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Overdose epidemic linked to the prescription of opioid analgesics in the United States

Epidemia de sobredosis relacionada con la prescripción de analgésicos opioides en Estados Unidos

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Until the 1980s, given their knowledge of the risk of addiction involved, physicians were more cautious regarding the prescription of opioids for treating pain in patients who were not terminal. However, an awareness-raising campaign aimed at US physicians and involving the dissemination of low quality evidence on the supposed efficacy and safety of opioid analgesics for the treatment of pain sparked the indiscriminate issuing of prescriptions and an even greater demand for opioid analgesics by patients.

A letter consisting of a single paragraph by Porter and Jick published in the New England Journal of Medicine in 1980 reported that 11,882 of 39,946 inpatients were prescribed an opioid, and that of only four who developed an addiction just one of them was severely addicted. The letter ended by saying that the development of addiction is rare in patients who do not have a history of addiction.

This letter has been cited 608 times over many years. In 72.2% of the citations it was taken as evidence that opioid addiction is rare, and 80.8% did not mention that the sample consisted of hospitalized patients. The message that the risk of addiction to opioid analgesics was small received widespread attention and may have contributed to the epidemic of opioid analgesics in North America. (Brauser, 2017; Leung, Macdonald, Stanbrook, Dhalla & Jauurlink, 2017).

The greater availability of opioids among the population triggered extensive growth in their use, with an attendant rapid increase in the rates of abuse, addiction and overdose. When measures were tried to contain the epidemic, some people went on to take illegal opioids such as heroin or fentanyl and their derivatives. The increase in the number of deaths due to overdose has alerted the government of the United States to reduce their prescription and increase the range of treatments available to people who have developed addiction and have overdosed (CDC, 2016; Madras, 2017).

During the last two decades, sales of prescription opioids have increased by 300%, and more than 50% have been prescribed for the treatment of chronic noncancerous pain. Almost half of those being treated for addiction to opioids have reported that their first contact was via a prescription for pain treatment, and 80% of those with heroin addiction went through an earlier stage of opioid analgesics abuse (Madras, 2017).

It is estimated that 30% of Americans suffer some type of pain, half of them daily and considered serious in a third, with lower back pain and osteoarthritis the most frequent forms of chronic pain. Although opioid analgesics are prescribed for 20%, these produce a reduction of only 8-12 points out of 100 in lower back pain, and the treatment dropout rate due to lack of efficacy or adverse effects is as high as 50%. The authors point out that they are probably being prescribed too frequently or for too long for acute pain, and that their long-term efficacy for chronic pain is limited (Lin & Vega, 2016).

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Between 1999 and 2014 the number of deaths by overdose in the United States has quadrupled, with 61% of them linked to opioids. The rapid increase of such deaths - particularly in 2014 and 2015 - is linked in 72.2% of cases to synthetic opioids such as fentanyl, and to heroin in 20.6% (Rudd, Seth, David & Scholl, 2016; NIDA, 2017).

The Center for Disease Prevention and Control (CDC) of the United States states that 20% of those initially prescribed a 10-day course of opioid analgesics will continue taking these drugs for more than a year, which points to their addictive power. And it is also recognized that the simultaneous use of opioid analgesics and benzodiazepines (BZD) quadruples the risk of death by overdose, compared with the consumption of opioids without BZD (CDC, 2016).

1. Opioid addiction

The dilemma surrounding opioid analgesics is that they are essential medicines to relieve certain types of pain, but can at the same time cause great suffering to people who develop addiction and/or those who overdose.

Repeated supraphysiological stimulation of the dopaminergic system produced by the continuous use of opioids can induce changes in the plasticity of the brain (at the level of the glutamatergic system in the circuits linking the prefrontal cortex with the striatum), resulting in a decrease in the inhibitory control of seek and consume behavior, which can then become compulsive (Kalivas & Volkow, 2005) and which we know as addiction.

Opioids also have a double reinforcing effect, positive and negative. The positive is due to the brain mechanism of drug reward and euphoria. The negative is a consequence of its pain relief effect, not only physical but also emotional or psychic, caused by stressful or traumatic events. People suffering from a mental disorder therefore obtain a more powerful negative reinforcing effect and this makes them more vulnerable to opioid addiction (Guardia, Surkov & Cardús, 2010).

The risk of addiction also increases when their use diverges from the prescription made by the physician, either with higher doses or using a more direct administration route than the oral, or when they are consumed alongside other drugs or alcohol because dangerous synergies occur, with a high risk of overdose from such combinations (NIDA, 2012).

Epidemiology of opioid analgesic use

The United States has suffered an epidemic of opioid overdose deaths. In this country 91 people die every day as a result of overdosing on either prescribed opioid analgesics or illegal opioids. In 2016 there were more than 64,000 overdose deaths, including more than 15,000 involving heroin and more than 20,000 from synthetic opioids. The increase in overdose deaths that has occurred in the last decade has accelerated in recent years and it seems that it may even result in a reduction in life expectancy of the United States population (NIDA, 2017).

This opioid abuse involves a cost of $20 billion a year incurred by emergency services and hospital care. All this despite the lack of scientific evidence that these drugs are effective for the treatment of chronic pain, and the fact that they can also produce serious negative consequences, such as addiction, overdose, falls and injuries caused by accidents (Case & Deaton, 2015).

Heroin adulterated with fentanyl or its derivatives without the buyer's knowledge is increasingly sold on the black market. The risk of death from overdose is therefore much greater, given the power of fentanyl and its derivatives to suddenly paralyze the respiratory centers of the brain (EMCDDA, 2017).

Fentanyl is a synthetic opioid with 50 to 100 times the potency of morphine. Fentanyl derivatives, such as acetyl fentanyl, furanyl fentanyl, sufentanil, alfentanil, remifentanil, carfentanil, 3-methyl fentanyl, acrylfentanyl, butyryl fentanyl, parafluorofentanyl and others, can be a hundred times stronger than fentanyl itself. In particular, carfentanil is 10,000 times more potent than morphine and is used to immobilize and capture or anesthetize large animals (O'Donnell, Halpin, Mattson, Goldberger & Gladen, 2017).

Traces of several fentanyl derivatives can appear in the same person cases of in death by overdose. In the eastern states of the United States, half the deaths caused by opioid overdose tested positive for fentanyl and nearly half the overdoses from fentanyl or derivatives did not test positive for other illegal opioids, which suggests that fentanyl and derivatives may be emerging as illicit drugs in their own right. Since they are very powerful and have a very rapid effect, loss of consciousness and death are almost instantaneous and require immediate treatment with high or repeated doses of naloxone. In addition, in one in five deaths from fentanyl and derivatives there was no evidence of injection, with the drug being administered by other routes. Indeed, fake opioid analgesics tablets containing fentanyl or derivatives are in circulation (O'Donnell et al., 2017).

The number of overdose deaths involving prescription opioids has quadrupled since 1999, and since 2007 exceeds the number of deaths from heroin and cocaine overdoses combined. More than 77% of adolescents who have used heroin had previously taken opioid analgesics (vicodin, Percocet or OxyContin), which means that these drugs could be considered an entry drug to heroin for adolescents in the United States. The opioid analgesics that are most frequently abused are hydrocodone (Vicodin) - one in 12 - and oxycodone (OxyContin) - one in 20 (NIDA, 2017).

In Europe, overdose deaths have also been detected as a result of the administration of potent fentanyl derivatives among people with a history of heroin use (Hikin, Smith,

Ringland, Hudson & Morley, 2017), as well as an increase in non-fatal poisoning notifications involving powerful synthetic opioids such as fentanyl and derivatives (EMCDDA, 2017).

3. Overdose

Shortly after the administration of opioids, symptoms may occur of drowsiness, disorientation, sedation, sweating, miosis, and a severe slowing of breathing that may lead to respiratory arrest.

When we talk about overdoses, people think they must be heroin induced, and the media at times claim that they are due to bad quality or adulterated heroin. However, there are more overdoses in the United States today caused by opioid analgesics than heroin. The risk of overdose rises with greater heroin purity and when combined with fentanyl or derivatives, benzodiazepines or alcohol.

Although isolated benzodiazepine use does not usually produce clinically significant respiratory depression, it can exacerbate respiratory depression caused by opioids, and the risk of death from overdose increases substantially when benzodiazepines are prescribed to people already taking opioid analgesics (Horsfall & Sprague, 2016).

Jones & McAninch (2015) state that the prescription drugs most frequently behind overdose deaths are opioid analgesics and benzodiazepines (BZD) used simultaneously. According to the Center for Disease Prevention and Control (CDC) in the United States, the proportion of overdose deaths caused by opioid analgesics associated with benzodiazepines increased from 13% in 1999 to 31% in 2011. Between 2006 and 2011, deaths with BZD involvement increased 14% per year, while those involving opioid analgesics (without BZD) remained at the same level (Paulozzi, Jones, Marck & Rudd, 2011; Chen, Hedegaard & Warner, 2014). Moreover, half the patients suffering an overdose had received the prescription of both drugs from the same prescriber, even on the same day (Hwang, Kang, Kornegay, Staffa, Jones, & McAninch, 2016). That is to say that the co-prescription of opioids and benzodiazepines increases the risk of overdose and also of deaths due to overdose, with people suffering from respiratory diseases, cardiovascular diseases, and elderly or debilitated people at increased risk.

In a recent study involving 13,089 people suffering from chronic noncancerous pain, 42.3% had received a prescription of benzodiazepines (BZD) in the 30 days prior to death (Olfson, Wall, Wang, Crystal & Blanco, 2017). Another recent study has found that in 23.5% of cases, the prescription of opioids and BZD was simultaneous, despite the intensifying effect of BZD on opioid-induced respiratory depression (Horsfall et al., 2017). Moreover, the US Drug Abuse Warning Network (DAWN) has also confirmed that the simultaneous use of opioids with benzodiazepines or alcohol increases the risk of overdose from 24% to 55%, compared to the isolated consumption of benzodiazepines (SAMHSA, 2014).

The risk of opioid overdose may be four times higher when benzodiazepines are involved than with isolated opioid use (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015) and they could be one of the causes of death in one out of every six opioid-related fatalities (Corkery, Schifano, Ghodse & Oyefeso, 2004). Finally, the risks of co-prescribing opioids with benzodiazepines are confirmed by the recent increase in the frequency of such co-prescription (Hwang et al., 2016) and by a disproportionate increase in deaths due to opioid overdose with benzodiazepine involvement (NIDA, 2017).

The US Centers for Disease Control and Prevention recommends providing naloxone to patients taking opioid analgesics combined with benzodiazepines, or if they have a history of alcohol or drug abuse, since they are at greater risk of overdose (CDC, 2016).

When a person suffers their first opioid overdose, they should start specialized treatment of their opioid disorder immediately because addiction is a disease that increases the risk of overdose and is therefore potentially life-threatening. Specialized treatment after a first overdose can prevent future accidental death. However, opioid analgesic users are unlikely to be diagnosed with opioid use disorder, and opioids often continue to be prescribed, even though a person has overdosed (Madras, 2017).

In Europe, overdose is the leading cause of death among high-risk drug users. Men make up 78% of such cases, with an increase in older users between 2007 and 2015 and a decrease in the group of younger users, reflecting the aging of the opioid-using population. In 2015, there were 8,441 deaths due to an overdose involving an illegal drug, which represents an increase of 6% compared to 2014. Spain also experienced an increase in overdose deaths between 2012 and 2015 (EMCDDA, 2017).

The Spanish public health system has some advantages that could help prevent a future epidemic of opioid analgesics and overdoses. The computer network linking hospital care services with primary health care and mental health and drug addiction centers allows access to unified clinical histories, which facilitates the coordination of the different physicians involved. The electronic prescription, to which all physicians in the public health service have access, avoids duplication and facilitates the supervision and control of prescription guidelines for medications. The computer registration of methadone prescription is also visible for any doctor in the network of drug addiction centers. The availability of treatment centers in the drug addiction network for people with substance addiction facilitates specialized treatment for their addiction. Finally, access to the public health system is free for the entire population, providing simultaneous treatment not only of addiction

but also of the medical and psychiatric comorbidities that addiction sufferer may have.

Nevertheless, we should beware of a certain trivialization and ignorance regarding the risks of co-prescription and polydrug use which increases the risk of accidents and overdoses. For example, in some hospitals, intravenous morphine is easily administered "on demand" to patients suffering severe pain. This regimen of opioid administration, which can be maintained for many days of hospitalization and sometimes until the patient leaves hospital, carries a greater risk of addiction, especially for people who already have a history of other addictive behaviors or a greater vulnerability towards them.

There is also a serious lack of knowledge regarding addiction as a common disease that can affect anybody and that requires specialized treatment. Such treatment frequently requires specific drugs, but some of these are not paid for by the public health system and others involve various difficulties in terms of prescription or acquisition, especially when obtaining them represents a burden for the patient or when the medication has a high price.

Other risk factors for fatal overdose lurking in our environments and which could emerge in the coming years are the prescription of high potency synthetic opioids - such as fentanyl and its derivatives - and the co-prescription of opioid analgesics and benzodiazepines. The consumption of benzodiazepines is very high in Spain, affecting 15.3% of women and 7.6% of men, increasing with age and rising to 27% of women and 11.3% of men in the 55 - 65 year age range (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2013).

4. Prevention

Treating pain long-term with opioid analgesics carries the risk of the patient developing tolerance and needing increased doses, of hyperalgesia and addiction. Follow-up and monitoring allows potential signs of abuse or misuse to be detected when the patient does not follow the prescribed prescription properly.

In 2015, the Department of Health and Social Services of the United States began a campaign to reduce the prescription of opioid analgesics and overdose deaths with three strategies: (1) educating and training doctors in pain treatment to reduce opioid prescription, (2) facilitating access to naloxone and (3) expanding the availability of treatment for opioid medication addiction, which also includes minors (Dowell, Haegerich, & Chou, 2016).

An electronic program to monitor opioid prescriptions and promote safe prescription practices has been developed. The CDC has developed a guide for prescribing opioids with the following recommendations: (1) limit the onset of abuse and addiction to opioid analgesics through better control by physicians, (2) expand drug treatments (based on evidence) for people who have developed opioid addiction, (3) protect people addicted to opioids by providing easy access to naloxone in case of overdose, and (4) coordinate the actions of all professionals who serve them to optimize the detection of and treatment response for people who have suffered some overdose (CDC, 2016).

Other recommendations are the preferential choice of normal analgesics for the treatment of chronic pain, restricting the prescription of opioid analgesics to those cases in which the benefits in terms of pain and functionality are greater than the associated risks, setting treatment goals with patients including the possibility of withdrawing them if the benefits do not outweigh the risks, prescribe the minimum effective dose, carefully re-assessing benefits and risks if thinking of exceeding a daily 50 mg dose of morphine or equivalent, and avoiding prescription and simultaneous use of other opioids or benzodiazepines whenever possible. Doctors should also enter the prescription data into an electronic program that warns of possible doses or combinations of risk. And access to specialized treatment programs and medications such as buprenorphine or methadone should be offered and facilitated for people who have developed opioid addiction (Dowell, et al., 2016).

Opioid addiction is a mental disease that can be treated effectively, although several treatment episodes are sometimes required for the patient to recover completely. Treatment requires the administration of opioid receptor agonist drugs, such as methadone or buprenorphine (NIDA, 2012).

It is also worth weighing up whether the benefits of opioid analgesics are only small or moderate in the short term and uncertain in the long term, compared to their potential serious adverse effects. For example, the expected benefits of opioids probably do not outweigh the potential risks when treating headache or fibromyalgia, while ordinary analgesics combined with antidepressants and/or anticonvulsants may even be more effective and less risky. There is no evidence to show that opioid analgesics bring long-term pain benefit and, conversely, considerable proof of their possible negative consequences, such as addiction, overdose and injuries due to traffic accidents. Furthermore, there is some evidence to suggest certain benefits of non-pharmacological treatments, which are also more innocuous (Dowell et al., 2016).

In the treatment of severe acute pain, opioids may be necessary for bone fractures, nephritic colic, myocardial infarction and similar. However, for minor pain such as lower back pain, headache, fibromyalgia or toothache, normal analgesics, rest and physiotherapy may be even more effective than opioids (Lligoña, López, Henche, Guardia, Tuca, et al., 2017).

In the case of chronic pain opioid analgesics should not be considered as routine or first-line treatment, with the

exception of active cancer, palliative care or terminally ill patients. It is advisable to avoid their indiscriminate prescription whenever possible and as a first option it is preferable to use ordinary analgesics, which can be combined with adjuvant drugs such as anticonvulsants and antidepressants (Guardia Serecigni, 2017).

It has also been recommended that patients be warned of the adverse effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence and withdrawal symptoms when their administration is interrupted. Patients should also be alerted to their interference in the ability to drive safely, especially at the beginning of treatment, when the dose is increased or when other depressants, such as anxiolytics, hypnotics or alcoholic drinks are taken at the same time (CDC, 2016).

Given that the United States is suffering from an overdose epidemic caused by a period of indiscriminate prescription of opioid analgesics, and given that we still have time to prevent a similar epidemic in our country, we consider it appropriate to disseminate this information not only among medical professionals but also among the entire population because together we can all contribute to avoiding it.

Conflict of interests

The author has received financial assistance from the Lundbeck Laboratory to carry out a study on the reduction of alcohol consumption with nalmefene which is unconnected to this editorial.

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Remediation therapy in patients with alcohol use disorders and neurocognitive disorders: A Pilot Study

Terapia de rehabilitación cognitiva en pacientes con trastorno por consumo de alcohol y trastorno neurocognitivo. Estudio piloto

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Abstract

Many alcohol-dependent patients suffer from cognitive impairment of variable severity, manifested by alterations in retrograde and anterograde memory, visuospatial processing, cognitive abilities and attention, some of which are reversible. In this context, cognitive remediation therapies could significantly improve patients' performance; therefore, these are considered a valuable alternative. The aim of this study was to implement cognitive remediation therapy in patients with alcohol dependence and cognitive impairment and evaluate its viability and effectiveness. The participants were sixteen abstinent, alcohol-dependent patients (mean age of 59 years, 63% males) from the Addictive Behaviours Unit of a tertiary hospital. Over 6 months, a nurse led 1-hour weekly sessions (24 sessions in total) during which exercises for improving functional, social and cognitive performance were completed. Patients were assessed at baseline, at the end of the study and 6 months later, using the Mini-Mental State Examination (MMSE) and the Memory Alteration Test (M@T). Their respective scores were 26.4 (SD 3.16), 29 (SD 1.67) and 27 (SD 3.1) for the MMSE and 38.7 (SD 6.81), 45.7 (SD 5.6) and 41.1 (SD 7.86) for the M@T. Changes were assessed with both Friedman and Wilcoxon signed-rank tests, with mostly statistically significant differences ($p < 0.05$). Assistance and satisfaction were high. Therefore, the therapy was viable, widely accepted and effective.

Key words: Alcohol dependence; Cognitive impairment; Cognitive remediation; Alcohol-related brain damage.

Resumen

El deterioro cognitivo es común en los pacientes alcohólicos. Éste se manifiesta por alteraciones en la memoria anterógrada y retrógrada, el procesamiento visual-espacial, y en las habilidades cognitivas y la atención, siendo algunas reversibles. Las terapias de rehabilitación cognitiva podrían mejorar el rendimiento de los pacientes, siendo una alternativa terapéutica de interés. El objetivo de este estudio piloto fue evaluar la implementación, viabilidad y efectividad de la terapia de rehabilitación cognitiva en pacientes con dependencia al alcohol y deterioro cognitivo asociado. Se trata de un estudio piloto con 16 pacientes (63% hombres, edad media de 59 años) seguidos en la Unidad de Conductas Adictivas de un hospital de tercer nivel. Siendo la abstinencia un requisito para la inclusión, durante 6 meses una enfermera realizó sesiones semanales de una hora (24 sesiones), realizándose ejercicios de psico-estimulación para la mejora del rendimiento cognitivo, funcional y social. Se evaluó a los pacientes al inicio, al final y pasados 6 meses, mediante las escalas MMSE (test Mini-mental de Lobo) y T@M (test de Alteración de Memoria). Sus puntuaciones medias respectivas fueron 26.4 (DE 3,16), 29 (DE 1,67) y 27 (DE 3,1) para MMSE y 38,7 (DE 6,81), 45,7 (DE 5,6) y 41,1 (DE 7,86) para T@M. Los datos se analizaron mediante la prueba de Friedman y se comparon los distintos periodos temporales mediante la prueba de rangos con signo de Wilcoxon, siendo la mayoría de comparaciones significativas ($p < 0,05$). La asistencia y la satisfacción fueron elevadas. Así pues, la terapia fue viable, ampliamente aceptada y mostró ser efectiva.

Palabras clave:: Dependencia de alcohol; Deterioro cognitivo; Rehabilitación cognitiva; Daño cerebral asociado al alcohol.

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The DSM-V (American Psychiatric Association, 2013) defines alcohol use disorders as a condition related with ongoing consumption of alcohol in excessive amounts or during a long period over one's lifetime; it is also associated with the appearance of behavioural and physical symptoms, including tolerance, abstinence, lack of control over use, and health, family and social problems (American Psychiatric Association, 2013; Schuckit 2009). The European Union, a region in which alcohol production and use is strongly rooted, has one of the world's highest per capita use rates (approximately 23 million adults/year are alcohol-dependent) (Rosón Hernández, 2008). In Spain, alcohol use has remained stable since the eighties, though the proportion of female drinkers has increased.

The World Health Organization (WHO) associates the disorder with physical and mental deterioration. This entails a significant increase of both mortality and morbidity (Varela-Rey, Woodhoo, Martinez-Chantar, Mato, & Lu, 2013), including neurological, cardiovascular, metabolic and neoplasic diseases.

Alcohol use disorder generates a socioeconomic impact, particularly low productivity and health-related expenses. In turn, the disorder is strongly correlated with sexual risk situations, injuries, suicide, homicide and automobile accidents, the costs of which are difficult to evaluate (Miller et al., 2008; Surkan, Fielding-Miller, & Melchior, 2012; Varela-Rey et al., 2013).

Alcohol-related brain damage (ARBD) is currently the focus of special attention (Soler-González, Balcells-Oliveró, & Gual-Solé, 2014). Behavioural alterations, cognitive deficits, amnesia and degenerative changes to the cerebellum are worth highlighting. Neuroimaging has related excessive alcohol use with the appearance of structural (e.g., loss of volume of brain and cerebellum tissue) and functional (e.g., dysfunction of the frontal and temporal lobes and their connections) changes (Glass et al., 2009; Yeh, Gazdzinski, Durazzo, Sjöstrand, & Meyerhoff, 2007). These changes have been related to alterations of episodic memory, attention, visuospatial processing, and emotional processing and decision-making (Pedrero-Perez, Rojo-Mota, Ruiz-Sanchez de Leon, Llanero-Luque, & Puerta-Garcia, 2011). On this basis, a patient with alcohol use disorder may develop a Neuro-cognitive Disorder (NCD) characterized by deficits that last longer than the usual duration of acute abstinence, and which are more likely in older patients (Gongvatana et al., 2014). It is estimated that between 50-70% of alcohol-dependent persons have some degree of cognitive deterioration (Glass et al., 2009; Miller et al., 2008). The DSM-5 uses the categories "Mild (MND) and major neurocognitive disorders associated with substance abuse".

The more frequent MND entails difficulty in performing some daily tasks that require paying attention and following instructions. Ongoing use, with the appearance of secondary brain damage, associated with lower neuronal plasticity and other age-related changes, could cause patients difficulty in learning and implementing new information (Pedrero-Perez et al., 2011). These changes are related to poor compliance with rules and guidelines, lower adherence to treatment, early relapses and few skills for refusing alcohol (Bates, Buckman, & Nguyen, 2013; Pedrero -Perez et al., 2011).

Executive functions and memory, given their close relationship with abstinence and the success of treatments for alcohol dependency, have been the most widely studied areas in the field of alcohol. Working memory and the capacity for inhibiting response (both based on frontal circuits) are highly vulnerable to alcohol use (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). Other skills, such as conceptualization, abstraction and problem-solving are also frequently affected (Rupp et al., 2006). Despite the existing patterns as regards impact, it is absolutely necessary to emphasize the important heterogeneity among patients, due to the methodological limitations of published research, as well as to the numerous determinant factors underlying individual cognitive capacities, such as age, gender, cultural level or genetic influence (Bates, Bowden, & Barry, 2002).

Decades of research and clinical experience have focused current treatment for alcohol use on helping patients to reduce or stop their alcohol use through medication, behavioural therapies, brief interventions and social skills training (Huebner & Kantor, 2010). Studies with patients with alcohol use disorder and mild NCD show that the latter may interfere with treatment efficiency. Nevertheless, lost cognitive functions may be recovered, at least to a great extent (Rojo-Mota et al., 2009). To achieve this, continuous abstinence is a critical, though probably insufficient, element.

In this regard, functional and cognitive rehabilitation therapy acquires increasing importance. To date, most programs have focused on improving executive functions, memory, and other cognitive skills (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Bickel, Yi, Landes, Hill, & Baxter, 2011; Houben, Wiers, & Jansen, 2011; Levine et al., 2011) with the goal of evaluating their effect on both cognitive skills per se, as well as with regards to their impact on variables associated with alcohol use. Recently, rehabilitation models based on changing automatic and implicit processes have also been proposed (Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Alternative programs include the use of heart rate variability biofeedback (Bates & Buckam, 2013), aerobic physical training (Brown et al., 2014) or mindfulness (Chiesa, Calati, & Serretti, 2011).

Though the concept is not new, most studies on this issue are already relatively outdated (Allen, Goldstein, & Seaton, 1997; Goldman, 1990). Though some recent studies (Rupp, Kemmler, Kurz, Hinterhuber, & Fleischhac-

ker, 2012) contribute promising results, notable controversy arises as to these programs' real efficiency, structure and organization (Bernardin, Maheut-Bosser, & Paille, 2014). In addition, there is still important vagueness as to the real mechanisms implied in these rehabilitation programs' observed improvements, with different studies suggesting different mechanisms (Houben, Havermans, Nederkoorn, & Jansen, 2012; Houben & Wiers, 2009). We must also mention the critique of both methodologies applied and external validity of cognitive rehabilitation programs in the field of alcoholism (Houben et al., 2011; Houben & Wiers, 2009). Altogether, this suggests that evidence on this issue is far from conclusive, and further research is required.

