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Postmodernity, addictive societies, cannabis and suicidal behaviour: Towards a brave new world?

Posmodernidad, sociedades adictivas, cannabis y comportamiento suicida: ¿Hacia un mundo feliz?

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"Is happiness not merely the freedom to follow
the dictates of one's own will or desire?"

Critique of modernity, Alain Touraine

"The postmodern moment is much more than a fashion;
it reveals the process of pure indifference in which all tastes,
all behaviours can exist side-by-side without excluding one another;
everything can be had with ease, the most practical, the most esoteric things,
old as well as new, the simple-ecological life as well as the hypersophisticated life,
in a lifeless time with no stable reference points, with no guiding coordinates."

The age of emptiness, Gilles Lipovetsky

Suicidal behaviours - ideation, intent, and completed suicide - are a public health problem of the highest order (Saiz & Bobes, 2014). They generate significant economic expense in Western societies (Czernin *et al.*, 2012). More important than the economic impact, however, is the human cost: up to 20 million people attempt suicide, and about one million complete it annually worldwide (WHO, 1999); indeed, suicide is the second cause of death among the world's young population (WHO, 2014). Considering that substance use is a risk factor for suicidal behaviour, and that cannabis is consumed mainly by young people, it is striking that the role the endocannabinoid system (ECS) plays in suicidal behaviour has been relatively little studied.

Recently two "epidemics" linked to substance use have been of concern in the Spanish media: the "silent epidemic" on the one hand, in which a significant part of the general Spanish population takes anxiolytics or even opioids on medical prescription (Zuil, 2017); on the other hand, the imported epidemic of smoked heroin that claimed more than 33,000 lives in the US in 2015 and which, as expected, has reached on our shores (Rego, 2017). The opioid epidemic that devastated American society at the beginning of the century led the Obama administration to limit the legal prescription of opioids as of 2010. This led opioid addicts to begin using heroin and synthetic opioids, such as fentanyl, which are cheaper and easier to acquire. In other words, legal use was replaced by illegal use (Tedesco *et al.*, 2017). In Spain, the fact that the use of opioids had multiplied by a factor of 14 since 1992 had already been reported in 2008; the authors also pointed out how fentanyl was replacing morphine (Garcia del Pozo *et al.*,

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2008). Unfortunately, it is only to be expected that the pattern of opioid use in the US - the transition from legal to illegal opioids - may be reproduced in Spain.

These two epidemics have at least two common elements: firstly, they are epidemics imported from the same country (US), one that has established itself as a social reference point for postmodern Western societies; secondly, it is possible that both epidemics are related to the existential void which is characteristic of postmodern societies (Blasco-Fontecilla *et al.,* 2015, Lipovetsky, 1986), and the inability of many of its inhabitants to endure it. It is possible that to face this void many citizens resort to taking different substances, whether legal or illegal. As Antonio, the protagonist of the article, points out to the El Mundo journalist after smoking a dose of heroin: "You see? This is peace, there are no bad thoughts or pain, only an immense tranquility ... " (Rego, 2017).

In addition to these two media concerns, cannabis is a new source of worry, at least in the health field. Cannabis is the third most widely used drug in the world, and the most heavily used illegal drug, with consumption increasing dramatically in the last two years (Casajuana *et al.,* 2017). It contains around 500 chemical substances and 100 cannabinoids, the most frequently found being delta-9-tetrahydrocannabinol (9-THC), up to 40%, which is a partial CB_1 agonist with a euphoric effect, and cannabidiol (CBD), a CB_1 receptor antagonist with analgesic and anti-inflammatory effects and without psychotropic effects but with modulators of other endocannabinoids (Casajuana *et al.,* 2017). Cannabis use has spread alarmingly in different countries, including ours, particularly among the youngest (see Figure 1).

Although the reasons for this increase are certainly complex, among them we may find: 1) the trivialization of the potentially harmful effects of cannabis; 2) the magnification of the therapeutic potential of some of its components, which has led to the commercialization of Sativex®, an oromucosal spray with identical proportions of 9-THC

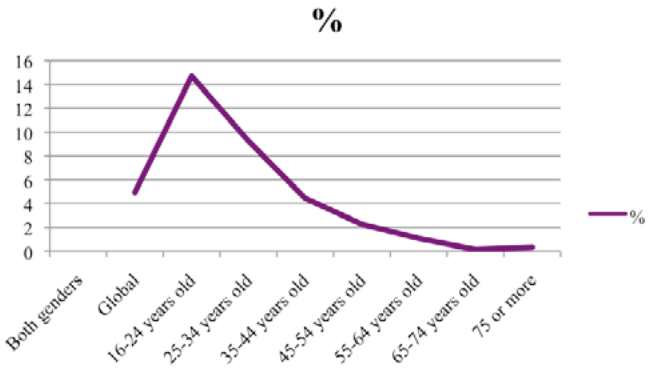

Figure 1. Cannabis use during the previous 12 months by sex and age group in % (population aged 16 and over) (year 2009, compiled by author, SOURCE: INE [Spanish Office for National Statistics]).

and cannabidiol; 3) the fact that it is a relatively poorly studied drug, linked to recreational use and to which severe effects are not attributed (Casajuana *et al.,* 2017); and 4) its legalization in different states of the US and countries around the world (Alvarez *et al.,* 2017). This legalization is a reflection of the trivialization regarding the use of cannabis. While in the early 1990s there was no legislation on the medicinal use of cannabis in the US, today more than a third of US states have some law in this regard, and perception of the risks of cannabis has been relaxed. It is clear that the medicinal use of marijuana may have benefits for some patients. But it is equally obvious that it is having negative outcomes at the public health level. Thus, in recent years there has been an increase in the illicit use of cannabis and disorders related to its use in the US (Hasin *et al.,* 2017). The authors of this study point out that this laxity in the laws resulted in an increase of 1.1 million adult "illicit" cannabis users from 1991 to 2012 and half a million adults with mental disorders derived from cannabis use in the US.

Among the potential therapeutic effects of cannabis in general, we can mention: 1) treatment of chemotherapy-induced nausea, or of chronic neuropathic pain in multiple sclerosis, diabetic neuropathy or other conditions [60], with Sativex® approved for the treatment of central neuropathic pain in multiple sclerosis and intractable cancer pain (Russo *et al.,* 2016); 2) reduction of positive symptoms and severity of symptoms in schizophrenia (Murray *et al.,* 2017, Zuardi *et al.,* 2012); 3) utility when treating epilepsy with animal (Huizenga *et al.,* 2017, Kaplan *et al.,* 2017b) and clinical models (Devinsky *et al.,* 2017, Kaplan *et al.,* 2017a); 4) treatment of some anxiety disorders, particularly post-traumatic stress disorder (Walsh *et al.,* 2017). Indeed, the authors postulate that rather than acting as a gateway for the use of other drugs, using cannabis could function as a way of getting off them; 5) CBD could attenuate the positive reinforcement exerted by opioids by interfering with the cerebral mechanisms responsible for the acute reinforcing properties of opioids except cocaine (Hurd, 2017); and 6) the chronic consumption of low doses of 9-THC has reversed cognitive decline in "mature or elderly" mice, doing so by a glutamatergic mechanism mediated by the CB_1 receptor and histone acetylation (Bilkei-Gorzo *et al.,* 2017).

Nevertheless, the use of cannabis, particularly when regular, and in large high-strength doses (with high levels of 9-THC), has been linked to the following detrimental effects: 1) reduction in bone mineralization, which could increase the risk of osteoporosis and bone fractures in adulthood (Sophocleous *et al.,* 2017); 2) periodontal disease in adulthood (Meier *et al.,* 2016); 3) greater likelihood of death below the age of 60 (Manrique-Garcia *et al.,* 2016); 4) prenatal cannabis exposure has been linked to greater frontal cortex thickness among children and adolescents, affecting the development of executive functions (El Ma-

rroun *et al.,* 2016), and generating greater aggression and attention problems among 18-month old girls (El Marroun *et al.,* 2011); 5) damage to the white matter of the corpus callosum, which may lead to diminished inter-hemispheric communication (Rigucci *et al.,* 2016); 6) greater susceptibility to false memories and less activity in the brain regions associated with the processing of attention and performance (parietal and frontal regions), and memory (temporal and medial temporal areas) (Riba *et al.,* 2015); 7) an increase in accidental poisoning among children. In a retrospective multicenter study conducted in France with 235 children aged under 6 who came to the hospital emergency department for accidental cannabis poisoning between 2004 and 2014, the authors noted that the rate of accidental poisoning by cannabis among young children had increased by 133%, and that calls to poison control centres had increased by 312% (Claudet *et al.,* 2017). The authors pointed out that the proportion of serious cases had risen from 7% in the period 2004-2009 to 19% during 2010-2014, and attributed this to the increasing concentrations of THC in cannabis, which rose from 9.3% (2004) to 20.7% (2014); 8) THC increases the risk of negative feelings such as anxiety, depression, worry, and negative self-evaluation, a reduced working memory, and paranoia (Freeman *et al.,* 2015); 9) the use of cannabis, especially in adolescence and early youth, a period in which brain maturation is still taking place, would increase the risk of psychosis. But not only this. A recent prospective study conducted with 245 patients who were followed for two years after their first psychotic episode found that the continued use of cannabis was associated with a poor prognosis and an increased risk of relapse, which was linked to the poorer treatment adherence of the patients involved (Schoeler *et al.,* 2017); 10) In another study, with a follow-up of 130 men and 90 women conducted for two years after their first psychotic episode, the authors reported that the relapse rate was higher among patients who had continuously used cannabis after the first psychotic episode, (59.1%), compared to those who had done so intermittently (36.0%) or had not used it (28.5%) (Schoeler *et al.,* 2016); and 11) contrary to what many people think, the regular consumption of high-strength cannabis generates dependency (Freeman & Winstock, 2015).

In terms of anxiety, this is regulated biphasically by the ECS, which could explain why cannabis can have a relaxing effect in certain situations, while generating anxiety in others. An example of the regulation of the biphasic response to anxiety is that THC has an anxiolytic effect in the prefrontal area, while it can be anxiogenic in the basolateral amygdala (Ruehle *et al.,* 2012). Since the action of CB_1 agonists inhibits the release of GABA, a simplistic assumption would be that CB_1 agonists could trigger an anxious response (Ruehle *et al.,* 2012), but as these authors point out, CB_1 agonists also inhibit the release of glutamate, and regulate the action of other receptors. Thus, anxiety regulation mediated by CB_1 receptors has to do with three factors: localization, basal activation, and sensitivity. Because the ECS also mediates monoaminergic neurotransmission, ECS stimulation could increase the neurotransmission of noradrenaline, which would be linked to increased anxiety. Furthermore, through the serotonergic system, mild stimulation of the ECS would have an anxiolytic effect, while strong stimulation would have an anxiogenic effect (Ruehle *et al.,* 2012). In situations of emotional stress, for example, when a patient is faced with a life event that can trigger suicidal behaviour, there is a glutamatergic excitatory excess. This would result in a down regulation of the CB_1 receptor exclusively in GABAergic neurons, which would in turn moderate the hyperactivation of the glutamatergic system. In conclusion, the effect of cannabis on anxiety can be very variable depending on the subject and their emotional state in different circumstances, as well as the composition of cannabis, among other factors.

Despite the growing use of cannabis worldwide, its role in suicidal behaviour has scarcely been explored. As we have noted in a systematic and as yet unpublished review focusing on the relationship of cannabinoid receptors and suicidal behaviour (Colino *et al.,* 2018), the ECS is involved in the regulation of pain, and since pain may be considered an intermediate endophenotype of suicidal behaviour (de Leon *et al.,* 2015), this suggests that the ECS could play a role in suicidal behaviour. The first suspicion that the ECS could be involved in suicidal behaviours came via *rimonabant*, a CB_1 receptor antagonist that produced anxiety, dysphoria and autolytic ideation in some obese patients (Christensen *et al.,* 2007), leading to its withdrawal from the market in 2008. Furthermore, when comparing identical twins who had used cannabis and those who did not in a recent study of 13,986 twins (6,181 monozygotic, 7,805 dizygotic), the authors found that cannabis use was linked to: 1) a 100 times greater risk of suicidal ideation; and 2) an almost 7 times greater risk of attempted suicide (Agrawal *et al.,* 2017). An alarming statistic revealed by this study was that the use of cannabis had increased from 30.4% in the 1st wave (1992-1993) to 69% in the 3rd wave (2005-2009). At the same time, average onset age had fallen, while frequent use had risen. Finally, in the aforementioned review we suggested that cannabinoid agonists could be tested as potential treatments for suicidal behaviour (Colino *et al.,* 2018) given that: 1) the majority (>90%) of people who attempt suicide speak of mental (psychological) pain (Blasco-Fontecilla *et al.,* 2015); 2) mental pain is what unifies and gives meaning to suicidal behaviour (de Leon *et al.,* 2015); and 3) Sativex® has been approved for the treatment of different types of chronic pain (Hauser *et al.,* 2017, Russo *et al.,* 2016). Moreover, given that the ECS appears to have a certain regulatory role over the opioid system (Hurd, 2017), this role and the potential use of Sativex® could be particularly interesting in

the context of the theory of addiction in suicidal behaviours (Blasco-Fontecilla, 2012, Blasco-Fontecilla *et al.,* 2014, Blasco-Fontecilla *et al.,* 2016). Either way, any approach in this regard has to be cautious because the use of Sativex® could also increase the risk of suicidal behaviour among some patients (Etges *et al.,* 2016).

In conclusion, cannabis use has become widespread in much of the world, particularly among young people, who are precisely those most vulnerable to its negative effects. Indeed, scientific evidence in animal models suggests that the potential benefits at brain level would only occur if used in adulthood or old age (Bilkei-Gorzo *et al.,* 2017). In addition, it is important to remember that there are more than 100 different cannabinoids (Casajuana *et al.,* 2017). While it is true that some cannabinoids, such as CBD, may play a therapeutic role in some clinical situations, it is no less true that other cannabinoids, such as 9-THC, have psychotropic effects and are related to increased psychiatric morbidity. In addition, while it is possible that some cannabinoids may play a therapeutic role in suicidal behaviour, the limited evidence available suggests that we should be prudent, since it could also increase the risk of suicidal behaviour. It is worth reflecting on the fact that suicidal behaviour has been associated both with the use of a CB_1 antagonist (rimonabant) (Christensen *et al.,* 2007) and with a drug (Sativex®), which is a mixture of an agonist and a CB_1 antagonist (Russo *et al.,* 2016).

I would like to conclude by saying that the high rates of all types of drug use - particularly cannabis - and of suicidal behaviour among young people are likely to be related to the kind of hedonistic and consumption-addicted societies that we construct together. We live in the age of emptiness (Lipovetsky, 1986) - in the age of "anything goes", in which there are hardly any valid reference points for young people aside from consumerism, in societies characterized by haste, lack of limits and low tolerance of frustration because of hyperabundance and oversaturation of the senses. We believed that living under the affirmation *I have, therefore I am* would make us happier. But this has not been the case and emptiness has been our punishment. Given this vacuum, it is not surprising that some young people resort to cannabis or suicidal behaviour. Postmodernism has also brought us an expansion of the "traditional" limits of medicine and the psychiatrization of everyday life (Blasco-Fontecilla, 2014, 2017). Because at the end of the day, "*society still looks to the medical profession for help and for hope during difficult times*" (Murthy, 2016). We are heading towards the ironically brave new world that Huxley predicted in his masterpiece; or are we perhaps we already living in his dystopia? One wonders if this is the kind of society that we would wish for ourselves, our children, and the generations to come. Because remember, as I point out in the essay *Hacia un mundo feliz* "in the brave new world of Huxley, Shakespeare was an author yet to be civilized" (Blasco-Fontecilla, 2017).

Conflict of interest

The author has received financial compensation for scientific talks for AB-Biotics, Praxis Pharmaceuticals, Rovi, and Shire in the last two years.

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Reduction of mortality following better detection of hypertension and alcohol problems in primary health care in Spain

Reducción de la mortalidad mediante una mejor detección de la hipertensión y los problemas con el alcohol en la atención primaria de salud en España

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Abstract

Through a simulation study, we estimated the potential effects of better detection of hypertension and improved screening for alcohol problems with subsequent interventions. Results showed that if 50% of Spanish males between 40 and 64 years of age who are currently unaware of their hypertension become aware of their condition and receive the usual treatment, and 50% of these males with hypertension are screened for alcohol and are treated for hazardous drinking or alcohol use disorders, then the percentage of uncontrolled hypertension among men with hypertension decreases from 61.2% to 55.9%, i.e. by 8.6%, with about 1/3 of the effect due to the alcohol intervention. For women, likewise, these interventions would decrease the percentage of women in the same age group with uncontrolled hypertension by 7.4% (about 40% due to the alcohol intervention). The reduction of blood pressure in the population would avoid 412 premature CVD deaths (346 in men, 66 in women) within one year. Therefore, better detection of hypertension and screening for alcohol with subsequent interventions would result in marked reductions of uncontrolled hypertension and CVD mortality.

Keywords: Blood pressure; Hypertension; Alcohol use; Alcohol use disorders; Primary health care; Screening; Detection; Intervention, simulation.

Resumen

Se estudian mediante una simulación los potenciales beneficios que puede comportar una mejora en la detección y tratamiento de la hipertensión y de los problemas relacionados con el alcohol. Los resultados muestran que si el 50% de los varones españoles entre 40 y 64 años que desconocen que padecen hipertensión fuesen detectados y recibiesen tratamiento; y si en el 50% de los varones hipertensos se realizase el cribado de consumo alcohólico y recibieran consejo para la reducción de consumos o tratamiento cuando procediera, el porcentaje de hipertensión no controlada descendería del 61,2% al 55,9% (una reducción del 8,6%). Un tercio del efecto es atribuible a la intervención sobre el alcohol. De forma similar, las mismas intervenciones en mujeres de los mismos grupos etarios implicarían una reducción del 7,4% de la hipertensión no controlada (40% debido a la intervención sobre alcohol). La reducción de la presión arterial en la población permitiría evitar 412 muertes prematuras por patología cardiovascular (346 varones y 66 mujeres) anualmente. Una mejor detección de la hipertensión y el cribado de consumos alcohólicos con las consiguientes intervenciones resultarían en una marcada reducción de la hipertensión no controlada y de las muertes de origen cardiovascular.

Palabras clave: Presión arterial; Hipertensión; Consumo de alcohol; Trastornos por consumo de alcohol; Atención primaria de salud; Cribado; Detección; Intervención; Simulación.