A wide range of health professionals manage these programs, but nurses deserve special attention because they assume a key role in both detecting and treating alcohol dependency. Patient care by nurses combines psychosocial interventions, where mental health nurses assume leadership, given their more direct and frequent contact with patients (Ryan & Rothwell, 2010). When providing orientation, the nurse takes advantage of the therapeutic relationship to boost the patient's motivation and interest in rehabilitation therapy.

The purpose of this pilot study was to evaluate the implementation of rehabilitation therapy within the framework of nursing, in alcohol-dependent patients with associated cognitive deterioration, and to evaluate the therapy's viability and effectiveness.

Resources and methods

Pilot study to evaluate the implementation, acceptability and preliminary efficiency of a cognitive rehabilitation program for patients with alcohol dependence and mild NCD. Longitudinal prospective design without control group. The study was comprised of a total of 24 alcohol-dependent patients seeking treatment through outpatient visits to the Addictive Behaviours Unit (see inclusion criteria) upon agreeing to participate and signing the informed consent.

Criteria for participation in the study was as follows. Inclusion criteria: outpatient services patient, alcohol use disorder (DSM-5) with a minimum of 6 months of abstinence beforehand, significant NCD: M@T below 43 and MMSE below 28. Exclusion criteria: Serious NCD or any other condition (per clinical diagnosis) that prevents correctly participating in, or assimilating, the cognitive therapy.

During 6 months, the Unit nurse led a total of 24, 1-hour weekly sessions. The group was comprised of 8-9 patients who always held group sessions with the participation of all of its members in each. Mental stimulation resources and exercises were used to improve cognitive, functional and social performance. Written language (prints) and spoken language (recall of participants' names, previous tasks, etc.) were alternated. The tasks were completed in a classroom specifically adapted for group work, and the patients occupied the same place to facilitate name retention. The contents of the resources used were adapted to the patients to the extent possible, regardless of their sociocultural level.

The areas object of the intervention were:

1. Attention: practiced through visuospatial recognition exercises, word searches and differences between pictures.
2. Memory: different memory types were addressed:
   a. Semantic memory: implying conceptual information, referring to aspects related to the meaning of the information, addressed in the group through exercises involving general knowledge without the recall of specific events, such as holidays and celebrations.
   b. Episodic memory: worked on using information that allows for assigning dates and spatially locating information in relation to the patients themselves and to other events, specifying where and when a given information was presented in regard to one's personal biography. This was done by asking questions about each patient's life events, such as: "What did you do yesterday?" "What have you eaten for breakfast?" "What colour was the shirt you wore yesterday?"
   c. Autobiographical memory: the recall of first-hand events experienced by each patient was addressed through the recall of specific episodes from their lives, based on personal and family photographs or objects.
   d. Immediate memory: the recall and/or recognition of information received was addressed based on repeating word lists and describing previously presented images.
3. Language:
   a. Automatic language: based on automatic verbal production tasks through exercises to recall the months of the year, numerical series, and popular sayings or proverbs in which the beginning of the saying was presented, and the patient had to complete the sentence and then try to explain its meaning.
   b. Recall: to evaluate and work on aspects related with verbal fluency in which the person named the elements comprising a category (colours, animals, pieces of clothing, cities).
   c. Spontaneous language: through exercises to describe images, prints, situations and occurrences.
   d. Denomination: addressing the content of terms and words based on exercises that entailed naming objects and the components of objects.
4. Reading and writing: reading and writing exercises were completed based on reading newspaper articles, books and short texts.

5. Executive functions: practiced through exercises to detect similarities and differences, logical series and numerical processing exercises. Though the targets were attention and memory, other fields, such as language and executive functions, were alternated as well to maintain adherence and retention during the one-hour session.

Three evaluations were completed: at baseline, at the end of the sessions (6 months) and 12 months later. The initial evaluation gathered sociodemographic data, medical and psychiatric background and the level of cognitive deterioration using the MMSE (Mini-Mental State Examination) and the M@T (Memory Alteration) scales. The two latter ones were also evaluated at 6 and 12 months, as well as the patients' attendance in the therapy sessions and satisfaction (Annex 1).

Instruments

No specific validation exists for screening cognitive deterioration in patients with alcohol use disorder. Most published studies, as well as in clinical practice, use those tests that are most widely applied in other fields (such as dementias). In our case, we used the MMSE and the M@T.

MMSE: The Mini-Mental State Examination is a test for screening dementias, also used for follow-up of their progress. It is most commonly used to detect and evaluate the progress of a Cognitive Disorder associated with neurodegenerative diseases, like Alzheimer (Crum, Anthony, Bassett & Folstein, 1993). It includes five sections: orientation, attention, concentration and calculation, memory and language. The administration of this simple, structured scale requires no more than 5-10 minutes. The maximum, total score is 30 points. A score of < 23 points in a geriatric patient or of < 27 points in the general population is considered cognitive deterioration (Crum et al., 1993).

M@T SCALE: The Memory Alteration Test (M@T) is a cognitive screening test with high sensitivity and specificity for mild cognitive deterioration similar to amnesia, and for mild Alzheimer disease, among the general population. It is short, easy to administer and score. It evaluates several memory subtypes through five sections: immediate memory, temporal orientation memory, semantic remote memory, free recall memory, and recall memory with cues. Administration varies between 5-10 minutes for both healthy patients and those with mild cognitive deterioration. Correct answers are summed (1 point). A global score over the 50 maximum possible points of the test is recommended. A score of < 43 points represents significant cognitive deterioration (Rami, Molinuevo, Sanchez-Valle, Bosch, & Villar, 2007).

Data analysis

Microsoft Office Excel sheets were used to gather and analyse the data. SPSS (V.19) was used for statistical analysis. Given the sample size and non-normal data, the Friedman test was used as a non-parametric method for repeated measures to evaluate the global significance of the study for both scales. Post-hoc analysis was completed with the Wilcoxon signed-rank test, comparing the baseline results with the results upon completing the therapy and with those 6 months later. A 95% confidence interval was used for data analysis for $p < .05$ to contrast the proposed hypothesis.

Results

Table 1 displays sociodemographic data and the medical and psychiatric background of patients who attended therapy. A total of 24 patients participated, 58.3% were male and 41.7% were female. The average age was 62 years (minimum 41, maximum 83). Of these, 4.2% were single, 54.2% were married, 33.3% were divorced and 8.3% were widowed. As regards educational level, 54.2% had completed elementary schooling, and the remaining patients had completed secondary or upper education. As to employment, 45.8% were retired, 4.2% were currently unemployed but had worked previously, 33.3% had no paid job at the time, and 16.6% were currently employed. As regards socioeconomic level, 33.3% of the patients currently or previously experienced difficulties. As to household composition at the time of becoming a member of the therapy group, 29.2% of the patients lived alone, while the remaining lived with the family, mainly with a partner or children.

Patient health was assessed as to the presence or absence of cardiovascular risk factors (CRF), noteworthy neurological diseases and associated psychiatric diagnoses, independent of alcohol dependence. As to cardiovascular risk factors, 58.3% of the patients were smokers, and approximately one third of the sample showed dyslipidaemia. A lower percentage of patients had diabetes mellitus or obesity. No patients had primary neurological disorders. As to a history of neurological diseases, 20.9% of the sample showed some type of diagnosis; among these, two patients had a diagnosed cerebrovascular disease, one epilepsy and another Huntington's disease. A dual pathology diagnosis was common; 66.7% of the patients had a mental disorder, depression being predominant (33.3%), followed by personality disorder (16.75%), anxiety disorder (12.5%) and bipolar disorder (4.2%).

Table 2 displays the results of the MMSE and M@T scales over the course of the study. The global analysis of the Friedman test found statistically significant differences between the successive values of the MMSE ($X^2(2) = 22.86$; $p < .001$) and the M@T ($X^2(2) = 36.02$; $p < .001$). The post-hoc analysis was completed with the Wilcoxon signed-rank test and the Bonferroni correction, which established statistical significance at $p < .0125$. As regards the MMSE scale, the medians and interquartile range for the values at baseline, upon completion of the treatment, and 6 months later were 27 (from 25.25 to 28), 29 (from 28 to

Table 1. *Sociodemographic data of the sample.*

Variable	Characteristics of the sample Mean (*SD*) or percentage
Age	61,83 (12.25)
Gender (% female)	41.7%
Marital status	
unmarried	4.2%
married	54.%
divorced	33.3%
widowed	8.3%
Level of education	
primary	54.2%
secondary	16.7%
occupational training	16.7%
3-year university degree	8.3%
5-year university degree	4.2%
Employment status	
unemployed	33.3%
unskilled worker	8.3%
skilled worker	8.3%
unemployment benefits	4.2%
pensioner	45.8%
Socioeconomic level	
lower class	33.3%
middle class	66.7%
Household composition	
alone	29,2%
spouse	41,7%
spouse and children	12,5%
children	12,5%
parents/siblings	4,2%
Comorbid psychiatric disorder	66,7%
Pharmacological treatments	
antipsychotics	20.8%
benzodiazepines	12.5%
antidepressants	33.3%
interdictor	37.5%
Smokers	41.7%

Note. SD = Standard Deviation.

30) and 28 (from 27 to 30). Significant differences were found between the values at baseline and at the end of the treatment ($z = -4.05$; $p < .001$), while no significant differences were found between the values at baseline and at 6 months after the end of the treatment ($z = -2.392$; $p = .017$). As regards the M@T scale, the medians and interquartile range for the values at baseline, upon completion of the treatment, and 6 months later were 40 (from 37 to 45.5), 47.5 (from 44 to 49) and 44.5 (from 40 to 48). Significant differences were found between the values at baseline and at the end of the treatment ($z = -4.3$; $p < .001$), as well as between the values at baseline and at 6 months after the end of the treatment ($z = -2.6$; $p = .009$).

Missed attendance was anecdotal: 7%. As regards satisfaction with the therapy, 3% of the patients was satisfied and 97% was very satisfied. During follow-up of the study, all of the patients remained abstinent, according to the usual urine tests and self-reports completed by patients and their family members.

Table 2. *Values of the MMSE and M@T at baseline, end of treatment and 6 months.*

Scale	Baseline Mean (*SD*)	End Mean (*SD*)	At 6 months Mean (*SD*)
MMSE	26.58 (2,7)	28.92 (1,4)	27.71 (2,8)
T@M	39.79 (6,4)	46.00 (4,8)	42.21 (7,5)

Note. SD = Standard Deviation. MMSE = Mini-Mental State Examination. M@T = Memory Alteration Test.

Discussion

The results of this pilot study suggest how cognitive rehabilitation therapy, when integrated in the treatment for alcohol dependency, could facilitate improved cognitive functioning in patients with cognitive deterioration associated with alcohol use, in accordance with general cognitive screening tests, like the M@T and the MMSE. The data collected over the course of the study suggest that the improvement observed upon completion of the study tends to be lost at 6 months after the end of the intervention.

It is important to highlight the pilot nature of this study, implying the absence of a control group and a small sample size. This means that the observed cognitive improvements cannot be definitely attributed to the direct effects of the therapy. Any type of intervention that facilitates social interaction and fosters some cognitive effort could have caused improvements in the patients' cognition or mood state, and this could have acted as a confounding variable in our analysis. Furthermore, other secondary effects, such as a greater presence of or closer supervision by the health professionals in relation to the patients, also exist. We must also mention that part of the improved progress observed could be spontaneous, as it is known that some cognitive functions improve spontaneously during prolonged periods of abstinence. Even so, we consider that the fact that patients remained abstinent 6 months before and 6 months after the intervention increases the validity of the results. Again, given that this is a pilot study without a control group, conclusions cannot be drawn as to whether the observed improvement contributed toward maintaining abstinence in subsequent months, a fact confirmed by other studies (Rupp et al., 2012). Special mention must also be made of the use of instruments like the M@T and the MMSE, lacking high specificity and usually used as screening methods. Nevertheless, these are widely-used instruments validated in many contexts and have been shown to partially correlate with broader neuropsychological batteries (Rami et al., 2009), wherefore they may be considered an acceptable approximation of the cognitive state of the study's participants.

The fact that both levels of attendance and patient satisfaction were high suggests that the intervention was widely accepted. The fact that these patients' nurse led the

intervention could be an important variable in explaining this high satisfaction and acceptance. This could have significant implications as regards future research, suggesting that the implementation of the therapy by the patients' attending health professionals could improve its implementation and, therefore, facilitate or contribute toward achieving higher efficiency.

The study has major limitations derived of the criteria used for selecting patients to participate in the therapy. Based on the demand of patients and their family members as well as of professionals, with regards to the detection of cognitive impairment symptoms, the patient sample was quite heterogeneous, mostly in health-related issues. In this sense, the presence of patients with and without neurological disorders, as well as others with a dual diagnosis, could justify the scarce homogeneity of results in the MMSE and M@T scales. All of this hinders drawing conclusions on causality as regards the possible aetiology of the cognitive deterioration. Though it is true that all patients met criteria of alcohol dependency, it is quite likely that, in many cases, the observed deterioration had a mixed source. Another significant limitation is general and not study-specific: the absence of neurocognitive evaluation tests validated specifically in alcohol-dependent populations and which, furthermore, have proven their sensitivity to changes in the long term. Many authors have emphasized this, and it should be a focus of future research. Finally, given the pragmatic and exploratory study design, the effect of learning could not be controlled in patients in which it could have resulted of completing the same test several times over 12 months.

Conclusions

This pilot study shows how cognitive rehabilitation therapy in patients with cognitive deterioration and alcohol use disorder is viable and widely accepted by the patients. The study's important methodological limitations hinder obtaining valid conclusions about its efficacy. Nevertheless, preliminary exploratory data suggest that the intervention could contribute toward improving this population's cognitive functioning. The promotion of research in this field is of critical importance, given its potential positive impact on a highly relevant health problem. To this end, it would be convenient to first validate neurocognitive screening and evaluation tests in patients with alcohol use disorder that are sensitive to changes over time; then, to carry out prospective longitudinal studies with comparison groups for different rehabilitation approaches.

Conflict of interests

The authors declare the inexistence of conflicts of interest with regard to this study.

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Academic outcomes and cognitive performance in problematic Internet users

Rendimiento académico y cognitivo en el uso problemático de Internet

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Abstract

Only few studies have examined the relationship between problematic Internet use (PIU) and cognitive and academic performance in adolescents. The aim of this study was to analyze the differences in academic and cognitive performance (perception, attention, memory, verbal fluency and abstract reasoning) between adolescents with and without PIU. A total of 575 students from different high schools of the region of Alicante participated. Students were divided into two groups: adolescents with and without PIU (PIU and NPIU, respectively). Several questionnaires were administered to assess problematic Internet use, as well as students' academic performance. Substance use (alcohol / cannabis) was also assessed as exclusion criteria. A battery of neuropsychological tests was used to assess cognitive abilities. On the one hand, PIU users group obtained poorer academic results than NPIU, in terms of lower marks and more failed subjects. On the other hand, PIU group had a better hit ratio in the perception test than NPIU group. However, PIU adolescents got higher error rates for the abstract reasoning test. This greater number of errors, plus a similar number of hits compared to the NPIU group, could indicated a higher response rate for the PIU group, which may might be associated with greater impulsivity. As occurs in other addictive and non-substance-related problems studies, these results could mean difficulties in impulse control and regulation of response inhibition circuits in PIU users group. Future research is needed to analyze in depth the results presented in this paper.

Keywords: Internet Problematic Use; Cognitive Performance; Academic Outcomes; Adolescents; Alcohol.

Resumen

Son escasos los estudios que hayan analizado la relación entre el uso problemático de Internet (UPI) y el rendimiento cognitivo y académico en adolescentes. El objetivo de este estudio fue analizar las diferencias en rendimiento académico y cognitivo (percepción, atención, memoria, fluidez verbal y razonamiento abstracto) en una muestra de estudiantes de Secundaria con y sin UPI. Participaron un total de 575 estudiantes de diferentes institutos de la provincia de Alicante, que fueron divididos en dos grupos: adolescentes con y sin uso problemático de Internet (UPI y NUPI, respectivamente). Se administraron varios cuestionarios para evaluar el uso problemático de Internet de los sujetos, su rendimiento académico, su consumo de sustancias (alcohol/cannabis) como criterios de exclusión, así como una batería de pruebas neuropsicológicas para evaluar sus habilidades cognitivas. Por un lado, los adolescentes con UPI mostraron un peor rendimiento académico que los estudiantes del grupo NUPI, presentando una nota media más baja y un mayor número de asignaturas suspendidas. Por otro lado, el grupo UPI obtuvo una mayor tasa de aciertos en el test de percepción que el grupo NUPI. Sin embargo, los adolescentes con UPI obtuvieron una mayor tasa de errores para el test de razonamiento abstracto. Este mayor número de errores, sumado a un número similar de aciertos que NUPI, indicaría una mayor tasa de respuesta total para el grupo UPI, que podría estar asociada a mayor impulsividad. Concretamente, tal y como se ha observado en otros problemas adictivos con y sin sustancia, estos resultados podrían indicar en los sujetos del grupo UPI dificultades en el control de impulsos y en la regulación de los circuitos de inhibición de respuesta. Resultan necesarios, no obstante, futuros estudios que profundicen en las conclusiones presentadas en este trabajo.

Palabras clave: Uso problemático Internet; Rendimiento cognitivo; Rendimiento académico; Adolescentes; Alcohol.

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The use of Information and Communication Technologies (ICTs) is becoming ever more widespread in our society, especially among the adolescent population. According to data from the National Institute of Statistics, in 2015 99% of boys and girls between 16 and 24 years of age used the Internet in the previous month, and 92.8% used it daily in the previous 3 months on at least 5 days a week (Instituto Nacional de Estadística, 2015).

Such massive Internet use has given rise to the appearance of negative effects related to its excessive use (Herrera, Pacheco, Palomar & Zavala, 2010; Secades-Villa et al., 2014), which in recent years has led in turn to an increase in the number of studies that have attempted to define this complex phenomenon, often categorized under the name "Problematic Internet Use" (PIU) (Jelenchick & Christakis, 2014; Rial, Gómez, Isorna, Araujo & Varela, 2015; Starcevic, 2010).

PIU has been defined in the scientific literature in terms similar to substance use disorders and pathological gambling, as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 2013). More specifically, PIU has been conceptualized in relation to the negative effects caused by excessive use, including symptoms such as tolerance, a negative effect on daily life (eg. reducing other activities), loss of control, and the desire to be online (Beranuy, Chamarro, Graner & Carbonell, 2009). However, in contrast to Internet gaming disorder or video game addiction (Bertrán & Chamarro, 2016; Carbonell, 2014; Li, O'Brien, Snyder & Howard, 2016), it is important to note that PIU has not yet been included in the DSM-5 classification.

In terms of prevalence, rates ranging from 3.7% to 9.9% have been estimated for Spain, with greater problematic use among the youngest users (Carbonell, Fúster, Chamarro & Oberst, 2012).

The negative consequences of PIU have been the focus of various studies, some of which have concentrated on the impact such use has on the brain functioning of excessive users. This approach has seen different investigations using neuroimaging techniques to verify alterations in the prefrontal cortex in subjects with PIU, which results in problems of cognitive flexibility (Dong, Lin, Zhou & Lu, 2014), decision making (D'Hondt, Billieux & Maurage, 2015), working memory (Dong, Devito, Du & Cui, 2012) and executive control. These characteristics are consistent with disorders found in other behavioral addictions, such as pathological gambling (Brand, Young & Laier, 2014). Some studies have also analyzed the cognitive functioning of these subjects using classical neuropsychological tests, such as the Stroop test (as a measure of response inhibition ability) or general intelligence questionnaires where longer reaction times, more frequent errors, as well as difficulties in comprehension were found in the PIU group in comparison with a control group (Dong, Zhou & Zhao, 2011; Rücker, Akre, Berchtold & Suris, 2015). Furthermore, significant differences were found between subjects with and without problematic Internet use in terms of their verbal fluency, with PIU subjects faring worse in tasks that evaluated verbal semantic fluency (Nie, Zhang & Liu, 2017).

In light of such data, numerous studies have suggested that neurobiological substrates and cognitive functioning in PIU may resemble not only that found in other behavioral addictions but also that observed in substance use disorders (Bauernhofer, Papousek, Fink, Unterrainer & Weiss, 2015; Brand et al., 2014; Yuan et al., 2016; Zhang et al., 2015).

In addition, research has also found a relationship between PIU and academic performance among students. On the one hand, PIU has been shown to be a predictor of poor academic performance due to lack of sleep and concentration related to Internet abuse (Stavropoulos, Alexandraki & Motti-Stefanidi, 2013). On the other hand, low school performance has been found to cause PIU (Huang et al., 2009). Given cross-sectional nature of most of these studies, the direction of influence of both variables is still unclear.

Despite the growing interest in the influence of PIU on the cognitive skills and academic performance of young people, studies that have linked these variables are still few and far between, and conclusive evidence has yet to be found (Park et al., 2011). Also, there is a scarcity of studies investigating these variables through specific neuropsychological tests. The objective of the present study is therefore to analyze the relationship between the problematic use of the Internet and the academic and cognitive performance of a sample of secondary students.

Our variables have been selected on the basis of previous evidence in the field of neuropsychological assessment and academic performance, both in regard to PIU and other addiction disorders. Given these previous studies, our hypotheses are: (a) students with PIU will achieve worse academic outcomes in terms of lower average school grades and a greater number of suspended subjects than adolescents who use the Internet in a non-problematic way (NPIU); (b) students with PIU will reveal worse cognitive performance in all neuropsychological tests used, in the form of a higher rate of errors and a lower hit rate, than the adolescents with NPIU.

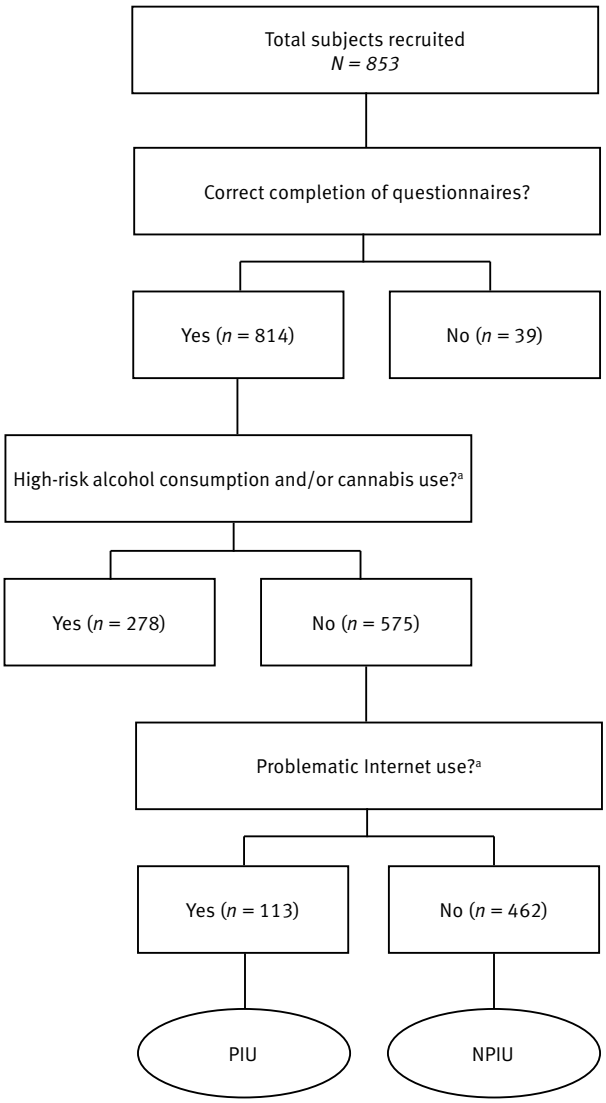
Method

Participants

Initially, 8 public secondary schools (IES) were selected, randomly chosen from among the 40 high schools in the cities of Alicante and Elche. The random procedure was performed by rolling a die and using the numbers produced to select the different schools from a list.

Two of the schools contacted refused to take part in the study, so finally the sample was taken from 6 schools. The participating schools were all state funded and located in neighborhoods of average socioeconomic level. With a total of 31,280 students enrolled in these high schools at the time of sample collection, and taking into account the estimated average prevalence of PIU in Spanish adolescents of 10% (95% confidence, ± 2.5 margin of error), the minimum sample required for this study was 544 participants. After receiving the authorization of the heads of study of each school, 47 classes of the 3rd and 4th years of compulsory secondary education (ESO) were randomly selected, resulting in an initial total of 853 students recruited.

Since different studies have shown that both cannabis use (Shrivastava, Johnston & Tsuang, 2011) and excessive alcohol consumption (Geil et al., 2014; Parada et al., 2012) have a negative effect on cognitive performance, the following exclusion criteria were set to eliminate possible biases in measuring cognitive abilities: (a) cannabis use once a month or more and (b) high-risk alcohol consumption. These variables were assessed using a questionnaire based on the ESTUDES survey of the National Plan on Drugs (Ministerio de Sanidad, Servicios sociales e Igualdad, 2013) to collect data on the frequency of alcohol and cannabis use during their lifetime, in the last month, and the last week. In the case of alcohol, the intensity of use was also collected, measured in SDUs consumed in the last month.



Note. PIU: Students with problematic Internet use
NPIU: Students with non-problematic Internet use
[a] Cannabis: once a month or more; Alcohol: ≥ 6/4 SDUs (boys and girls, respectively).
[b] Score ≥ 34 on IREQ.

Figure 1. Sample selection

In this study, high-risk alcohol consumption is understood as binge drinking, which involves the consumption of at least 6 standard drink units (SDU) (1 SDU = 10 grams of pure ethanol) in the case of boys and 4 SDUs in that of girls concentrated within the space of two hours (National Institute on Alcohol Abuse and Alcoholism, 2004).

An exploratory analysis of the initial sample thus resulted in a total of 278 cases (32.5%) being rejected for not meeting the inclusion criteria to participate in the study or for not correctly completing the tests, leaving a final sample of 575 participants. The participants were between 13 and 17 years old, with a mean age of 14.67 ± 0.79 years, and 55.7% (n = 314) of them were in the 3rd year of compulsory secondary education at the time of the study. The average mark for the previous school year of the total sample was 7.08 ± 1.58, while the number of fails stood at an average of 0.93 ± 2.12. Girls made up 42.1% (n = 239) of the sample.

As for Internet use, 82.6% (n = 470) of the total sample reported using the Internet on a daily basis, and 21.2% (n = 121) reported being online for more than three hours per day. In terms of the preferred use of the Internet, the adolescents mainly used social networks when online (87.4%, n = 450).

Participants were classified into two groups according to whether they had PIU (19.7%; n = 113) or not (NPIU) (80.3%; n = 462). To measure this classification criterion the Internet-Related Experiences Questionnaire - IREQ (Beranuy et al., 2009) was used, in which a cut-off score of greater than or equal to 34 is considered an indication of PIU. The sample selection diagram is shown in Figure 1.

Variables and instruments

A series of self-reports and neuropsychological tests were used to measure problematic Internet use, frequency and type of use, alcohol and cannabis consumption, as well as the cognitive and academic performance of subjects. The instruments were chosen on the basis of their use in other similar studies conducted on addictive disorders (Carballo, García, Jáuregui, Marín & Pérez-Jover, 2011; Carballo et al., 2013) and on their ease of use when applied in a group format. The different types of variables assessed were as follows:

- *Sociodemographic variables*: Information was collected regarding the sex, age and school year of the participants.
- *Internet use*: An ad-hoc three-item questionnaire was used to measure the frequency of Internet use during the week and the number of hours spent online daily, as well as the preferred type of Internet use (social networks, study, online games, etc.).
- *Problematic Internet use*: This was assessed with the Internet-Related Experiences Questionnaire - IREQ (Beranuy et al., 2009), a 10-item self-administered questionnaire with a 4-point Likert-type response scale, based on DSM-IV-TR criteria for substance abuse and pathological gambling. The questionnaire addresses different aspects such as increased tolerance, negative effects arising from the problematic Internet use, reduction of activities, loss of control, avoidance, and desire to be online. Scores range from 0 to 40, with 34 or higher signaling problematic Internet use. The questionnaire has been shown to have an internal consistency of 0.77 in the Spanish sample (Beranuy et al., 2009).
- *Academic outcomes*: The average school mark was calculated on a scale from 0 to 10, as well as the number of subjects failed in the last year. Both data were reported by the students.
- *Variables related to cognitive performance*: A battery of neuropsychological instruments was used to measure perceptual acuity, attention span, verbal memory (immediate and delayed recall), verbal fluency, and abstract reasoning. The hits and errors of all tests were collected.
- *Perceptual acuity*: This was measured with the WAIS-III Symbol Search Subtest (Wechsler, 1995), in which participants have to identify the presence of certain symbols in a sequence of several elements. The test was applied for one minute.
- *Attention*: The Symbol Digit Modalities Test (SDMT) (Smith, 1982) was used. This test evaluates sustained attention and concentration, requiring complex visual scanning and visual tracking. It consists of indicating the numbers corresponding to each symbol (from one to nine) beneath it, in a list of randomly distributed symbols and following a certain order. Subjects had one minute and thirty seconds to complete the test.
- *Immediate and delayed verbal recall*: Immediate and delayed recall was assessed by using of a list of twelve standard words extracted from the Weschler Memory Scale (1945). A list of the words was read to the participants with an interval of two seconds between each word. They were then asked to write down those they remembered in two attempts, one immediately after hearing the list, and another five minutes later. Between the two attempts a distractor was introduced in the form of the SDMT.
- *Verbal fluency*: semantic fluency was assessed (Buriel, Casanova, Rodés, Fombuena & Böhm, 2004) with the spontaneous production of names of fruits and vegetables in one minute.
- *Abstract reasoning*: we used the DAT (Differential Aptitude Test) (Bennett, Seashore & Wesman, 2000), which consists of 32 items. The subjects were presented with a series of images ordered consecutively and logically and had to infer from the alternatives presented which would be the next one to follow in the sequence. A total of three minutes was provided to complete the test.

Procedure

After receiving the relevant permits from the Conselleria d'Educació of the Generalitat Valenciana (Education Department of the Regional Government of Valencia) and the heads of study of the schools, the questionnaires used in this cross-sectional descriptive study were administered in groups in the schools themselves during school hours. Student participation was subject to consent from parents or legal guardians, and was voluntary, anonymous and confidential. All neuropsychological and self-report tests were applied at the same time, in a single session of between 30-50 minutes. After being given a brief explanation of the aims of the study, the students responded to the instruments according to the instructions provided for the correct completion of the same. The study was approved by the Ethics and Research Commission of the Miguel Hernández University in Elche.

Data analysis

The data obtained were coded and analyzed using the statistical software IBM SPSS Statistics 20.0 for Windows. Descriptive analyses of means and frequencies were performed in order to detect and exclude those cases that did not meet the study's inclusion criteria, as well as to identify the sociodemographic profile of the participants (eg. sex), their use of the Internet (eg. days online) and academic performance (eg. average grade). Likewise, descriptive analyses were made to differentiate between those subjects with problematic Internet use (PIU) and those without (NPIU).

In order to study the frequency differences in non-continuous variables, the chi-square test was used, while for the analysis of mean differences in continuous variables a non-parametric (Mann-Whitney U) analysis was used for independent samples, since the variables did not fit the normal distribution. Effect size was found with the Rosenthal *r* (*r*) for comparisons between groups (Rosenthal, 1991), with the following value settings: 0.10 (small effect size), 0.30 (moderate effect size) and 0.50 (large effect size) (Ro-

senthal, 1991). The confidence level applied in these statistical tests was 95%. To minimize the type I error that can occur with multiple analyses, we used the Bonferroni correction for an alpha of 0.05 in groups of related variables.

Finally, for an in-depth analysis of the relationship between problematic Internet use and academic and cognitive performance, a hierarchical linear regression analysis was conducted. The variable problematic Internet use was used as a dummy control variable. Interaction terms were calculated using differential scores to control multicollinearity problems.

Results

First, we analyzed the sociodemographic differences between PIU and NPIU, applying the Bonferroni correction for the three sociodemographic variables analyzed, and obtaining an α of 0.0167 (0.05/3).

As in Table 1 shows, no statistically significant differences were found between the two groups in terms of sex, mean age or school year.

We also performed a differential analysis of the two variables related to academic performance across PIU and NPIU (Table 2). Again, the Bonferroni correction was performed for these variables, obtaining α = 0.025 (0.05/2). Statistically significant differences were found both in relation to the mean grades (z = -4.52, p = .0001) and to the number of subjects failed in the previous course (z = -2.47, p = .01). In this way, the group with problematic Internet use obtained a lower average grade (6.47 ± 1.42) than the NPIU group (7.23 ± 1.58), as well as a greater number of failed subjects (PIU = 1.22 ± 2.11; NPIU = 0.86 ± 2.12), although the size of the effect was small in both cases (r = 0.20 and r = 0.11, respectively).

Table 1. *Sociodemographic differences between PIU and NPIU*

	PIU (19.7%; *n*=113)	NPIU (80.3%; *n*=462)	X^2/*z(p)*
%(*n*) *Boys*	59.3 (67)	57.6 (262)	0.11 (.74)
Mean age	14.79 ± 0.86	14.63 ± 0.78	- 1.53 (.12)
%(*n*) *3rd year*	51.8 (58)	56.6 (256)	0.85 (.35)

Note. *Significant for α=0.0167 (Bonferroni correction)

Table 2. *Differences in academic outcomes (means) between PIU and NPIU*

	PIU	NPIU	*z(p)*	*r*
Grade[a]	6.47 ± 1.42	7.23 ± 1.58	- 4.52 (.0001)*	.20
Failed subjects[b]	1.22 ± 2.11	0.86 ± 2.12	- 2.47 (.01) *	.11

Note. *Significant for α=0.025 (Bonferroni correction)
[a]N = 521; PIU = 101; NPIU = 420
[b]N = 545; PIU = 107; NPIU = 438

Finally, we analyzed the differences between PIU and NPIU with regard to cognitive performance (Table 3). Mean differences in the number of hits and errors in attention span tests, perception, memory (immediate and delayed recall), verbal fluency, and abstract reasoning were evaluated. The α was 0.0042 (0.05/12) after performing the Bonferroni correction on these twelve variables.

As shown in Table 3, we found statistically significant differences between the two groups in relation to the success rate on the perceptual acuity test (z = -2.89, p = .0039), with the PIU group obtaining a higher number of hits (19.18 ± 5.41) than the NPIU group (17.55 ± 5.8). Likewise, differences were found in the error rate of the abstract reasoning test (z = -3.15, p = .002), with a higher rate in the PIU group (5.84 ± 4.00) compared to those with NPIU (4.45 ± 3.20). In both cases, the effect size was small (r = 0.12 and r = 0.13, respectively). No statistically significant differences were found in the hit and error rates of the other neuropsychological tests applied.

Table 3. *Differences in academic outcomes (means) between PIU and NPIU.*

	PIU (*n*=113)	NUPI (*n*=462)	*z* (p)	*r*
Perception				
Hits	19.18 ± 5.41	17.55 ± 5.80	-2.89 (.0039)*	.12
Errors	0.65 ± 1.14	0.69 ± 1.51	-0.36 (.71)	
Immediate recall				
Hits	6.57 ± 1.94	6.46 ± 2.11	-0.34 (.73)	
Errors	0.50 ± 0.84	0.51 ± 0.5	-0.06 (.94)	
Delayed recall				
Hits	5.73 ± 1.85	5.80 ± 2.01	- 0.27 (.78)	
Errors	0.67 ± 1.25	0.67 ± 2.07	- 1.11 (.26)	
Verbal fluency				
Hits	12.73 ± 2.80	12.34 ± 3.31	- 0.92 (.35)	
Errors	0.12 ± 0.38	0.15 ± 0.80	- 0.42 (.66)	
Attention				
Hits	32.65 ± 9.47	32.84 ± 8.55	-0.49 (.61)	
Errors	1.42 ± 8.39	2.55 ± 12.26	- 0.12 (.89)	
Abstract reasoning				
Hits	6.85 ± 3.29	6.69 ± 3.43	-0.62 (.53)	
Errors	5.84 ±4.00	4.45 ± 3.20	-3.15 (.002)*	.13

Note. *Significant for α=0.0042 (Bonferroni correction)

Finally, to eliminate any confounding bias that cognitive performance might have on academic performance, hierarchical linear regression analyses were performed in which those cognitive performance variables were incorporated as predictors of academic performance in which statistically significant differences were found.

In the first regression analysis (Table 4), stratified according to problematic or non-problematic Internet use, the existence of a positive and statistically significant association between the hit rate in the perceptual acuity test and average school grade ($p < .05$) was found in the NPIU group, as well as between the error rate in abstract reasoning and the number of failed subjects ($p < .01$). Likewise, a statistically significant negative association between the error rate in abstract reasoning and the average school grade ($p < .01$), and between the hit rate in perception and the number of failed subjects ($p < .05$) were observed. However, in the PIU group, the only statistically significant standardized coefficient was the errors in abstract reasoning variable, which again was negatively associated with average grades ($p < .05$).

Given the results obtained, a new regression model was run with the complete sample incorporating the interactions of each predictor with the problematic Internet use variable, which was also included as a predictor. As shown in Table 5, PIU as well as the perception hit rate and error rate in abstract reasoning are statistically significant predictors of the average grade, with PIU being the variable which explains the highest percentage of variance. Regarding the number of failed subjects, perceptual acuity and errors in abstract reasoning are the only statistically significant predictors, with each of these variables contributing only a small amount. Furthermore, in the interaction analysis, no evidence has been found that problematic Internet use moderates the association between cognitive performance and academic outcomes ($p > .05$).

Table 4. *Regression analysis of academic outcomes (mean grade and failed subjects) in relation to cognitive performance*

	Mean grade			Failed subjects		
Variables	**B (SE)**	**β**	**sr² (%)**	**B (SE)**	**β**	**sr² (%)**
NPIU						
Hits perception	.03 (.01)	.11*	1.17%	-.04 (.02)	-.11*	1.14%
Errors abstract reasoning	-.07 (-.03)	-.13**	1.72%	.11 (.03)	.16**	2.56%
PIU						
Hits perception	.04 (.03)	.15	2.31%	-.05 (.04)	-.15	2.19%
Errors abstract reasoning	-.08 (.04)	-.22*	4.54%	.07 (.05)	.13	1.64%

Note. B= non-standardized coefficient , SE= standard error, β=standardized coefficient, sr=semipartial
*p<.05,**p<.01

Discussion

The aim of this study was to analyze the relationship between the problematic use of the Internet and academic and cognitive performance of a sample of secondary school students. The results obtained showed worse academic outcomes of subjects with PIU, as well as statistically significant differences in the tests of perception and abstract reasoning between subjects with and without problematic Internet use.

First, students were divided into two groups according to their use of the Internet, with a 19.7% ($n = 113$) prevalence of PIU found in the sample assessed. While this figure is within the range found in international investigations (Aboujaoude, 2010; Kamal & Mosallem, 2013; Wang et al.,

Table 5. *Linear hierarchical regression for the analysis of the link between academic outcomes, cognitive performance and problematic Internet use*

Variables	**B (SE)**	**β**	**sr² (%)**	**B (SE)**	**β**	**sr² (%)**
Step 1						
Hits perception	.03 (.01)	.12**	1.30%	-.04 (.02)	-.12**	1.30%
Errors abstract reasoning	-.07 (-.02)	-.15**	2.05%	.10 (.03)	.15**	2.25%
PIU	-.70 (.18)	-.17**	2.89%	.25 (.23)	.05	0.20%
Step 2						
Hits perception	.03 (.01)	.11**	0.96%	-.04 (.02)	-.11**	0.94%
Errors abstract reasoning	-.07 (.02)	-.14**	1.39%	.11 (.03)	.17**	2.10%
PIU	-.70 (.18)	-.17**	2.76%	.29 (.24)	.05	0.27%
Perception*PIU	.01 (.03)	.01	0.01%	-.01 (.04)	-.02	0.02%
Abstract reasoning *PIU	-.02 (.05)	-.02	0.02%	-.04 (.06)	-.04	0.09%

Note. B= non-standardized coefficient , SE= standard error, β=standardized coefficient, sr=semipartial
*p<.05,**p<.01

2011), it is notable for being higher than that observed in other studies with the Spanish population (Carbonell et al., 2012). This discrepancy may be related to the increase in Internet access in recent years (Gómez, Rial, Braña & Varela, 2014), as well as to the different types of measures and diagnostic criteria used to evaluate PIU.

With reference to the hypotheses set out at the beginning of this study, it was suggested firstly that students with PIU would experience worse academic outcomes in terms of lower average grades and a greater number of failed subjects than the adolescents with NPIU. This hypothesis has been confirmed in its entirety for the sample assessed, the results being consistent with the findings of previous studies, in which a positive relationship between PIU and scholastic failure has been observed (Huang et al., 2009; Tsitsika et al., 2011; Stavropoulos et al., 2013).

Regarding the second hypothesis, it was thought that, in comparison with adolescents with NPIU, students with PIU would show worse cognitive performance in all the neuropsychological tests applied, measured in terms of higher rates of error and lower hit rates. This hypothesis has only been partially confirmed for the abstract reasoning test, where the PIU group scored a higher number of errors. This higher error rate, coupled with a similar hit rate to the NPIU group, would indicate a higher total response rate among adolescents with problematic use. A high response rate has been described as an indicator of greater impulsivity (Lozano & Pérez, 2012) and is frequently observed in studies with a substance-addicted population (De Wit, 2009). This result is furthermore consistent with previous evidence linking PIU to difficulties in impulse control and in the regulation of response inhibition circuits, with subjects experiencing this problem failing in the inhibition of unwanted actions and presenting worse impulse control than those without PIU (Dong et al., 2012, Dong, Zhou & Zhao, 2010, Li et al., 2014). In any case, these results merely indicate trends which should be analyzed in depth in future research.

With regard to the perceptual acuity test, it is interesting to note that the results illustrated a tendency running counter to the predicted hypothesis. Thus, it was found that the adolescents presenting PIU obtained higher hit rates in the perception test than the NPIU group. This improved perceptual performance in subjects with PIU could be due to greater exposure to and training with visual stimuli resulting from a more extensive use of the Internet and computers, as some previous studies have suggested (Castel, Pratt & Drummond, 2005; Green & Bavelier, 2003, 2007). However, it should be noted that the evidence relating to this aspect is still controversial (Murphy & Spencer, 2009; Park et al., 2011).

With the aim of minimizing biases in the results, and based on previous studies that link academic outcomes and cognitive performance (Stelzer & Cervigni, 2011), the association between both variables was assessed. Although significant associations were found between them, specifically in the case of average school grade, it is important to note that it was PIU that explained the greatest percentage of variance. Further studies are nevertheless needed to analyze these relationships in more depth.

Having presented these findings, however, it is necessary to point out that the results of this research should be treated with caution, since it is an exploratory study suffering from a series of limitations that need to be taken into account for future research.

Firstly, this is a descriptive, cross-sectional study and the results have therefore been analyzed and interpreted only in terms of the trends displayed by the variables of interest. Moreover, the small effect sizes yielded by the relationships found mean that the results shown should be interpreted with extreme caution.

Secondly, in relation to the measuring instruments used, it is worth emphasizing the limitations inherent in self-reports (eg. social desirability). It would be interesting here to be able to include sincerity scales that would make it possible to assess the validity of the responses of adolescents.

Similarly, with regard to the neuropsychological assessments, it is important to remember that performance in such tests could be influenced by other extraneous variables, such as, for example, previous training of subjects through the frequent playing of video games, or participation in psycho-pedagogical improvement programs, which commonly use some of the tasks applied in this study. In relation to these instruments it would also be advisable to redefine or improve their characteristics in order to establish specific tests that reliably assess cognitive abilities in this area, as has been achieved in the field of other addictive problems (Szczebak & Glisky, 2011).

Although extensive control of extraneous variables that might contaminate outcomes (eg. substance use) was carried out, future studies should consider the possible influence of other factors on cognitive performance, such as variables interfering at the time of the test (eg. anxiety state). It would likewise be of interest to include other comparison groups in the assessment of cognitive variables, such as non-students or adolescents with other addictive disorders or problems (eg. alcohol abuse). Furthermore, it would be advisable to consider longitudinal designs with broader samples that allow the analysis of how performance and PIU of adolescents develops, the assessment of the cognitive performance of subjects before they start using the Internet for the first time, as well as the analysis of relationships with variables such as impulsivity, time online or type of Internet use.

Despite these limitations, it is important to note that the results of this study provide new data in a field of research of growing interest but in which conclusive evidence has yet to be established. Also, unlike other studies in the area

of PIU which have focused on neuroimaging techniques, this paper presents comparative data from performance in neuropsychological tests, providing results on specific cognitive functions. In this way, the trends observed in this study may lead to the start of future lines of research that will allow us to deepen our knowledge of the consequences of PIU on cognitive abilities, as well as their implications in the neuropsychological development of subjects who initiate problematic use early on.

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Conflict of interests

The authors of this paper declare that they have no conflicts of interest.

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Intangible costs of alcohol dependence from the perspective of patients and their relatives: A contingent valuation study

Costes intangibles de la dependencia alcohólica desde la perspectiva de los pacientes y sus familiares: un estudio de valoración contingente

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Abstract

Alcohol dependence causes multiple problems not only for the person suffering dependence but also for others. In this study, the contingent valuation method is proposed to measure the intangible effects of alcohol dependence from the perspective of the persons directly involved: the patients and their relatives. Interviews were conducted with 145 patients and 61 relatives. Intangible effects of alcohol dependence were determined based on willingness to pay for a hypothetical treatment for dependence, with different success scenarios (100% and 50%). The mean monthly willingness to pay among the alcohol-dependent population was €129 and €168, respectively, for the treatments with 100% and 50% success. The willingness to pay of relatives was greater in both scenarios (€307 and €420, respectively), which could be explained by their greater perception of the family, labour, and health problems resulting from alcohol dependence. Regression analysis showed that patients' willingness to pay is positively related to treatment efficacy, personal income and moderate health deterioration, and negatively related to feeling discouraged and depressed. The results from this study can be applied to economic valuation studies that aim to measure the benefits of programs intended to reduce the prevalence of alcohol dependence. The intangible costs estimated can be added to the direct and indirect costs commonly used.

Keywords: Alcohol; Dependence; Family; Contingent valuation; Willingness to pay.

Resumen

La dependencia alcohólica produce múltiples problemas no sólo a la persona que la padece sino también a su entorno. En este estudio se utiliza la valoración contingente para valorar los efectos intangibles de la dependencia alcohólica, desde la perspectiva de las personas directamente implicadas: pacientes y familiares. Se ha entrevistado a 145 pacientes y 61 familiares. Los efectos intangibles de la dependencia alcohólica se obtienen a partir de la disponibilidad a pagar por un hipotético tratamiento para la dependencia, ante dos escenarios de éxito (50% y 100%). La disponibilidad a pagar media mensual de la población alcohólica es de 129€ y 168€, respectivamente, por los tratamientos con un 50% y un 100% de éxito. La disponibilidad de los familiares es mayor en ambos escenarios (307€ y 420€, respectivamente), lo cual podría ser explicado por su mayor percepción de los problemas familiares, laborales y de salud generados por la dependencia alcohólica. El análisis de regresión realizado muestra que la eficacia del tratamiento, la renta personal y tener un deterioro moderado de la salud influyen positivamente en la disponibilidad a pagar de los pacientes, e influye negativamente estar desanimado y deprimido. Los resultados de este estudio pueden ser aplicados a estudios de evaluación económica cuyo objetivo es medir los beneficios de programas destinados a reducir la prevalencia de la dependencia alcohólica. Los costes intangibles estimados pueden ser añadidos a los costes directos e indirectos habitualmente utilizados.

Palabras clave: Alcohol; Dependencia; Familia; Valoración contingente; Disposición a pagar.

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The excessive consumption of alcoholic beverages is highly prevalent. It is estimated that about 15% of the European population consumes alcohol excessively (Rehm et al., 2004) and about 1.2–3% suffers from alcohol dependence (Anderson & Baumberg, 2006; Rehm, Rehm, Shield, Gmel & Gual, 2013). The effects of excessive alcohol consumption have innumerable direct as well as indirect economic costs (Anderson et al, 2006; Baumberg, 2010). Direct costs refer to expenditures that could have been put to some other productive use, primarily those resulting from greater medical expenses (Johansson et al., 2006). Indirect costs refer, primarily, to the loss of resources caused by reduced participation in the labour market and the lower productivity of workers with alcohol problems (Petersen et al, 2005).

Alcohol dependence also has numerous intangible, or non-financial, costs, such as lowered life expectancy and reduced quality of life (pain, suffering, physical health problems, etc.), for the dependent person, as well as for the persons around them. "These costs are non-financial because they do not have a monetary value, in the sense that you cannot sell or exchange pain. Nevertheless, individuals and society would be prepared to pay something to avoid them, which means they do have a (non-financial) value" (Baumberg, 2010). Most studies that have analysed intangible costs have focused on the effects on the drinker's health in terms of mortality (Collins & Lapsley, 2008; John et al., 2013) and quality of life. One of the most frequently used quality of life measure is the *quality-adjusted life year*. This measure has been applied to assess both the impact of alcohol dependence (Kraemer et al., 2005; Maheswaran, Petrou, Rees & Stranges, 2013; Petrie, Doran, Shakeshaft & Sanson-Fisher, 2008; Saarni et al., 2007; Sanderson, Andrews, Corry & Lapsley, 2004; Stouthard, Essink-Bot & Bonsel, 2000) and the benefit of interventions aimed at their treatment or prevention (Chisholm, Rehm, Van Ommerem & Monteiro, 2004; Corry, Sanderson, Issakidis, Andrews & Lapsley, 2004; Mortimer & Segal, 2005; Parrott, Godfrey, Heather, Clark & Ryan, 2006; UKATT Research Team, 2005). In Spain, although the clinical guidelines provide an ample description of the intangible consequences, few studies have focused on measurement of these effects. The recent review by García-Pérez et al. (2014) found two studies that quantify the impact of alcoholism on the quality of life (Fernández et al., 2010; Grandes, Montoya, Arietaleanizbeaskoa, Arce & Sanchez, 2011) and Mosquera & Rodríguez-Míguez (2015) provide new empirical evidence about the effects of alcohol dependence on the quality of life of the dependent and those around them.

However, the intangible effects on well-being caused by alcohol go well beyond direct effects on the drinker's health. Thus, alcohol dependence has additional effects on the drinker such as suffering, isolation, family problems, social exclusion, etc. Moreover, this disease has considerable effects on the drinker's surroundings (Laslett et al., 2010). Although alcohol is considered the addictive substance that inflicts the most damage to others (Nutt, King & Phillips, 2010), few studies have analyzed these intangible effects. Except some studies have estimated the quality of life lost by cohabiting relatives (Jarl et al., 2008; Mosquera et al, 2015), most of the research in this field focuses on the measurement of direct and indirect costs. So, the research has concentrated on the study of foetal alcohol syndrome and the impact of alcohol abuse on victims of crimes and traffic accidents, using the cost of illness as the primary measurement method (for a review of these studies, see Navarro, Doran & Shakeshaft, 2011). Failure to consider the intangible effects of alcohol consumption can result in significant underestimation of the effects of the disease, as well as of the benefits associated with treatment.