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The major non-communicable diseases caused more than half of the deaths worldwide in the year 2012 (38 million out of the almost 56 million; World Health Organization, 2014; based on Global Health Estimates by the World Health Organization: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html). To reduce this burden, a global action plan has been implemented, which foresees the overall target of a 25% relative reduction in risk of premature mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases (World Health Organization, 2013), plus specific targets for the major risk factors. Both hypertension and the harmful use of alcohol are among these targets, with expected reductions of 25% and 10%, respectively. Both risk factors are closely associated in a dose-response fashion; i.e., the higher the alcohol consumption, the higher the blood pressure (Briasoulis, Agarwal, & Messerli, 2012; Taylor et al., 2009). The effect of alcohol has been shown to be causal: increases and decreases in alcohol consumption have been shown to result in subsequent changes in blood pressure in observational studies and controlled clinical trials (for overviews: O'Keefe, Bhatti, Bajwa, DiNicolantonio, & Lavie, 2014; Xin et al., 2001; see also Saunders, 1987, for an early review including clinical recommendations). The dose-response relationship is not linear, as the association gets stronger (steeper) in the higher drinking levels, and thus heavy drinking and alcohol use disorders have a large impact on elevated blood pressure and hypertension (Rehm et al., 2015b; Saunders, Beevers, & Paton, 1979; Saunders, Paton, & Beevers, 1981; Taylor et al., 2009).

In light of the strong impact of heavy drinking on hypertension, it does not come as a surprise, that screening, monitoring and subsequent interventions for this risk factor has been recommended already in the 1980s in the management of hypertension (Saunders, 1987); and reduction of drinking is now part of the recommended lifestyle changes in hypertension treatment (Mancia et al., 2013a; Mancia et al., 2013b). However, screening of alcohol consumption does not seem to be a routine part of the general practice in hypertension management in primary health care yet. In fact, alcohol consumption in general or heavy drinking in particular are relatively rarely broached as issues in primary care, independent of hypertension (Brotons et al., 2012; Drummond et al., 2013; for Spain see also http://www.papps.es/suplemento_ap_09.php). Despite current practice, primary health care seems to be the natural setting for screening and intervening with alcohol-related hypertension problems, since the majority of the population seek treatment for all kinds of medical conditions on a yearly basis (Miller, Anton, Egan, Basile, & Nguyen, 2005; Rehm et al., 2014). Moreover, hypertension is one of the most common, if not the most common diagnosis in primary care in many high-income countries (e.g., Minas, Koukosias, Zintzaras, Kostikas, & Gourgoulianis, 2010; Ministry of Health and Social Policy, 2010; Wändell et al., 2013), and is a chronic illness for which many patients may see their providers regularly.

Thus, it was the aim of this contribution to model what could happen if:

- the rate of awareness of for hypertension increased (see Banegas et al., 2012; Catalá-López, Ridao, Sanfélix-Gimeno, & Peiró, 2013; Llisterri et al., 2012 for current level of awareness and control of hypertension in Spain).
- screening for alcohol would be introduced, with brief interventions for hazardous and harmful drinking, and formal treatment for alcohol use disorders (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001; Room, Babor, & Rehm, 2005).

The consequences modelled comprise the distribution of systolic blood pressure and the risks for cardiovascular diseases linked to hypertension (Singh et al., 2013).

Methods

Exposure of hypertension in Spain

The blood pressure distributions among people with hypertension in Spain was modelled based on the results of Banegas and colleagues (Banegas et al., 2012; also see Catalá-López et al., 2013; Llisterri et al., 2012). In the Banegas study (Banegas et al., 2012), BP was measured by certified trained personnel, using standardized procedures, with validated automatic devices. Two sets of BP readings were made separated by 90 minutes. In each set, BP was measured 3 times at 1- to 2-minute intervals, after resting at least 3 minutes in a seated position. In the analyses, BP was calculated as the mean of ≥3 of the last 5 readings. We restricted our modelling to ages 40-64, as this is the age group, where there is already a considerable prevalence or hypertension, with less awareness than in older age groups (Banegas et al., 2012). In addition, in this age group prevalence of hazardous and harmful drinking and alcohol use disorders is high (Rehm et al., 2015a; Rehm et al., 2014): in a representative study of more than 13,000 patients of primary health care in 6 European Union countries, the following prevalence was found: hazardous drinking and other alcohol problems indicating the need of a brief intervention: women 14.1%-16.1%; men 14.2%-19.8%; alcohol dependence indicating the need for a therapy: women 3.9%-5.8%; men 11.1%–16.7 %).

Modelling the distribution of blood pressure: The "belly curve"

In order to estimate the change in blood pressure distribution among the sub-population of people with hypertension, a new distribution was designed as an alternative to a simple normal distribution. This distribution which we refer to as the "belly curve" is an attempt to model the asymmetric

distribution of blood pressure among people with hypertension (Pater, 2005)

1. The belly curve was designed according to the following rules about its shape:
2. The shape of the belly curve is made up of one half of a normal distribution to the right and left of its modus.
3. The standard deviation of the normal distribution making up the right half of the belly curve is twice that of the other.

The two normal distribution halves are multiplied by constants so as to yield a continuous distribution.

Based on these assumptions, it is possible to reverse engineer the required normal distributions if the overall mean and standard deviation of the final belly curve are known, therefore it is possible to obtain a belly curve fitting the mean and standard deviations found in surveys or other data.

The standard deviation of the normal distribution on the left of the modus of the belly curve s_{left}, the modus of the belly curve, the mean of the of the belly curve, μ, and the standard deviation of the belly curve, s_{belly}, are linked through the following expressions:

$$Modus = \mu - \sqrt{\frac{2}{\pi}} \cdot \sigma_{left}$$

$$\sigma_{belly}{}^2 = \mu^2 + Modus^2 + 2 \cdot Modus \cdot \sqrt{\frac{2}{\pi}} \cdot \sigma_{left} + 3 \cdot \sigma_{left}{}^2 - 2 \cdot Mean \cdot \left(Modus + \sqrt{\frac{2}{\pi}} \cdot \sigma_{left} \right)$$

We validated the curve by reproducing the actual distributions of blood pressure among people with hypertension (controlled and uncontrolled) in Finland (Koskinen, Lundqvist, & Ristiluoma, 2012; Laatikainen et al., 2013), Germany (Neuhauser, Thamm, & Ellert, 2013), Spain (Banegas et al., 2012; Catalá-López et al., 2013; Llisterri et al., 2012) and the UK (Joffres et al., 2013).

Modelling the effects of treatment and intervention

The above expressions allow us to derive a belly curve for any given mean and standard deviation. To estimate the effects of interventions, 1'000'000 samples were created from the belly curve and a proportional decrease in blood pressure is applied to a subset of the samples, as given by the percentage of patients with hypertension receiving the respective intervention.

Overall, three steps are required for a comparison of the current status with an ideal scenario where all patients with hypertension are screened and receive blood pressure interventions (mainly medications), and where the people with alcohol problems receive additional interventions either in form of brief interventions (Kaner et al., 2007) or formal treatment including pharmacotherapy.

1. An initial belly curve is created using the current known mean and standard deviation of high blood pressure among people with hypertension.
2. The effects of systematic screening are assessed by attributing the mean blood pressure of the group of patients who had been aware and in treatment for their blood pressure (based on empirical information including those, where the intervention did not lead to a control of hypertension) to all people with hypertension.
3. Finally, the effect of brief interventions and formal treatment for alcohol use disorder was assessed by decreasing blood pressure of a randomly sampled subset of the belly distribution from step 2. The subset was chosen to reflect the prevalence of people with hazardous alcohol drinking and alcohol use disorders among people with hypertension (Rehm et al., 2014) specified above. The size of the decrease was modelled based on the meta-analysis of (Xin et al., 2001): using the mean effect of all interventions used in Xin and colleagues (2001) for hazardous drinking, and using the effect specified for formal therapies for the effect of therapies of alcohol dependence.

The main analysis assumes a reduction of people unaware of their hypertension by 50% and coverage rates of alcohol interventions by 50% as well. We also performed two sensitivity analyses: in the first we assumed coverage rates of alcohol interventions by 100%; and in the second coverage rates for hypertension and alcohol by 100%. While the latter goals seem hard to reach, it gives us the maximum effect which could be reached with the interventions suggested.

Modelling the effect of the changed distribution of blood pressure on cardiovascular diseases

To estimate the amount of deaths avoided with the interventions described here, we have to compare the blood pressure distributions before and after the interventions in combination with the relative risk functions associated with blood pressure. It is further assumed, that people without hypertension have a relative risk of 1.

In the case where the blood pressure distributions are known before and after the interventions, the avoided deaths can be computed as follows:

$$DeathsAvoided = \frac{\int P_{HT_{AfterInt}}(BP) * RR(BP)\, dBP - \int P_{HT_{BeforeInt}}(BP) * RR(BP)\, dBP}{P_{normotensive} + \int P_{HT_{BeforeInt}}(BP) * RR(BP)\, dBP}$$

Where $P_{normotensive}$ is the proportion of people that do not have hypertension, $P_{HTAfterInt}$ (BP)is the blood pressure (BP) distribution after all the interventions, $P_{HTBeforeInt}$ (BP) is the blood pressure distribution before any intervention and RR(BP) is the relative risk of dying of a given disease for a blood pressure BP.

In our case, the final BP distribution has been estimated using 1 million samples. The integral was therefore replaced by the mean value of the relative risk function applied to each sample. The mortality data for Spain were taken from the WHO Global Health Estimates for 2012 (http://www.who.int/healthinfo/global_burden_disease/en/).

Results

Main result for reduction of uncontrolled hypertension

Table 1 gives the results on the proportion of people with controlled and uncontrolled blood pressure after the two interventions described above. If 50% of Spanish men between 40 and 64 years of age currently not aware about their hypertension, could be made aware of their condition and received interventions to change their blood pressure distribution; and if 50% of people with hypertension who have alcohol problems or alcohol use disorders, receive interventions (either brief interventions for hazardous or harmful drinking or therapy for alcohol use disorders), the percentage of uncontrolled hypertension among men with hypertension would decrease from 61.2% to 55.9%, i.e. by 8.6%. This is equivalent to a reduction of men aged 40 to 64 with uncontrolled hypertension in the general population by 2.2 percentage points (from 25.7% to 23.5%). Controlled hypertension here is defined as having a systolic blood pressure below 140 mm Hg. Alcohol interventions contributed about one third of this effect.

Similarly, for women, these interventions would decrease the percentage of women in the same age group with uncontrolled hypertension by 7.4%, reducing the proportion of such women in the general population from 17.8% to 16.5%, i.e., by 1.3 percentage points. Alcohol interventions contributed about 40% of this effect.

Reduction in CVD mortality

Overall, within one year, 412 out of 9,912 cardiovascular deaths in the age group 40-64 could be avoided (data are based on 2012). The overwhelming majority of these deaths would be in men, and in ischemic heart disease, followed by stroke.

Sensitivity analyses

We conducted 2 sensitivity analyses in addition to the main analysis to get an idea of how each change affects the bottom line outcome. The first sensitivity analysis assumed that 50% of Spanish between the age of 40 and 64 who were unaware of their hypertension were made aware and changed their blood pressure distribution accordingly, and that all people having alcohol problems or alcohol use disorders received interventions.

The second sensitivity analysis assumed that all Spanish between the age of 40 and 64 unaware were shifted to the distribution of people aware of their hypertension, and furthermore, that all people having alcohol problems or alcohol use disorders received interventions.

For each of the sensitivity analyses, the computations were again split in 2 steps, as for the main analyses. The results are summarized in Table 3.

Table 1. *Shifts in systolic blood pressure among people with hypertension (controlled and uncontrolled) in Spain after two hypothetical interventions (based on (Banegas et al., 2012)*

	Women 40-64 years of age				Men 40-64 years of age			
	Mean systolic blood pressure (BP)	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population	Mean systolic BP	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population
Before	146,0	40,4	-	17,8	146,8	38,8	-	25,7
After increasing awareness (50%)	144,8	43,0	2,6	17,0	145,3	42,2	3,5	24,2
After increasing awareness (50%) and alcohol interventions (50%)	144,1	44,8	4,4	16,5	144,5	44,1	5,3	23,5
Proportion of effect due to alcohol intervention	40,5%	40,6%		38,5%	33,5	33,4%		31,8%

Note. & defined as systolic blood pressure ≥ 140 mm HG.

Table 2. *Expected cardiovascular mortality gains within one year from the interventions via the reduction of blood pressure (based on (Singh et al., 2013)*

	Women 40-64 years of age		**Men 40-64 years of age**	
	Number of avoided deaths	% of all deaths	Number of avoided deaths	% of all deaths
Ischemic heart disease	20	2,5%	180	4,2%
Hypertensive heart disease	9	9,9%	33	14,3%
Rheumatic heart disease	1	0,7%	1	1,2%
Inflammatory heart disease	1	0,7%	13	2,2%
Ischaemic Stroke	6	4,3%	24	6,7%
Haemorrhagic Stroke	25	5,1%	66	7,7%
Other CVD	8	1,5%	36	2,6%
Total	66	3,0%	346	4,5%

Note. The effects were modelled for 2012. They comprise reductions in mortality within one year based on the effect of both interventions on blood pressure.

Table 3. *Shifts in systolic blood pressure among people with hypertension (controlled and uncontrolled) in Spain after two hypothetical interventions (Banegas et al., 2012) – sensitivity analyses*

Assumption: 50% of unware -› aware;
100% of people with alcohol problems get interventions.

	Women 40-64 years of age				**Men 40-64 years of age**			
	Mean systolic blood pressure (BP)	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population	Mean systolic BP	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population
Before	146,0	40,4	-	17,8	146,8	38,8	-	25,7
After increasing awareness (50%)	144,8	43,0	2,6	17,0	145,3	42,2	3.5	24,2
After increasing awareness (50%) and alcohol interventions (100%)	143,3	46,4	6,0	16,0	143,6	45,9	7.1	22,7
Proportion of effect due to alcohol intervention	55,6%	56,7%		55,6%	53,1%	51,4%		50,0%

Note. & defined as systolic blood pressure ≥ 140 mm HG

Assumption: 100% of unware -› aware;
100% of people with alcohol problems get interventions.

	Women 40-64 years of age				**Men 40-64 years of age**			
	Mean systolic blood pressure (BP)	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population	Mean systolic BP	% controlled[&] among hypertensives	Increase in control delta%	Systolic BP ≥ 140 mmHg in population
Before	146,0	40,4	-	17,8	146,8	38,8	-	25,7
After increasing awareness (100%)	143,7	45,5	5,1	16,2	143,7	45,8	7.0	22,8
After increasing awareness (100%) and alcohol interventions (100%)	142,2	49,0	8,6	15,2	142,1	49,3	10.5	21,3
Proportion of effect due to alcohol intervention	39,5%	40,7%		38,5%	34,0%	33,3%		34,1%

Note. & defined as systolic blood pressure ≥ 140 mm HG.

Discussion

Overall, it could be shown, that alcohol interventions in primary care patients with hypertension, i.e. brief interventions for harmful and hazardous drinking and treatment or referral to specialized treatment for alcohol use disorders (Babor et al., 2010; Babor et al., 2007) promises public health gains in terms of reducing blood pressure levels and subsequent cardiovascular disease (see also Gual, Zarco, Colom, & Rehm, 2015). With respect to reducing blood pressure levels it could be shown, that up to 17% of existing hypertension in men and 15% in women could be controlled, if unawareness is reduced maximally and if alcohol interventions are initiated (see results sensitivity analysis 2). In this scenario, the current differences between men and women would also disappear (for recent assessments of gender differences in Spain see (Banegas et al., 2008; Gijón-Conde & Banegas, 2012; Ortiz Marrón et al., 2011).

The impact of the interventions on cardiovascular mortality was also pronounced. More than 400 cardiovascular deaths could be avoided by the main scenario within one year (see Table 2 for details), mainly in men. In addition, and not explicitly modelled here, reduction in alcohol consumption will be associated with sizable short term reduction of morbidity and mortality for many disease outcomes (Rehm & Roerecke, 2013; Rehm, Shield, Rehm, Gmel, & Frick, 2013; specifically for Spain: Rehm, Rehm, Shield, Gmel, & Gual, 2013; Soler González, Balcells Oliveró, & Gual Solé, 2014; for a complete listing of alcohol-attributable diseases see Rehm et al., 2010). To give a sense of the magnitude of such reductions for formal treatment: if alcohol consumption was reduced, including, but not limited to reaching abstinence, the risk for all-cause mortality will be reduced by about 60% overall within 9 years (results based on a comprehensive meta-analyses of all treatment studies with the relevant information - Roerecke, Gual, & Rehm, 2013). These effects included the effects on cardiovascular diseases via hypertension, however.

In sum, the impact of better awareness and alcohol interventions could be marked. What keeps the current system from not achieving them? First, awareness of hypertension is still seen as a problem of the elderly. Clearly, the older the population, the better the awareness (Banegas et al., 2012): whereas two thirds of the people younger than age 45 in Spain was not aware of their hypertension, the majority of the population older than 65 (again about 2/3) was aware of this disease condition. For primary health care physicians, screening for hypertension in younger people, especially in younger males with heavy alcohol use (Org et al., 2011), is worth the effort. Second, screening for alcohol use and applying brief interventions or treatment could make a marked difference in the control of hypertension. Primary health care centres would be the ideal point where to apply these screenings and early interventions: not only do primary health care physicians recognize heavy drinking and alcohol use disorders (Rehm et al., 2015a), but in this environment both brief interventions and treatment for less severe alcohol use disorders are possible (Rehm et al., 2016; Rubio, Jiménez-Arriero, Martinez, Ponce, & Palomo, 2010; Segura Garcia, Gual Solé, Montserrat Mestre, Bueno Belmonte, & Colom Farran, 2006). Third, if such interventions are given, also the rate of treatment resistant hypertension (for a definition Boswell, Pascual, & Oliveras, 2015; for Spain: Oliveras & de la Sierra, 2014) could probably be reduced (Calhoun et al., 2008; Denolle et al., 2014). In addition, alcohol interventions may have an effect on medication intake (Miller et al., 2005), not only in people with hypertension (Grodensky, Golin, Ochtera, & Turner, 2012), and alcohol reduction will reduce the risk and severity of other co-morbidities (Diaz et al., 2014; Rehm, Manthey, Struzzo, Gual, & Wojnar, 2015d; Rehm & Roerecke, 2013).

No modelling is without limitations. First, we based our prevalence data and means of a large study with careful assessment of hypertension by trained personnel (Banegas et al., 2012). However, the chance of "white coat" or "isolated office/study hypertension" could only be excluded if 24-hour ambulatory blood measurements, for example as stipulated in UK guidelines of the National Institute for Clinical Excellence, were taken (Mayor, 2011). While our data may overestimate the real prevalence of people with hypertension, this effect seems to amount to not more than 10% (Banegas et al., 2015, based on an older sample). Second, while the belly curve has been shown to portray the distribution of blood pressure in Spain fairly well, any model is a simplification with some bias. Thirdly, the results of the meta-analyses between blood pressure and cardiovascular outcomes (Singh et al., 2013) were used for Spain, thus assuming that the risk relations hold true. This assumption is standard in global burden of disease modelling (Ezzati, Lopez, Rodgers, & Murray, 2004; Rehm et al., 2009); it should be checked with local data wherever possible (e.g., Roerecke et al., 2015). We found no data for Spain detailing the increase in risk for the various cardiovascular risk categories examined, and thus had to use the global risk relations (Singh et al., 2013). The error introduced does not seem to be too large, as most of the underlying studies were from high income countries, and as the relationships are mainly based on biological mechanisms.

Overall, the modelling and the sensitivity analyses clearly show that interventions to increase awareness of hypertension and to screen and intervene for alcohol problems and alcohol use disorders will lead to public health-relevant reductions of people with blood pressure values above 140 mm Hg systolic blood pressure. The best place for these interventions seems to primary health care, where hypertension is controlled in most cases anyway. For an implementation, three requirements should be in place: firstly, primary care physicians should be trained to do these alcohol inter-

ventions (Rehm et al., 2016); secondly, they should be given enough time in their daily schedule to carry out brief interventions and formal treatment for alcohol dependence, and thirdly, there should be appropriate incentive structures (Anderson et al., 2014; O'Donnell et al., 2014).

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Information and Communications Technologies (ICT): Problematic use of Internet, video games, mobile phones, instant messaging and social networks using MULTICAGE-TIC

Tecnologías de la Información y la Comunicación (TIC): uso problemático de Internet, videojuegos, teléfonos móviles, mensajería instantánea y redes sociales mediante el MULTICAGE-TIC

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Abstract

Use/abuse of Information and Communications Technologies (ICT) has in recent years become a topic of great interest. Current discussion addresses whether it must be considered addictive behaviour and if it is a problem that primarily affects adolescents and youth. This study aims to understand the problems that affect people of all ages in controlling the use of these ICTs and whether they are related to mental health problems, stress and difficulties in executive control of behaviour. A survey was administered through social networks and email, using the MULTICAGE-ICT, a questionnaire that explores problems in the use of Internet, mobile phones, video games, instant messaging and social networks. Additionally, the Prefrontal Symptom Inventory, General Health Questionnaire and Perceived Stress Scale were administered. The sample was comprised of 1,276 individuals of all ages from different Spanish-speaking countries. The results indicate that about 50% of the sample, regardless of age or other variables, presents significant problems with the use of these technologies, and that these problems are directly related to symptoms of poor prefrontal functioning, stress and mental health problems. The results reveal the need for reconsidering whether we are facing an addictive behaviour or a new problem demanding environmental, psychological, sociological and sociopolitical explanations; therefore, it is necessary to reformulate actions to be implemented to address and refocus our understanding of the problem.

Keywords: Behavioural addiction; Information and communications technologies; Perceived stress; Dysexecutive syndrome; Mental health.

Resumen

El uso/abuso de las Tecnologías de la Información y la Comunicación (TIC) es un tema que suscita enorme interés en los últimos años. Está en discusión si debe recibir la consideración de conducta adictiva y si es un problema que afecte prioritariamente a adolescentes y jóvenes. El presente estudio pretende conocer los problemas que afectan a las personas de todas las edades en el control del uso de estas TICs y si están relacionados con problemas de salud mental, estrés y dificultades en el control superior del comportamiento. Se realiza una encuesta a través de redes sociales y correo electrónico, en el que se administra el cuestionario MULTICAGE-TIC, que explora problemas en el uso de Internet, teléfono móvil, videojuegos, mensajería instantánea y redes sociales. Adicionalmente se administra el Inventario de Síntomas Prefrontales, el Cuestionario de Salud General y la Escala de Estrés Percibido. Se obtiene una muestra de 1.276 sujetos de todas las edades y diferentes países de habla hispana. Los resultados apuntan a que alrededor del 50% de la muestra presenta importantes problemas en el uso de estas tecnologías, y que esos problemas se relacionan directamente con síntomas de mal funcionamiento prefrontal, estrés y problemas de salud mental, independientemente de la edad u otras variables. Estos resultados sugieren reconsiderar si se trata de una patología adictiva o si estamos ante un problema novedoso que requiere de explicaciones de índole ambiental, psicológica, sociológica y sociopolítica, debiendo reformular las acciones a emprender para reorientar la comprensión y el abordaje del problema.

Palabras clave: adicciones comportamentales; tecnologías de la información y la comunicación; estrés percibido; disfunción ejecutiva; salud mental.

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Over the last two decades, the so-called "behavioural addictions" have become increasingly important and have generated ongoing research. For example, a query of the PubMed database using the descriptor "*behavioural addiction*" shows an increase from 304 studies in 1995 to 2,583 in 2014, an uninterrupted exponential growth. Marks (1990) defined the concept of "behavioural addictions" as a group of behaviours characterised by the repeated need for assuming behaviours with known negative consequences, developing behavioural sequences that generate stress and recurrent phases of urgency until they are completed, together comprising a syndrome that is activated by external and internal signals and that ultimately entails difficulty in one's everyday functioning. Over time, concepts have been refined, empirical evidence has been gathered on similarities across behavioural addictions and those related to substances with regards to their natural evolution, phenomenology, tolerance, associated psychopathology, contribution of genetics, neurobiological mechanisms, and response to treatment, among others (Grant, Potenza, Weinstein & Gorelick, 2010).

A significant number of these neuroscientific studies have found that, as occurs with substance addiction, deficits in the functioning of the prefrontal cortex are central elements of behavioural addictions that explain the loss of executive control over problematic behaviour (Blum et al., 2015; Brand, Young & Laier, 2014; de Ruiter, Oosterlaan, Veltman, van den Brink & Goudriaan, 2012) and that important similarities may be found between both modalities in brain structures such as white matter (Yip et al., 2016).

Other studies have focused on finding evidence of the differences among many of these behavioural addictions and those entailing the use of substances. For example, one 5-year longitudinal study (Konkolÿ Thege, Woodin, Hodgins & Williams, 2015) found that the development of these excessive behaviours is usually short-term and that, in most cases, they are abandoned naturally. However, this is not proof of differences, given that most substance addicts also recover spontaneously and without professional assistance (Brevers & Noel, 2015). Some authors denounce that our determination in assimilating excessive repetitive behaviours with criteria for diagnosing psychiatric disorders leads to the assumption of absurd categories that lack specificity and clinical validity and result in overpathologizing everyday life (Billieux, Schimmenti, Khazaal, Maurage & Heeren, 2015), ignore ideographic aspects (Spada, 2015), elude individual differential characteristics (Kardefelt-Winther, 2015) and functionality (Brevers & Noel, 2015), in addition to the behaviours' environmental, social and cultural determinants (Blaszczynski, 2015; Van der Linden, 2015). For these reasons, the concept of behavioural addiction is fiercely questioned (Sinclair, Lochner & Stein, 2016) and, given our actual knowledge, referring to these as compulsive habits seems more appropriate (Potenza, 2015).

The so-called Information and Communications Technologies (ICTs) have been object of the greatest attention. In recent decades, humanity has witnessed two global revolutions of enormous scales. The first, in the final years of the last century, was the popularisation of and unlimited access to the Internet, with the arrival of modems to the home. But, just shortly later, halfway through the first decade of the current century, the second revolution occurred: the transformation of pocket-sized, portable mobile phones into platforms that provide access to an immense number of possibilities.

This emergence of opportunities has entailed great advantages, but also important risks and problems. Based on the concept of Internet addiction (Fernández-Villa et al., 2015; Griffiths, Kuss, Billieux & Pontes, 2016; Young, 2017) or mobile phone addiction (Pedrero-Pérez, Rodríguez-Monje & Ruiz-Sánchez de León, 2012), this study has shifted from supports to specific applications: instant messaging (Dlodlo, 2015; Sultan, 2014), social networks (Schou Andreassen, 2015), online games (Bertran & Chamarro, 2016; Chen & Leung, 2015; Griffiths, 2015), among many others. Studies coincide in finding a relationship between the abuse of some of these modes of online interaction and indicators of poor daily functioning, problems related to self-esteem, and decreased school performance (Grover et al., 2016; Hawi & Samaha, 2016; Ko, Yen, Yen, Chen & Chen, 2012; Schou Andreassen et al., 2016; Soroush, Hancock & Bonns, 2014).

Most of these studies have focused on adolescents or the population of youth under the age of 30, in interpreting that the vulnerabilities that may lead to abuse or addiction become apparent at these ages. However, the penetration of these technologies across all societal levels worldwide allows for hypothesising that all ages may be affected. Scarce evidence supports a relationship between the problems associated with abuse of ICT and psychopathological symptoms or problems in daily activities beyond youth.

The purpose of this study is to detect the frequency of problems associated with use and abuse of Information and Communications Technologies (ICTs) in all age groups and in different geographical and cultural settings. To this end, first the psychometric quality of a previously-used survey was evaluated and adapted to the problems object of the study. Furthermore, given that all of the available models for characterizing behavioural addictions allude to a dysfunctional prefrontal cortex as an antecedent of the loss of executive control over behaviour, we hypothesized a direct relationship between the problematic use of ICTs and the symptoms of prefrontal dysfunction in everyday life, as well as other psychological symptoms and perceived stress.

Method

Participants and procedure

Given that the target population was comprised of frequent users of ICTs, a survey was created using Google Docs® (available at https://goo.gl/4UAyIw) and anonymous and voluntary participation was requested via instant messaging applications (WhatsApp®), social networks (Facebook®) and e-mail. Likewise, the Respondent-Driven Sampling technique was used, requesting participants to disseminate the survey to their contacts. Given that the survey was comprised of 56 items, a minimum of 20 subjects was estimated per item, doubling the usual requirements of the rule of 10 subjects per item (Velicer & Fava, 1998), requiring a minimum of 1,120 subjects. When this figure was reached, a week was given for the study to be completed. Data collection took place between March 8-24, 2016 (n = 1,290). Exploratory data analysis was performed, excluding 14 surveys: 12 had identical responses, 1 was incomplete and 1 was an outlier (all responses reflected the most negative alternative). The final sample was comprised of 1,276 subjects.

Instruments

MULTICAGE-TIC, 20-item survey, comprised of 5 scales, posed questions on problematic use of Internet, Video Games, Mobile Phones, Instant Messaging and Social Networks. It is based on MULTICAGE CAD-4, a survey used for screening compulsive behaviours, with and without substances (Pedrero-Pérez et al., 2007), that has been used in primary care (Garrido-Elustondo, Reneses, Navalón, Martín, Ramos & Fuentes, 2016; Reneses et al., 2015; Rodríguez-Monje, Pedrero-Pérez, Fernández-Girón, Gallardo-Alonso & Sanz-Cuesta, 2009), behavioural addictions (Estevez, Herrero-Fernández, Sarabia & Jauregui, 2015; Estévez Gutiérrez, Herrero Fernández, Sarabia Gonzalvo & Jáuregui Bilbao, 2014) and substance addiction (Navas, Torres, Cándido & Perales, 2014; Martínez-González, Munera-Ramos & Becoña-Iglesias, 2013; Pedrero-Pérez, 2010). This new version's design comprised four questions with dichotomous answers (Yes/No) for each problematic behaviour, asking about: item 1, estimated excessive time dedication; item 2, excessive time estimated by significant others; item 3, difficulty in refraining from the behaviour; item 4, difficulties in voluntarily interrupting the behaviour. Given the newness of the survey, its psychometric properties were tested with the sample itself.

Prefrontal Symptoms Inventory, screening version (ISP-20; Pedrero-Pérez, Ruiz-Sánchez de León, Morales-Alonso, Pedrero-Aguilar & Fernández-Méndez, 2015c) that explores symptoms of malfunction in daily life related with neuropsychological alterations attributable to the prefrontal cortex. Responses are given on a Likert scale (0: never or almost never; 1: sometimes; 2: sometimes yes and sometimes no; 3: frequently; 4: always or almost always). Factorial analysis found a three-factor solution: problems in behavioural control, problems in emotional control and problems in social behaviour. Validation for the general population and for addicts in treatment reported sufficient internal consistency of all of the subscales ($0.87 < a_s < 0.89$), clinical validity (Ruiz-Sánchez de León, Pedrero-Pérez, Gálvez, Fernández-Méndez & Lozoya-Delgado, 2015), ecological validity (Pedrero-Pérez et al., 2016) and transcultural validity (Cuello Prato & Mendoza Carmona, 2014; González Roscigno, Mujica Díaz, Terán Mendoza, Guerrero Alcedo & Arroyo Alvarado, 2016). In the study sample, multivariate consistency was $\alpha_s = 0.91$ for the complete test and $0.81 < \alpha_s < 0.90$ for the scales.

General Health Questionnaire, 12-item version (*General Health Questionnaire*, GHQ-12; Goldberg & Williams, 1998), Spanish version (Rocha, Pérez, Rodríguez-Sanz, Borrell & Obiols, 2011) is a self-administered screening instrument used to detect indicators of mental illness and possible cases of psychopathological disorders in primary care contexts or in the general population. Responses are given on a four-option Likert scale. It may be corrected in several ways; the following two were adopted for this study: GHQ-Likert, scores between 0 and 3, where higher scores correspond with worse health indicators; and GHQ criterion-referenced scores, assigning the values 0, 0, 1, 1 to item responses. In the study sample, the consistency of the test was $\alpha_s = 0.90$.

The "Escala de Estrés Percibido" (EEP), the Spanish version (Remor & Carrobles, 2001) of the Perceived Stress Scale (PSS) by Cohen, Kamarck & Mermelstein (1983). The complete PSS is comprised of 14 items that measure the degree to which, in the last month, persons have felt unsure or concerned about, or to the contrary have felt certain about, their capacity for controlling their personal problems. A brief, 4-item version is also available, with adequate psychometric properties in the Spanish population, with an internal consistency of $\alpha = 0.83$ in the general population and clinical samples (Pedrero-Pérez et al., 2015b). Responses are given on a 5-item Likert scale, ranging from 0 ("Never") to 4 ("Very frequently"), with scores of between 0-16 and with higher scores corresponding to higher perceived stress. This study used the 4-item version (PSS-4), with an internal consistency of $\alpha_s = 0.81$.

Participants were also asked to specify their age, level of studies, gender, country of birth and actual country of residence.

Data analysis

First, the psychometric properties of MULTICAGE-TIC were analysed. Initially, the distributions for each item were obtained and whether these were distributed in line with the multivariate normality criteria of Mardia (1970). Given that this property was not guaranteed, the tetrachoric correlations matrix was used, and the ω= McDonald's

Omega and α_s= standardized Cronbach's Alfa were used as internal consistency estimates, according to the most recent recommendations (Dunn, Baguley & Brunsden, 2014). The FACTOR 10.3.01 program (Lorenzo-Seva & Ferrando, 2006) was used for these tests. Then, a confirmatory factorial analysis was performed of the theoretical proposal of 5 scales for the data obtained, and the unweighted least squares (ULS) method was used, with indicators of fit provided by the AMOS 18 application (RMR = Root Mean Square Residual, with acceptable values below 0.06; GFI = General Fit Index; AGFI = Adjusted Goodness of Fit Index; NFI = Normed Fit Index; RFI = Relative Fit Index, all with acceptable values above 0.90; PNFI = Parsimonious Normed Fit Index and PGFI = Parsimony Goodness of Fit Index, both acceptable with values above 0.7). Partial correlation tests were performed, controlling for covariables, and using the Bonferroni correction for multiple correlations to avoid committing a type 1 error. Stepwise linear regression was done using the Durbin-Watson test to control for prediction errors. MANCOVA was performed to compare subgroups, using the partial eta-squared (η^2) to estimate the effect size and the "rules of thumb" proposed by Cohen (1988): 0.01 small effect size, 0.06 medium effect size and 0.14 large effect size. For these analyses, gender was the dummy variable, with values 0 and 1. Analyses was performed using the SPSS 19 statistics package.

Table 1. *Descriptive variables of the sample.*

	Country of origin		Residence
	n	%	Country of origin (%)
Spain	960	75.2	97.8
Colombia	138	10.8	86.2
Venezuela	94	7.4	89.4
Other countries			
Europe	27	2.1	0
North America	2	0.2	0
Other countries of Latin America	48	3.8	60.4
Asia	3	0.2	0
Africa	4	0.3	0
Gender			
Males	425	33.3	
Females	851	66.7	
Level of studies			
Primary or lower	28	2.2	
Secondary	65	5.1	
Higher secondary	176	13.8	
University student	193	15.1	
University graduate	814	63.8	
Age			
‹ 18	57	4.5	
18 - 25	272	21.3	
25 - 30	129	10.1	
30-45	393	30.8	
45 - 60	365	28.6	
› 60	60	4.7	

Results

Characteristics of the sample

Table 1 displays the complete sample's descriptive variables.

Psychometric properties of MULTICAGE-TIC

Table 2 displays the descriptive variables for the MULTICAGE-TIC items, in addition to each scale's Goodness of Fit Index (GFI) and internal consistency measures. All scales have adequate internal consistency, though lower, yet still acceptable (> 0.70) for the Mobile Telephone scale, at the expense of low communality of the third item ("*On a day that you don't have your mobile phone with you, do you feel uneasy or as if something very important is missing?*") with the scale's remaining items.