Contingent valuation studies using the willingness to pay (WTP) method have proven to be a useful tool for assessing the effects of certain treatments providing benefits extending beyond health. The WTP method allows valuation of the intangible costs of alcohol dependence based on the maximum amount a person is willing to pay to reduce, eliminate, or avoid the situation. This methodology has been widely applied in the valuation of health consequences (Byrne, O´Malley & Suarez-Almazor, 2005; Fautrel et al., 2007; Greenberg, Bakhai, Neumann & Cohen, 2004; Gueylard-Chenevier & Leloier, 2005; Pinto-Prades, Farreras & de Bobadilla, 2008), as well as clinical procedures (Bergmo & Wangberg, 2007; Boonen et al. 2005; He et al., 2007; Jimoh, Sofola, Petu & Okorosobo, 2007; Sadri, Mackeigan, Leite & Einarson, 2005; Walsh & Bartfield, 2006; Whynes, Frew & Wolstenholme, 2003; Yasunaga, Ide, Imamura & Ohe, 2006; Unutzer et al., 2003) (for a review of studies prior to 2002, see Smith, 2003). Application of this methodology to the area of drugs in general (Bishai et al., 2008; Tang, Liu, Chang & Chang, 2007; Zarkin, Cates & Bala, 2000) and to alcohol dependence in particular has been quite limited. To our knowledge, only two published contingent valuation studies have used the WTP method to measure the effects of abusive alcohol consumption. Jeanrenaud and Pellegrini (2008) utilized a sample of 236 subjects from the general Swiss population to determine the WTP for a curative treatment for alcohol dependence of a hypothetical cohabiting relative. Petrie, Doran & Shakeshaft (2011) used a sample from the general Australian population to determine the WTP for 10% and 20% reductions in damages caused by alcohol within the population. However, we do not know any study that had obtained the WTP of the patients themselves or their relatives. It can be important because there is abundant empirical evidence that shows that the preferences of the general population and the persons directly involved can be quite different (Brazier et al., 2005; Gabriel et al., 1999; Mann, Brazier & Tsuchiya, 2009; Ubel, Loewenstein & Jepson, 2003).

The aim of this study is to quantify the intangible costs of alcohol dependence, from the perspective of the patients themselves and their relatives, in 2010 in Spain. In line with the studies mentioned above, our study applies the WTP method to estimate these intangible effects in an ample sense, not just effects on health. However, unlike them our study measures those effects from the perspective of the persons directly involved, who were personally interviewed by the first author.

Materials and methods

Samples

The patients and relatives were contacted at an alcohol treatment unit within the National Health Service. This care unit treats patients with alcohol dependence from the sanitary area of Vigo (Spain). The sample of patients, all of whom met the DSM-4R criteria for alcohol dependence, included all those who came in for consultation for two months, starting in January of 2010. Participation in the study was voluntary and anonymous. The exclusion criteria were refusal to participate, undergoing the first consultation at the centre, acute alcohol intoxication or untreated mental disorder at the time of the interview, and sufficient cognitive deterioration to hinder comprehension of the questionnaire (in the therapist's opinion). The sample of relatives included all individuals who accompanied the patients participating in the interview on the day it was conducted. If the patients came in for consultation alone at the time of inclusion in the study, the person who usually accompanied them (if there was one) was contacted by telephone to invite them to participate voluntarily. There were no other exclusionary criteria besides the refusal to participate. During the recruitment period, 161 patients came in for consultation. Two patients were excluded for alcohol intoxication, two for untreated mental illness, and six for cognitive deterioration. In addition, five patients were excluded from the analysis because they did not provide a WTP. One subject declined to participate. In only 66 cases were we able to interview a relative (in the remaining cases, no relative was involved in the treatment process). One relative declined to participate and four were excluded because they did not provide a WTP. The first coauthor interview personally and independently to participants, to address potential problems during the interview.

Questionnaire

In the first part of the interview, the participant was informed regarding its voluntary and anonymous nature and informed consent to participate was obtained. At the same time, the participants were also explained that the proposed scenarios were hypothetical and that the answers given would in no way influence the care received. In the second part of the interview, the following scenario was described to the subject:

"Imagine a hypothetical situation, a situation that is not real. Suppose there is a new treatment to solve the problems related to alcohol. This treatment is not always effective. In 5 out of 10 people (i.e. half of treated patients) is effective, that is, they stop drinking alcohol and have no desire to do so. In the other half of the patients, the treatment is not effective. The effects of the treatment remain for a year. After one year, the subject would have to receive the treatment again with the same probability of success. The treatment is not free, that is, it is not financed by the National Health Service. What is the maximum annual amount you would pay to receive such treatment? Think calmly your answer. You must take into account your level of income. Please note that this payment would mean giving up the consumption of other goods or would reduce their ability to save money".

In addition, as proposed by Blumenschein, Johannesson, Yokoyama & Freeman (2001), a follow-up question was included. After the participants provided the maximum amounts they would be willing to pay for the treatment, they were asked to choose between two answers: "*I'm absolutely certain I would pay it"* and "*I think I would pay but I am not sure"*. If they chose the second answer, they were asked again to provide an amount they were sure they would pay. Next, another scenario was proposed in which the efficacy of the hypothetical treatment was 100% but the patient would have to continue treatment indefinitely, because otherwise there would be a relapse, reverting to the initial situation. As in the previous scenario, the participants were again asked for the maximum they would be willing to pay per month, followed by the follow-up question.

In the third part of the interview, the participants were asked for a subjective opinion regarding the consequences of their alcohol dependence in four areas: health, family relationships, occupational consequences, and legal problems. The possible answers in each case were 'hardly any', 'moderate/some', and 'severe/many'. We also know the date in which the actual treatment started as well as the level of consumption (measured in standard drink units), in a normal day, at that date. Next, standard sociodemographic questions were asked to the participants. Finally, the patients as well as the relatives were asked to complete the 36-item Short-Form Health Survey (SF-36), a generic health-related quality of life questionnaire (information needed for another study underway).

Statistical analysis

The intangible cost of alcohol dependence was estimated based on the mean and median values provided by participants after the follow-up question for both success scenarios. Next, a linear regression was estimated to identify the variables correlated with the WTP. The independent variable was the WTP provided by the participants after the follow-up question and the explanatory variables were

the variables that, a priori, might be related to the WTP. A regression model with random effects was used to take into account that the participants provided two responses, one for the treatment with a 50% probability of success and the other for the treatment with a 100% probability of success.

Validity analysis

There is a consensus that contingent valuation studies, at a minimum, should show a positive correlation between WTP and income level. Therefore, the sign of the regression coefficient for this variable is used as the theoretical validity test. The lack of prior literature regarding an alcohol-dependent population's WTP presents a considerable challenge to our formulation of the hypotheses regarding the remaining variables. In any case, it would seem reasonable that, ceteris paribus, the worse the consequences of dependence are, the greater the WTP for treatment should be. Another expected result is for the WTP to be sensitive to the quantity and/or quality of the good (Arrow et al., 1993), known as sensitivity to scale. In our study, we analyse whether or not the WTP for the treatment with 100% success is significantly greater than that for the treatment with 50% success. Failure to support this hypothesis would raise serious doubt about the validity of the results (Diamond & Haussman, 1994).

Compliance with the two preceding analyses of validity is a necessary but not a sufficient condition to guarantee the validity of the results. Criterion validity is the most important validity test, because it analyses the extent to which the results for a hypothetical scenario match those obtained in a real transaction. Since a hypothetical treatment was proposed in our study as a mechanism for obtaining the intangible costs of alcohol dependence, the criterion validity cannot be tested. The impossibility of testing criterion validity is common to other WTP studies (in fact, the lack of a real market is one of the reasons that justifies performing WTP study). However, this test is relevant because the differences between the WTP in a real and a hypothetical situation can be quite large. The study of Blumenschein et al. (2001) on WTP for an asthma treatment found that the overestimation obtained from the hypothetical scenario (compared to a real purchase scenario) was corrected by asking the interviewees if they were absolutely certain they would make the payment they had mentioned. For this reason, to minimize the potential difference between the real and hypothetical WTP, we asked a follow-up question assessing the certainty with which the interviewees would pay the amounts they initially provided.

Results

Description of the samples

Table 1 summarizes the characteristics of the 145 patients and 61 relatives selected. Males dominate the patient sample and about half live with a wife or partner. The mean personal income is €766 and 20 subjects gave their income as €0 (in seven cases, the family income was also €0). We compared information from the patient sample for sex, mean age and education, with information provided by the institution for all patients under its care and found no significant differences. More than half of the sample of relatives consists of women, spouses of the dependent person. Table 1 also reports the mood (downhearted and depressed) of the dependent person during the last four weeks (obtained from the SF-36) and the percentage that had family support (patients were considered to have family support if we contacted a family member for inclusion in the study).

With regard to the perception of the interviewees regarding the consequences of alcohol dependence, it seems that patients as well as relatives agreed that family problems, followed by health problems, are the most frequent. However, except for legal problems, relatives perceived significantly greater problems than expressed by patients (this conclusion holds when we compare the sample of relatives to the subsample of 61 patients whose relative was interviewed).

All data are available by request to the corresponding author.

WTP results

Table 2 gives the mean and median WTP and Figure 1 provides the WTP distribution. The mean monthly WTP for a treatment with 50% efficacy was €135 after the first question and €129 after the follow-up question. In 23 cases, the answer was €0. The monthly WTP for the treatment with 100% effectiveness was €168, rejecting the existence of insensitivity to scale. Since only one individual changed the response after the follow-up question, the final WTP was practically the same as before. In 22 cases, the answer was €0.

Among patients who were unwilling to pay anything, there is no evidence that their answers can be considered "protest" responses. To start with, 55% of interviewees with zero WTP for the treatment with 100% success had no personal income and 29% had no family income either (they got by with help from other persons or non-governmental institutions). These percentages are slightly reduced (to 52% and 27%, respectively) when the treatment had a 50% success rate. In addition, if we examine only the participants who did have personal incomes, the mean income is 23% greater among those who had a positive WTP, compared to those who provided a zero WTP response. Finally, the participants who provided a zero WTP mentioned their low level of income as the reason for this response. Therefore, we believe that there is not a clear justification for considering these responses as "protest" responses and they have been included in the analysis.

The WTP for the sample of relatives was significantly greater, with a mean monthly WTP of €307 when the

Table 1. *Description of samples of patients and relatives*

		Patients (n = 145)	**Relatives** (n = 61)
Sex (% males)		69.66	18.03
Age distribution (%)	18 to 29 years old	5.59	6.56
	30 to 44 years old	30.34	31.15
	45 to 59 years old	48.28	39.34
	60 years old and older	15.86	22.95
Mean personal income (€/month)		765.93	854.16
Mean family income (€/month)		1301.03	1826.57
Level of education (%)	Elementary or less	66.9	68.85
	Secondary	25.52	16.39
	Higher	7.59	14.75
Living with a partner (%)		45.52	85.24
Downhearted and depressed (%)	None/a little of the time	37.93	50.82
	Some/most/all of the time	62.07	49.18
Family consequences (%)	Hardly any	17.93	8.2
	Moderate/some problems	36.55	31.15
	Severe/many problems	45.52	60.66
Health consequences (%)	Hardly any	31.03	19.67
	Moderate/some problems	40.69	44.26
	Severe/many problems	28.28	36.07
Legal consequences (%)	Hardly any	69.66	78.69
	Moderate/some problems	15.86	8.2
	Severe/many problems	14.48	13.11
Occupational consequences (%)	Hardly any	69.66	52.46
	Moderate/some problems	17.24	22.95
	Severe/many problems	13.10	24.59
Alcohol intake before treatment (%)	‹4 units/day (men)/ ‹3 (women)	12.41	
	›4 and ‹8 (men) / ›3 and ‹6 (women)	18.62	
	›8 units/day (men)/ ›6 (women)	68.97	
Duration of treatment (months)	‹ 4	12.41	
	4 - 6	7.59	
	7 - 12	15.17	
	12 - 24	35.86	
	› 24	28.97	
Has family support (%)		42.76	
Relationship with dependent (%)	Spouse		67.7
	Son/daughter		4.6
	Sibling		10.8
	Parents		12.3
	Others		4.6

Table 2. *Mean and median monthly willingness to pay (WTP) values for patients and relatives*

	Patients (n = 145)			**Relatives (n = 61)**		
	Mean (stand. error)	**Median (min, max)**	**Percentiles 25 and 75**	**Mean (stand. error)**	**Median (min, max)**	**Percentiles 25 and 75**
Initial WTP 50% success	135.41 (14.06)	100 (0-1000)	30–200	322.95 (48.70)	200 (0-2000)	80–400
Final WTP 50% success	128.95 (14.01)	90 (0-1000)	30–150	306.72 (48.87)	200 (0-2000)	55–300
Initial WTP 100% success	167.59 (18.05)	100 (0-1000)	30–200	420.25 (65.21)	300 (0-2000)	100–475
Final WTP 100% success	167.53 (18.05)	100 (0-1000)	30–200	420.25 (65.21)	300 (0-2000)	100–475

treatment efficacy was 50% and a mean monthly WTP of €420 when the efficacy was 100%. Only four relatives provided a zero WTP. The median is lower than the mean but shows the same pattern, with higher values for the 100% success treatment than for the 50% success treatment and higher valuations from relatives than patients.

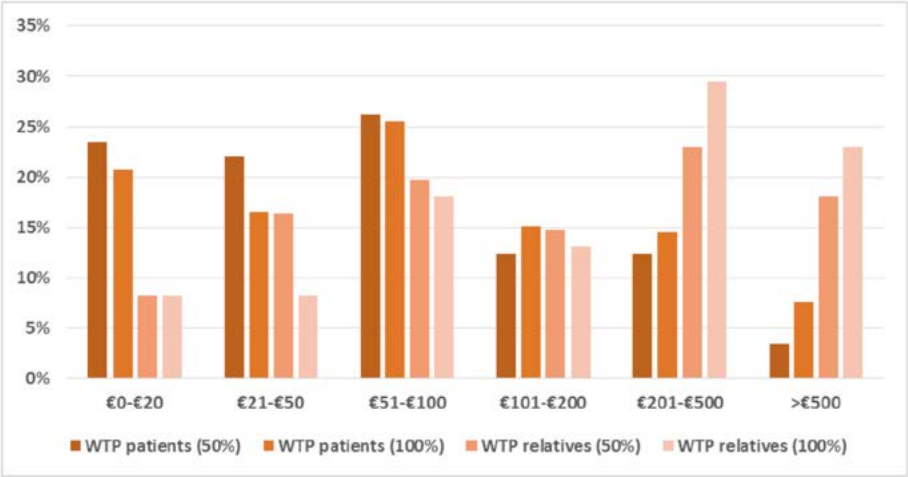

Figure 1: Distribution of willingness to pay (WTP)

Determinants of the WTP

Table 3 shows the results from the regression analysis performed to identify possible determinants of patients' WTP. WTP is positively correlated with treatment efficacy (sensitivity to scale). Accordingly, interviewees were willing to pay an additional €39 for treatment that guaranteed success, compared to one with only a 50% success rate. Personal income is also positively correlated with WTP, supporting the theoretical validity of the results. The WTP is also positively related to having family support (was able to contact a relative involved in treatment) and negatively related to feeling downhearted and depressed during the last four weeks.

[Insert Table 3]

With regard to the effects of alcoholism on health, it was found that persons for whom alcohol dependency had caused moderate health problems were willing to pay €108 more than those who hardly any had health problems. However, when alcohol dependence had caused serious health problems, WTP, although positive, was not significant. In any case, the result that might a priori seem most surprising is the negative correlation between the presence of serious family problems and WTP. This result combined with the fact that WTP is negatively related to feeling downhearted and depressed may be related to the influence of the subject's self-efficacy on his or her expectations. In other words, to pay more for a treatment, there must be some degree of optimism about the possibility of success, which could be less plausible in highly deteriorated family situations. However, these results hold even for the 100% probability of success, which may indicate limited motivation to improve one's life among patients in highly deteriorated situations.

The variable "alcohol intake" (see table 1) has been excluded from regression analysis because it refers to the date in which the actual treatment started, which is not representative of the current situation. In any case, we estimated the regression with this variable and it was not significant, obtaining similar results in the rest of variables. We also estimated the model excluding the patients who had no personal income. Similar results were obtained with regard to the sign and the significance of parameters, except that *severe family consequences* was not significant (p=0.127).

The results of the regression performed on data from relatives (not shown) indicate that none of the variables examined significantly influences WTP, except for the probability of success and income (both significant at the 5% level). In any case, we must be very cautious with these results, given the small size of the sample of relatives.

Discussion

The objective of this study is to obtain a monetary valuation of the intangible costs of alcohol dependence by means of a contingent valuation study conducted with the patients and their families. Although, to our knowledge, no prior study of these characteristics has been conducted, the study with the greatest similarity to ours is that of Jeanrenaud et al (2007), conducted with a sample of the general Swiss population. The authors found that the mean WTP for a curative treatment for alcohol dependence of a hypothetical cohabiting relative accounts for about 7% of the average monthly household income, a percentage that is significantly lower than that obtained in our sample of relatives (23% of the income). This difference may reflect the discrepancy between assuming one has and actually having an alcoholic relative. Our sample of patients also provides, in relative terms, greater WTP (13% of the family income) than that of the Swiss population.

The lower WTP for the dependents than for their relatives could have different explanations. First, the income of the

Table 3. *Determinants of monthly willingness to pay (WTP)*

	Coefficient	p-value	95% Conf. Interval
Treatment efficacy (ref. 50%)	38.59	.001	22.67 — 54.50
Sex (ref. male)	1.90	.955	-63.86 — 67.65
Age	-1.23	.430	-4.29 — 1.83
Education (ref. elementary school or less)			
Secondary school	-2.55	.944	-73.26 — 68.16
University	5.43	.927	-110.97 — 121.82
Monthly personal income	0.10	.001	0.04 — 0.15
Health consequences (ref. hardly any)			
Moderate/some	108.29	.002	40.71 — 175.87
Severe/many	23.98	.562	-57.08 — 105.03
Family consequences (ref. hardly any)			
Moderate/some	-64.27	.138	-149.23 — 20.69
Severe/many	-70.97	.099	-155.42 — 13.47
Legal consequences (ref. hardly any)			
Moderate/some	-8.42	.855	-98.78 — 81.94
Severe/many	25.05	.591	-66.32 — 116.42
Occupational consequences (ref. hardly any)			
Moderate/some	-24.80	.580	-112.77 — 63.14
Severe/many	-7.02	.888	-104.96 — 90.92
Downhearted and depressed (ref. none/a little)	-74.56	.015	-134.63 — -14.50
Duration of treatment	-0.46	.769	-3.54 — 2.62
Has family support (ref. no support)	54.34	.077	-5.90 — 114.58
Constant	151.06	.173	-66.08 — 368.20

Note. R-sq= 0.265. Number of participants, 145; number of observations, 290

patients was lower than that of relatives and so it is to be expected that the WTP would be lower. However, we find those differences to be very large. One should consider that, while the personal income of relatives is 11% greater than that of patients, the WTP is more than double for both scenarios. Second, differences in the perception of problems generated by dependence (relatives perceive these problems to be significantly more severe than the dependent persons themselves do) could reflect another important part of these differences. In other words, these differences could be partly motivated by differences in the perceived gain in well-being. Finally, there is evidence that individuals may be willing to pay more to avoid a risk or treat the disease of a relative than to protect their own health (Amin & Khondoker, 2004; Viskusi, Magat & Huber, 1987).

It is arguable whether the WTP obtained is capturing solely intangible costs, as was our objective, or, instead, is also capturing tangible costs (direct or indirect). Since Spain has a public health care system that requires minimal copayment for services, it is assumed that the direct cost incurred by the dependence treatment was not incorporated by the interviewees (or, if so, only marginally). However, the WTP could well be capturing part of the indirect costs resulting from loss of productivity (loss of employment, lower income from absenteeism, premature disability pension, etc.). Although we do not know if participants took these effects into account at the time they provided their WTP, we have information suggesting that any influence they may have had was small. Namely, only 13% of the patients considered that drinking has had severe consequences in their work (although this value increased to 26% if we consider the opinions of relatives).

The lack of an increasing positive correlation between the severity of the consequences of alcohol dependence and the WTP should be emphasized. The results suggest that patients with serious problems provide a significantly lower WTP than those with moderate problems. These results relate to phenomena highly relevant to treating drug dependencies, namely, the perception of self-efficacy (Burling, Reilly, Motzen & Ziff, 1989). Self-efficacy has to do with the perception that the addict has of his or her chances of success and, obviously, the higher those chances are, the more they will pay. This is more likely to come into play for patients with less severe problems (in the very initial phases, with greater control of the situation, etc.) and encouraged than for patients with more problems who may have failed in previous attempts for a cure or for patients who have adapted to their situation. The potential influence of these aspects is apparent in the 50% scenario (patients may perceive their personal probability to be greater or less than

that provided). However, secondary regression analyses indicate these results hold when only the answers referring to 100% success scenario are considered. Consequently, factors such as a lower perception of the seriousness of the problem by patients who have more severe problems (and probably a more severe addiction) may have a greater impact on these results. Our study suggests that there is greater willingness to be treated among alcoholic subjects in the less evolved stages of alcohol dependence, with family support, encouraged, and when a large number of secondary problems are not associated.

Our results are subject to several limitations. First, our sample of people with alcohol dependence is small and it is not taken from the general population, which could cause selection bias. If selection bias is present, we do not know in what direction it would alter the composition of the sample. There could be a bias towards subjects with more serious alcohol dependence, as would be the case with those coming into a centre specialized in the treatment of alcoholism. However, the bias could also come from the exclusion of patients with very severe pathology, linked in many cases to situations of social exclusion, who do not come in for treatment. In any case, our sample has some advantages with respect to an extracted sample of the general population. On the one hand, our recruitment method guarantees that all the patients interviewed are alcohol dependent, as diagnosed by a specialist. On the other hand, the type of contact (within an alcoholism treatment unit) and the interview format (direct interview rather than a mail or telephone interview) provided a response rate and valid questionnaire percentage that were very high compared to those ordinarily encountered in this kind of study (Petrie et al., 2008; Saarni et al., 2007), avoiding the bias that a low response rate could cause.

Second, a considerable portion of patients has no relatives committed to the treatment. This resulted in a particularly small sample of relatives and could introduce selection biases that are hard to evaluate. In addition, the small size of the sample of relatives may have contributed to the result that, among the variables measured, only income and probability of treatment success influenced the WTP. Another possible limitation is the question design. Since one of the scenarios proposed a 100% cure rate, it is possible that the WTP values obtained are strongly conditioned by budget constraints. Obviously, any WTP study faces a budget constraint. When participants have to state how much they would pay for a good, this amount is limited by their income and by what they want to consume with the remaining assets. The problem arises when the benefit is so great that the value the participants assign to the good exceeds their income producing an underestimation of the benefit or insensitivity of WTP values to changes in the quantity of the good. To avoid this, the scope of the good being valued is often decreased by introducing, for example, a probability of obtaining the good lower than 100%. In our study, an additional scenario was proposed in which the probability of success was 50%. The result is that participants were willing to pay 30% more to guarantee the success of treatment (37% more in the case of relatives). Since the differences are significant, we believe that, at least in the first question (50% success), the participants' WTP was not exhausted, because in the second question the amount was increased. The constraint imposed by the 100% cure is hard to assess. In any case, our results agree with the literature. The study of Neuman and Johannesson (1994), for example, analysing WTP for an in vitro fertilization treatment, found that participants were willing to pay between 37% and 47% more (depending on the perspective taken) for a program that ensured 100% success than for one that only had a 50% probability of success.

Finally, the WTP obtained could be influenced by the open-ended question format utilized. This format is especially suitable when the sample size is small (Carson & Hanemann, 2005), as in our study. However, there is empirical evidence that the types of elicitation techniques can influence the values estimated. Relevant literature indicates that values obtained with an open-ended or payment card format are often lower than the results from dichotomous choices (Gyrd-Hansen, Jensen & Kjaer, 2014). In addition, in the area of health services, it has been found that the open format, when compared to the payment card format, produces either lower valuations (Whynes et al. 2003; Donaldson, Thomas & Torgerson, 1997) or no significant differences (Gyrd-Hansen et al., 2014). These results suggest that our study should be providing conservative valuations of the intangible costs of alcohol dependence.

The results obtained can be used —with all necessary precautions given the previously mentioned limitations— in the area of economic valuation, specifically in cost–benefit analysis studies. Our study provides a range of values that could be utilized to approximate the benefits derived from programs focused on the prevention, treatment, or cure of the alcohol dependence. However, the selection of a single value is not easy, since one must decide whether to utilize mean or median values, the results from the 100% or the 50% success scenario (in the last scenario, the benefit from curing dependence is assumed to be twice the value provided), or, finally, answers from relatives or patients. Depending on this decision, the annual value for curing one case of alcohol dependence could range from €1200 – the median provided by patients for a 100% cure rate– up to €7361, twice the mean WTP provided by relatives for a 50% cure rate. We suggest that the annual benefit of curing (or preventing) a case of alcoholic dependence should initially be approximated by using the mean values from the 50% cure scenario (€3095 from the perspective of the patients and €7361 from the perspective of the relatives), with a subsequent sensitivity analysis using the remaining

values. The reason for this choice is that cost–benefit analysis usually utilizes mean values and that we assume that the values estimated for the 100% cure scenario could be strongly restricted by the participants' budget constraints. In any case, these values should be taken with caution. This study shows a methodology to evaluate the intangible costs and provides a first approach to these values, but our findings need to be validated by future studies with larger samples and in other settings.

This study suggests that the contingent valuation approach can be a suitable method for measuring the intangible costs resulting from alcohol dependence, from the perspective of patients and relatives. The results show that the valuations obtained are very different, depending on the perspective taken. Although a vast literature in the area of economic valuation shows disparities between the patients' and the general population's perspectives, these results add new empirical evidence regarding disparities between patients and relatives. In our opinion, future investigations on the measurement of intangible effects of alcohol dependence in particular and of drugs in general should study these differences in greater depth. Since dependent patients may distort the true magnitude of the problem, the perspective of relatives could be especially relevant in that context.