The model was tested as a whole, with confirmatory factorial analysis to verify the fit of the 5-scale theoretical

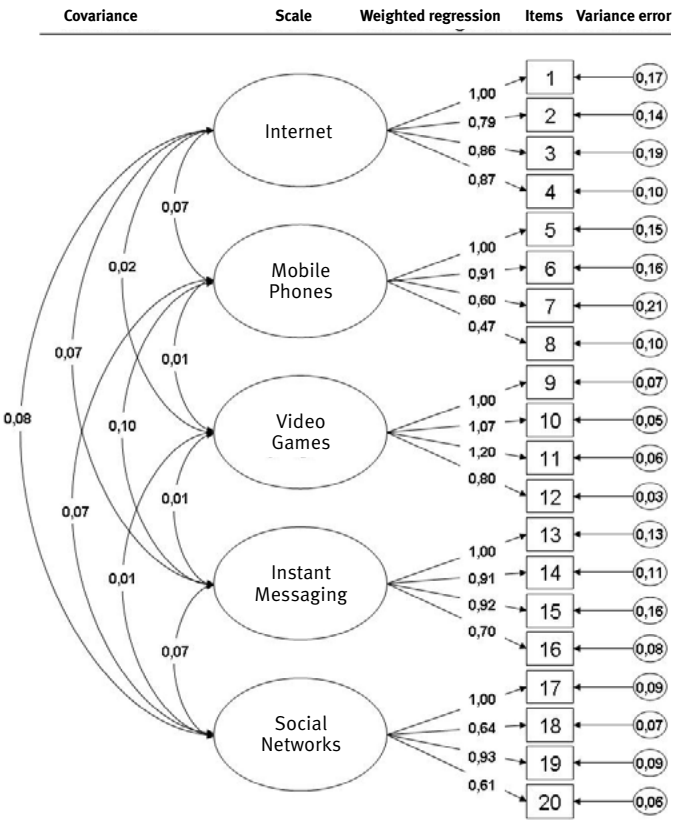

Figure 1. MULTICAGE-TIC structural model.

Table 2. Descriptive variables and indicators of fit and internal consistency of the MULTICAGE-TIC scales.

Scale	Item	Median	Mean	95% confidence interval	Variance	Asymmetry	Kurtosis	Communalities	r_{it}	GFI	ω	α_s
Internet	1	1	0.51	(0.48 - 0.55)	0.25	-0.04	-2.00	0.62	0.45	0.99	0.81	0.80
	2	0	0.26	(0.23 - 0.29)	0.19	1.11	-0.76	0.43	0.38			
	3	1	0.51	(0.47 - 0.54)	0.25	-0.02	-2.00	0.35	0.36			
	4	0	0.21	(0.18 - 0.24)	0.16	1.45	0.11	0.68	0.46			
Mobile Phone	1	1	0.60	(0.57 - 0.64)	0.24	-0.42	-1.82	0.72	0.41	1.00	0.74	0.72
	2	0	0.38	(0.34 - 0.41)	0.23	0.52	-1.73	0.50	0.38			
	3	0	0.64	(0.60 - 0.67)	0.23	-0.56	-1.68	0.11	0.21			
	4	0	0.15	(0.13 - 0.18)	0.13	1.93	-1.73	0.43	0.30			
Video Games	1	0	0.12	(0.10 - 0.14)	0.11	2.34	3.48	0.75	0.56	1.00	0.91	0.90
	2	0	0.10	(0.08 - 0.12)	0.09	2.62	4.86	0.76	0.57			
	3	0	0.13	(0.11 - 0.15)	0.11	2.21	2.89	0.60	0.46			
	4	0	0.05	(0.03 - 0.06)	0.05	4.16	15.32	0.71	0.49			
Instant Messaging	1	0	0.41	(0.37 - 0.44)	0.24	0.38	-1.86	0.77	0.60	1.00	0.89	0.89
	2	0	0.29	(0.26 - 0.32)	0.21	0.94	-1.13	0.65	0.56			
	3	0	0.51	(0.48 - 0.55)	0.25	-0.05	-2.00	0.58	0.49			
	4	0	0.17	(0.14 - 0.19)	0.14	1.80	1.22	0.71	0.49			
Social Networks	1	0	0.31	(0.27 - 0.34)	0.21	0.83	-1.31	0.92	0.68	1.00	0.93	0.93
	2	0	0.14	0.12 - 0.17)	0.12	2.03	2.11	0.68	0.55			
	3	0	0.27	(0.24 - 0.31)	0.20	1.02	-0.97	0.81	0.66			
	4	0	0.13	(0.10 - 0.15)	0.11	2.26	3.12	0.71	0.54			

Note. r_{it}= corrected item-test correlation; GFI = Goodness of Fit Index; ω= McDonald's Omega; α_s= standardised Cronbach's Alpha..

Table 3. Affirmative responses for each item of the MULTICAGE-TIC and the percentage of subjects with affirmative responses to a given number of questions.

	Affirmative responses (%) Item				% Affirmative responses for all items			
Scale	1	2	3	4	0-1	2	3	4
Internet	51.1	25.7	50.5	20.6	51.1	25.7	50.5	20.6
Mobile Phone	60.3	37.5	63.6	15.3	60.3	37.5	63.6	15.3
Video Games	12.0	10.3	12.9	4.9	12.0	10.3	12.9	4.9
Instant Messaging	40.8	28.8	51.3	16.6	40.8	28.8	51.3	16.6
Social Networks	30.8	14.4	27.4	12.5	30.8	14.4	27.4	12.5

model to the data obtained. None of the surveys met multivariate normality criteria (Mardia $p < 0.05$ in all cases). Therefore, the unweighted least squares (ULS) method was used. Indicators of fit were satisfactory (RMR = 0.012; GFI = 0.96; AGFI = 0.95; NFI = 0.94; RFI = 0.92; PGFI = 0.73; PNFI = 0.79) and the third item of the Mobile Phone scale would just slight improve the model's fit (RMR = 0.011; GFI = 0.97; AGFI = 0.96; NFI = 0.94; the others remain unchanged). Figure 1 shows the resulting structural model.

Table 3 displays the percentage of affirmative response for each item and the percentage of subjects with affirmative responses to a given number of questions. While for Video Games only 10.9% respond affirmatively to 2 or more items, the percentage increases to 45.1% for the Internet and 57.5% for Mobile Phones.

Table 4 shows that the ISP, whether as a whole or by subscales, correlates with all of the MULTICAGE-TIC scales, once implementing corrections to avoid type 1 error (Bonferroni) and controlling for age, gender and level of studies. The effect size is small or medium in all cases ($0.06 < r^2 < 0.01$). The case is the same for the GHQ ($0.04 < r^2 < 0.01$), while with the PSS it only occurs in relation to three scales ($0.02 < r^2 < 0.01$), but not with the other two ($r^2 < 0.01$).

Table 5 displays the results of joint regression of the items of the ISP-20, GHQ-12 and PSS-4, marking those with predictive capacity ($R^2 * 100 > 1$) for MULTICAGE-TIC sca-

Table 4. *Partial correlations (controlling for gender, age and level of studies) between the MULTICAGE-TIC and the ISP-20, GHQ-12 and EEP questionnaires.*

	Internet	Mobile Phone	Video Games	Instant Messaging	Social Networks
ISP-20	0.24*	0.17*	0.17*	0.22*	0.19*
Executive problems	0.22*	0.15*	0.16*	0.19*	0.18*
Social Behaviour Problems	0.16*	0.11*	0.13*	0.18*	0.13*
Emotional Control Problems	0.16*	0.13*	0.08	0.15*	0.13*
GHQ-12					
Likert Scores	0.19*	0.09	0.12*	0.14*	0.12*
Criterion-referenced score	0.19*	0.12*	0.13*	0.17*	0.14*
EEP-4					
Perceived Stress	0.15*	0.09	0.09	0.15*	0.11*

Note. *Significant correlation after applying the Bonferroni correction for multiple correlations.

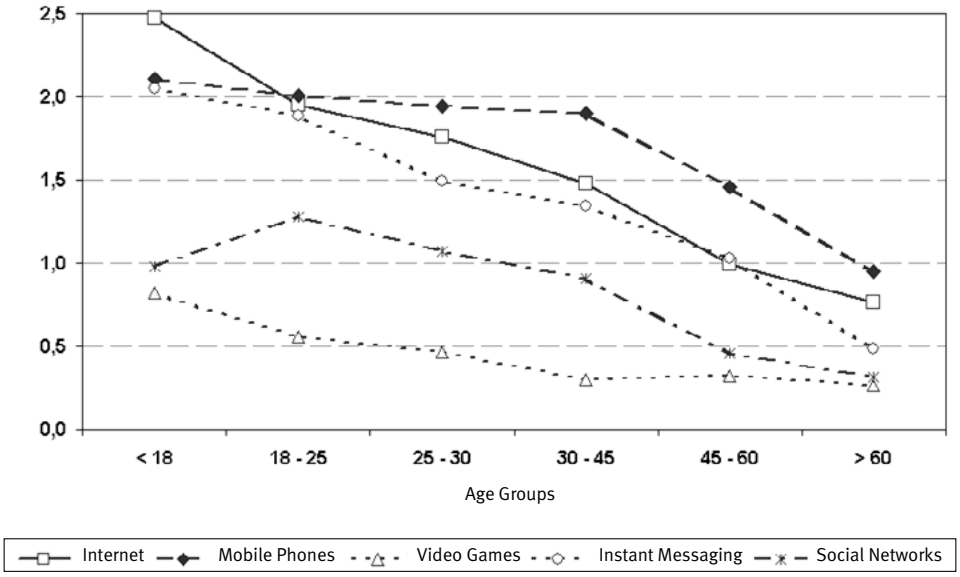

Figure 2. Average scores in the MULTICAGE-TIC scales by age groups.

les. Problems with concentration, difficulties with emotional control, motivational deficits and disinhibited social behaviour are the problems most-related with the different scales on the use of ICTs, though it cannot be determined whether they cause, or result of, problematic use.

When subjects are categorized according to the number of affirmative responses to the MULTICAGE-TIC scales, it is observed (Table 6) that the prefrontal symptoms increase almost in parallel, somewhat similar to what occurs with the scores in the GHQ and the PSS.

Figure 2 shows the average scores by age groups. The highest scores are obtained by the youngest age groups (except for the Social Networks scale, which peaks between the ages of 18-25), showing a gradual decrease, except for Mobile Phones, in which similar levels are maintained until the age of 45.

Gender differences

Table 7 displays the average scores and dispersion of the estimated variables by surveys and gender. Significant differences are found for all variables, with low to moderate effect sizes. Females obtain higher scores in the scales on the use of Mobile Phones, Instant Messaging, and Social Networks, while males obtain higher scores in the use of the Internet and Video Games. Females also obtain higher scores in prefrontal symptoms (though only at the expense of declaring more symptoms related with poor emotional control), risk of poor mental health and perceived stress.

Table 5. *Items with predictive capacity (R2*100› 1) of the items of the ISP-20, GHQ-12 and EEP-4 for the MULTICAGE-TIC scales.*

Items	Internet	Mobile Phone	Video Games	Instant Messaging	Social Networks
It is difficult for me to concentrate on anything	6.5	1.0		1.0	
Have you been able to concentrate well on your activities over the last few weeks?					1.0
Have you constantly felt overwhelmed and stressed?					1.0
I laugh or cry too easily	1.0	3.0		2.2	1.4
Many times I am incapable of doing things unless someone tells me I must do them	2.0	1.9	1.8		3.9
I forget that there are things I must do but I remember when reminded			1.0		
I feel lethargic, sleepy				4.1	
I make very personal comments in front of others				1.2	
I make inappropriate sexual comments	1.2				
I tell unsuitable jokes in inappropriate situations			3.0		

Table 6. *Scores on prefrontal symptoms, mental health and perceived stress according to the number of affirmative responses in each scale of MULTICAGE-TIC (controlling for gender, age and level of studies).*

MULTICAGE-TIC			Number of affirmative responses						
			0	1	2	3	4	F_7	η^2
Internet	ISP-20	M	14.65	15.84	19.57	21.47	24.63	25.21*	0.12
		SD	*9.327*	*10.28*	*10.64*	*10.42*	*12.59*		
	GHQ-12	M	9.25	10.21	10.39	11.81	12.96	10.78*	0.06
		SD	*4.25*	*4.49*	*4.95*	*5.90*	*6.89*		
	EEP-4	M	4.15	4.59	5.16	5.86	6.18	17.34*	0.09
		SD	*3.05*	*2.88*	*3.19*	*3.24*	*3.29*		
Mobile Phone	ISP-20	M	14.63	16.98	17.57	19.91	23.81	20.31*	0.10
		SD	*9.76*	*10.26*	*10.36*	*10.94*	*12.75*		
	GHQ-12	M	9.81	10.22	10.02	11.15	12.24	6.06*	0.03
		SD	*4.62*	*4.58*	*5.06*	*5.55*	*6.15*		
	EEP-4	M	4.13	4.82	4.78	5.57	5.63	15.05*	0.08
		SD	*3.08*	*3.13*	*3.09*	*3.12*	*3.36*		
Video Games	ISP-20	M	16.90	19.28	22.04	25.85	23.87	18.85*	0.09
		SD	*10.52*	*9.81*	*11.38*	*10.77*	*15.06*		
	GHQ-12	M	10.12	10.94	11.55	13.39	11.88	6.15*	0.03
		SD	*4.88*	*5.25*	*5.62*	*6.19*	*7.30*		
	EEP-4	M	4.72	5.26	5.74	6.41	5.38	15.54*	0.07
		SD	*3.10*	*2.96*	*3.68*	*3.36*	*2.79*		
Instant Messaging	ISP-20	M	15.15	17.23	17.85	21.64	24.05	23.84*	0.12
		SD	*9.83*	*10.67*	*10.06*	*10.46*	*12.04*		
	GHQ-12	M	9.73	10.21	10.08	11.62	12.40	7.59*	0.04
		SD	*4.37*	*4.94*	*4.96*	*5.86*	*6.31*		
	EEP-4	M	4.27	4.80	4.89	5.73	6.22	17.60*	0.09
		SD	*3.02*	*3.12*	*2.97*	*3.31*	*3.12*		
Social Networks	ISP-20	M	16.22	18.94	18.70	21.83	25.26	21.26*	0.11
		SD	*10.30*	*10.80*	*9.51*	*10.79*	*12.97*		
	GHQ-12	M	9.93	10.79	10.89	11.35	12.60	6.11*	0.03
		SD	*4.48*	*5.67*	*5.16*	*6.19*	*6.91*		
	EEP-4	M	4.57	5.08	5.11	5.89	6.15	15.33*	0.08
		SD	*3.05*	*3.23*	*2.96*	*3.37*	*3.47*		

Note. M= Mean; SD = Standard Deviation; * p ‹ 0.001; η^2= Partial eta-squared for estimating the effect size.

Table 7. *Gender differences in the different scales (controlling for age and level of studies).*

	Males		Females			
MULTICAGE-TIC	M	SD	Females	SD	F_3	η^2
Internet	1.55	1.25	1.44	1.28	55.74*	0.12
Mobile Phone	1.60	1.19	1.85	1.16	26.08*	0.06
Video Games	0.53	1.03	0.34	0.79	15.41*	0.04
Instant Messaging	1.06	1.24	1.53	1.40	49.77*	0.11
Social Networks	0.71	1.15	0.92	1.31	26.69*	0.06
ISP-20	17.51	11.01	18.08	10.68	30.69*	0.07
Executive problems	11.63	7.89	11.49	7.38	18.69*	0.04
Social Behaviour Problems	2.50	2.77	1.68	2.11	24.99*	0.06
Emotional Control Problems	3.37	2.82	4.90	3.25	59.17*	0.12
GHQ-12						
Likert Scores	10.11	4.75	10.60	5.27	7.34*	0.02
Criterion-referenced score	1.46	2.41	1.77	2.76	16.95*	0.04
EEP-4						
Perceived Stress	4.66	3.02	5.03	3.22	29.91*	0.07

Note. NOTE: M= Mean; SD = Standard Deviation; * $p < 0.001$; η^2= Partial eta-squared for estimating the effect size.

Geographical differences

To study geographical differences, subjects that resided in their country of origin were selected and the three sufficiently numerous populations were compared (Spain, Colombia and Venezuela). Table 8 shows that Venezuelans obtained higher scores in the scales on the use of ICTs and prefrontal symptoms, but not in those of poor mental health and perceived stress. The Colombian sample assumed an intermediate position, except for perceived stress, which was lower compared with the other two samples.

Discussion

The purpose of this study was to detect the frequency of problems associated with the use and abuse of Information and Communications Technologies (ICTs) in all age groups and in different geographical and cultural settings. To this end, it was necessary, first, to find evidence of validity of the survey to be used in exploring these issues. The MULTICAGE-TIC has shown adequate internal consistency and evidence of validity. Only item 3 ("*On a day that you don't have your mobile phone with you, do you feel uneasy or as if something very important is missing?*") of the Mobile Phone scale showed low communality with the other three. It is possible that, in the case of Mobile Phones, unavailability fails to have a relationship with the remaining problems explored by the scale. This is probable because, in today's society, doing without a mobile phone in everyday life entails a notable loss, even when someone makes adequate use of the device. Someone may forego playing video games, chatting or checking their social networks, but the mobile phone offers infinite additional functions that may have transformed it into an indispensable object in our everyday activities. A recent report by Telefónica provides data on the increasing importance of the smartphone in everyday life of the Spanish population, which checks it an average of 150 times per day, reflecting an unstoppable trend: it is increasingly difficult for us to live without a smartphone (Telefónica, 2015).