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Conflict of interest

The authors declare that they have no conflicts of interest in the research.

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Relationship between the rs1414334 C/G polymorphism in the HTR2C gene and smoking in patients treated with atypical antipsychotics

Relación entre el polimorfismo rs1414334 C/G del gen HTR2C y tabaquismo en pacientes tratados con antipsicóticos atípicos

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Abstract

An association has been found between the C allele of the rs1414334 polymorphism in the HTR2C gene and the metabolic syndrome in psychiatric patients. However, no study has yet evaluated whether this allele is associated with smoking. To assess this issue, therefore, we performed a cross-sectional study with a sample of 166 adult patients treated with atypical antipsychotics in 2012-2013 in a region of Spain. The primary variable was the presence of the C allele of the rs1414334 polymorphism in the HTR2C gene. Secondary variables were the number of pack-years (number of cigarettes per day x number of smoking years ÷ 20), age, gender, schizophrenia, years since diagnosis, metabolic syndrome criteria and SCORE. A stepwise binary logistic regression model was constructed to determine associations between primary and secondary variables and their area under the ROC curve (AUC) was calculated. Of the total sample, 33 patients (19.9%) had the C allele of the polymorphism analyzed. Mean cigarette consumption was 11.6 pack-years. The multivariate analysis showed the following factors as associated with the polymorphism: higher cigarette consumption, being a woman, and not having abdominal obesity. The AUC was 0.706. An association was found between increased cigarette consumption over the years and the presence of the C allele of the rs1414334 polymorphism in the HTR2C gene.

Keywords: Smoking; Pharmacogenetics; Alleles; Psychiatry.

Resumen

En pacientes psiquiátricos, otros autores han encontrado una asociación entre el alelo C del polimorfismo rs1414334 del gen HTR2C y el síndrome metabólico. Ninguno de ellos ha valorado si este alelo se asocia con el consumo de tabaco, por lo que se decidió realizar un estudio en una región española valorando esta cuestión. Estudio observacional transversal de una muestra de 166 pacientes adultos tratados con antipsicóticos atípicos en 2012-2013. Variable principal: presencia del alelo C del polimorfismo rs1414334 del gen HTR2C. Variables secundarias: número de paquetes-año (número de cigarrillos al día x número de años fumando ÷ 20), edad, sexo, esquizofrenia, años con el diagnóstico, criterios de síndrome metabólico y SCORE. Se construyó un modelo de regresión logística binaria por pasos para determinar asociaciones entre la variable principal y las variables secundarias del estudio y se calculó su área bajo la curva ROC (ABC). Del total de la muestra, 33 pacientes presentaron el alelo C del polimorfismo analizado (19,9%). El consumo de tabaco medio fue de 11,6 paquetes-año. El modelo multivariante arrojó los siguientes factores asociados al polimorfismo: mayor consumo tabáquico, ser mujer y no tener obesidad abdominal. El ABC fue de 0,706. Se ha encontrado asociación entre un mayor consumo de tabaco a lo largo de los años y la presencia del alelo C del polimorfismo rs1414334 del gen HTR2C. Se requiere otros estudios que corroboren nuestros resultados.

Palabras clave: Tabaquismo; Farmacogenética; Alelos; Psiquiatría.

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The HTR2C receptor has various functions, including appetite regulation and glucose homeostasis. It is also associated with the use of psychoactive substances, as well as being linked to diseases such as cyclothymic disorder, suicide or premature ejaculation (The Weizmann Institute of Science Crown Human Genome Centre, 2014).

The existing literature on the *HTR2C* rs1414334 polymorphism focuses on the relationship between the presence of the C allele of this polymorphism in psychiatric patients receiving antipsychotics and the possible link with the development of the metabolic syndrome, assessing each of the components of this syndrome individually as well as altogether. The results of these studies generally show an association between the C allele of this polymorphism and the metabolic syndrome (Gregoor et al., 2010; Hoekstra et al., 2010; Houston et al., 2012; Klemettilä et al., 2010; Ma et al., 2014; Mulder et al., 2007a; Mulder et al., 2007b; Mulder et al., 2009; Rico-Gomis et al., 2016; Risselada et al., 2012). In other words, these patients have an increased cardiovascular risk. Moreover, we must bear in mind that there is another major risk factor in the development of cardiovascular disease that is not contemplated in the criteria for the metabolic syndrome, which is smoking (Conroy et al., 2003; Wilson et al., 1998). None of the previous studies have evaluated whether patients with this allele have an association with smoking (Gregoor et al., 2010; Hoekstra et al., 2010; Houston et al., 2012; Klemettilä et al., 2010; Ma et al., 2014; Mulder et al., 2007a; Mulder et al., 2007b; Mulder et al., 2009; Rico-Gomis et al., 2016; Risselada et al., 2012). This is an important issue because animal models have shown that the *HTR2C* receptor modulates nicotine addiction in mice and that stimulation of the *HTR2C* receptors reduces dopamine function at the mesolimbic level (Guy and Fletcher, 2014), decreasing the stimulating effects of nicotine (Fletcher, Lê & Higgins, 2008). Given the lack of studies (Gregoor et al., 2010; Hoekstra et al., 2010; Houston et al., 2012; Klemettilä et al., 2010; Ma et al., 2014; Mulder et al., 2007a; Mulder et al., 2007b; Mulder et al., 2009; Rico-Gomis et al., 2016; Risselada et al., 2012), the possible association between smoking and this receptor, and that tobacco dependence has been found with other genes (Barrot, Sánchez, Abellana, Ortega & Gené, 2013; Fletcher et al., 2008; Guy and Fletcher, 2014; Saccone et al., 2007; Verde et al., 2011; Walton, Johnstone, Munafò, Neville & Griffiths, 2001), we decided to conduct a study to evaluate the possible association between smoking and the C allele of the *HTR2C* rs1414334 polymorphism in psychiatric patients with atypical antipsychotics. The results will help to provide scientific evidence on consumption of toxic substances in these patients and to improve the clinical guidelines for dual pathology and thus improve the success of cessation treatments in this population (San et al., 2016).

Methods

Ethical considerations

Before participating in the study all patients were properly informed and signed an informed consent prior to their inclusion in the study. The study was approved by the Ethics and Research Committee of the General University Hospital of Elche on November 20, 2012. All the procedures followed were in accordance with the Helsinki Declaration, as revised in 2004.

Study population

The study population comprised psychiatric patients treated with atypical antipsychotics in the Department of Health 20 (General University Hospital of Elche). This department is located in the Valencian Community, which is a Mediterranean region of approximately 5 million inhabitants, located in southeast Spain. In this department, health coverage for psychiatric patients is universal and free.

Study design and participants

This was a cross-sectional study of a sample of all adult patients attending the mental health services of Health Department 20 between December 2012 and June 2013 who agreed to participate in the study voluntarily. Inclusion criteria required that patients had to be diagnosed by their psychiatrist with at least one of these conditions: 1) schizophrenia; 2) schizophreniform disorder; 3) schizoaffective disorder; 4) other psychotic disorders; 5) bipolar disorder with treatment that included continuous antipsychotic medication (American Psychiatric Association, 2000). Additionally, all patients had to be on treatment with atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpride, asenapine and paliperidone), for at least three months. Patients taking this type of drug were chosen because the HTR2C receptor is involved in its mechanism of action and this gene is in turn associated with the use of psychoactive substances (The Weizmann Institute of Science Crown Human Genome Centre, 2014).

Variables and measurements

The primary study variable was the presence of the C allele of the rs1414334 polymorphism in the *HTR2C* gene. A venous blood sample was obtained from each selected patient (EDTA tube). Genomic DNA was isolated and purified from buffy coat samples using the semi-automated QIAcube system (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Extracted DNA was used for genotyping. Analyses of the polymorphism (rs1414334 C/G) were performed using a Taqman allelic discrimination assay (C_7455701_10, Applied Biosystems, Madrid, Spain) on a real-time PCR apparatus (Applied Biosystems 7300) (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1414334).

The secondary variables were: age (years), gender, schizophrenia (yes/no), years since diagnosis of the disorder, number of pack-years (number of cigarettes per day × number of years of smoking ÷ 20), metabolic syndrome criteria (abdominal obesity, hypertriglyceridemia, hypertension, abnormal HDL-c and insulin resistance) and SCORE (%) (Conroy et al., 2003; Grundy et al., 2004). The main diagnosis and its duration, age and gender were obtained from the patients' medical records. The number of cigarettes and the time each subject had smoked was obtained by personal interview. The metabolic syndrome criteria were obtained through measurements of blood pressure (systolic and diastolic), blood tests (total cholesterol, HDL-c, triglycerides and fasting glucose) and abdominal circumference. These measurements were performed according to the applicable clinical guidelines (American Diabetes Association, 2012; National Institutes of Health, 1998; Mancia et al., 2007; National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002). Finally, the SCORE was calculated using systolic blood pressure, age, gender, atherogenic index (total cholesterol ÷ HDL-c) and smoking as a binary variable (smoking or no smoking).

Sample size

Given that an a priori calculation of sample size was not performed, we calculated the statistical power of the sample during the study period: 166 patients, of whom 33 had the C allele of the polymorphism. To estimate an area under the ROC curve (AUC) different from 0.5, assuming an AUC of 0.70 and a confidence level of 95%, a power of 94.43% was obtained (Hanley & McNeil, 1982).

Statistical methods

Qualitative variables were described by absolute and relative frequencies, and quantitative variables using means and standard deviations. Raw odds ratios (ORs) were calculated to determine possible associations between the secondary variables and our primary variable. To obtain the adjusted ORs, a stepwise binary logistic regression model was constructed, considering that we could only enter a maximum of 3 variables (one for every 10 events). The steps were to obtain all possible combinations of the explanatory variables (231) and to calculate the AUC of the resulting model with that combination, keeping the combination with the highest AUC (the model with the greatest discriminatory power) (Azrak et al., 2015; Gutiérrez-Gómez et al., 2015; López-Bru, Palazón-Bru, Folgado-de la Rosa & Gil-Guillén, 2015; Ramírez-Prado et al., 2015). The type I error was set at 5% and for each relevant parameter its associated confidence interval (CI) was calculated. The statistical packages used were R 2.13.2. and IBM SPSS Statistics 19.

Results

Of a total of 166 patients treated with atypical antipsychotics, 33 had the C allele of the polymorphism analyzed (19.9%, 95% CI: 13.8-26.0%). Table 1 shows the descriptive and analytical characteristics of our patient sample. We highlight a mean age of 43.1 years, 55.4% with schizophrenia and mean number of years with the primary diagnosis of 14.9. Tobacco consumption was 11.6 pack-years on average. Finally, the metabolic syndrome criteria were highly prevalent (abdominal obesity, 66.3%; hypertriglyce-

Table 1. *Descriptive and analytical characteristics of the patients diagnosed with psychiatric disorders in a Spanish region: analysis of the rs1414334 C polymorphism in the HTR2C gene.*

Variable	**Total** n=166 n(%)/x±s	**Raw OR** (95% CI)	**p-value**	**Adj. OR** (95% CI)	**p-value**
Age (years)	43.1±11.5	1.02(0.98-1.05)	0.318	N/M	N/M
Gender, female	67(40.4)	2.40(1.11-5.22)	0.027	4.31(1.67-11.17)	0.003
Schizophrenia	92(55.4)	0.52(0.24-1.12)	0.094	N/M	N/M
Years with the disorder	14.9±9.6	0.99(0.95-1.03)	0.486	N/M	N/M
Number of pack-years	11.6±17.5	1.02(1.00-1.04)	0.057	1.03(1.01-1.05)	0.008
Abdominal obesity[a]	110(66.3)	0.70(0.31-1.58)	0.399	0.39(0.15-1.01)	0.053
Hypertriglyceridemia[a]	64(38.6)	0.53(0.23-1.23)	0.130	N/M	N/M
Hypertension[a]	58(34.9)	0.76(0.33-1.73)	0.511	N/M	N/M
Abnormal HDL-c[a]	55(33.1)	0.85(0.37-1.94)	0.698	N/M	N/M
Insulin resistance[a]	31(18.7)	0.54(0.18-1.67)	0.261	N/M	N/M
SCORE (%)	0.80±1.51	1.20(0.96-1.50)	0.107	N/M	N/M

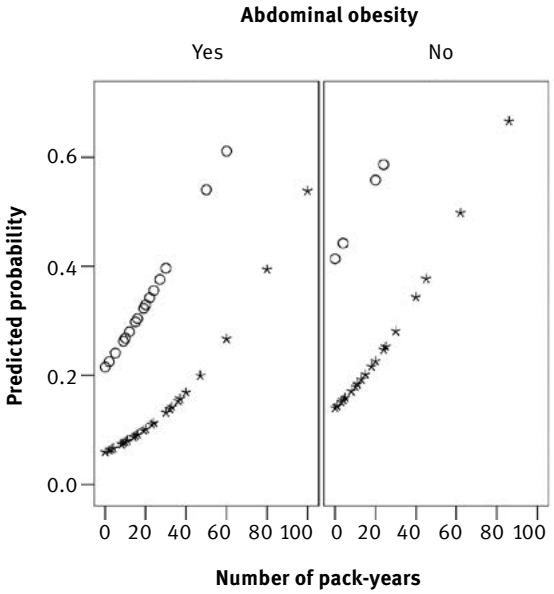
Nota. n(%), absolute frequency (relative frequency); x±s, mean ± standard deviation; Adj. OR, adjusted odds ratio; Raw OR, raw odds ratio; CI, confidence interval; N/M, not in the model. Goodness-of-fit of the multivariate model: X^2=14.80, p=0.002; area under the ROC curve=0.706 (95% CI: 0.603-0.810, p<0.001). [a] Criteria for Clinical Diagnosis of the Metabolic Syndrome (ATP III).

ridemia, 38.6%; hypertension, 34.9%; abnormal HDL-c, 33.1%; insulin resistance, 18.7%).

Univariate analysis of the associated factors (Table 1) showed a statistically significant association ($p<0.05$) between the C allele of the polymorphism and being a woman and greater tobacco consumption, while not having schizophrenia remained close to statistical significance ($0.05< p<0.10$). After adjusting with the best combination of factors (AUC=0.706), we found that higher tobacco consumption, being a woman and not having abdominal obesity were associated with the allele analyzed. The model that included these factors was highly significant ($p=0.002$).

Figure 1 shows the predicted probabilities of the presence of the C allele of our polymorphism. These probabilities increased as the patient's tobacco consumption increased. Moreover, being a woman and not having abdominal obesity indicated a greater likelihood of having this allele.

Figure 1. Predicted probabilities of the presence of the C allele of the HTR2C rs1414334 polymorphism according to specific variables in the multivariate model.



Note. Gender: * Male; O Female.
Goodness of fit: p=0.002.

Discussion

Summary

In an innovative way, this study identified the association between tobacco consumption measured in pack-years and the presence of the C allele of the rs1414334 polymorphism in the *HTR2C* gene. This association was direct; that is, the higher the patient's tobacco consumption, the higher the probability of having this allele. Moreover, it was found that being a woman and not having abdominal obesity were associated with having this allele.

Strengths and limitations of the study

The main strength of this work is the research question addressed. We found no studies determining the association between smoking and the C allele of the polymorphism studied, such that our results are novel. Furthermore, all possible combinations of variables were tested to obtain the best multivariate model and the power of the sample was near 95%, when most studies use powers of 80% and 90%.

To minimize selection bias, patient data were collected over a specific period of time. Regarding information bias, the data were carefully and exhaustively collected by the research team. Finally, confounding bias was minimized using the best combination of a total of 231.

Our finding is probably related to the X-bound character of HTR2C (i.e., men are hemizygotes) and loss of statistical power. In addition, some second-generation antipsychotics, including asenapine, clozapine, olanzapine and sertindole, are relatively potent 5-HT receptor antagonists and others, including amisulpride, asenapine, clozapine, amisulpride, lurasidone and risperidone, have high affinity for 5-HT receptors. The effects of these second-generation antipsychotics may distort a possible relationship with genetic variations in receptor activity. Therefore, the relationship between the 5-HT2C polymorphism and smoking is possibly due to camouflage by receptor binding caused by the current drug treatment. On the other hand, smoking was measured by interview, instead of expired CO.

Comparison with the existing literature

When assessing the association between tobacco consumption and the allele examined, we found no studies with which to compare our results because previous studies did not consider smoking among their variables (Gregoor et al., 2010; Hoekstra et al., 2010; Houston et al., 2012; Klemettilä et al., 2010; Ma et al., 2014; Mulder et al., 2007a; Mulder et al., 2007b; Mulder et al., 2009; Rico-Gomis et al., 2016; Risselada et al., 2012). We believe that this association may be related to the role of the *HTR2C* receptor in modulating nicotine in the brain, since similar behavior has been seen in animal models using mice (Fletcher et al., 2008; Guy & Fletcher, 2014). However, this should be corroborated through genetic and experimental studies.

With respect to the other associations found, gender is consistent, since this gene is located on chromosome X. Finally, the association between abdominal obesity and this allele (not significant in our study) is not clear in the previous two studies published on the subject, since one of them found a direct association and the other found no association between these two variables (OR close to 1) (Mulder et al., 2007a; Risselada et al., 2012).

The C allele was present in approximately one in every five patients treated with atypical antipsychotics, which is

similar to the results found by others (Hoekstra et al., 2010; Mulder et al., 2007a; Mulder et al., 2007b; Mulder et al., 2009; Risselada et al., 2012).

Implications to research and practice

Given that tobacco consumption was associated with the C allele of the *HTR2C* rs1414334 polymorphism, if these results are confirmed by other studies, we will be able to determine which patients are most likely to have high tobacco consumption and carry out early intervention to attempt to partially decrease or completely eliminate the patient's smoking habit. In turn, this would reduce their cardiovascular risk (Prescott, Hippe, Schnohr, Hein, y Vestbo, 1998), which is higher than in the general population (McEvoy et al., 2005; Newcomer & Hennekens, 2007; Saha, Chant & McGrath, 2007). According to the results obtained, a study could be carried out analyzing the C allele in a sample with a high number of subjects, comparing the smoking population with the nonsmoking population, including men and women, and stratifying by psychiatric history and by metabolic syndrome. Additionally, variables related to smoking, such as cessation attempts, success/failure in discontinuation and drugs used for smoking cessation could be included.

Conclusions

This study found a direct association between increased consumption of tobacco over the years and the presence of the C allele of the rs1414334 polymorphism in the *HTR2C* gene. Since we have found no reports evaluating this association, studies to corroborate our results are needed. If this association is verified, we will know which patients treated with atypical antipsychotics are more likely to have a high tobacco consumption.

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Conflict of interest statement

Nothing to declare.

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Psychometric validation of the POSIT for screening alcohol and other drugs risk consumption among adolescents

Validación psicométrica del POSIT para el cribado del consumo de riesgo de alcohol y otras drogas entre adolescentes

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Abstract

La detección precoz del consumo abusivo de alcohol y otras drogas en adolescentes resulta decisiva no sólo para una derivación e intervención rápida en los casos de riesgo, sino también como un indicador a utilizar en la evaluación de los programas de prevención y en las políticas públicas de reducción del consumo. Uno de los instrumentos de *screening* más utilizados a nivel internacional es el *Problem Oriented Screening Instrument for Teenagers* (POSIT) (Rahdert, 1991), cuya subescala de Uso y Abuso de Sustancias ($POSIT_{UAS}$) constituye una herramienta breve de enorme potencial aplicado. Sin embargo, en España no existe todavía ningún estudio de validación empírica que permita garantizar su adecuado funcionamiento psicométrico. El objetivo del presente trabajo consiste precisamente en analizar las propiedades psicométricas del $POSIT_{UAS}$ en adolescentes españoles. Para ello fueron entrevistados de forma personal 569 estudiantes de entre 12 y 18 años (M = 14,71; DT = 1,79), seleccionados a partir de un muestreo bietápico. Los resultados obtenidos, utilizando la *Adolescent Diagnostic Interview* (Winters & Henly, 1993) como criterio, permiten informar que la versión española del $POSIT_{UAS}$ posee un excelente comportamiento psicométrico, tanto a nivel de consistencia interna (a=,82), como de sensibilidad (94,3%) y especificidad (83,9%), con un área bajo la curva ROC de ,953. Asimismo, la realización de un Análisis Factorial Confirmatorio permite constatar el carácter unidimensional de la escala. Como consecuencia se pone a disposición de investigadores y profesionales del ámbito de las conductas adictivas el $POSIT_{UAS}$, que puede ser utilizado en adelante con las garantías psicométricas requeridas.

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

Resumen

Early detection of alcohol and drug abuse among adolescents is decisive not only for rapid referral and intervention in cases of risk, but also as an indicator for use in the evaluation of prevention programs and public policies to reduce consumption. One of the most widely-used screening instruments in the world is the *Problem Oriented Screening Instrument for Teenagers* (POSIT) (Rahdert, 1991), whose substance use and abuse subscale ($POSIT_{UAS}$) is a brief tool of enormous applied potential. However, there is still no empirical validation study that would ensure its good psychometric performance in Spain. The aim of this paper is to analyse the psychometric properties of $POSIT_{UAS}$ among Spanish adolescents. For this purpose, 569 students aged between 12 and 18 years (M = 14.71; SD = 1.79) were personally interviewed. The study sample was selected through two-stage sampling. The results obtained, using the Adolescent Diagnostic Interview (Winters & Henly, 1993) as the gold criterion, allow us to inform that the Spanish version of the $POSIT_{UAS}$ has excellent psychometric behaviour, both at the level of internal consistency (a = .82) as well as regards sensitivity (94.3%) and specificity (83.9%), with an area under the ROC curve of .953. Also, the realisation of a Confirmatory Factor Analysis allows for verifying the one-dimensional character of the scale. As a result, $POSIT_{UAS}$ is made available to researchers and professionals in the field of addictive behaviours for use with a minimum of psychometric guarantees.

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

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The use of alcohol and other substances by adolescents is one of Spain's main healthcare problems. Despite the fact that the results of the most recent National Survey on Drug Use among Secondary School Students [ESTUDES 2014-2015] (National Drug Plan, 2016) reveal a decrease in the consumption of different substances over the last few years, the prevalence rates among students continue to be high. About 76.8% of students between the ages of 14-18 drank alcohol in the last year (68.2% in the last month); 31.4% reported having smoked tobacco in the last year (25.9% in the last month) and 25.4% reported having smoked cannabis (18.6% in the last month). Other substances explored, such as cocaine, ecstasy, amphetamines or hallucinogens, have much lower prevalence rates, under 3%.

Among all of the substances analysed by ESTUDES 2014-2015, alcohol continues to be the psychoactive substance most consumed by adolescents. Within this context, issues that continue to be of concern for professionals and researchers is binge drinking (Farke & Anderson, 2007; Parada et al., 2011) of alcohol, together with the early age of onset of alcohol use by adolescents. According to ESTUDES 2014-2015, 32.2% of adolescents participated in binge drinking in the last month, and 22.2% also report having got drunk. An abundance of literature reveals that this widely extended pattern of use among adolescents today entails serious consequences, not only for the organism (López-Caneda et al., 2014), but also a greater likelihood of involvement in risky behaviours (Huang, Jacobs & Deverensky, 2010; Matali et al., 2016; Miller, Naimi, Brewer & Jones, 2007; Windle, 2003) and of developing a pattern of polydrug use or, possibly, of alcohol dependence/disorder in adulthood (Jones, Oeltmann, Wilson, Brener & Hill, 2001; Petit, Maurage, Kornreich, Verbanck & Campanella, 2014). One variable that influences the likelihood of appearance of many of these consequences and of their seriousness is the age of onset of alcohol consumption (Motos, Cortés, Giménez & Cadaveira, 2015). Such is the case that delaying the age of onset is contemplated as one of the goals of the 2013-16 National Drug Plan (National Drug Plan, 2009a) (general objective 4), as well as of different regional plans, like the 2011-2016 Addiction Disorders Plan of Galicia (Xunta de Galicia [Regional Government of Galicia], 2010) (objective 1.3).

Of no less concern is the abovementioned rate of cannabis use, positioning it as the illegal drug most-used by adolescents. In addition to the levels of use revealed by ESTUDES 2014-15, we must mention that 2.5% (approximately 53,701 adolescents) were identified using the Cannabis Abuse Screening Test (CAST) (Legleye, Piontek & Kraus, 2011) as problematic or users at risk of developing a possible dependency (National Drug Plan, 2016).

In this context, early detection of the use of alcohol and other drugs among adolescents is decisive, not only to favour fast referrals and intervention in risk cases, but also as an indicator for use when evaluating prevention programs and public policies to reduce use. Therefore, it is necessary to have available screening instruments that have been sufficiently compared on an international level, properly translated and adapted to our culture and, likewise, with sufficient empirical-psychometric guarantees (García, Novalbos, Martínez & O'Ferrall, 2016; Tiburcio et al., 2016).

One of the most widely used instruments in this field has been the Problem Oriented Screening Instrument for Teenagers (POSIT). The POSIT, presented in a publication of the National Institute on Drug Abuse (Rahdert, 1991), is one of the instruments comprising the Adolescent Assessment/Referral System (AARS), the design and development of which had begun in 1987. It was created for the purpose of achieving the timely detection of specific problems in adolescents who used/abused drugs. It is comprised of 139 items with dichotomous (Yes/No) answers, grouped into 10 subscales that evaluate different functional areas of an adolescent's life that may be affected by drug use, one of which is the Substance Use and Abuse Subscale ($POSIT_{UAS}$). This subscale is comprised of 17 items with the objective of screening adolescents that could be at risk of developing a possible substance use disorder or dependence.

Currently, several studies exist on the validation and utility of the POSIT, for the entire scale (Dembo et al., 1996; Knight, Goodman, Pulerwitz & DuRant, 2001; McLaney, Del Boca & Babor, 1994) as well as for some of its subscales (Knight, Sherritt, Harris, Gates & Chang, 2003; Latimer et al., 2004; Latimer, Winters & Stinchfield, 1997; Rumpf, Wohlert, Freyer-Adam, Grothues & Bischof, 2013). The use of the POSIT as a screening tool with adolescents has been pointed out by different authors and institutions, scientific journals, guides and manuals, highlighting the instrument's reliability and validity (Center for Substance Abuse Treatment, 2012; Fuller & Cavanaugh, 1995; McPherson & Hersch, 2000; World Health Organization, 1997; Timken, 2007).

Specifically with regards to the Substance Use and Abuse subscale ($POSIT_{UAS}$), relatively few studies have reported its psychometric properties (Knight et al., 2001, 2003; Latimer et al., 2004, 1997), and, to date, no empirical validation study has been performed in Spain (Bobes et al., 2013). In general, research carried out in other countries has, nevertheless, reported excellent psychometric properties for this scale, conferring it enormous potential on the applied level, given its brevity and simple application.

In conclusion, despite having become one of the most-used evaluation and screening tools worldwide, empirical validation is inexistent for knowing, in reality, the psychometric behaviour of the Substance Use and Abuse Subscale ($POSIT_{UAS}$) with Spanish adolescents. This is, precisely, the main goal of this study. Specifically, two hypotheses will be the object of the empirical study: first that the $POSIT_{UAS}$ is

an adequate tool, in psychometric terms, for the early detection of problems with the use of alcohol and/or other substances by Spanish adolescents and, second, we will verify its one-dimensional character with regards to its internal validity or factorial structure.

Method

Participants

To address these issues, we applied a selective methodology comprised of a personal interview with students of Compulsory Secondary School (ESO), High School and Vocational Training in the autonomous region of Galicia (Spain). Bi-level sampling was used to select the sample: by conglomerates, for selecting the first-level units (school centres) and by quotas, according to gender and level, for selecting the second-level units (individuals).

Though initially 600 adolescents were interviewed, the final sample was comprised of 569 students; 31 were withdrawn due to incomplete interviews or incoherent answers. To guarantee both the absence of bias and randomness in the distribution of the missing cases, we verified that the percentage of the missing cases was similar to the different segments of the sample according to sex, age group, ownership of the school and residential area, therefore calculating $\chi 2$ statistics for comparative purposes.

Males comprised 57.1% and females 42.9% of the sample, aged 12-18 years (M = 14.71; SD = 1.79). Participants were randomly selected from a total of 33 schools (22 public and 11 private). Of these, 69.8% were enrolled in ESO (34.8% in the first year and 35% in the second year), 20.4% were high school students and 9.8% were undergoing basic professional training (Initial Professional Qualification Programmes) or a mid-level Training Programme. Finally, 43.1% lived in urban setting and 56.9% in rural or semirural settings.

Instruments

Data was collected using a structured interview, supported by a survey that included: the Substance Use and Abuse Subscale of the Problem Oriented Screening Instrument for Teenagers ($POSIT_{UAS}$) (Rahdert, 1991), the Adolescent Diagnostic Interview (ADI) (Winters & Henly, 1993) and the CRAFFT Substance Abuse Screening Test (Knight et al., 1999). To prevent possible bias with regards to the order in which these instruments were completed, the interview was properly counterbalanced.

The Spanish language version of the $POSIT_{UAS}$ was used, as provided by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (1998), comprised of 17 dichotomous (Yes/No) answers and theoretical scores between 0-17. The Adolescent Diagnostic Interview (ADI) (Winters & Henly, 1993) was used as the criteria for calculating the sensitivity and specificity of the $POSIT_{UAS}$, comprised of a diagnostic interview with 213 items adapted to DSM-5 criteria (American Psychiatric Association [APA], 2013) for the identification of substance use disorders in adolescents. Prior to its use in this study, the interview was both translated and back-translated under the supervision of its original authors. The different scales analysed obtained a high internal consistency ($\alpha = 0.84$ for the alcohol use disorder diagnosis; $\alpha = 0.87$ for the cannabis use disorder diagnosis and $\alpha = 0.88$ for the substance use disorder diagnosis). Finally, as an additional indicator of criterion validity we also included the CRAFFT, a scale comprised of just 6 items and specifically designed for the screening of hazardous use of alcohol and other substances by adolescents. It was both translated and back-translated under the supervision of its original authors and empirically validated in the study by Araujo et al. (2015), with an internal consistency (Cronbach's α) of 0.74, quite similar to that obtained in the original validation study by Knight, Sherritt, Shrier, Harris & Chang (2002) ($\alpha = 0.72$).

Procedure

Data was collected through a personal interview at the schools themselves, in offices specifically prepared for this purpose, by a team of psychologists experienced with these types of research studies. Each interview lasted between 45-60 minutes. The participants were informed of the purpose of the study, anonymity and confidentiality of their responses. Consent and collaboration was granted by the directors of the educational centres as well as by the respective students' parent associations. Participation was completely voluntary and without remuneration. The Bioethics Committee of the University of Santiago de Compostela approved the study.

Data analysis

First, a descriptive analysis was performed by calculating percentages, and measures of central tendency and dispersion were obtained. Means were compared by gender (using Student's t test) and age group (using a one-way ANOVA and a Tukey's post-hoc comparison). The suitable KR-20 index for dichotomous variables (Kuder & Richardson, 1937) was calculated to evaluate internal consistency. Confirmatory Factor Analysis (CFA) was performed, based on the tetrachoric correlations matrix, to verify the scale's one-dimensional structure. Given the data metrics themselves and their abnormality, the Unweighted Least Squares (ULS) method was used, which in addition to robustness requires no further assumptions as to its distribution (Jöreskog & Sörbom, 1989). The model's Goodness of Fit was evaluated with the following indexes: GFI (Goodness of Fit Index), the AGFI (Adjusted Goodness of Fit Index) and the NFI (Normed Fit Index).

To analyse the scale's psychometric properties, we calculated sensitivity and specificity indexes as well as the

area under the ROC (Receiver´s Operating Characteristics) curve, as a complement, to define the optimal cut-off point. Finally, to evaluate criterion validity, we analysed the degree of concordance between the $POSIT_{UAS}$ and both the ADI and the CRAFFT. The IBM SPSS Statistics 20 (IBM Corp. Released, 2011) and AMOS 21 (Arbuckle, 2012) software packages were used for data analysis.

Results

Descriptive statistics

First, Table 1 displays the direct responses of the 569 adolescents to each of the 17 items comprising the $POSIT_{UAS}$, with the percentage of affirmative responses to each. The highest percentages correspond to item 6 ("Do your friends take drugs to parties?") and to item 2 ("Do your friends feel bored at parties where alcohol is not served?"), with 30.2% and 29.3% of affirmative responses, respectively. Furthermore, item 1 ("Do you get into trouble because you use drugs or drink alcohol at school?") and item 10 ("Have you had a car or motorcycle accident while under the effect of alcohol or drugs?"?) resulted in the lowest percentage of affirmative responses (0.5% and 0.7%, respectively).

As to the descriptive statistics for the scale's total score, we must highlight that the overall mean of the $POSIT_{UAS}$ is 1.52 and the standard deviation is 2.34, with the observed scores ranging between 0-15. Statistics for asymmetry and standardised kurtosis reveal the existence of notable positive asymmetry (A = 21.36) and leptokurtic distribution (C = 28.10), thereby revealing that the scores do not adhere to a normal distribution. The absence of normality is also reflected in the distribution of percentiles. Specifically, the 95th percentile corresponds to a score of 6.5 (below the midpoint of the scale). Noncompliance with normality was verified using the Kolmogorov-Smirnov test, with the corresponding Lilliefors correction (K-S = 0.26; $p < .001$).

Table 2 displays the frequency distribution and cumulative percentages for the different scores. Using the scale's original cut-off point (≥ 2), 32.9% of the sample has a positive result in the $POSIT_{UAS}$.

When comparing mean scores by sex, though women obtain lower scores than men (1.40 vs 1.62), this difference is not statistically significant ($t(563) = 1.15$; $p = .25$). With regards to age, the differences among the established groups (12-14, 15-16 and 17-18 years) are statistically significant ($F(2\text{-}566) = 80.44$; $p < .001$; $\eta 2p = .22$), with the group aged 17-18 years having the highest average (3.13), followed by the group aged 15-16 years (2.02) and the group aged 12-14 years (0.41).

Consistency of scores

Internal consistency was calculated as evidence of reliability of the $POSIT_{UAS}$. Given the dichotomous nature

Table 1. *Percentage of affirmative responses to each item of the $POSIT_{UAS}$, standardised factor loadings and p-value*

Item	% yes	λ	*t*
Do you get into trouble because you use drugs or drink alcohol at school?	0.5	.16	5.38***
Do your friends feel bored at parties where alcohol is not served?	29.3	.42	7.20***
Have you accidentally hurt yourself or someone else while under the effect of alcohol or drugs?	4.7	.47	10.08***
Are you sometimes unable to participate in activities because you have no money due to having spent it on drugs or alcohol?	3.7	.41	10.34***
Do you sometimes feel that you are addicted to alcohol or drugs?	3.7	.47	10.53***
Do your friends take drugs to parties?	30.2	.60	9.43***
Have you started consuming higher amounts of drugs or alcohol each time to obtain the desired effect?	7.6	.51	10.25***
Do you sometimes leave parties because there are no alcohol or drugs?	3	.46	9.64***
Do you constantly feel the urge to drink alcohol or take drugs?	1.2	.30	7.95***
Have you had a car or motorcycle accident while under the effect of alcohol or drugs?	0.7	.28	8.20***
Do you forget the things you did while using alcohol or drugs?	13.9	.66	10.10***
Does using alcohol or drugs provoke fast mood changes, like shifting from being happy to feeling sad, or vice versa?	19.3	.67	10.03***
Have your family members or friends ever told you that you should reduce your use of alcohol or drugs?	9.5	.57	10.68***
Do you have serious discussions with your family members or friends about your use of alcohol or drugs?	3	.36	8.99***
When you drink alcohol or use drugs, do you tend to do things you normally would not, like disobey rules, break the law or arrive home late?	16.9	.70	10.42***
Do you have difficulties in your relationships with any of your friends due to your use of alcohol or drugs?	1.6	.25	6.23***
Do you sometimes feel that you are unable to control the urge to drink alcohol or take drugs?	3.5	.42	7.95***

Note. *** p < .001.

Table 2. *Frequency distribution for the total POSIT$_{UAS}$ scores.*

Total Score	Frequency	Valid percentage	Cumulative percentage
0	288	50.6	50.6
1	94	16.5	67.1
2	61	10.7	77.9
3	33	5.8	83.7
4	35	6.2	89.8
5	15	2.6	92.4
6	15	2.6	95.1
7	9	1.6	96.7
8	9	1.6	98.2
9	2	0.4	98.6
10	3	0.5	99.1
11	1	0.2	99.3
12	2	0.4	99.6
14	1	0.2	99.8
15	1	0.2	100

of these items, it was evaluated by calculating the KR-20 index, obtaining a value a of .82. Pardo and Ruiz (2001) usually consider values above .80 as meritorious. The consistency of each item was also analysed individually using the Corrected Homogeneity Index (CHI), resulting in values between .20 and .60. Items 1 and 16 showed the least consistency with the scale as a whole. However, deleting either one did not improve the scale's global consistency at all (Table 3).

Validity evidence of internal structure

Literature hardly addresses the dimensionality of the POSIT$_{UAS}$. Most studies offer a global score that is interpreted on the basis of a cut-off point, assuming the scale's one-dimensional structure, supported by its high internal consistency. This study attempts to take a step further in this regard by performing a Confirmatory Factorial Analysis (CFA) to provide evidence of internal validity, corroborating its one-dimensional structure. The obtained GFI (Goodness of Fit Index); AGFI (Adjusted Goodness of Fit Index) and NFI (Normed Fit Index) showed quite acceptable values (GFI = .983; AGFI = .978 and NFI = .962) in accordance with the criteria of Byrne (2009) and Kline (2005), and were practically identical for men (GFI_M = .979; $AGFI_M$ = .973 and NFI_M = .958) and women (GFI_W = .977; $AGFI_W$ = .971 and NFI_W = .944). Nevertheless, we performed an analysis of factorial invariance in accordance with the guidelines set forth by Byrne (2009), and found that comparing the different models or levels of restriction suggest the same factorial structure for male and female adolescents with regards to factorial saturation (Δc^2 = 24.79; p = .13), though this was not the case for measurement errors (Δc^2 = 126.78; p < .001).

Sensitivity, specificity and ROC curve

Table 4 displays the values for sensitivity and specificity for the different cut-off points. As shown, cut-off point 2 has the greatest equilibrium between sensitivity (94.3%) and specificity (83.9%). In other words, the subscale is capable of detecting true positives in 94.3% of the cases, and of rejecting real negatives in 83.9% of the cases; both results are highly acceptable. Complementarily, we performed a ROC (Receiver Operating Characteristic) curve analysis, obtaining an area under the curve of .95 (Figure 1).

Adopting cut-off point 2 and analysing the psychometric properties of the POSIT$_{UAS}$ according to sex, the results are very similar, though the specificity of the scale is slightly penalised in the case of women (80.4%). As regards age, the results are acceptable for the three age groups considered, especially for the group aged 12-14 years (sensitivity = 100% and specificity = 94.4%), with worse specificity for the two other groups.

Validity evidence of correlation with external variables

To study criterion validity, we first compared the percentage of adolescents with positive results in the POSIT$_{UAS}$ and in the ADI (32.9% and 21.4%, respectively), obtaining a Kappa concordance index of .66 (p < .001). Second, we performed the same comparison of the POSIT$_{UAS}$ and the CRAFFT, with the percentage of positive results in the latter of 22.8%, obtaining a Kappa concordance index of .63 (p < .001). Finally, we also calculated the Pearson correlation coefficient for both CRAFFT and the POSIT$_{UAS}$ scores,

Tabla 3. *Consistency of POSIT$_{UAS}$ items.*

Item	KR-20 if the item is deleted	CHI
1	.822	.204
2	.824	.362
3	.810	.468
4	.812	.452
5	.810	.478
6	.810	.513
7	.807	.497
8	.812	.466
9	.819	.322
10	.819	.337
11	.801	.565
12	.802	.562
13	.804	.540
14	.814	.395
15	.798	.602
16	.820	.260
17	.811	.461
GLOBAL	0.821	

the results of which were quite high and statistically significant (rxy = .80; p <.001).

Discussion

Adolescence is a critical period during which youth typically start using and experimenting with psychoactive substances (Gonzálvez, Espada, Guillén-Riquelme, Secades & Orgilés, 2016). In Spain, abusive consumption of alcohol and other drugs among minors has become one of the country's main public health problems, as reflected in the 2009-2016 National Strategy on Drugs (National Drug Plan, 2009b). According to experts, the success of prevention policies, to a great extent, depends on promoting early detection of risk cases, as well as in periodically monitoring the detected levels.

Though the POSIT is one of the evaluation and screening tools most used by professionals and researchers worldwide in the field of addictive behaviours, we still lack specific psychometric data that enables our use of this instrument with certain guarantees to date in Spain.

The analyses performed on the basis of a sample of 569 students from the region of Galicia allows us to verify that the $POSIT_{UAS}$ has good psychometric behaviour. First of all, its internal consistency is actually high (α= .82), in line with the findings of other validation studies that coincide in highlighting that the $POSIT_{UAS}$ is one of the most consistent tools (Knight et al., 2001; Mariño, González-Forteza, Andrade & Medina-Mora, 1998).

Second, in terms of screening, it displays a meritorious equilibrium between sensitivity (94.3%) and specificity (83.9%) for cut-off point 2 mentioned in literature. Furthermore, the results obtained by segments show that the $POSIT_{UAS}$ has excellent behaviour for both male and female adolescents, as well as across different age groups, though specificity is slightly lost as age increases, which suggests considering the possibility of raising the cut-off points. However, it is important to highlight that, as mentioned by Latimer et al. (1997), when faced with a screening tool, maximising sensitivity is most critical, given that the priority of these types of instruments is to prevent the erroneous lack of detection by the screening (false negative) of an adolescent with a drug abuse problem.

The high sensitivity of the $POSIT_{UAS}$ has also been shown when comparing the percentage of positives obtained with this tool (32.9%) with those obtained with the CRAFFT (22.8%), as already pointed out in the study by Golpe et al. (2016). Even so, high concordance with both the CRAFFT and the ADI evidences its high criterion validity.

As regards the subscale's dimensionality, though literature hardly addresses the issue, the performance of a CFA allowed for verifying its one-dimensional structure, thereby providing new support for studies like those by Knight et al. (2001), Latimer et al. (1997), Mariño et al. (1998) and Rumpf et al. (2013), which implicitly assume this one-dimensional structure.

In consequence, given our results, we may confirm the satisfactory psychometric behaviour of the Substance Use and Abuse Subscale ($POSIT_{UAS}$), which may be used with guarantees by researchers and professionals in Spain in the field of addictive behaviours.

From the applied perspective, this study's results entail some interesting implications. First, the validation of the $POSIT_{UAS}$ for use with Spanish adolescents is interesting to the extent that it may be included in future editions of the official information system available in Spain on substance use among Secondary School Students, the ESTUDES. Second, counting with a validated instrument for early de-

Table 4. *Psychometric properties of the $POSIT_{UAS}$ for different cut-off points.*

		Sensitivity (%)	Specificity (%)	ROC CURVE
Cuf-off ≥ 1	99.2	64.2	.953	
Cuf-off ≥ 2	94.3	83.9		
Cuf-off ≥ 3	79.5	93.5		
Cuf-off ≥ 4	66.4	97.3		
		Sensitivity (%)	Specificity (%) Cuf-off ≥ 2	ROC CURVE
Sex	Males	94.8	86.7	.963
	Females	93.3	80.4	.938
Age	12-14 years	100	94.4	.997
	15-16 years	90.2	73	.899
	17-18 years	96.8	64.4	.917

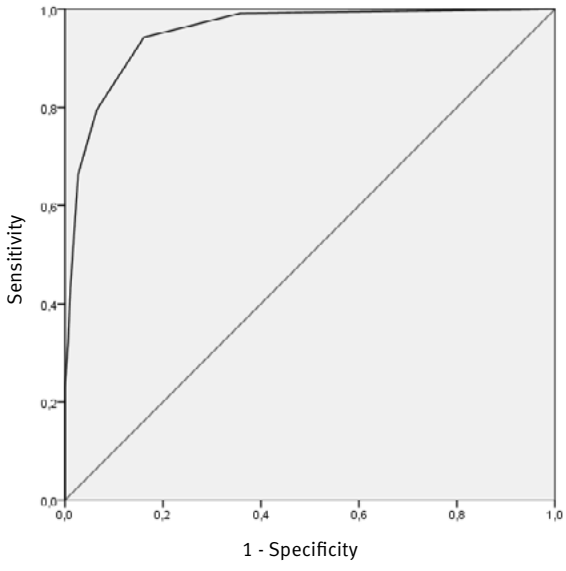

Figure 1. Curva ROC del $POSIT_{UAS}$

tection of the hazardous use of alcohol and other drugs by adolescents, such as the $POSIT_{UAS}$, could be the basis for developing an early detection and brief intervention system in Spain, similar to the SBIRT (Screening, Brief Intervention and Referral to Treatment) used in the United States of America (Laespada, 2014). This procedure is used for detection, prevention, intervention and referral to treatment for adolescents with problematic substance use. Last of all, the availability of screening tools that have been properly adapted and validated in our country would contribute toward a more thorough and objective evaluation of implemented prevention programs, and toward regular follow-up of the detected hazardous consumption levels.

Nevertheless, it is important to point out some of this study's limitations. From the point of view of the sample, we must mention that, despite the size of almost 600 adolescents (a sample size similar to, or even higher than, other validation studies) (Knight et al., 2001, 2003; Latimer et al., 1997), it is still insufficient for assessing the instrument according to different sociodemographic segments. On another hand, the fact that the sample comprised exclusively adolescents from the autonomous community of Galicia in itself is a determinant factor of external validity. Even though students from both public and private schools were included, residents of urban and rural or semirural settings, obviously future studies must consider analysing the psychometric behaviour of the subscale in other communities.

It would also have been interesting to have information available about some clinical aspects of the sample, such as a diagnosis of comorbid disorder, family history of the disorder, etc. However, we must also draw attention to the fact that this has been the initial validation study performed in a school setting, the context in which the most immediate use of the instrument is intended.

Finally, the fact that data collection took place in schools instead of through clinical interviews per se in healthcare settings results in self-reporting of all variables; therefore, it is impossible to know with absolute certainty the extent to which the adolescents may have actually underestimated or overestimated their consumption levels. Nevertheless, as already previously mentioned by different experts in the field of addictive behaviours, self-report measures have proven to be reliable and even better than other methods for evaluating levels of consumption of alcohol and other drugs (Babor, Kranzler & Lauerman, 1989; Winters, Stinchfield, Henly & Schwartz, 1990).

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Conflict of interests

The authors of this article declare the inexistence of conflicts of interest.

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Psychoactive constituents of cannabis and their clinical implications: a systematic review

Constituyentes psicoactivos del cannabis y sus implicaciones clínicas: una revisión sistemática

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Abstract

Objective This systematic review aims to summarize current evidence on which naturally present cannabinoids contribute to cannabis psychoactivity, considering their reported concentrations and pharmacodynamics in humans.

Design Following PRISMA guidelines, papers published before March 2016 in Medline, Scopus-Elsevier, Scopus, ISI-Web of Knowledge and COCHRANE, and fulfilling established a-priori selection criteria have been included.

Results In 40 original papers, three naturally present cannabinoids (Δ-9-Tetrahydrocannabinol, Δ-8-Tetrahydrocannabinol and Cannabinol) and one human metabolite (11-OH-THC) had clinical relevance. Of these, the metabolite produces the greatest psychoactive effects. Cannabidiol (CBD) is not psychoactive but plays a modulating role on cannabis psychoactive effects. The proportion of 9-THC in plant material is higher (up to 40%) than in other cannabinoids (up to 9%). Pharmacodynamic reports vary due to differences in methodological aspects (doses, administration route and volunteers' previous experience with cannabis).

Conclusions Findings reveal that 9-THC contributes the most to cannabis psychoactivity. Due to lower psychoactive potency and smaller proportions in plant material, other psychoactive cannabinoids have a weak influence on cannabis final effects. Current lack of standard methodology hinders homogenized research on cannabis health effects. Working on a standard cannabis unit considering 9-THC is recommended.

Keywords: Delta(9)-Tetrahydrocannabinol; Cannabinol; Cannabis; Cannabinoids; Psychotropic drugs.

Resumen

Objetivo Esta revisión sistemática pretende resumir la actual evidencia sobre qué cannabinoides naturalmente presentes contribuyen a la psicoactividad final del cannabis, considerando sus concentraciones registradas y su farmacodinamia en humanos.

Metodología Siguiendo las guías PRISMA, se revisaron artículos científicos publicados antes de marzo 2016 en Medline, Scopus-Elsevier, Scopus, ISI-Web of Knowledge y COCHRANE, que cumplieran unos criterios establecidos a-priori.

Resultados En 40 artículos científicos, se identificaron tres cannabinoides naturalmente presentes (Δ-9-Tetrahydrocannabinol, Δ-8-Tetrahydrocannabinol y cannabinol) y un metabolito humano (11-OH-THC) con relevancia clínica. De éstos, el metabolito produce los efectos psicoactivos más potentes. El cannabidiol (CBD) no es psicoactivo, pero sí ejerce un efecto modulador sobre los efectos psicoactivos del cannabis. La concentración 9-THC en derivados cannábicos (hasta 40%) supera en gran medida la de otros cannabinoides (hasta 9%). La farmacodinamia descrita varía, dada la heterogeneidad en aspectos clave de la metodología (dosis, rutas de administración y experiencia previa con cannabis de los participantes).

Conclusiones Los resultados evidencian que el 9-THC es el cannabinoide que más contribuye al efecto psicoactivo del cannabis. Otros cannabinoides psicoactivos contribuirían mínimamente, dada su menor potencia psicoactiva y su baja concentración en los derivados cannábicos. La falta de estándares metodológicos dificulta el avance en los conocimientos sobre los efectos del cannabis en la salud. Establecer una unidad estándar de cannabis basada en 9-THC ayudaría a superar estas limitaciones.

Palabras clave: Delta(9)-Tetrahidrocannabinol; Cannabinol; Cannabis; Cannabinoides; Drogas psicoactivas.

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Introduction

Cannabis is the third most widely used drug worldwide (United Nations Office on Drugs and Crime, 2015), being its lifetime prevalence of use about 80.5 million Europeans (European Monitoring Centre for Drugs and Drug Addiction, 2012). Many European countries reported an increase in cannabis use during the last two decades (WHO, 2016). Considered the most widely abused illicit drug, Cannabis sativa *(Cannabis Sativa L.)* is one of the oldest plants harvested by man (Appendino, Chianese, and Taglialatela-Scafati, 2011) and has been always accompanied by controversy due to its psychotropic effects- defined by the WHO as the "ability to change an individual's consciousness, mood or thinking processes" (WHO, 2004).

Cannabis use has been associated with psychiatric, physical, and social impairment (Hall and Degenhardt, 2009; Hall, 2009; Volkow, Baler, Compton, and Weiss, 2014). Otherwise, several potential therapeutic effects of cannabis have been found (Mechoulam and Hanuš, 2000). While knowledge on and its therapeutic potentials has grown considerably in the last decades, its use is still polemic due to its potential harmful effects and its marked recreational use (Adams and Martin, 1996). Moreover, difficulties in separating psychotropic effects from the therapeutic effects have been reported (Borgelt, Franson, Nussbaum, and Wang, 2013; Greenwald and Stitzer, 2000).

One reason is cannabis' complex composition, containing more than 500 compounds from almost all the chemical classes, as for example mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids, simply fatty acids, among others (Appendino et al., 2011; ElSohly and Slade, 2005). Exclusive of cannabis are the phytocannabinoids, being Δ-9-Tetrahydrocannabinol (9-THC) the most studied cannabinoid due to its known psycho activity (Dewey, 1987; Gaoni and Mechoulam, 1964; Hollister, 1987). The rest of cannabinoids, around 100, have commonly been neglected (Mechoulam, 2005). This is especially worrisome as consumers mostly smoke or ingest whole plant material, which presents variable proportions of cannabinoids.