Second, the results show high percentages of people who experiment difficulties with the use of these devices and resources. MULTICAGE was initially based on CAGE (Ewing, 1984), the validation studies of which established that affirmative responses to 2, 3 or 4 items corresponded with hazardous drinkers, harmful use of alcohol and alcohol dependency, respectively. However, for ICTs, no classification criteria are available for determining the item content, nor universally established gold standard tests for determining cut-off scores. If we assume, even provisionally, CAGE scores, the results would be as follows: 57.5% of survey participants obtained scores in problematic use of Mobile Phones (7.9% dependency), 45.1% in problematic use of the Internet (8.6% dependency), 39% in problematic use of Instant Messaging (10.7% dependency), 25.3% in problematic use of Social Networks (6.1% dependency) and 10.9% in problematic use of Video Games (1.9% dependency). Furthermore, though these percentages achieve their peak in subjects under the age of 18, they remain

Table 8. *Differences by geographic location (controlling for age and level of studies).*

	Spain (n = 939)		**Colombia (n = 119)**		**Venezuela (n = 84)**			
	M	SD	M	SD	M	SD		
MULTICAGE-TIC							F_4	η^2
Internet	1.38	*1.23*	1.41	*1.26*	2.00	*1.40*	42.84*	0.13
Mobile Phone	1.69	*1.13*	1.78	*1.33*	2.50	*1.12*	23.80*	0.08
Video Games	0.36	*0.81*	0.41	*1.01*	0.77	*1.21*	12.95*	0.04
Instant Messaging	1.30	*1.32*	1.45	*1.49*	2.21	*1.34*	40.76*	0.13
Social Networks	0.67	*1.13*	1.18	*1.44*	1.63	*1.47*	32.78*	0.10
ISP-20	17.61	*10.47*	17.20	*12.01*	19.42	*10.51*	17.35*	0.06
Executive problems	11.32	*7.33*	11.17	*8.26*	12.15	*7.15*	11.25*	0.04
Social Behaviour Problems	1.94	*2.28*	1.78	*2.53*	2.18	*2.76*	13.29*	0.04
Emotional Control Problems	4.35	*3.15*	4.25	*3.12*	5.08	*3.44*	31.11*	0.10
GHQ-12								
Likert Scores	10.62	*4.86*	9.15	*6.14*	9.07	*5.00*	7.75*	0.03
Criterion-referenced score	1.61	*2.66*	1.66	*2.66*	1.63	*2.07*	10.78*	0.04
EEP-4								
Perceived Stress	5.01	*3.10*	3.76	*3.23*	5.02	*3.09*	23.70*	0.08

Note. M= Mean; SD = Standard Deviation; * p ‹ 0.001; η2= Partial eta-squared for estimating the effect size.

quite stable, though with a continued decline, through successive age groups, and are higher in university students. Even if the responses necessary for considering problematic use or dependency are limited to 3 or 4, problematic use would still be the case in 27.7% of the subjects with Mobile Phones, 22.7% with the Internet and 24% with Instant Messaging.

Dispersed percentages also predominate in previous studies. According to the criteria and instruments applied, a review found that prevalence of addiction to the Mobile Phone varied between 0 and 38% (Pedrero-Pérez, Rodríguez-Monje & Ruiz-Sánchez de León, 2012) and that addiction to the Internet varied between 0.8% and 18.8% (Pontes, Kuss & Griffiths, 2015). Results are insufficient as regards the use of Social Networks and Instant Messaging.

It may be argued that this study sample was comprised of subjects who were already users of these devices and applications, and was not extracted from the general population. In addition, most prior studies were completed using convenience samples, usually university students or adolescents, and applied a wide range of instruments and diagnostic criteria (Pedrero et al., 2012; Pontes et al., 2015). Furthermore, according to studies of the National Statistics Institute, 74.4% of Spanish households are connected to the Internet, 76.2% of the population uses the Internet, 77.1% access the web via Mobile Phone, and 51.1% use Social Networks. The most striking fact is that the percentage of Internet users rose almost five points in just one year, compared with 2013. Therefore, this study overcomes some of the limitations of previous studies in relation to sample size and participant variability.

Another of this study's goals was to explore the relationship between problematic use and psychopathological variables. The results reveal a positive, linear relationship between problematic use of all devices or resources explored and symptoms of prefrontal dysfunction in everyday life, risk of poor mental health and perceived stress. This relationship is consistent and highly significant, despite a low to moderate effect size. In other words: people with difficulties in managing their relationship with ICTs show difficulties in managing their everyday activities, not only those related with ICTs. What others prefer to interpret as evidence of pathology remains a redundant argument. The task of managing ICTs involves personal characteristics, like personality (Wilmer & Chein, 2016), and personality traits are strongly supported by prefrontal lobe functioning (Pedrero-Pérez, Ruiz-Sánchez de León & Llanero Luque, 2015a; Pedrero-Pérez et al., 2013). The data also raises another question, though it remains unanswered, given the study's methodology: does prefrontal dysfunction precede difficulties with ICTs and, therefore, represents a vulnerability, or does it result of excessive immersion in these types of devices or applications, negatively impacting everyday life?

Results suggest that males and females very frequently have problems with controlling their use of these devices and resources, but with some differences: males obtain higher scores on the Internet and Video Game scales, whi-

le females do so in the Mobile Phone, Instant Messaging and Social Networks scales. The effect size for Internet and Instant Messaging is quite considerable and points to solid differences which may be associated with different levels of use and problems with controlling use. Males declared more prefrontal symptoms in general, but females score higher in problems related with Emotional Control. These differences are common in all studies; likewise, it is normal for females to score higher in symptoms of mental illness and perceived stress (Davis, Matthews & Twamley, 1999). Gender differences in the completion of self-reports must always be kept in mind to refrain from generating erroneous interpretations.

There are also differences in the participants' place of origin. An analysis was performed of three samples with a sufficient number of subjects, born in and residents of three different countries. Though we have already alluded to individual differences in ICT management styles, it is also necessary to point out that different sociocultural backgrounds entail, without a doubt, another notable source of variability.

When we study the predictive capacity of the items of the MULTICAGE scale scores, we find that four groups of items have this capacity: those referring to problems with maintaining attention, those referring to emotional instability, those alluding to motivational problems, and those reflecting lack of control as regards disinhibited social behaviour. As is the case with the remaining results, a dual explanation is possible: that these problems favour lack of control, or that these result of excessive immersion in these resources. For example, it is worth questioning whether problems with concentrating favour the problematic use of the Internet, or if this difficulty in concentrating in one's everyday life results of excessive browsing of the Web. In any case, the fact that just one item has the capacity for predicting 6.5% of a scale's total variance is grounds for developing new hypotheses and lines of research.

All of these data require reflection. While the psychiatric perspective tends to include substanceless addictions in diagnostic classifications (this has already been achieved for Gaming in the recent DSM-5), create new terms associated with the abuse of ICTs (*nomophobia, phubbing, vibranxiety, FoMO*) and pathologise any excess, other trends warn of the absurdity of this procedure, the effect of which is the overpathologication of everyday life (see Billieux et al., 2015 and all of the following commentaries in the same Journal number). In fact, many authors advocate for studying other issues, like the functionality of these technologies in the lives of individuals and groups, the socioeconomic and sociopolitical conditions that favour new uses and new problems, the improvements these contribute to everyday life and the pressures that may lead to an excessive use of these technologies or to feeling coerced to decrease their use. When a "problem" affects 50% of the population, or even merely 25%, considering it "psychopathological" may seem hardly adequate, and much less referring to "social pathology" of "epidemic" proportions, terms customarily used in mass media but that lack scientific relevance. It is probably necessary to accelerate the paradigm shift suggested by some authors, abandoning the trend toward the psychiatrisation of any occurrence and refocusing research on environmental elements that foster new behaviours (Pemberton & Wainwright, 2014), urgently demanded since years ago in the field of addictions specifically (Deacon & McKay, 2015; Hall, Carter & Forlini, 2015). As occurs in substance addiction, the first focus is expected to accumulate evidence of "comorbidity" and "dual diagnosis", which contributes little or nothing to our understanding and problem-solving (Seo, Kim & David, 2015), while the second focus may serve to understand excessive behaviours from an evolutionary perspective, and contributes educational and therapeutic elements (Kwan & Leung, 2015).

This study's main limitation refers to the method used for obtaining the sample. Dissemination using social networks does not allow for controlling the quality of participation, the participants' motivation, nor, of course, for generalizing results. The only way to control, at least globally, the quality of the responses, is to obtain a sufficiently large sample so that the percentage of inadequate responses will lose specific weight in the global results. For this purpose, a minimum value of 20 participants/item was estimated, doubling the strictest requirements in similar studies (Velicer & Fava, 1998). Nevertheless, the Respondent-Driven Sampling technique is recommendable when it is difficult to access the target population, or when large sample sizes are desired. Like all sampling methods, it entails risks that must be considered (Bowling, 2005). Internal consistency of tests, on both item and scale levels, is the main evidence that the data has been adequately obtained, at least for the most part.

In summary, the data of this study report the high frequency of problems associated with excessive use and immersion in the so-called Information and Communications Technologies (ICTs), a fact that is generalised across different countries, both genders, and all ages and cultural levels. This excessive use is related to difficulties in controlling behaviours, emotions and socializing in everyday activities, as well as to risk symptoms for developing mental health problems and for experimenting higher stress levels. Future studies should explore the directionality of these relationships to determine whether they are vulnerabilities for or consequences of abuse, or if both probabilities reinforce one another. Classifying these excessive behaviours as mental disorders will hardly favour understanding them and most likely will extend the borders of the psychiatric diagnosis to a disproportionate percentage of the population, which, no doubt, is an unacceptable ex-

cess and entails important consequences (pathologisation of everyday life, expansion of pharmacological treatments, etc.). Studies are needed that consider environmental circumstances (sociological, political, economic, ethical), individual predisposition (personality, social values, goals) and the interaction between both elements to understand what was originally a revolution in human communications and has evolved much faster than the scientific knowledge available for explanatory and predictive purposes.

Conflict of interests

The authors declare the inexistence of conflicts of interest.

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Appendix 1. *MULTICAGE-TIC*

		YES	NO
1	Do you spend more time than you think you should connected to the Internet for purposes other than work?		
2	Have your family members complained about the number of hours you dedicate to the Internet?		
3	Is it difficult for you to remain away from the Internet for several consecutive days?		
4	Do you have problems in controlling your impulse to connect to the Internet, or have you failed in trying to reduce the time you dedicate to being connected?		
5	Do you use the mobile phone more often or for longer time periods than you should?		
6	Have your family members or friends at any time commented that you make too much use of the mobile phone for chatting or sending messages?		
7	On a day that you don't have your mobile phone with you, do you feel uneasy or as if something very important is missing?		
8	Have you tried to reduce your use of the mobile phone without achieving this in a satisfactory way?		
9	Do you dedicate more time than you think you should to playing Video Games, using a console, computer or mobile phone?		
10	Does your family complain that you dedicate too much time to playing Video Games, using a console, computer or mobile phone?		
11	Is it difficult for you to be several days without playing Video Games using the console, computer or mobile phone?		
12	Have you failed in trying to reduce the time you dedicate to playing Video Games, using a console, computer or mobile phone?		
13	Do you spend more time than you think you should chatting with your contacts via WhatsApp (or similar application) over the mobile phone?		
14	Do your family members or friends complain that you dedicate too much time to chatting via WhatsApp (or similar application)?		
15	Is it difficult for you to spend time without checking if you have new messages in WhatsApp (or similar application)?		
16	Have you failed in trying to reduce the time you dedicate to WhatsApp (or similar application)?		
17	Do you dedicate more time than you think you should to participating in social networks, like Facebook, Twitter, Instagram or similar networks?		
18	Do your family members or friends complain that you dedicate too much time to checking and communicating via Facebook (or Twitter, Instagram or similar networks)?		
19	Is it difficult for you to spend time without checking Facebook (or Twitter, Instagram or similar networks) to check whether there is new information?		
20	Have you failed in trying to reduce the time you dedicate to Facebook (or Twitter, Instagram or similar networks)?		

Illicit drug policy in Spain: the opinion of health and legal professionals

Política de drogas ilegales en España: la opinión de los profesionales del ámbito sanitario y del legal

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Abstract

The high frequency of criminal behaviour and related legal problems associated with substance addiction generates a field of interaction between legal and healthcare systems.

This study was developed as a multicentre project to investigate the opinions of professionals from legal and healthcare systems about policies on illegal drugs and their implementation in practice. A multiple choice questionnaire designed ad hoc was administered to a sample of 230 professionals from legal and healthcare fields working in the cities of Barcelona, Granada and Bilbao. The questionnaire included sociodemographic and work-related data, and assessed interviewees' information about the response to drug-related crime and opinion on drug policy issues. This article presents the results from Spain.

The main results showed that both groups of professionals value alternative measures to imprisonment (AMI) as useful tools to prevent offenses related to drug use and claim a broader application of AMI. They also evaluated positively the regulations on cannabis use in effect. Though the attitude of healthcare professionals towards the application of AMI is more permissive, both groups favour restricting these sanctions in cases of recidivism. Both groups show mild satisfaction with the current addiction healthcare system and express dissatisfaction with actual drug policies in Spain.

Keywords: Addiction; criminal liability; drug policies; decriminalizing; healthcare system.

Resumen

La elevada frecuencia de conductas delictivas y problemas legales relacionados con las adicciones a sustancias genera un terreno de interacción entre los ámbitos legal y sanitario. En este contexto se ha llevado a cabo un estudio multicéntrico de las opiniones de los profesionales tanto del ámbito legal como del sanitario sobre la legislación relacionada con las drogas y su implementación en la práctica de acuerdo al marco legal vigente.

Se administró a 230 profesionales tanto del ámbito legal como del sanitario de Barcelona, Granada y Bilbao un cuestionario de respuesta múltiple diseñado ad hoc, con datos sociodemográficos y laborales y preguntas para valorar la opinión de los encuestados sobre la respuesta a la delincuencia relacionada con drogas y su postura en relación con la política en materia de drogas.

Los principales resultados mostraron que ambos grupos de profesionales valoran las medidas penales alternativas (MPA) como herramientas útiles para prevenir los delitos relacionados al consumo, apostando por la ampliación de su aplicación. También coinciden en valorar positivamente la actual regulación del consumo de cannabis. Los profesionales del ámbito sanitario muestran una actitud más permisiva de cara a la aplicación de MPA, pero ambos grupos reconocen oportuno endurecer la sanción en caso de reincidencia delictiva. Los dos grupos muestran una satisfacción relativa con el sistema de atención a las adicciones en los aspectos estudiados y expresan insatisfacción con las políticas actuales sobre drogas.

Palabras clave: Adicción; responsabilidad penal; legislación sobre drogas; despenalización; sistema sanitario.

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Substance addictions and their treatment imply a challenge for professionals, given both the complexity and seriousness of their clinical characteristics as well as the secondary social and legal problems associated with their use. For a long time, delinquency related with substance use has been grounds for stigmatising addictions. The high frequency of criminal behaviour and the related legal problems in patients with addiction disorders generates a field of interaction between legal and healthcare fields (Esbec & Echeburúa, 2016). Current knowledge in the field of addictions allows for the unambiguous definition of certain criminal behaviours as a result of a more complex pathology. Therefore, we must advance our knowledge about and approach toward an issue of major relevance in terms of socioeconomic costs (European Monitoring Centre for Drugs and Drug Addiction, 2007).

A uniform judicial framework across the different countries of the European Union on the use of illegal substances is inexistent (European Monitoring Centre for Drugs and Drug Addiction, 2015). Member states, like Poland, criminalise substance use, wherefore a patient with a substance use disorder is considered the author of an offence at the time of committing a criminal act. In Spain, as we will address further below, the criminal act is independent: when they are for personal use, the production/distribution of a substance and the possession of drugs are not criminalised. This difference impacts the practice of both legal and healthcare professionals, and is reflected in these professionals' opinions on this issue.

Brief reference to the legal framework in Spain: regulation and available data

In reference to criminalisation, unlike other European and American jurisdictions, Spain's legislation has refrained from imposing criminal punishment for neither personal use of drugs nor for possession of drugs in small quantities for personal use. However, criminal punishment does apply for the cultivation, elaboration or illegal trafficking of toxic drugs, narcotics, and psychotropics (Chapter III of crimes against public health, Title XVII of crimes against public safety, from the Criminal Code approved by Organic Law 10/1993, dated 23 November). Administrative law, however, penalises illegal possession and the use of toxic drugs, narcotics, and psychotropics in public places (Organic Law 4/2015, dated 30 March, on the protection of civilian security).

Criminal law, furthermore, proposes differentiated, specific sanctions when the person that has perpetrated a crime has done so under the influence of drugs or as a result of addiction to these (Annex I). As a result of the application of this legislation, those individuals convicted for a crime with a drug-related problem detected prior to the conviction, included in the sentence as a mitigating circumstance, may face one of the following situations as alternative measures: loss of liberty consisting of internment in a detoxication centre; participation in day treatment under parole or probation, in lieu of imprisonment; and suspension of imprisonment for drug addicts. This series of responses are included within a broader concept known as Alternative Measures to Imprisonment (AMI). In Spain, in 2013 the Sentence and Alternative Measures Management Service managed 24,865 AMI sentences, corresponding to suspensions and substitutions for convictions. Of these, 58% were for gender-based violence; 5% for crimes related with road safety, and 37% for other crimes, including those related with the use of addictive substances (DGPNSD - Governmental Delegation for the National Drug Plan, 2013).

Nevertheless, it is possible that the addiction-related problem goes undetected or unaddressed at the judicial level during sentencing, therefore resulting in the imprisonment of an offender as a result of addiction or addiction-related problems. In these cases, the penitentiary system offers several alternatives for prevention, risk reduction and treatment (Annex I). In 2014, 4,783 persons sentenced to prison were included in substance addiction treatment programs in the context of parole and the third grade prison regime (General Secretariat of Penitentiary Institutions, 2014).

The existence of sanctions other than prison that are sensitive to problems associated with substance addiction entails that there are persons who, in compliance with a judicial verdict, serve a sentence or fulfil security measures by participating in an out-of-prison detoxication treatment. This requires the multidisciplinary coordination of agencies and professionals from the judicial, penal enforcement, social, education, and healthcare systems to apply what simultaneously comprises a judicial verdict and medical treatment. In turn, this entails the presence of a technician, usually a psychologist or social worker, dependent on the General Secretariat of Penitentiary Institutions or the Justice Department in Cataluña, in charge of the execution of the judicial verdict and who, by following up with the corresponding healthcare professionals, reports to the judge as to the degree of compliance with said verdict.

In practice, this requires the cooperation of professionals from different backgrounds in terms of training and culture, and with objectives and rationalities that are not always in alignment: on one hand, professionals from the judicial or legal/criminal systems (judges, prosecutors, public defenders) and, on the other hand, healthcare or therapeutic professionals (doctors, social workers, psychologists, nurses). Specifically, the research findings highlighted below focus on the opinion of these diverse groups of professionals on the regulation and application of sanctions other than prison in response to drug addiction.