This knowledge gap has also complicated cannabis health assessment. As no reliable and homogeneous registration systems exist, cannabis assessment remains focused on the frequency of consumption. One example is the definition for risky cannabis users given by the EMCDDA, which bases only on the frequency of cannabis use in the last month (European Monitoring Centre for Drugs and Drug Addiction, 2012). Meanwhile the consumed quantity of cannabis, and more concretely the quantity of cannabinoids, remains unexplored.

One option already defined for other drugs as alcohol are standard units (Gual et al., 1999; Stockwell, Blaze-Temple, and Walker, 1991), which consider the main constituent with implication on health. However for cannabis, consensus on which cannabinoids, other than 9-THC, may have implications on the sought psychoactive effects on humans, is still needed. Information on the influence of other cannabinoids on cannabis effects, considering their concentrations and effects on cannabis pharmacodynamics is still required.

In order to analyze the contribution of other cannabinoids to cannabis final health effects, we conducted a systematic literature review, which is intended to conclude which naturally present cannabinoids have shown psychoactive effects, considering their concentrations and their pharmacodynamics in humans.

Methods and materials

The information for this systematic review was gathered with an advanced document protocol in accordance with the PRISMA guidelines (Liberati et al., 2009; Urrútia and Bonfill, 2010). Electronic research was performed consulting the following four scientific data bases: Medline (1950-March 2016), Scopus- Elsevier (2004- March 2016), Web of Science (1900- March 2016) and COCHRANE (1991-March 2016). A combination of the following truncated terms were used as keywords to conduct the search: "Cannab*", "marijuana", "hash", "chemical", "structure" "constituent", "psycho" and "effect".

Selection criteria

All studies published before October 2015 were taken into account following the next parameters: (1) Studies on psychoactivity in humans with cannabinoids which are naturally present in cannabis or their pure synthetic alternative, (2) Pharmacodynamical properties of cannabinoids contributing to cannabis final psychoactive effects, (3) Reports of cannabis potency. Exclusion criteria: (1) Studies focusing mainly on pharmacokinetic properties of cannabinoids (2) Reviews or monographs. No language or publication date restrictions were applied.

Data extraction

Data was extracted by two reviewers (CC and HL) and two senior researchers (AG and MB) were asked in case of doubts. From the selected articles, the following data was extracted: authorship, year of publication, identified psychoactive substances, doses, administration forms, psychoactive effects, plant material used for the study and volunteers previous experience with cannabis.

Results

A total of 1484 unique entries were found, beyond those 87 fulfilled our inclusion criteria. After full-text-revision, 54 were rejected due to meet exclusion criteria, mostly because of being previous reviews (N=41). Finally, as shown

in Figure 1, 40 articles were included in the literature review. The results are divided in three parts: 1) Naturally present cannabinoids affecting cannabis psycho activity; 2) Pharmacodynamical effects; and 3) Reported potencies of naturally present psychoactive constituents.

1) Naturally present cannabinoids affecting cannabis psycho activity

- *Direct effects*

Delta-9-trans-Tetrahydrocannabinol (9-THC) dose-dependent psychoactive effects were observed on subjects after using the intravenous, oral and inhaled routes of administration (Table 2). Also other administration routes like vaporization (Zuurman et al., 2008) and drinking cannabis tea (Hazekamp, Bastola, Rashidi, Bender, and Verpoorte, 2007) have been reported.

Delta-8-Tetrahydrocannabinol (8-THC) and Cannabinol (CBN) produce psychoactive effects in humans but with less intensity than 9-THC (Table 1) (De Souza, Karniol, and Ventura, 1974; Hollister and Gillespie, 1973; Karniol and Carlini, 1973; Pérez-Reyes, 1973). Potency ratio for 8-THC was estimated to be between 1:2 and 2:3 (8-THC: 9-THC) (Hollister and Gillespie, 1973; Karniol and Carlini, 1973). Psychoactive effects of 8-THC were observed after intravenous and oral administration. CBN has a potency ratio of 1:10 (CBN: 9-THC), but psychoactive effects were not present after oral administration (Hollister, 1973).

One metabolite of 9-THC -11-OH-THC- has psychoactive effects by its own if injected pure intravenously, observing faster and stronger psychoactive effects than after the administration of 9-THC (Lemberger, Martz, Rodda, Forney, and Rowe, 1973).

- *Indirect effects*

Cannabidiol (CBD) administration was not followed by psychoactive effects neither after oral nor intravenous administration. CBD presents a modulating effect on 9-THC psychoactive activity, which has shown to depend on several factors. One example is the ratio CBD:9-THC or the order of administration of the cannabinoids, which affects the intensity of the modulating effect (Dalton, Martz, Lemberger, Rodda, and Forney, 1976; Ilan, Gevins, Coleman, ElSohly, and de Wit, 2005; Zuardi, Shirakawa, Finkelfarb, and Karniol, 1982).

Another cannabinoid influencing 9-THC psychoactive effects is Δ-9-tetrahydrocannabivarin (THCV), which potency was estimated to be 25% of 9-THC psychoactive potency (Hollister, 1974). However, evidence on THCV effects on 9-THC is still limited and contested, and suggest that THCV may have a mixed effect on 9-THC. A recent study showed that pre-treatment with THCV resulted in potentiating some of the effects produced by 9-THC, while minimizing others (Englund et al., 2016).

2) Pharmacodynamical effects

Pharmacodynamical effects of naturally present psychoactive cannabinoids have shown to include psychological and systemically effects (Table 2).

- *Psychological measures*

Pure 9-THC and whole plant material produced dose-dependent effects and feelings of intoxication and stimulation were the most often described. Other effects frequently observed were anxiety, sedation, deviations of psychomotor performance, memory impairment, worse-

Table 1. *Psychoactivity of naturally present cannabinoids and related metabolites in humans, identified in the selected articles.*

Molecule	Author	Administration route	Psychoactive potency
Naturally present psycho active cannabinoids			
9-THC	All authors	Smoked Intravenous Oral	Naturally present cannabinoid with the highest psychoactive potency
8-THC	Hollister (1973)	Oral Intravenous	Potency ratio: 2:3 (8-THC : 9-THC)
	Karniol and Carlini (1973) De Souza (1974)	Smoked	Potency rate: 1:2 (8-THC : 9-THC) Less potent than 9-THC
CBN	Pérez Reyes (1973)	Intravenous	1:10 (CBN : 9-THC)
		Oral	No psychoactive effects
THCV	Hollister (1974)	Intravenous	Potency ratio: 1:4 (THCV: 9-THC)
Directly related psychoactive metabolites of cannabis			
11-OH- 9-THC	Lehmberger (1973)	Intravenous	Greater psychological effects than 9-THC with earlier onset.

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; 8-THC: 8-Delta-Tetrahydrocannabinol; CBN: Cannabinol; THCV: Δ-9-Tetrahydrocannabivarin, 11-OH-9-THC: 11-Hydroxy-Delta-9-Tetrahydrocannabinol.

Table 2. *Human pharmacodynamical properties of cannabinoids described in the selected articles.*

Author	Volunteer characteristics	Administration route	Doses	Observed effects after the consumption
Administration of pure 9-THC				
Curran (2002)	Experienced cannabis users with no current consumption	Oral	9-THC: 7.5, 15 mg	Dose-dependent effects on Impairment of episodic memory and learning, perceptual priming and working memory.
D'Souza (2008)	Current frequent users	Intravenous	9-THC: 2.5, 5 mg	Dose-related perceptual alterations, impaired memory and attention, amnesia, increased subjective effects of "high" and tachycardia.
Martín-Santos (2012)	Cannabis use less than 15 times in lifetime	Oral	9-THC: 10 mg	Positive and negative symptoms like anxiety, dysphoria, sedation and subjective intoxication. 5% of the patients became paranoid and anxious. Increased heart rate and differences in diastolic blood pressure at 2 hours post-administration
Zuurman (2008)	Cannabis use not more than once a week during the previous 6 months	Intrapulmonary (vaporization)	9-THC: 2 mg, 4 mg, 6 mg and 8 mg	Alertness, "feeling high", external perception, tachycardia, changes in body sway and pupil size.
Studies with administration of whole plant material or combinations of cannabinoids				
Bhattacharyya (2010)	Mean lifetime cannabis use	Intravenously	CBD: 5 mg 9-THC: 1.25 mg	Pre-treatment with CBD resulted in reduced psychological/psychotic effects of 9-THC versus pre-treatment with placebo.
Dalton (1976)	Previous cannabis users	Smoking	25 µg/kg of 9-THC together with either placebo or 150 µg/kg of CBD	Combined administration of CBD and 9-THC resulted in significantly attenuated subjective response and intoxication feelings than following the administration of 9-THC. Pretreatment with CBD failed to block 9-THC-induced euphoria.
Greenwald (2000)	Regular marijuana users	Smoking (Marihuana)	9-THC: 3.55 %	Antinociception and behavioral symptoms. Subjective effects showed high variability between participants.
Englund (2013)	Volunteer having consumed at least once in their lifetime	Oral (CBD) Intravenous (9-THC) 1.5mg	CBD 600 mg 9-THC 1.5 mg	Pretreatment with CBD resulted in less psychotic symptoms, paranoia and better episodic memory. Positive psychotic symptoms were lower if pre-treatment with CBD had been present, however in comparison to placebo, differences did not reach not statistical significance
Englund (2016)	Males who have not consumed cannabis more than 25 times in their lifetime	Oral (THCV) Intravenous (THC)	THCV 10mg capsules 1 mg of 9-THC	Pre-treatment with THCV inhibited some effects of THC (for example less subjective intense effects of 9-THC), while potentiating others (anxiogenic effects of 9-THC).
Haney (2015)	Cannabis users of at least half a cannabis cigarette 4 or more times per week in the last month	Oral (CBD) Smoking (THC)	Pretreatment with oral CBD (200 mg, 400 mg or 800 mg) Smoking half of an inactive or active (5.30–5.80% 9-THC) cannabis cigarette was smoked 90 min later	Oral CBD pretreatment does not alter the subjective, reinforcing, or cardiovascular effects of smoked cannabis relative to placebo in cannabis smokers
Hunault (2008)	Cannabis users (2-9 joints/month)	Smoking (Marihuana and tobacco)	9-THC: 9.8%, 16.4%, 23.1%	Increased doses raised heart rate and drowsiness, produced vomiting, changes in blood pressure and tachycardia.
Hunault (2009)	Cannabis users (2-9 joints/month)	Smoking (Marihuana and tobacco)	9-THC: 9.8%, 16.4%, 23.1%	Increased doses slowed down response time and worsened both linearly motor control. Some participants showed no impairment in motor control even at serum concentrations higher than 40 ng/mL. Subjective effects (high feeling and drowsiness) differed significantly between treatments.
Ilan (2005)	Previous cannabis experience (more than 10 times in lifetime)	Smoking (Marihuana)	9-THC: 1.8-3.6% CBC: 0.1-0.5% CBD: 0.2-1%	Varying concentrations of CBD and CDC do not affect significantly the effect of 9-THC. CBD tended to antagonize only if 9-THC was present in high concentration.
Morgan (2010)	Cannabis used at least once a month during the previous year	Smoking	Participants own cannabis	Acute deficits in prose recall and memory impairment, being more evident if CBD concentrations were low.

Author	Volunteer characteristics	Administration route	Doses	Observed effects after the consumption
Morgan (2012)	Current cannabis smokers	Smoking	Participants own cannabis.	High THC concentrations increased rates of depression and anxiety and resulted in worse prose recalls and source memory. In recreational users, presence of CBD decreased presence of psychosis-like symptoms. In daily users, CDB presence resulted in better recognition memory.
Ramesh (2013)	Current daily marijuana consumers	Smoking	1 to 6 puffs: 9-THC: 5.5%, 6.2%	Feeling "high", impaired psychomotor performance and decreased accuracy of immediate recall. Participants also presented decreased Carbon Monoxide levels.
Schaefer (1977)	Occasional and habitual smokers	Smoking	9- THC: 1.5%, 2.2%	Increased heart rate and slower reaction time. Subjective effects were dose-dependent.
Schwope (2012)	Heavy and chronic cannabis smokers	Smoking	9- THC: 6.8%	Feelings of "high", stimulation, sedation, slurring speech, shakiness. Increased food intake and dry mouth.
Zuardi (1982)	Cannabis use at least on 15 days prior to the study	Oral	9-THC: 0.5 mg/kg CBD: 1 mg/kg Combination of 9-THC (0.5 mg/kg) and CBD (1 mg/kg)	THC anxiogenic, CBD antagonized subjective psychotropic effects of THC, pulse rate was not affected.
Studies comparing administration of pure 9-THC and whole plant material				
Wachtel (2002)	Cannabis use at least once in the last two months and at least 10 times in their lifetime.	Oral and smoking	9-THC: 8.4 mg, 16.9 mg CBN: 0.30% CBD:0.05%	*Oral group:* Volunteer report higher drug effect after pure 9-THC than after taking marijuana. *Smoking group:* Pure 9-THC induces less drug effects than smoking marijuana, especially at the lower dose.
Chait (1992)	Experienced cannabis users	Oral vs smoking	Oral: 10mg, 15mg Smoked: 2.6%, 3.6%	Smoking and oral ingestion resulted in similar subjective effects. Smoking marihuana was rated in overall greater drug effects, greater heart rate and lower food intake.
Hart (2002)	Current cannabis smokers, with average of 6 joints/day	Oral vs smoking	Oral: 20 mg of 9-THC Smoking: 3.1 % of 9-THC	Smoking and oral ingestion resulted in similar subjective effects. Slightly more pronounced subjective effects with slower decrease over time were observed after smoking marijuana. Negative subjective effects and abstinence were identified only in the smoking group and not in the oral administration group.

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; 8-THC: 8-Delta-Tetrahydrocannabinol ; CBN: Cannabinol; CBD: Cannabidiol; CBC: Cannabichromene.

ned prose recall, mood changes and decreased perceptual accuracy (Curran, Brignell, Fletcher, Middleton, and Henry, 2002; D'Souza et al., 2008; Hunault et al., 2009; Martin-Santos et al., 2012; Ramesh, Haney, and Cooper, 2013; Schaefer, Gunn, and Dubowski, 1977).

Articles comparing the effects of cannabis in different administration routes (oral vs smoked) conclude that oral administration of pure 9-THC produces lower subjective ratings than smoking whole plant material (Chait and Zacny, 1992; Hart et al., 2002) and does not result in craving and abstinence symptoms (Hart et al., 2002).

When comparing the effects of pure 9-THC and whole plant material within same administration routes, minor differences in subjective effects were observed (Wachtel, ElSohly, Ross, Ambre, and Wit, 2002). Basing on visual analog scales (Folstein and Luria, 1973), orally ingested marihuana produces less subjective effects than pure oral 9-THC. In contrast, when smoked, marihuana resulted in greater subjective effects than smoking pure 9-THC. These results are consistent with other study results which have shown that cannabinoids as CBN lose their psychoactive effects if taken orally (Pérez-Reyes, 1973).

Studies analyzing the influence of specific cannabinoids on 9-THC effects mostly focused on CBD. Although devoid of psycho activity (Pérez-Reyes, 1973), several studies included in our review suggest that CBD has an potential influence on cannabis final effects. CBD has shown to antagonize and to modulate 9-THC effects, as for example memory impairment and prose recall (Morgan, Schafer, Freeman, and Curran, 2010). Also anxiety and psychotic-like symptoms induced by 9-THC seem to be affected if CBD is present (Morgan et al., 2012; Zuardi et al., 1982). However, CBD role seems complex as its effects not to depend only on its own concentration but also on the concentration of 9-THC as well the administration order (Bhattacharyya et al., 2010; Ilan et al., 2005).

- *Systemic effects*

Dose-dependent cardiovascular effects, characterized by marked increases in heart rate were found in most of the volunteers participating in the cannabis studies. Smoking pure 9-THC induced less tachycardia than smoking whole plant material (Wachtel et al., 2002). Other systemic symptoms were feeling hungry (Schwope, Bosker, Ramaekers, Gorelick, and Huestis, 2012), increased body sway as well as pupil size (Zuurman et al., 2008).

Effects on the respiratory system were not described in the selected articles. Because cannabis is commonly smoked along with tobacco, some studies analyzed the potential interaction between the two drugs. Although little, available information indicates that tobacco increases the proportion of released cannabinoids (Van der Kooy, Pomahacova, and Verpoorte, 2009).

3) Reported potencies of naturally present psychoactive constituents

- *9-THC*

With only a few exceptions, 9-THC is the cannabinoid present in the highest proportion. The highest concentrations of 9-THC identified in the review were in English cannabis powder (40.63%) and Dutch hashish (39.85%). Lower concentrations of 9-THC were reported in herbal cannabis, with a maximum of 25.5% of 9-THC found in New Zealand. Studies analyzing changes in 9-THC concentrations over time, describe high increases in the proportion of the main psychoactive cannabinoid (Bruci et al., 2012; Burgdorf, Kilmer, and Pacula, 2011; ElSohly et al., 2000, 2016; Mehmedic et al., 2010) (Table 3).

- *Other cannabinoids contributing to cannabis psychoactivity*

Concentrations of psychoactive cannabinoids other than 9-THC, were not always registered (Table 3). When present, concentrations were generally low in comparison to 9-THC. One example is CBN, which maximum registered was of 7.7% present in confiscated hashish oil in the USA (Mehmedic et al., 2010).

In contrast, although not psychoactive, concentrations of CBD were frequently registered. Over time, percentages of CBD in cannabis show a negative tendency, which is especially visible in herbal cannabis (ElSohly et al., 2016; Mehmedic et al., 2010; Niesink, Rigter, Koeter, and Brunt, 2015; Potter, Clark, and Brown, 2008). In resin cannabis variable potencies were found depending on the origin of the derivate (Niesink et al., 2015; Pijlman, Rigter, Hoek, Goldschmidt, and Niesink, 2005; Tsumura et al., 2012).

Discussion

Our review summarizes the current evidence on which naturally present cannabinoids contribute to cannabis final psychoactive effects. We have identified three cannabinoids (9-THC, 8-THC and CBD) and one human metabolite of 9-THC (11-OH-THC) which have shown psycho active effects. Beyond naturally present psychoactive constituents, 9-THC has the strongest psychoactive effects and is present in the highest concentration. Its metabolite 11-OH-THC produces more intense effects with an earlier onset. Cannabis psychological and systemically effects are primarily induced by 9-THC, while the contribution of other psychoactive cannabinoids is estimated to be very low.

Burdens in cannabis pharmacodynamical reports

Included studies present huge differences in crucial aspects of methodology, hindering direct comparison and more exhaustive analysis, as for example a meta-analysis. One of these aspects is volunteer's previous experience, which varied largely (going from cannabis use more than 10 times in lifetime to heavy and chronic cannabis users). When studying cannabis pharmacodynamia, previous experience is determinant to estimate acute and long-term effects, due to the presence of depot levels and tolerance (Abood and Martin, 1992; De Souza et al., 1974; Sharma, Murthy, and Bharath, 2012). Methodological differences also affect how outcomes have been measured, going from self-ratings of subjective marihuana-like effects in the older studies (Pérez-Reyes, 1973) to much more complex descriptions using validated scales in the most recent retrieved articles (Englund et al., 2016).

Another important aspect to be considered is the administration route. With direct impact on cannabinoids pharmacokinetic, differences play a key role in cannabis effects. One example is CBN which produces psychoactive effects if injected intravenously but not after oral administration (Pérez-Reyes, 1973). Another example are abstinence symptoms which appeared after smoking marihuana but not after oral ingestion of pure 9-THC (Hart et al., 2002). As cannabis extract is commonly smoked, these studies have important implications for the evaluation of cannabis health effects.

Moreover, 9-THC doses in the selected articles differed widely. In consequence, as cannabis has dose-dependent effects (D'Souza et al., 2008; Wachtel et al., 2002), variable symptoms were described. We cannot reject that due to cannabis complex composition even whole plant material containing similar 9-THC levels may have been different in regard to other cannabinoids. Characteristics as the origin of the plant material, part analyzed or cannabis derivate product should always be considered. Meanwhile, in order to permit comparisons between studies, also data on other cannabinoids but 9-THC should be registered.

Evaluating the role of other cannabinoids but 9-THC

Our review highlights that, by now, 9-THC is considered the main cannabinoid responsible for cannabis psychoactive effects. Research has focused on 9-THC although canna-

Table 3. *Registers of cannabinoids concentrations given in the selected articles.*

Author	Origin and year	Derivate type	Registered concentrations of analyzed cannabinoids					
Bruci et al (2012)	Albania, 2011	Herbal	9-THC: 1.07%- 12.13 % CBD: 0.65% -2.02% CBN: 0.02% - 1.12%					
Burgdorf et al (2011)	USA; 1996-2008	Not indicated	9-THC: 11.75 % CBD: 0.08 %					
ElSohly (2000)	USA, 1980-1997	cannabis, hashish, or hash oil	Marijuana samples had less than 1.5% 9-THC in 1980 and rose to 4.2% 9-THC in 1997. Hashish and hash oil showed no specific potency trends. Other cannabinoids CBD, CBN and CBC showed no significant change in their concentration over the years.					
ElSohly (2016)	USA, 1995-2014	marihuana, hashish, or hash oil	9-THC potency in herbal cannabis has risen over time from approximately 4% 9-THC in 1995 to approximately 12% in 2014. Other cannabinoids with significant content are CBD and CBN (in hashish oil approximately 2-5%). CBD content in plant material has fallen on average from approximately 0.28% in 2001 to ‹0.15% in 2014. In resin derivate CBD maintains on average below 5%.					
Knight (2010)	New Zealand	Hydroponic grown cannabis plants	9-THC: 4.3% -25.2%					
Mehmedic (2010)	USA, 1993-2008	Marijuana Sinsemilla Ditch weed Hashish Hash oil	%	Marijuana	Sinsemilla	Ditch weed	Hashish	Hash oil
			9-THC	3.4-6.1	5.8-13.4	0.3-0.5	2.5-29.3	6.5-31.5
			CBD	0.2-0.5	0.2-0.5	1.5-2.4	0.8-4.9	0.1-1.3
			CBN	0.2-0.4	0-0.2	0-0.2	1.3-2.3	0.6-7.7
			CBC	0.2-0.3	0.2-0.3	0.1-0.2	0.5-0.9	0.3-1.6
			CBG	0.1-0.3	0.1-0.5	‹0.1	0.3-1	0.2-1.2
			THCV	‹0.1	‹0.1	‹0.1	0.1-0.4	0.1-0.7
Niesink (2015)	The Netherlands, 2005-2015	Herbal cannabis (Nederwiet and imported herbal cannabis), cannabis resin (Nederhasj and imported cannabis resin)	Herbal Cannabis: Nederwiet showed high doses of THC but hardly any CBD; fewer than 1% of these samples contained more than 1% CBD. Mean potencies of the most popular and the strongest Nederwiet were 16.0±4.0%, 17.0±3,9%. Imported herbal cannabis had lower 9-THC potencies (6.5±3.5%). Imported cannabis resin had 16.5±6.3% and Nederhasj presented higher 9-THC levels (30.2±16.4%).					
van der Pol (2013)	Netherlands, year not indicated	Herbal cannabis and resin cannabis joints	Herbal: 9-THC: 12.4% (range 1.1–19.5, SD= 3.0); CBD: 0.2% (range: 0.0–0.5, SD= 0.1)					
Pijlman (2005)	Netherlands, 2000-2004	Imported marijuana, home-grown marijuana, imported hashish and home-grown hashish	%	Imported Marihuana	Home-grown Marihuana	Imported Hashish	Home-grown Hashish	
			9-THC	7.2	21.5	18.5	39.8	
			CBN	0.7	0	1.5	0.6	
			CBD	0.20	0.25	8.10	0.60	
Potter (2008)	England, 2005	Resin	%	Herbal	Resin	Sinsemilla	Powder	
			9-THC	2.14	3.54	13.98	40.63	
			CBD	‹0.1	4.17	‹0.10	0.18	
			CBC	0.22	0.34	0.2	0.41	
			THCV	0.17	0.10	‹0.03	0.29	
			CBG	0.21	0.29	0.41	1.59	
			CBN	0.55	1.55	0.16	0.57	
Tsumura (2012)	Japan, 2010-2011	Leaves	%	Leaves	Seeded buds	Seedless buds	Powder	
			9-THC	1.8	3.8	8.3	8.9	
			CBN	0.5	1.1	1.3	1.2	
			CBD	0.2	0.2	0.1	0.1	
Turner (1974)	Different origins, 1970s	Cannabis plants	Nepal: 2.81% THC, 0.21% CBD Mexico: 1.68% THC, 0.27% CBD Pakistan: 1.30% THC, 1.14% CBD USA: 0.35% THC, 1.42% CBD Other cannabinoids found were: CBC, THCV and CBL.					

Note. 9-THC: 9-Delta-Tetrahydrocannabinol; CBN: Cannabinol; CBD: Cannabidiol; CBC: cannabichromene; CBG: cannabigerol; THCV: Tetrahydrocannabivarin; CBL: Cannabicyclol.

bis is mostly consumed as whole plant material. In order to avoid conflicting pharmacological reports, several authors have indicated that other plant cannabinoids need to be considered when evaluating cannabis effects (Eichler et al., 2012; Mechoulam, 2005; Turner, 1974). Our review shows that in most occasions other psychoactive cannabinoids are not even analyzed.