Therefore, based on the hypothesis that whether professionals belong to legal or healthcare fields would impact their opinion on the suitability of AMI aimed at offences

Annex I. *Summary chart of criminal and penitentiary-related legislation specifically for persons dependent on toxic drugs.*

	Institution	Applicable circumstance	Disposición normativa
Determination of criminal liability	Grounds for exemption of criminal liability	Complete intoxication or abstinence syndrome at the time of committing the criminal act, that impedes the comprehension of the act or of acting in accordance with that comprehension	Article 20.2, Criminal Code
	Grounds for incomplete exemption of criminal liability	Complete intoxication or abstinence syndrome at the time of committing the criminal act, without meeting all of the requirements for complete exemption	Article 21.1 in relation with Article 20.2 , Criminal Code
	Mitigating circumstance of criminal liability	Acting as a result of a serious addiction to toxic substances	Article 21.2, Criminal Code
Specific sanctions	Internment in a detoxification centre as a security measure	Persons with complete or incomplete exemption of liability, Article 20.2 or 21.1, Criminal Code	Article 102.1 and 104, Criminal Code
	Parole or probation with the obligation of participating in an outpatient detoxification treatment program as a security measure	Persons with complete or incomplete exemption of liability, Article 20.2 or 21.1, Criminal Code	Article 106.1.k, Criminal Code
	Suspension of imprisonment with the obligation of participating in a detoxification treatment program	Persons sentenced to prison for up to 5 years, with the condition that they refrain from further offences and that they remain in treatment during the term of suspension	Article 80.5, Criminal Code
Specific responses of the penitentiary system	Specific programs in prison	Persons sentenced to prison and imprisoned in penitentiary centres may benefit from the following programs developed by the penitentiary authorities: Health prevention and education program; Needle exchange program; Methadone treatment program; Detoxification Program; and Social reinsertion program	General Secretariat of Penitentiary Institutions, http://www.institucionpenitenciaria.es/web/portal/Reeducacion/ProgramasEspecificos/drogodependencia.html
	Serving the prison sentence at a detoxification centre	Inmates in the third grade prison regime with an addiction to toxic substances	Article 182, Penitentiary Regulations

committed by drug addicts, the IDDO-Europe project (Illicit drugs and drug offences - new challenges and developments for European criminal law politics) (Soyer & Schumann, 2015) was launched in Austria, Poland and Spain. Its objective was to evaluate the opinions of professionals from legal and healthcare fields on some aspects of drug-related legislation and its implementation in practice. This article presents the main findings of this study in Spain.

Materials and methods

This study's sample consisted of 230 professionals in direct contact with illegal substance users, from legal (prosecutors, judges, lawyers, police) and healthcare (drug addiction treatment centres: psychiatrists, psychologists, nurses and social workers) fields in Barcelona, Granada and Bilbao. They all completed an *ad hoc* self-administered, multiple choice questionnaire (Soyer & Schumann, 2015) that included (a) sociodemographic and employment-related data: age, sex, profession, position at the workplace, years of experience in the field of substance use, percentage of the job shift dedicated to issues related with delinquency and drug use; (b) opinion on the response to delinquency related with drugs in practice, specifically, factors that promote or hinder the implementation of AMI, types of offences that facilitate the application of AMI, response to recidivists; level and goodwill of actual cooperation between professionals from legal and healthcare fields; level of quality of the drug addiction treatment centres; (c) opinion of the professional as regards policies on drugs: opinion on sanctions for personal use of drugs; usefulness of AMI in crime prevention; suitability of current regulations on AMI; opinion on the degree of suitability of the application of AMI to offenders addicted to drugs; usefulness of decriminalizing substances like cannabis; suitability of Opioid Replacement Therapy (ORT) and opinion on drug-related legislation in force in Spain. The Clinical Research Ethics Committee of Parc de Salut Mar approved the study (201 114420/1).

The SPSS Statistics 17.0 package was used for data analysis. The mean and standard deviation (SD) for continuous demographic data and frequencies for discrete, variable data were calculated. The Chi-squared test was used to calculate the differences of the various items included in the questionnaire according to profession. The significance level of $p > 0.005$ was set as the cut-off for the chi-squared distribution.

Results

Sociodemographic and employment-related characteristics

The mean age of the 230 interviewees was 43 (SD 9.2; range 21-65) and 122 (53%) were female. The professions were distributed as follows: 69 (32%) from the legal field (21 judges, 21 lawyers, 19 prosecutors and 8 police) and 161 (68%) from the healthcare field (71 nurses, 59 doctors, 16 psychologists, 15 social workers). Most of the professionals, about 73%, worked in direct contact with persons with legal problems related with substance abuse, while only 27% held management positions. Analysis by subgroups did not yield significant differences in the distribution by sex, except for the groups of police agents (100% male) and nurses, predominantly female (65%). As to years working in the sector of substance abuse-related problems, 24% of the professionals that completed the questionnaire had specific experience under 5 years, 30% between 5 and 10 years, 25% between 10 and 20 years, and, finally, 15% over 20 years.

Comparison of professionals from legal and healthcare fields

Opinion on the response to delinquency related with drugs in practice.

The factors and substances object of abuse that promote or hinder the implementation of AMI and the opinion on the degree of suitability of the application of AMI to offenders addicted to drugs, according to the two groups of professionals, are described in Table 1. As regards the factors that favour the implementation of AMI, professionals from both fields consider that a stable social environment and employment are factors that favour the implementation of AMI. However, differences were found by profession as regards relevance whether the offence or AMI was the first one: legal professionals assigned higher relevance to the fact of an offence being an initial one and that the person had not previously been sentenced to serve AMI (Table 1).

Likewise, most of the professionals agree in considering that recidivism and the absence of a stable social environment are factors that hinder the application of AMI; however, their opinions differ as regards the lack of income or of having completed AMI previously: legal professionals consider that unemployment and a prior AMI impede the application of AMI (Table 1).

In relation to the type of substance implied, most legal professionals consider that AMI are pertinent for offenders who abuse cannabis, heroin and cocaine (54-75%), but only a minority consider that these are suitable in response to the use of amphetamines and other synthesis drugs (39%). To the contrary, healthcare professionals did not differentiate the substances, and considered that AMI are applicable to all (65-76%).

The majority of the interviewees considered that the application of AMI was dependent on the type of offence committed: possession/use and property crimes were the most likely candidates for AMI. Violent crimes are considered the least suitable for the implementation of AMI, though differences arise between both fields: legal professionals are less inclined toward applying AMI in these cases (Table 1). Likewise, the majority of the professionals from both groups (90 and 72%, respectively) consider that the most common reaction unto recidivists is the application of a more severe measure, while only 3% and 8% of these professionals consider that repeating AMI is applicable.

Most of the professionals advocate for a heightened cooperation across the fields of action, considering the current situation deficient both in terms of the existing cooperation as well as the willingness to cooperate of the two groups (Table 1).

Opinion on drug-related policies.

No substantial differences were found across both groups of professionals in response to questions on different aspects of Spain's drug-related policies in force. Therefore, as to their opinion on sanctions for personal use of drugs, merely a third of the interviewees considered this measure useful for preventing subsequent drug use, drug use by others, or for reducing drug-related crime. As to their opinion on the effectiveness of AMI for preventing recidivism, the majority of the professionals (97% of both legal and healthcare fields) considered that these could prevent crime. As to their opinion of Spain's AMI-related legislation in force, most of the professionals from both fields considered it inadequate and that the frequency of application of AMI should be increased (Table 2).

As to regulations on the use of cannabis in our country, about half of the professionals from both fields were in agreement with the current legislation, and only a minority (approximately 10%) considered the need for increasing its severity.

Finally, only 15% of legal professionals and 17% of healthcare professionals were satisfied with drug-related legislation in force.

Opinion on treatment for addictions.

The questionnaire included two questions addressing aspects about treatment currently offered for addictions. In this regard, professionals from both legal and healthcare fields were relatively satisfied - 58 and 54%, respectively - with the quality of the drug treatment centres. Likewise, over 80% were satisfied with current long-term Opioid Replacement Therapy (ORT) programs.

Table 1. *Opinions of interviewees on the response to delinquency related with drugs, according to professional field. Spain 2015*

	Legal (%)	Healthcare (%)	X2	p
Factors that favour the implementation of AMI				
Stable social environment	68	73	0,638	ns
Employment	58	62	0,250	ns
Substance abuse	44	42	0,069	ns
First offence	75	58	6,005	0,014
First AMI	67	33	22,438	0,000
Factors that hinder the implementation of AMI				
Fragile social environment	60	62	0,087	ns
Unemployment	1	26	19,288	0,000
Substance abuse	23	32	1,686	ns
Recidivism	77	80	0,321	ns
Prior AMI	52	38	4,042	0,044
Substances that favour the implementation of AMI				
Cannabis	75	76	0,028	ns
Heroin	65	70	0,421	ns
Cocaine/crack	54	66	3,064	ns
Amphetamines/other	39	65	12,777	0,000
Substances that hinder the implementation of AMI				
Cannabis	29	24	0,742	ns
Heroin	25	26	0,018	ns
Cocaine/crack	33	27	0,843	ns
Amphetamines/other	48	22	14,916	0,000
Types of offences that favour the implementation of AMI				
Possession/use	73	79	1,097	ns
Trafficking	42	40	0,104	ns
Property crimes	70	52	6,087	ns
Violent crime	3	15	7,298	0,007
Response to recidivism				
New AMI	3	8		
AMI + sanction	7	20	10,5	0,005
More severe sanction	90	72		
Existing level of cooperation between professionals from legal and healthcare fields				
Sufficient	23	8		
Insufficient	64	76	8,597	0,014
None	13	16		
Willingness to cooperate between professionals from legal and healthcare fields				
Sufficient	41	18		
Insufficient	52	72	12,721	0,002
None	7	10		
Sufficient level of quality of the drug addiction treatment centres				
Yes	58	54	61	ns

Note. AMI: Alternative Measures to Imprisonment.

Discussion

The evaluation of the opinions of professionals from both legal and healthcare fields on Spanish legislation in effect on drug use and drug-related crime demonstrates, first, that both groups share similar opinions on matters addressed by the study.

As to the application of AMI, healthcare professionals assign lesser relevance to the fact of whether or not the offence is the initial one, or whether or not AMI has been applied previously. Along the same lines, healthcare professionals' recognition of addiction as a chronic illness entailing recidivism possibly contributes toward their less punitive attitude toward recidivist offenders with relapses in their drug use. For healthcare professionals, furthermore, the decision of whether or not to impose AMI is not dependent on the type of substance, while legal professionals associate the application of AMI to offenses related with the use of heroin, cocaine or cannabis more so than to those related with amphetamines or synthesis drugs. This is, probably, a reflection of the erroneous perception that amphetamines and other synthesis drugs are substances without analogous addiction-related problems, compared with other substances like heroin, cocaine and cannabis. In this regard, it is worth highlighting that the demand for treatment for the use of

Table 2. *Opinions of interviewees on drug-related policies, according to professional field. Spain 2015.*

	Legal (%)	Healthcare (%)	X2	p
Opinion on punishment for personal use of drugs				
Adequate prevention of subsequent use	38	39	0,023	ns
Adequate prevention of use by others	35	31	0,275	ns
Contributes to reducing drug-related offences	33	29	0,481	ns
Usefulness of AMI for preventing delinquency				
Yes, always	10	7		
Yes, sometimes	87	90	0,58	ns
No, never	3	3		
Suitability of current legislation on AMI				
Yes	16	10	1,969	ns
The implementation of AMI should				
Be increased	75	72		
Be limited	13	13	1,215	ns
Remain the same	12	14		
Be abolished	0	1		
Usefulness of decriminalizing cannabis				
Yes, for personal use	24	34		
Yes, for selling	16	14	2,795	ns
No, legislation is adequate	50	41		
No, legislation should increase in severity	10	11		
Suitability of long-term Opioid Replacement Therapy (ORT) programs				
Yes	84	82	1,32	ns
Opinion on legislation in effect on drug-related policies				
Yes	15	17	0,116	ns

Note. AMI: Alternative Measures to Imprisonment.

amphetamines and other synthesis drugs is much lower than that demanded for heroin, cocaine and cannabis (DGPNSD - Governmental Delegation for the National Drug Plan, 2014). Likewise, both groups of professionals agree in the difficulty inherent to the application of AMI in cases of violent crimes and acknowledge that not only are offences of use and possession suitable for implementing AMI, but that property crimes are suitable as well. Most of the interviewees consider it possible to prevent recidivism, and advocate for broadening the scope of application of AMI. These results suggest that these professionals have a favourable opinion of the efficiency of a legal system, like Spain's, based on recognising addictions as illnesses and, consequently, promoting AMI as a key tool of the process for responding to drug-related crime, advocating for a more solid interaction across legal and healthcare fields in the face of drug treatment.

One particularly relevant result of the study is the opinion of the interviewees on the issue of decriminalizing cannabis. Most favour abolishing punishment for personal use and explicitly point out the usefulness of decriminalizing personal use of cannabis, in line with Spain's legislation in force. This fact is confirmed independently in that only a minority of the interviewees prefer more severe legislation. Given the current, international debate on the decriminalization/deregulation of cannabis use, this opinion shared by both legal and healthcare professionals as regards cannabis users in Spain (Babín Vich, 2013) may contribute information that is interesting and relevant for other countries (Banys, 2016; Volkow et al., 2016; Wall et al., 2016).

Furthermore, bearing in mind that Spain is one of the countries with the broadest coverage of ORT programs, including its availability in prisons (Torrens, Fonseca, Castillo, & Domingo-Salvany, 2013), the fact that 80% of the professionals interviewed were satisfied with the characteristics of ORT programs available in our country also seems to support this vision more oriented toward considering the user a patient.

Finally, though both groups consider that their cooperation is insufficient, healthcare professionals feel so more strongly. In general, this perception of lack of cooperation may arise from the fact that, in practice, legal professionals do not communicate with healthcare professionals directly but rather through social workers, a minority group within the healthcare field. To the contrary, the fact that these intermediaries in the communication are not the healthcare professionals directly responsible for the clinical cases themselves facilitates the independence of medical decisions in relation to the legal situation.

When comparing our results with data obtained using the same methodology in Austria and Poland within the framework of the IDDO-Europe project, the attitude of legal policies for treatment in effect across the three countries is not the same: Spain's legislation is more permissive while that of Austria and Poland is more restrictive. In general,

healthcare professionals in all three countries are more critical as regards the effectiveness of criminalizing the management of addictions, though Spain's healthcare and legal professionals both advocate for the current legal system to consider the possibility of implementing AMI and request a subsequent review of current policies on illegal drugs.

The main limitation of this study is the representativeness of the sample, given that it does not encompass the entire country.

Nevertheless, this study of opinions on current legislation applicable to addiction to illegal substances from the perspective of healthcare and legal professionals demonstrates their similarity of opinions as well as main points of discrepancy as regards many of the aspects under study, and offers a framework for improving the interaction across both groups of professionals which would result, ultimately, in improving the approach toward addiction as an illness.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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Brief Sensation Seeking Scale: Latent structure of 8-item and 4-item versions in Peruvian adolescents

Escala breve de búsqueda de sensaciones (BSSS): estructura latente de las versiones de 8 y 4 ítems en adolescentes peruanos

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Abstract

This research intended to validate two brief scales of sensations seeking with Peruvian adolescents: the eight item scale (BSSS8; Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002) and the four item scale (BSSS4; Stephenson, Hoyle, Slater, & Palmgreen, 2003). Questionnaires were administered to 618 voluntary participants, with an average age of 13.6 years, from different levels of high school, state and private school in a district in the south of Lima. It analyzed the internal structure of both short versions using three models: a) unidimensional (M1), b) oblique or related dimensions (M2), and c) the bifactor model (M3). Results show that both instruments have a single dimension which best represents the variability of the items; a fact that can be explained both by the complexity of the concept and by the small number of items representing each factor, which is more noticeable in the BSSS4. Reliability is within levels found by previous studies: alpha: .745 = BSSS8 and BSSS4 =. 643; omega coefficient: .747 in BSSS8 and .651 in BSSS4. These are considered suitable for the type of instruments studied. Based on the correlation between the two instruments, it was found that there are satisfactory levels of equivalence between the BSSS8 and BSSS4. However, it is recommended that the BSSS4 is mainly used for research and for the purpose of describing populations.

Keywords: Sensation Seeking; Adolescents; Internal Structure; Validation; Reliability; Equivalence.

Resumen

El presente estudio tuvo el propósito de validar con adolescentes peruanos dos Escalas Breves de Búsqueda de Sensaciones: el de ocho ítems (BSSS8; Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002) y el de cuatro ítems (BSSS4; Stephenson, Hoyle, Slater, & Palmgreen, 2003). Los cuestionarios se aplicaron a 618 adolescentes que participaron voluntariamente, de 13. 6 años de edad promedio, de diferentes niveles de estudios de la secundaria, de colegios de gestión estatal y privada, pertenecientes a un distrito del sur de Lima. Se analizó la estructura interna de ambas versiones breves a través de tres modelos: unidimensional (M1), dimensiones relacionadas u oblicuas (M2) y el modelo bifactor (M3); los resultados hallados indican que ambos instrumentos tienen una sola dimensión que representa mejor la variabilidad de los ítems, hecho que puede ser explicado tanto por la complejidad del concepto como por la pequeña cantidad de ítems que representan a cada factor; aspecto que se potencia en el BSSS4; la fiabilidad cae dentro de los niveles que los estudios anteriores hallaron (Alfa: BSSS8= .745 y BSSS4= .643) y (Coeficiente Omega: .747 del BSSS8 y .651 del BSSS4) los mismos que se consideran adecuados para el tipo de instrumentos estudiados. A partir de la correlación entre ambos instrumentos, se encontró que existen niveles satisfactorios de equivalencia entre el BSSS8 y BSSS4. Se recomienda sin embargo que el BSSS4 se utilice fundamentalmente para trabajos de investigación y con propósitos de describir poblaciones.

Palabras clave: búsqueda de sensaciones; adolescente; estructura interna; validación; fiabilidad; equivalencia.

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Zuckerman (1981) began to investigate sensation seeking (SS) in the early 1960's and the first instrument designed to measure it as an independent construct was the SSS (Sensation Seeking Scale, Zuckerman, Kolin, Price & Zoob, 1964), revised in successive versions (II, III and IV). The last modification, the SSS-V (Sensation Seeking Scale, version V) proposed by Zuckerman, Eysenck and Eysenck (1978), is the most frequently used in research (Carretero-Dios & Salinas, 2008). It has been adapted for use in different places and cultures such as Spain (Pérez & Torrubia, 1986), Italy (Maná, Faraci & Como, 2013; Primi, Narducci, Benedetti, Donati & Chiesi, 2011), Canada (Rowland & Franken, 1986) and Israel (Birenbaum & Montag, 1987). An extensive review can be found in Aluja, García and García (2004). A further version (SSS-VI) was later published by Zuckerman (1984) himself and used by Torki (1993) in an intercultural study of American and Kuwaiti populations.

The SSS-V has modeled the construction of other SS measures that partially adopted its structure or contents in order to study them in different populations. A well-known examples is the Arnett Inventory of Sensation Seeking (AISS) (Arnett 1994; Carretero-Dios & Salinas, 2008; Ferrando & Chico, 2001), which demonstrated that the same construct was being measured. Recently, Palacios (2015) reported the psychometric properties of the Sensation Search Inventory for adolescents in Mexico (IBS-Mx) and found eight factors, including the four reported by Zuckerman. Other instruments consider SS to be a personality factor, such as the ZKPQ (*Zuckerman-Kuhlman Personality Questionnaire*, Aluja et al., 2006; Aluja, Kuhlman, & Zuckerman, 2010; Ledesma, Poó & Peltzer 2007), or the Impulsive Behavior Scale (UPPS-P), the factorial structure of which covers SS (Candido, Orduña, Perales, Verdejo-García, Billieux, 2012).

Practical research problems led to the reduction in size of the instrument without loss of reliability or validity, with Madsen, Das, Bogen and Grossman (1987) developing the Short Sensation-Seeking Scale, derived from SSS-IV and composed of 10 ipsative items. Later, Hoyle, Stephenson, Palmgreen, Lorch and Donohew (2002) presented the Brief Sensation Seeking Scale (BSSS-8), derived from SSS-V and demonstrating good psychometric properties. This version was adapted to study Latino workers in North America (Stephenson, Velez, Chalela, Ramirez & Hoyle, 2007). Subsequently, Stephenson, Hoyle, Palmgreen and Slater (2003) created a smaller scale of four items (BSSS-4) for use in epidemiological studies or those in which SS is not the main construct. Its creators consider that both versions exhibit stable psychometric properties regarding gender and educational level, that their scores are conceptually related to those of more longer measures, and that despite the scale's brevity, they lose very little of their predictive power and reliability.

The SSS-V, its adaptations and modifications were centred on the study of adolescent populations, with unsatisfactory results given that the discriminatory power of the items was found to be low, structural stability unacceptable, and recovery of factors weak (e.g. Maná et al., 2013). Several reasons may underlie these problems: using content originally developed for adults with adolescents, using concepts no longer socially relevant (Palacios, 2015), and the obtainment of moderately valid measures and low reliabilities (for example, Kafry, 1982; Pérez, Ortet, Pla & Simó, 1987; Russo, Lahey, Christ, Frick, McBurnnett, Loeber, Stouthamer-Loeber & Green, 1991; Russo, Stokes, Lahey, Christ, McBurnett, Loeber, Stouthamer-Loeber & Green, 1993). These results limit the use of SSS-V with adolescent populations because it adds irrelevant variance to the construct, reduces the common variance among its items, and does not guarantee its intercultural replicability.

In order to overcome the criticism of SSS-V when applied to adolescents, instruments such as the Arnett Sensation Seeking Inventory (AISS, Arnett, 1994) and others were developed, which contemplated, for example, the contents of the items (e.g. items that produce adverse reactions, such as those related to drug use or sexual activity), the invalidity of the construct when compared to impulsivity, the up-to-dateness of various item contents , the size of the instrument as well as the response format (Hoyle, et al., 2002; Jensen, Weaver, Ivic, & Imboden, 2011; Palacios, 2012). Nevertheless, the stability of the psychometric properties of the AISS with adolescents of certain cultures still seems to be limitated in terms of reliability (e.g. Smorti & Guarnieri, 2013), a problem which is repeated in studies with adult populations (Carter-Dios & Salinas, 2008). In addition, Stephenson, Palmgreen, Hoyle, Donohew and Colon (1999) created a version with 20 items starting from two instruments that were designed for adolescents (Huba, Newcomb & Bentler, 1981; Zuckerman et al., 1978), with internal consistency reliability of 0.82 for the total score. However, the report on this instrument had two important weaknesses: it did not report the reliability of the sub-dimensions, nor did it provide evidence of the validity of the internal structure of the instrument.

Some other instruments for children and adolescents also emerged with the idea of overcoming the methodological problems of SSS-V (Michel et al., 1998; Palacios, 2015; Pérez et al., 1987; Russo et al., 1993), or as independent developments but secondary to the main objectives of the study (e.g. Sargent, Tanski, Stoolmiller & Hanewinkel, 2010). With respect to the latter (Sargent et al., 2010), its brevity and psychometric efficiency is comparable to another short measure which is the focus of the present study (BSSS4; Stephenson et al., 2003). Its construction, however, appears to have followed an essentially rational method guided by practical convenience (brevity) instead of being a complete restructuring of the

measurement of SS and the application of multivariate psychometric analyses.

The proposed BSSS (Brief Sensation Seeking Scale, Hoyle et al., 2002), attempted to overcome problems related to the contents of the items and with psychometric aspects of SSS-V (e.g. Ridgeway & Russell, 1980), and currently seems to be the most used to quantify SS, since its age coverage fits well with adults and adolescents, its items are appropriate and relevant to both age groups and its content is related to current experiences. In some studies with adult speakers of English (Eachus, 2004; Litvin, 2008) and Spanish (López-Bonilla & López-Bonilla, 2010) it was found to have satisfactory psychometric properties regarding the internal validity of its items, its relationship to other constructs and its internal consistency. Also, some unpublished results (e.g. Cheah, 2003) indicated good psychometric properties which were similar to the original study by Hoyle et al. (2002).

To date, research carried out with adolescents (Banerjee, Greene & Yanovitzky, 2011; Donohew et al., 2000; Hoyle et al., 2002; Jensen, Imboden, & Ivic, 2011; Primi, Narducci, Benedetti, Donati & Chiesi, 2011; Stephenson et al., 2003) has been mainly with Anglo-Saxon samples. In these studies Hispanic groups were identified as ethnic minorities, whose origin status is that of immigrants. Even when the instruments were created in Spanish to measure SS (e.g. Arnett, 1994; Palacios, 2015; Palacios, Sánchez & Andrade, 2010) in an attempt to overcome the shortcomings of SSS-V, no publications have been found in Peru and other South American countries describing their construction and validation or provding psychometric analysis. There are also no published studies on BSSS with Hispanic adolescents in their own culture.

In this study, we present psychometric results with structural validity of two short versions of BSSS, of eight (BSSS8, Hoyle et al., 2002) and four items (BSSS4, Stephenson et al., 2003), with a sample of Peruvian adolescents. It is justified by its novelty and by the utility of brief scales for epidemiological studies (Stephenson et al., 2003) because SS is associated with increasingly widespread social problems, such as risky behaviors, problematic use of alcohol and substances, or abuse of the internet, video games, etc. (Cándido & Perales, 2014; Choliz & Marco, 2011; Cortés Tomás, Giménez Costa, Motos Sellés & Cadaveira Mahía, 2014; Motos Sellés, Cortés Tomás, Giménez Costa & Cadaveira Mahía, 2015; Navas, Torres, Candido & Perales, 2014), and also because these scales can be used to predict risky behaviors in different activities of daily life, and moreover in highly problematic social contexts such as Peru and Latin America. These brief measures of sensation seeking can be very valuable for professional practice and to rationalize research resources, since the small number of studies on this construct can be linked to the absence of instruments that have international support, are economical and dimensionally clear. Although the present study only focuses on Peruvian adolescents, it also contributes a baseline of psychometric properties that are testable and potentially generalizable to other Hispanic contexts.

Method

Participants

The sample consisted of 618 adolescents (females: 50.6%, without data: 17, 2.8%) coming from regular basic secondary schools, four of which were state managed (495, 80.1%) and nine prívate. All were located in a coastal district south of Lima's metropolitan area in Peru. The educational institutions were selected for their willingness to participate in the study, ease of access, and the authorization of their management regarding the time when the study could be carried out and compliance with the ethical aspects of the study. Participating students agreed to respond to the questionnaire voluntarily and only those that were present on the day the instrument was administered were included. All school grades were sampled (in Peru, secondary education consists of five grades or years) in order to obtain the highest statistical power with respect to inter-item covariance. The distribution of students in the school grades was: 1st (238, 38.5%), 2nd (107, 17.3%), 3rd (81, 13.1%), 4th (102, 16.5%) and 5th (90, 14.6%) . The mean age was 13.6 (SD = 1.79), and the age range was from 10 to 21. This extreme máximum age occurred in one of the public schools. While there were no differences in age distribution according to sex (Kolmogorov-Smirnov $Z = 0.839$, $p > 0.05$), differences were found according to school management ($t[616] = 4.84$, $p = 1.58E\text{-}6$), where adolescents from private institutions (M = 14.28, SD = 1.52) were moderately older ($d = 0.49$) than those from public schools (M = 13.42, SD = 1.81). Adolescents who did not agree to participate voluntarily or who did not complete at least 80% of the items were excluded.

Instruments

Brief Sensation Seeking Scale, BSSS8 (Hoyle et al., 2002). This scale was created for adolescents and consists of 8 items derived from the SSS-V that parsimoniously represent the four factors identified by Zuckerman for SS: the experience seeking (items 1 and 5), adventure and emotion seeking (2 and 6), disinhibition (3 and 7), and susceptibility to boredom (4 and 8) (see Appendix). It has an ordinal response format of five options, from *disagree completely* to *agree completely*. The respondent is instructed to assess their likes and preferences without reference to a specific moment. The internal consistency for the total score in previous studies with adolescents was around 0.75 (Banerjee, Greene & Yanovitzky, 2011; Donohew et al., 2000; Hoyle et al., 2002; Jensen, Imboden, & Ivic, 2011; Primi et al., 2011; Stephenson et al., 2003). The version

used in the present study was obtained from the work of Stephenson et al. (2007), which describes the pilot stage of sampling items translated into Spanish and the decisions taken regarding a problematic item for samples of young Latino adults.

Brief Sensation Seeking Scale, BSSS4 (Stephenson et al., 2003). This is a super-short version, developed for purposes of use in epidemiological work. It was created by selecting items with higher factor loads in the study of each dimension. It consists of four items (1, 2, 7 and 8), each representative of the four content areas of the BSSS8. The original study yielded a reliability of $\alpha = 0.66$, and a high correlation ($r = .89$) with the BSSS8, of which the items form part. Similarly, construct validity with behavioral risk and protective factors were found which were similar in direction and magnitude to those obtained for the BSSS8. Other studies have also yielded similar levels of reliability ($\alpha = .65$; Vallone, Allen, Clayton, & Xiao, 2007) to those found by Stephenson et al., 2003.

Procedure

The research was approved by the institution to which the researchers belonged, and by the directors of the adolescents' educational establishments. Given that it was the first application of BSSS8 in a Peruvian context, the items were examined in a small group of 6 adolescents to explore how the items were understood. In a single semi-structured interview, the adolescents stated that all items were perceived as perfectly comprehensible regarding content, extent, response options and instructions. Data collection was subsequently carried out in classrooms during regular morning hours. The administration of the instrument was supervised by two researchers for each group assessed. The instructions placed emphasis on giving answers that were honest, anonymous and focused on the content of the items. All the respondents agreed to complete the quesionnaire after consenting to participate.

Prior to the analysis, it was found that for each item the percentage of missing values was below 1% and apparently random. The missing values were therefore replaced by the corresponding modal value. With regard to the quantitative analysis, a confirmatory factor analysis was applied based on structural equation modeling (SEM, Bentler & Dugeon, 1996; Jöreskog, 1969), which verified the source of latent variance of BSSS items. The method used was the one of maximum verisimilitude with Satorra and Bentler scaling (1994; *SB-c*^{2}), since this is an effective procedure with non-normal distributions of the items (Boomsma, 2000; Lei & Wu, 2012; Tong & Bentler, 2013) and allows better approximation of the goodness-of-fit test to the c^2 distribution of Bentler and Dugeon, 1996. The structural analyses were based on the covariance matrix, given that the number of response alternatives of the items (five) is a sufficient characteristic for approximating to continuous variables without producing substantial biases in the estimated parameters even when using the máximum likelihood method (Beauducel & Herzberg, 2006; Dolan, 1994; Rhemtulla, Brosseau-Liard & Savalei, 2012). The covariance matrix S was used for the analysis (Table 1), estimated using the EQS 6.2 program (Bentler & Wu, 2012), which was used for all SEM analyses.

As is the norm in confirmatory factor analysis, structural specifications were imposed a priori (MacCallum & Austin, 2000): zero covariance between the item and factor error terms, each item belonging to a latent variable, and the first indicator of each factor was set at 1.0. Since this initial specification may require some flexibility during analysis in a posteriori framework (Boomsma, 2000), two criteria were established for this: one of a statistical nature through the study of the Lagrange indices (Sörbom, 1989), also known as modification indices; and one of a rational nature, which is the same with a conceptual and theoretical basis, and which is considered relatively more important (Boomsma, 2000; Lei & Wu, 2012) than the statistical criterion. The quantification of the goodness of fit was made using descriptive indices such as the comparative fit index (CFI ^{3} 0.95), standardized root mean square residual (SRMR £ 0.08) and root mean square error of approximation (RMSEA £ 0.05), with their confidence intervals set at 90% (McDonald, 1989). This set of indices for goodness of fit is recommended in assisting decision making on the models evaluated (Jackson, Gillaspay & Purc-Stephenson, 2009). The relative quality of the model was also evaluated with the Akaike information criterion (AIC Akaike, 1974).

In order to verify that the statistical properties were maintained across groups, an analysis of the measurement invariance (Meredith, 1993) of the BSSS was carried out. The classifying group was the sex of the adolescents. This was done using multiple-group confirmatory factor analysis (MGCFA), in which the parameters of the items, such as the number of dimensions (configurational invariance), factor loadings (weak invariance), intercept (strong) invariance and residual (strict) invariance are compared consecutively and cumulatively under the null hypothesis of equality between the groups compared. MGCFA was started with the evaluation of configurational invariance or the baseline model, i.e. the unidimensional structure jointly verified in males and females (configurational invariance). The reference point for this unidimensional model was what had previously been found in the total sample. Further, the factor variance to enable the total estimation of item parameters was set at 1. The comparison between the different forms of invariance was made using Cheung and Rensvold's (2002) criterion: $\Delta_{CFI} \leq 0.01$

Reliability was estimated using the *a* coefficient (Cronbach, 1951) and its confidence intervals using the Fisher method (Romano, Kromrey, Owens & Scott, 2011), and the *w* coefficient (McDonald, 1999). Both coefficients

were identified with two different reliability models respectively, essential and congeneric tau-equivalent (Haertel, 2006), which were modeled by the CFA-SEM method. Precision was also estimated using the direct score metric with standard measurement error (Nunnally & Bernstein, 1995), which should ideally be less than 0.5 (SD) to achieve the maximum tolerable measurement error around the observed scores (Wyrwich, Nienaber, Tierney & Wolinsky, 1999). Assuming that error variability is not necessarily constant in the different scoring levels of the measurment instruments (Feldt & Brennan, 1989), this error variation was examined for the BSSS8 across all scoring using the standard error of measurement (CSEM; Feldt & Brennan, 1989). This was calculated with the Mollenkopf method of polynomial regression (1949) requiring two equivalent halves of the instrument to be obtained. These halves were formed by the odd-even procedure, with the items sorted by their average responses. The CSEM method presents the information in the observed score metric.

Results

Item analysis

There were no floor or ceiling effects on items since all response options were used by the participants, and the spread of responses among them could be considered similar. Except for items 1 and 5, which show moderate asymmetry, the items approach distributional symmetry, an aspect that can be seen in the magnitude of the SSI coefficient (standardized asymmetry coefficient, Malgady, 2007), varying from 0 (symmetry) to 1 (strong asymmetry). There is a greater density of reponses in both items in the options indicating more intense SS. The kurtosis in the items was moderately heterogeneous.

Internal structure and measurement model

Several hypotheses of the internal structure of the BSSS were tested: unidimensional (M_1), related or oblique dimensions (M_2) and the bifactor model (M_3). This last model allows the separation of item variance in one related to a general common factor (FG), and another derived from specific factors, F_i (Reise et al., 2010; Reise, 2012). In accordance with the adjustment indices, the models are highly satisfactory with regard to BSSS8, as Table 2 shows. This is also borne out by the fact that the difference between them is small, which means that these models can be considered adequate. Nevertheless, comparatively the M_3 model shows the best fit, in which the residuals between the items yielded a range from 0.079 to -0.019, magnitudes that can be considered very small. All item parameters in the general factor of the M_3 model were statistically significant (t between 14.08 and 7.53), whereas the parameters of the specific factors were not statistically significant. With the exception of the general factor variance (1.536, $t = 13.32$, $p < 0.05$), the variance of the factors was between 0.00 and 0.271, and none was statistically significant ($t < 1.147$). This bi-factor model clearly states that specific factors (F_i) lose discriminatory power in the presence of a general factor (F_G). Indeed, the factor loadings (Table 3) of the specific factors vary between 0.000 and 0.414, while in the general factor the loads are moderately high (except item 4). Although the M_2 model also shows a good fit and is slightly lower than M_3, it should be noted that the interfactor correlations (Table 3) in this model ranged from 0.808 to

Table 1. *Descriptive statistics, items correlations (Pearson) and covariance.*

	bsss1	bsss2	bsss3	bsss4	bsss5	bsss6	bsss7	bsss8
bsss1	1.459	0.255	0.169	0.210	0.299	0.247	0.291	0.217
bsss2	0.390	1.575	0.341	0.254	0.275	0.278	0.322	0.329
bsss3	0.272	0.559	1.726	0.264	0.265	0.221	0.363	0.267
bsss4	0.319	0.406	0.436	1.577	0.187	0.133	0.202	0.139
bsss5	0.489	0.464	0.461	0.335	1.808	0.338	0.338	0.342
bsss6	0.403	0.439	0.374	0.207	0.583	1.699	0.338	0.338
bsss7	0.469	0.521	0.628	0.331	0.592	0.497	1.736	0.439
bsss8	0.324	0.494	0.427	0.207	0.558	0.339	0.697	1.493
M	3.872	2.670	2.848	3.076	3.215	3.697	2.730	2.709
SD	1.207	1.253	1.311	1.251	1.340	1.309	1.319	1.225
As.	-0.963	0.370	0.201	-0.139	-0.126	-0.734	0.277	0.289
Ku.	0.002	-0.806	-0.989	-0.968	-1.156	-0.643	-0.998	-0.759
SSI	-0.331	0.118	0.058	-0.044	-0.035	-0.214	0.080	0.096

Note. All correlations are p < 0.01. Diagonal and lower triangle for covariance matrix; upper triangle for Pearson correlations. SSI: standardized asymmetry index. As.: asymmetry coefficient. Ku.:kurtosis coefficient.