A common profile of cannabis effects could be found, including subjective effects (feeling 'high', stimulated) and systemic effects (changes in heart rate). Studies testing if 9-THC is the only responsible for cannabis psychoactivity conclude that administration of pure 9-THC and whole plant material produce similar effects, which do not significantly differ (Ilan et al., 2005; Wachtel et al., 2002). Clinical implications due to 9-THC interaction with CBD is still being contested, and included articles evidence that CBD's acute modulating effects depends on several factors, as for example the concentration ratio, the administration form or the order of administration (Englund et al., 2013; Haney et al., 2016; Ilan et al., 2005; Zuardi et al., 1982). Described effects reflect laboratory conditions, which may differ from real life conditions. In fact, reported data on concentrations of CBD indicate that especially in herbal cannabis, CBD is only present in minor concentrations. Therefore and as stated in previous reviews on the interaction of CBD and 9-THC, evidence suggests that CBD clinical implications on cannabis health outcomes need further research, that includes larger sample sizes and analyses of long-term effects (Haney et al., 2016; Hollister and Gillespie, 1975; Leweke, Mueller, Lange, and Rohleder, 2016; Zhornitsky and Potvin, 2012).

Cannabis potencies and implications for health

In our article selection, the highest concentration used to analyze pharmacodynamical effects was 69 mg of 9-THC (23%) (Hunault et al., 2008, 2009). Even though high concentrations used in research may be lower than some of the registered potencies, as samples containing between 30% and 40% of 9-THC were reported by several authors. However, due to the fact that some registries correspond to policy seizures, data on potency may not be representative of common street cannabis.

Some authors affirm that when growing for recreational use, getting stronger cannabis has become a common target (Knight et al., 2010; Mehmedic et al., 2010; Pijlman et al., 2005). Concentration changes have focused on 9-THC, while other cannabinoids maintain or decrease (Mehmedic et al., 2010). Concentrations of 9-THC were mostly higher than the concentrations of other cannabinoids, which did mostly not exceed 8%.

Information about which harmful effects of cannabis are expected to get worsened by higher doses, especially in cases of chronic heavy use, need further research. Nonetheless, our review shows that in research there is a tendency to simulate real conditions of cannabis consumption. One example is analyzing cannabis extracts mixed with tobacco (Hunault et al., 2008, 2009; Van der Kooy, Pomahacova, and Verpoorte, 2008; Van der Kooy et al., 2009) or volunteers' own preparations (Morgan et al., 2012; van der Pol et al., 2013).

Another issue of growing concern is the use of highly potent synthetic cannabinoids, which can result in serious harmful effects on health. Our review did not consider these compounds due to the fact that their prevalence of use in our context is much lower than the use of whole plant (Observatorio Español de la Droga y las Toxicomanías, 2015; Plan Nacional sobre Drogas, 2016).

Limitations and strengths of the systematic review

Our review has several potential study limitations. On the one hand, differences in study characteristics hindered equivalent data extraction for its comparison in a meta-analysis. On the other hand, publication bias and limitation of the data bases may have implicated some loss of information. However, our review was designed in order to find and assess relevant or high quality studies addressing the question of the review.

Our review has several positive aspects. To our knowledge it is the first systematic literature review focusing on psychoactivity, considering pharmacodynamical properties and potencies of several cannabinoids. Our study also points out that several aspects of cannabis psychoactivity are still unclear, mostly because research has not focused on how cannabinoids may influence individually on cannabis final effects.

Conclusions

Current evidence indicates that of cannabis naturally present constituents, 9-THC is the most potent psychoactive cannabinoid. Moreover, in comparison to other cannabinoids, its concentration in plant material is greatly higher. Therefore, when evaluating cannabis effects, 9-THC should be considered the main contributor to cannabis psycho activity.

Cannabis is the most abused illicit drug worldwide and constitutes an important public health problem. Standardized methodology is needed to overcome current burdens in cannabis research. Working on a standard cannabis unit which quantifies cannabis main cannabinoid with implication on psychoactivity is needed. This unit is expected to facilitate homogenization of cannabis registers, which is essential to improve epidemiological research and public health interventions.

Contributions

Cristina Casajuana Kögel, Hugo López-Pelayo, María Mercedes Balcells and Antoni Gual designed the study. Cris-

tina Casajuana wrote the first draft of the manuscript. All other authors contributed to the editing and final review of the manuscript. All authors approved the final paper.

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Impact of Binge Drinking (BD) in Adolescence. Are we doing it right?

Impacto del consumo episódico excesivo de alcohol en la adolescencia. ¿Lo estamos haciendo bien?

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Dear Editor,

Excessive alcohol use and alcohol use disorders are major causes of death and disability worldwide (WHO, 2014). According to the World Health Organization, 10% of adolescent deaths (those aged 15 to 19 years) in the European Region were attributable to alcohol (Drost et al. 2016).

Nowadays, one of the most prevalent patterns of alcohol consumption is called binge drinking (BD). In 2015 it was estimated that about 35% of European adolescents of 15–16 years old have had at least one BD occasion in the past 30 days (The ESPAD Group, 2016). Moreover, in Spain, the series of surveys on the use of drugs in adolescents of secondary education, ESTUDES 2014-2015, stated that 32.2% have performed at least one BD occasion in the last month (National Plan on Drugs, 2016) whereas a recent study by Golpe, Gómez, Braña, Varela & Rial (2017) concluded that 33.1% of Spanish adolescents were doing intensive consumption last year and 20% last month (3 or more alcoholic drinks per sitting and drunkenness). Moreover, 19.8% of adolescents were doing a risk alcohol consumption without significant differences by gender. Romo-Avilés, Marcos-Marcos, Tarragona-Camacho, Gil-García & Marquina-Márquez (2016) found small differences between the amount of alcohol consumed or in "botellón" participation between boys and girls. This suggests that intensive alcohol consumption and BD have increased in girls.

In the European Union, alcohol-attributable costs were estimated at €125 billion in 2003. In Spain, the total social costs of alcohol consumption can be around 1% of gross domestic product (more than 10.000 million euros) (Pulido, Indave-Ruiz, Ruiz-García, Bartroli & Barrio, 2014).

We did not find any study regarding costs associated with BD and underage drinking in Europe but previous works have shown youthful drinkers are at greater risk of: being victimized and perpetrating youth violence; low educational attainment; and low college expectations, putting a financial burden on the criminal justice system and educational sector. (WHO, 2014).

Based on the evidence, BD is mainly related to acute effects in young people, such as acute intoxication, accidental and intentional injuries, road crashes, scholar problems due to lower cognitive performance and brain alterations as well as school absenteeism caused by the symptoms caused by the hangover after acute alcohol intoxication, unprotected and unplanned sex, consumption of other drugs, legal problems due to the reduction of cognitive and verbal ability to resolve conflicts and developing an alcohol use disorder in adulthood (Pulido et al., 2014, Windle & Windle, 2017). In a research carried out by Windle & Windle in 2017 found that diagnostic accuracy of adolescent alcohol problems in predicting alcohol dependence 7 years later was 74%. In Spain, the annual prevalence self-informed about acute alcohol intoxication was higher than 30% in population between 15 and 34 years

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old in 2011, being higher in adolescents between 15 and 16 years old (Pulido et al., 2014).

However, all these adverse or acute events could be associated to economic consequences such as outpatient care, hospital stays, some of the direct costs associated with violence as emergency care, police services or criminal justice, traffic accidents with healthcare and scholar absenteeism (Pulido et al., 2014; WHO, 2014).

Given the high prevalence and health, social and economic consequences of alcohol use and BD, it seems clear that strategies aimed at the prevention must be carried out. Which measures are taken today for prevention of alcohol use? To date, different programs to prevent alcohol use in adolescents have been designed (Foxcroft y Tsertsvadze, 2012; Jander, Crutzen, Mercken, Candel & de Vries, 2016). Currently there are some web-based computer-tailored prevention programs but they are more extended usually at international level.

A meta-analysis of computer-tailored interventions for health behaviour change showed these interventions would have clinically significant impact on rates of behavioural risk factors (Krebs, Prochaska & Rossi, 2010). On the one hand, these interventions have the potential to reach many people from different social classes and ages. This is because a significant percentage of the population, today, has access to the internet. On the other hand, tailored information is perceived as more relevant than no tailored information (Schulz et al., 2014).

Despite of international and national interventions (Foxcroft y Tsertsvadze, 2012) aim to prevent the alcohol use, in very few occasions their cost-effectiveness and their efficiency has been assessed (Drost et al., 2016). In a limited budget situation studying the cost-effectiveness of interventions is a need to assess health decision making. Therefore, cost-effectiveness analysis is a useful tool to inform the interest of an intervention and influence policy and health planning.

In conclusion, there are important gaps in the information about social and health harms associated to alcohol consumption in Spain, especially in the estimation of mortality and morbidity burden, the prevalence of alcohol use disorders, the social costs of consumption and the efficiency of preventive interventions or programs. Therefore, there is a need to evaluate the economic burden and economic evaluation of interventions of BD.

Authorship contributions

AM Vargas-Martínez has prepared the first draft and coordinated the work. E Gil-García has reviewed the work and added the gender perspective. M Lima-Serrano and M Trapero-Bertran have contributed substantially to the text, have made critical revisions to its content. All the authors have approved the final version.

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Conflicts of interest

None.

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"Diazepam loading": ¿Can a strategy for preventing alcohol withdrawal be used to treat benzodiazepine use disorder?

"Carga de diazepam": ¿puede una estrategia para prevenir abstinencia al alcohol usarse con éxito para tratar la dependencia a benzodiacepinas?

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To the Editor,

Benzodiazepines (BZDs) are central nervous system (CNS) depressants which are widely used to treat insomnia and anxiety, despite having long-term adverse side effects. (Fortea González, Oriolo, Balcells Oliveró, Sánchez Del Valle & Castellvi, 2017). As with alcohol, continued use can lead to tolerance and dependence phenomena. Discontinuation in such cases can produce abstinence symptoms such as tremors, anxiety, seizures and, occasionally, death (Brett y Murnion, 2015).

Diazepam is a BZD used to treat and prevent alcohol withdrawal (Bird & Makela, 1994), as well as BZD withdrawal. Diazepam has a long elimination half-life (20-100 hours), as does its active liver metabolite, nordiazepam (36-200 hours) (Greenblatt, Shader, Divoll & Harmatz, 1981), which means that therapeutic concentrations can be present for prolonged periods even after short-term treatments (Muzyk, Leung, Nelson, Embury & Jones, 2013). It also has a highly lipophilic nature, making for rapid onset of action, with maximum concentration in the CNS being quickly reached.

Among the strategies for tackling alcohol withdrawal, the use of a BZD loading dose is considered valid (Lligoña, 2007; Wasilewski et al., 1996). The pharmacokinetic profile of diazepam allows a high initial loading dose to achieve an immediate and sustained treatment effect. Normally this load takes the form of 20 mg of diazepam doses orally every 2 hours until the patient is drowsy but reactive, producing therapeutic concentrations of diazepam and nordiazepam for more than 72 hours.

Nevertheless, despite its pharmacological properties and its use for alcohol withdrawal, the loading strategy has not been reported in the literature for treating BZD withdrawal, except as an initial strategy in the case of acute withdrawal symptomatology followed by a gradual descending pattern (Sellers, 1988).

We describe the case of a 51-year-old woman with a history of long-term BZD use disorder, who was successfully detoxified after receiving a loading dose of diazepam without the subsequent administration of benzodiazepines.

Her toxicological history featured abuse of snorted cocaine and cannabis in the past. She habitually smoked tobacco and drank alcohol sporadically. Personality disorder stands out in her medical history, with predominantly histrionic and borderline characteristics (DSM-5), and self-harming behaviors.

BZD use was initiated by medical prescription for panic attacks and subsequently developed into a pattern of dependence. She had two hospital admissions for detoxification, where a tapering dose of clonazepam was applied, with subsequent relapse. Recently she had been taking 5 mg of lorazepam and 100 mg of diazepam daily.

The patient was taken to the emergency room after an estimated overdose of 200 mg of diazepam with the intention of committing suicide. The toxic urine screen was negative for opioids and ethanol. During the observation

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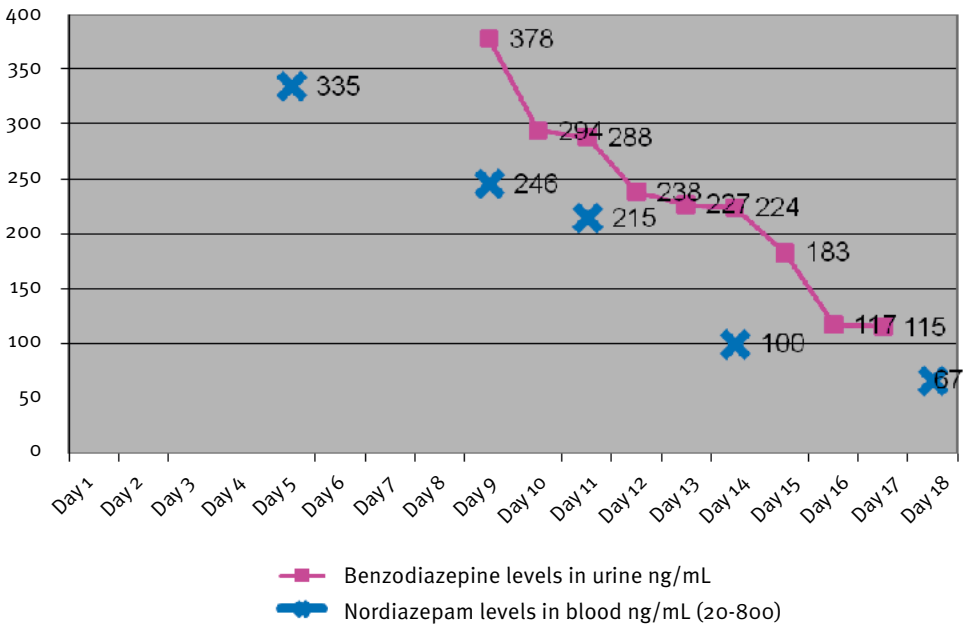

Figure 1. Monitoring of benzodiazepine levels in urine and nordiazepam in blood (the interval considered therapeutic by the laboratory is shown in brackets) during the time of admission. The presence of therapeutic levels of active metabolite in blood is noticeable over a prolonged period.

period she had respiratory depression, for which an intravenous perfusion of flumazenil was administered for 8 hours. Activated charcoal was not administered. She was subsequently admitted to the acute psychiatric unit.

Since flumazenil suppresses the effects of BZDs by inhibition but does not eliminate them from the organism, a diazepam loading strategy analogous to that used for alcohol detoxification was chosen to treat the patient's BZDs withdrawal syndrome. The loading dose was considered to be the earlier intake of 200 mg of diazepam.

She experienced neither symptoms nor severe signs of BZD withdrawal such as delirium or seizures. No signs or symptoms of abstinence were found or reported spontaneously beyond mild anxiety that gradually subsided, nor was a rescue dose required. On the fourth day, monitoring of BZDs in blood and urine was initiated. She was discharged after 18 days and has remained abstinent for 24 weeks.

In our experience, and consistent with its use for alcohol withdrawal, diazepam loading may be a valid strategy on its own for the prevention and treatment of BZD abstinence. The half-life of diazepam and its metabolites (such as nordiazepam) makes it possible to maintain elevated serum levels of active substance, enabling progressive reduction over time (Figure 1) and thereby preventing abstinence symptoms from appearing. In this way the administration of new doses of BZDs is avoided and substance-seeking behavior is not reinforced, as would be the case if BZDs were administered in split doses during several days.

Despite the patient's own overdose being taken as a loading dose in our case, such doses could be administered in a supervised manner to avoid subsequent complications. Thus, although new studies are needed to assess the safety, loading dosage and efficacy in comparison with conventional strategies for treatment and prevention of BZD withdrawal, diazepam loading could be an effective alternative that could also minimize the relapse into use of BZDs.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Chemsex: are we prepared?

Chemsex: ¿estamos preparados?

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To the Editor,

It was with great interest that we read the article published by Dolengevich-Segal (Dolengevich-Segal et al., 2017), which provides an interesting review of the emerging phenomenon known as chemsex and the different drugs used in this type of practice.

We would like to highlight the importance and usefulness of this paper, given the progressive increase in the prevalence of drug use in the context of sexual activity among men who have sex with men (MSM) in Western Europe (Fernández-Dávila et al,. 2016). This situation raises the need to launch epidemiological studies to assess the phenomenon - not only, however, from the point of view of mental health, but also from the field of infectious diseases and toxicology. We must not forget that this type of practice involves an increase in the risk of infection by sexually transmitted diseases and the problems that drug use can cause from the toxicological point of view. Both are causes of emergency room (ER) consultation, and more training in how to tackle the problems arising from chemsex should be provided.

Medication is the second biggest cause of ER visits (Bilbao Gómez-Martino et al., 2017). In addition to the impact on patient safety, adverse effects lead to greater demand for healthcare resources (Bilbao Gómez-Martino et al., 2017). Acute intoxication is a frequent reason for consulting these services, representing 0.5-1% of total visits (Supervía Caparrós et al., 2017). For these reasons, ERs should propose research and intervention programs on this problem, using their own research networks and always with the collaboration and understanding of the toxicology experts (Burbano Santos et al., 2017; González Del Castillo et al., 2017).

The consumption of mephedrone, GHB and methamphetamine for recreational uses, frequent in *chemsex* sessions, constitutes a health risk which is increased by the lack of a specific antidote for any of them (Coll et al., 2016). In addition, given the recent spread of these drugs, they have been little studied and not much is known about their toxicity and problems derived from long-term use. Intranasal methamphetamine can be a risk factor for transmission of the hepatitis C virus after sharing the materials (tubes or straws), not forgetting that the most dangerous route of administration is injection (Folch et al., 2015). Furthermore, protease inhibitors can increase GHB levels, and because methamphetamines use the same hepatic metabolic pathway as these, the likelihood of serious interactions between them is high (Hales et al., 2000). Deaths have been reported in patients with HIV who take methamphetamine during ritonavir treatment (Hales et al., 2000). The number of cases described is small but the risk is probably significant for people on ritonavir and cobicistat treatment.

Considering the increase in primary HIV infections in MSM, some health professionals propose pre-exposure prophylaxis (PrEP), a biomedical intervention, as a cost-effective way to reduce HIV transmission among men

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in this high-risk group and cheaper than post-exposure prophylaxis (PEP) and taking lifelong antiretrovirals. The PrEp, usually performed with Truvada, introduces a new drug into the cocktail and could have a cumulative toxicity effect or loss of efficacy due to potential drug interactions given polydrug use in chemsex sessions (Uglietti et al., 2012).

We believe that the above factors make it necessary to conduct research studies, enhance the training of ER doctors in these aspects and increase the information campaigns to the population in relation to the effects of all these substances, which have appeared recently in comparison to other better-known drugs, as well as the risks associated with the contexts in which they are used. With this type of sexual practices on the increase, such campaigns could be directed not only at the target population, but also involve leisure facilities and health personnel to promote educational therapy from primary care to ER.

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Desde el año 2012 sólo se admite la normativa APA.

Ante la preparación de un artículo de cara a su publicación se deben revisar y aplicar las normas extensas, que pueden ser consultadas en www.adicciones.es

Adicciones está editada por Socidrogalcohol, Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y otras Toxicomanías. Adicciones publica artículos originales sobre el tratamiento, la prevención, estudios básicos y descriptivos en el campo de las adicciones de cualquier tipo, procedentes de distintas disciplinas (medicina, psicología, investigación básica, investigación social, etc.). Todos los artículos son seleccionados después de pasar un proceso de revisión anónimo hecho por expertos en cada tema. Adicciones publica 4 números al año. Adicciones tiene las secciones de editorial, artículos originales, informes breves, artículos de revisión y cartas al director. La revista se publica en español, aunque admite artículos en inglés. Cuando publica un artículo en inglés, puede exigir su traducción también al español, pero no es la norma.

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NO existe un límite exacto de palabras para los trabajos que se presenten. Pero deberá cuidarse mucho que toda la información que se incluya sea estrictamente la necesaria.

Es importante que los artículos sean interesantes para la comunidad científica del campo de las adicciones. Se evitarán trabajos que se refieran a realidades muy concretas –a menos que precisamente en ello resida su interés-, o que sean básicamente descriptivos –a menos, nuevamente, que se trate de algo novedoso.

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

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TREVICTA®
palmitato de paliperidona
suspensión inyectable de liberación prolongada

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 de paliperidona oral a liberación prolongada a Xeplion: El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Xeplion debe iniciarse según se describe al principio de la sección 4.2 anterior. Cambio desde risperidona inyectable de acción prolongada a Xeplion: Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xeplion en lugar de la siguiente inyección programada. A partir de entonces, Xeplion se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y Xeplion 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. Dentro de los siete días de una 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 las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. Dentro 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. Dentro 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. Dentro 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. Dentro de la dosis de mantenimiento mensual: 1 mes o 5 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. Dentro de la dosis de mantenimiento mensual: 6 semanas o más: 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 o 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. Dentro 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. Pacientes 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. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos <1x10⁹/l) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia poscomercialización 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. **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 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vivo ni in vitro de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{max} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inalterado excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante periodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona 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 excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas 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 distonía. 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	neumonía, 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 aumentad	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 líbido, nerviosismo, pesadillas	estado confusional, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación/somnolencia, distonía[a], mareos, discinesia[a], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, convulsión[a], trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringolaringeo, 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. [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. **[e]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 y reflejo de la glabella anormal, 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 ciego 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. *Investigaciones.* En ensayos clínicos, se observaron medianos 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).

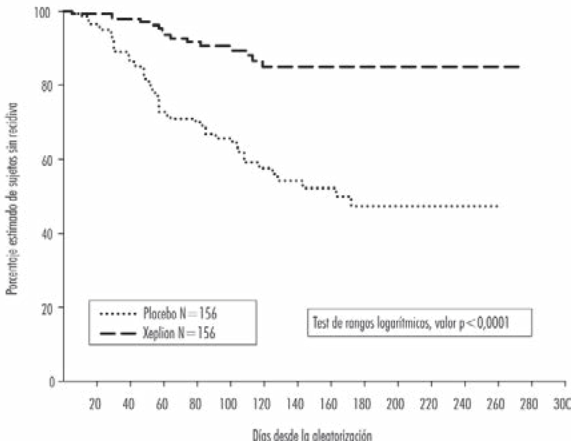
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 las primeras 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 radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 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 (días 8 y 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 los 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 las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una 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.** Poliisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. 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. Período de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefino-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: 171,61 €; PVP: 217,52 €; PVP (IVA): 226,22 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 223,08 €; PVP: 273,99 €; PVP (IVA): 284,95 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 274,59 €; PVP: 325,50 €; PVP (IVA): 338,52 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 411,88 €; PVP: 462,79 €; PVP (IVA): 481,30 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 11/2016. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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 FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a TREVICTA. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

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

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

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

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

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

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de paliperidona de liberación prolongada, se debe iniciar la administración diaria de los comprimidos 3 meses después de la última dosis de TREVICTA y continuar el tratamiento con los comprimidos de paliperidona de liberación prolongada según se describe en la tabla siguiente. La tabla siguiente indica las pautas recomendadas de conversión de las dosis para que los pacientes previamente 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 a 4 meses	Se administrará la inyección lo antes posible y a continuación se reanudará el calendario de inyecciones trimestrales.
de 4 meses a 9 meses	Se seguirá la pauta de reanudación recomendada que se indica en la tabla siguiente.
> 9 meses	Se reanudará el tratamiento con palmitato de paliperidona inyectable mensual según se describe en la ficha técnica del producto. Se podrá reanudar la administración de TREVICTA después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más.

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

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

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

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

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	Frecuencia no conocida[a]
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, onicomicosis, celulitis	infección oftálmica, 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[d]	agitación, depresión, ansiedad	trastornos del sueño, mania, disminución de la líbido, nerviosismo, pesadillas	estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[e], acatisia[e], sedación[f]/somnolencia, distonía[e], mareo, discinesias[e], 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[e], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardíacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolia pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión respiratoria, sibilancias, dolor faringolaringeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, distonía

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 lumbodorsal, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical	rabdomiólisis, hinchazón de las articulaciones	alteraciones posturales
Trastornos renales y urinarios			incontinencia urinaria, poliquiuria, 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[5], 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[6], 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		

[4] 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. [5] Ver el apartado 'Hiperprolactinemia' a continuación. [6] Ver el apartado 'Síntomas extrapiramidales' a continuación. [4] En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con palmitato de paliperidona inyectable mensual comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,65% en todos los pacientes tratados con palmitato de paliperidona inyectable mensual. [4] **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, emprostótonos, 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 cardíaco y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del QT y síntomas extrapiramidales. Se han descrito Torsades de pointes y fibrilación ventricular en un paciente expuesto a sobredosis de paliperidona oral. En caso de sobredosis aguda se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. Tratamiento. Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos y continuos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICTA contiene una mezcla racémica de paliperidona (+) y (–). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante el 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 aleatorizada, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o el final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

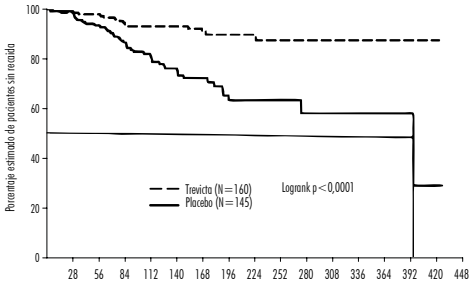


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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

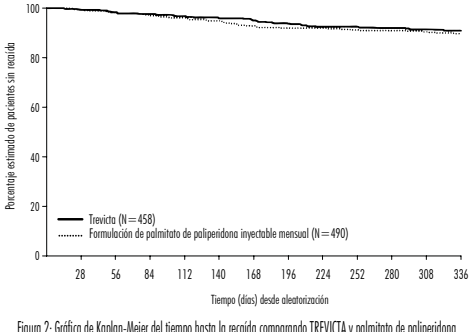


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{ss}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas in vivo, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe substancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_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 FARMACEUTICOS. 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: 515,00 €; PVP: 570,91 €; PVP (IVA): 593,75 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 670,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 824,00 €; PVP: 879,91 €; PVP (IVA): 915,11 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.236,00 €; PVP: 1.291,91 €; PVP (IVA): 1.343,59 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag Interntional NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2017. 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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