1,000, which implies a strong loss of their discriminative validity. In consequence, this model was not accepted. The M_1 model also presents a satisfactory fit and given its parsimony and the high similarity of the factor loadings with M_3, it is selected for the following analyses.

As for BSSS4 modeling, its internal structure exhibited an excellent fit. With the exception of item 1, the rest shows good discrimination level (factor loading > 0.50). It is also observed that, in general, the BSSS4 item loadings correspond to the BSSS8 items with high loadings, which suggests that the choice of Hoyle et al. (2002) to form BSSS4 with the items with the highest loadings in BSSS8 in their study is confirmed in the present sample. All BSSS4 items were statistically significant ($t > 2.00$).

Once the model (unidimensional) was identified, the measurement invariance between males and females was examined. The configurational invariance showed that the goodness-of-fit test was statistically significant, $SB\text{-}c^2$ (40) = 70.78 ($p < 0.01$). However, the fit indices can be considered satisfactory: CFI = 0.954, RMSEA = 0.050 (90% CI = 0.030, 0.069). Having shown that the dimensionality between the groups is consistent, the next step was to test the equality of the factor loadings, in which $SB\text{-}c^2$ (48) = 81.202 ($p < 0.01$) was obtained. The goodness-of-fit indicators were CFI = 0.951, RMSEA = 0.047 (90% CI = 0.030, 0.069), and were also considered satisfactory. The difference between both models (D_{CFI} = 0.003) was below the criterion (0.01) and it can therefore be claimed that both groups are invariant with respect to their item metrics. Since this type of invariance was maintained, the equality of the intercepts was examined, obtaining $SB\text{-}c^2$ (56) = 94.583 ($p < 0.01$); CFI = 0.949, RMSEA = 0.047 (90% CI = 0.030, 0.063). The difference between this model and the previous was D_{CFI} = 0.002, and did not degrade the fit by introducing this additional constraint. Finally, the restriction of equality of residuals between the items was applied to test strict invariance. Goodness-of-fit based on the $SB\text{-}c^2$ test (64) was 108.625 ($p < 0.01$), and the fit indices were CFI = 0.944, RMSEA = 0.048 (90% CI = 0.032, 0.062). The difference between the two models was D_{CFI} = 0.005, so that residual invariance between the items is maintained.

Regarding the assessment of the reliability model for the BSSS8 (Table 2), it was found that the tau-equivalent model fits slightly better than the parallel model given that the change in goodness-of-fit indices can be considered small. But compared to the congeneric model (model M_1), the difference in fit is notable. This indicates that the items may be better represented by a congeneric model, and the more accurate reliability coefficient should be obtained by means of *w*. Since the BSSS4 items are contained in the BSSS8, it was assumed that the invariance and reliability modeling results can be transferred to the BSSS4.

Reliability

Table 3 shows the *a* and *w* reliability coefficients. Although it can be seen that the congeneric model shows a better statistical fit, the practical significance of this adjustment does not seem to be shown in the calculated reliability coefficients. Therefore *a* and *w* can be considered very similar. The effect of the reduction of the items on the *a* coefficient was evaluated in two ways. First, the inferential hypothesis that the *a* coefficient of the short form is equal to that of the long form was tested using an ad hoc computer program (ALPHATEST; Lautenschlager & Meade, 1987),

Table 2. *Results of the internal structure fit test and measurement model.*

Internal stucture	SB-c2 (gl)	RMSEA (CI 90%)	CFI	TLI	SRMR	AIC
BSSS8						
M_1	49.170 ** (20)	0.049 (0.032, 0.066)	0.955	0.937	0.038	9.17
M_2	35.270** (14)	0.05 (0.030, 0.071)	0.967	0.934	0.058	7.270
M_3	26.039** (11)	0.047 (0.024, 0.071)	0.977	0.941	0.036	4.04
BSSS4						
M_1	4.564 (2)	0.046 (0.000, 0.102)	0.99	0.97	0.021	0.56
Reliability model (BSSS8)						
Parallel	96.459** (33)	0.056 (0.043, 0.069)	0.915	0.910	0.068	30.45
Tau-Equivalent	77.475** (26)	0.057 (0.042, 0.071)	0.921	0.921	0.036	25.47

Nota. $^{**}p < 0.01$. Models: M_1, unidimensional; M_2, oblique factors; M_3, bi-factor. BSSS8: 8 item scale. BSSS4: 4 item scale.

Table 3. *Individual parameters of the bifactor and unidimensional models.*

	BSSS8								BSSS4	
	Bifactor						Unidimensional			
	F_1	F_2	F_3	F_4	F_G	h^2	F	h^2	F	h^2
bsss1	0.211				0.447	0.244	0.459	0.210	0.417	0.174
bsss2		0.414			0.557	0.482	0.554	0.307	0.509	0.259
bsss3			0.295		0.510	0.347	0.520	0.271	-	-
bsss 4				0.000	0.363	0.132	0.363	0.132	-	-
bsss 5	0.250				0.555	0.371	0.562	0.316	-	-
bsss 6		0.022			0.465	0.217	0.467	0.218	-	-
bsss 7			0.128		0.637	0.422	0.644	0.414	0.679	0.462
bsss 8				0.000	0.569	0.324	0.564	0.318	0.626	0.392
Interfactorial correlation										
F1	1				-	-	-	-	-	-
F2	0.958	1			-	-	-	-	-	-
F3	0.808	0.913	1		-	-	-	-	-	-
F4	1.000	1.000	1.000	1	-	-	-	-	-	-
α	-	-	-	-	-	-	0.745	-	0.643	-
w	-	-	-	-	-	-	0.747	-	0.651	-
Descriptive statistics										
M	-	-	-	-	-	-	24.77	-	11.98	-
SD	-	-	-	-	-	-	6.17	-	3.47	-
As.	-	-	-	-	-	-	-0.05	-	0.09	-
Ku.	-	-	-	-	-	-	-0.09	-	-0.27	-

Note. h^2: communality. *a*: alpha coefficient. *w*: omega coefficient. BSSS8: 8 item scale. BSSS4: 4 item scale.

which applies the asymptotic procedure based on the *F* distribution (Feldt, 1980; Feldt, Woodruff & Salih, 1987). Using the uncorrected and spurious-corrected inter-form correlations (see following section), a statistical difference between the two coefficients was found: $c^2[1] = 55.79$ ($p < 0.0001$) and $c^2[1] = 21.97$ ($p < 0001$), respectively. Second, the 95% confidence interval (Feldt et al., 1987; Romano, Kromrey, Owens & Scott, 2011) was compared heuristically for the a of BSSS8 (0.71: 0.77) and BSSS4 (0.59: 0.68). Both analyses show that the reduction of internal consistency in BSSS4 is substantial and statistically significant. The reliability of BSSS8 is the same or only very slightly different from that reported in the American validation studies (Hoyle et al., 2002; Stephenson et al., 2003). When examining instrument accuracy in the measurement of the observed scores, the standard error of measurement in BSSS8 (3.11) and BSSS4 (2.07) compared to the maximum tolerable dispersion (3.08 and 1.73, respectively) was found to be slightly higher.

For the CSEM, the polynomial regression equation was calculated by multiplying each score by the coefficient b = 0.133 ($R^2 = 0.475$, $F[2, 615] = 89.73$, $p < 0.01$), given that the neither the constant nor the quadratic and cubic component were statistically significant. Table 4 shows the CSEM and the standardized CSEM (CSEM-S). It can be seen that the scores show less error variation in the lower and near average levels, and that this decline becomes more pronounced, with reliability falling to below 0.70 with scores above 26.

Equivalence BSSS8 and BSSS4

The equivalence and consistency between BSSS8 and its abbreviated version, BSSS4, was examined. The consistency between these measures, as shown by the correlations between them, was corrected by spurious or correlated errors (Bashaw & Anderson 1967; Levy, 1967). The spurious corrected correlation should be high (≥ 0.70, Petrides et al., 2003; Putnam & Rothbart, 2006) in order to argue for the linear dependence between forms (Smith et al., 2000). The observed correlation between BSSS forms was 0.89 (95% CI = 0.87: 0.90) and the corrected correlation was 0.68 (95% CI = 0.63: 0.72). With respect to the reference value (0.70), the corrected correlation was not statistically significant ($z = -0.94$, $p > 0.05$).

To examine the concordance between BSSS8 and BSSS4, the weighted kappa coefficient (K_W; Fleiss, Levin & Paik, 2003) was used with linear weights assigned to scores categorized in deciles. We obtained K_W = 0.679 (95% CI: 0.64, 0.70), a value that can be considered a good level of agreement and equal to the corrected correlation obtained in the previous paragraph. In order to identify the characteristics of the agreement between the versions, they can be better observed in the Bland-Altman plot (1986), contrasting the difference between BSSS8 and BSSS4 against the full version score (Krouwer, 2008). Figure 1 suggests that, in general, discrepancies between BSSS4 and BSSS8 occur within acceptable limits (± 1.96 SD of BSSS8-BSSS4 differences); The linearly increasing size of the differences is due to the joint increase of the scores of both versions and is therefore expected. However, it was found that in the lower decile scores there are more discrepancies, although they are infrequent compared to the total sample.

Table 4. *Conditional standard error of measurement for BSSS8 y BSSS4.*

	CSEM	
Score	BSSS8	BSSS4
4	-	1.38
5	-	1.54
6	-	1.69
7	-	1.83
8	1.06	1.95
9	1.20	2.07
10	1.33	2.18
11	1.46	2.29
12	1.60	2.39
13	1.73	2.49
14	1.86	2.58
15	2.00	2.67
16	2.13	2.76
17	2.26	2.84
18	2.39	2.64
19	2.53	2.69
20	2.66	2.74
21	2.79	-
22	2.93	-
23	3.06	-
24	1.79	-
25	1.82	-
26	1.86	-
27	1.89	-
28	1.93	-
29	1.96	-
30	2.00	-
31	2.03	-
32	2.06	-
33	2.09	-
34	2.13	-
35	2.16	-
36	2.19	-
37	2.22	-
38	2.25	-
39	2.28	-
40	2.31	-

Note. CSEM: Conditional standard error of measurement.

Discussion

The results of the structural validation of the BSSS (8 and 4 items) in Peruvian adolescents showed that a single dimension better represents the variability of the items. This strong support for the unidimensional structure may be determined by two factors: First, the correlations between the constructs (experience seeking, susceptibility to boredom, emotion and adventure seeking, and disinhibition) were very high, which generally suggests that the model does not meet the criterion of discriminative validity (Nunnally & Bernstein, 1995). Second, the introduction of the bifactor model clearly showed that the validity of the items is strongly associated with a single general factor, with higher factor loadings than on the specific factors. Therefore, the larger common variance in this general factor indicates unmistakeably that there is no statistical justification for interpreting dimensional scores separately (Reise et al., 2010; Reise, 2012). In contrast to other studies in which factor methods were applied, this is the first to advance in the identification of BSSS structure using bifactor

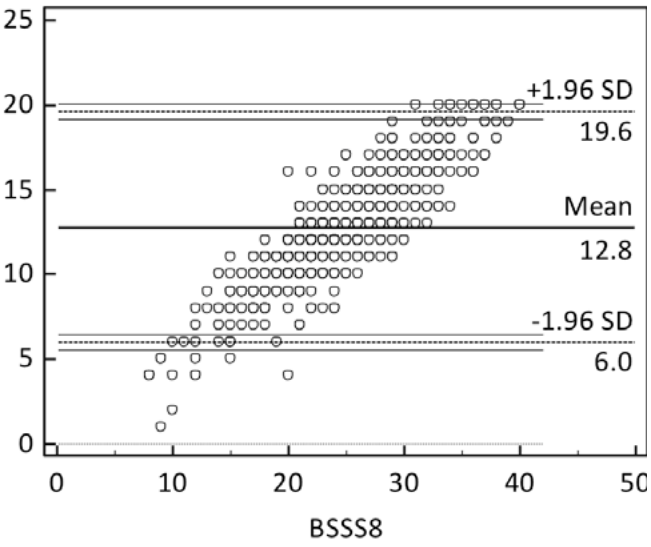

Figure 1. Bland-Altman plot of direct scores for BSSS8 and BSSS4..

modeling, which confirmed the unidimensional nature of the instrument.

Regarding the internal consistency estimates, those obtained in previous studies for the BSSS with adolescents and adults (cited in the present study), do not in general exceed 0.80, for either subscale scores or for total score. This pattern is also replicated in the results reported here, and may be a consequence of the origin of the construct since it is considered to be a biological trait influenced at the same time by interaction with the social environment; it is a complex construct composed of experiences and feelings (Chico, 2000; Hoyle et al., 2002; Pérez & Torrubia, 1986; Primi et al., 2011; Stephenson et al., 2003; Zuckerman & Neeb, 1980), which groups and represents heterogeneous behaviors with a common denominator: risk. This factor can be conceptually and empirically linked to variables and physical, legal, social, moral, financial, etc., issues (Horvath & Zuckerman, 1996; Ledesma, Poó & Peltzer, 2007). With this underlying feature, which originates in the definition of the SS construct and the discussion about its internal structure, it is reasonable that no higher levels of reliability are obtained. Yet with regard to comparing the internal consistency of our study with that of previous studies on BSSS8 and BSSS4 in adolescents (Banerjee & Greene, 2009; Hoyle et al., 2002; Stephenson, Morgan, Lorch, Palmgreen, Donohew, & Hoyle 2002; Stephenson et al., 2003; Vallone et al., 2007), very similar results were obtained. Thus there is evidence that the true variability of BSSS8 and BSSS4 seems to be mainly constant from an intercultural angle. This has direct implications for the accuracy of SS assessment using these brief measures, which, although not high enough for clinical use, may be the best option for developing epidemiological studies and describing groups in a scientific research context. Furthermore, taking into account that the standard error of measurement of the scores is close to the maximum acceptable, the user will have to decide if it is appropriate to apply an adjustment to the scores or statistics obtained with the instrument in order to mitigate the error of measurement (Nunnally & Bernstein, 1995). When interpreting the scores, it should also be taken into account that the scores below the average are more reliable, whereas higher scores are more likely to be affected by measurement error. Therefore, the description of a group or subject based on the BSSS8 scores, and even more so with the BSSS4, may be expressed with less bias when the adolescent subject's sensation seeking is of low intensity. At this point it is not known whether social desirability or other irrelevant response patterns have played a role, but it is an issue pending resolution in subsequent research.

In brief measures such as BSSS8 and BSSS4, it may be preferable to measure a general construct compared to multifactorial measurement, because the number of items in each specific factor is small and directly affects the magnitude of the reliability coefficients (Heartel, 2006). Moreover, it should be pointed out that in such brief measures of a construct as broad as SS, the internal consistency found can be considered satisfactory for certain contexts of use, such as those already mentioned: for studies and descriptions of groups, especially those of an epidemiological nature. The most demanding levels of reliability (eg scores of 0.90 or higher) for measurement instruments are reserved for contexts where decisions have to be made on the individual subject (e.g. diagnostics); measurements errors can be unacceptable in such contexts (Nunnally & Bernstein, 1995) and lead to consequences counter to the interests of individuals or groups and institutions (for example, a poor diagnosis of a depressive disorder, errors in the interpretation of a company's working environment). Given this view, BSSS8 and BSSS4 can safely be used in research or when work is done on groups of subjects. For more precise assessments, it will be necessary to use a combination of instruments or instruments with more items, which will provide a better appreciation of the internal consistency. For example, the SSS-V scale adapted for adolescents (Perez, et al., 1986, Pérez, et al., 1987) could be used as an aid in the diagnosis of this personality trait.

Furthermore, another relevant aspect of factor loadings indicates that the definition of the construct in BSSS8 and BSSS4 is similarly weighted by each item, and that the simple sum of the items can be accepted as an indicator of the construct. Conversely, the heterogeneity of the factor loadings would indicate that each item influences the definition of the construct differently, and therefore a better representation of the score may be obtained by weighting each item differentially. Fortunately, the similarity of discriminative power is satsfied in each item, and although they are not very high (e.g. 0.80 or more), they contribute with sufficient relevant variance to the construct for group descriptive purposes. This description can use the same measurement parameters found among males and females, as the instrument has fulfilled the increasingly demanding forms of invariance. Thus, an exhaustive comparison of the differences in the level of latent or observed scores appears to be assured.

Finally, the equivalence analyzed between BSSS8 and BSSS4 has been found to be satisfactory, and can be considered more precise than the convergent correlation between both, since the authors (Hoyle et al., 2002; Stephenson et al., 2003; Stephenson et al., 2007) did not adjust the correlation coefficient to effectively control the variance of correlated errors. The BSSS4 scale can be used for epidemiological studies or in research alongside other instruments, especially when the number of items, time limits and the availability of the subjects interact negatively to require abbreviated but valid measures.

The present study presents some limitations, such as the lack of evaluation of the invariance of measurement or the

differential operation of items, the characterization of the items through Item Response Theory modeling, and external links with other convergent and divergent constructs. These aspects are pending further research.

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Conflicts of Interest

The authors declare that the present manuscript, its conception and development are free from conflicts of interest.

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Design and validation of a Cannabis Use Intention Questionnaire (CUIQ) for adolescents

Diseño y validación de una escala de intención de consumo de cannabis (CUIQ) para adolescentes

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Abstract

In Spain, one in four 14 to 18-year-old adolescents has used cannabis during the last twelve months. Demand for treatment has increased in European countries. These facts have prompted the development of preventive interventions that require screening tools in order to identify the vulnerable population and to properly asses the efficacy of such interventions. The Theory of Planned Behaviour (TPB), widely used to forecast behavioural intention, has also demonstrated a good predictive capacity in addictions. The aim of this study is to design and validate a Cannabis Use Intention Questionnaire (CUIQ) based on TPB. 1,011 teenagers answered a set of tests to assess attitude towards use, subjective norms, self-efficacy towards non-use, and intention to use cannabis. CUIQ had good psychometric properties. Structural Equation Modelling results confirm the predictive model on intention to use cannabis in the Spanish adolescent sample, classified as users and non-users, explaining 40% of variance of intention to consume. CUIQ is aimed at providing a better understanding of the psychological processes that lead to cannabis use and allowing the evaluation of programmes. This can be particularly useful for improving the design and implementation of selective prevention programmes.

Keywords: Cannabis use; Intention; Questionnaire validation; Attitude; self-efficacy; Theory of planned behaviour.

Resumen

En España, uno de cada cuatro jóvenes de 14 a 18 años declara haber consumido cannabis en el último año. La demanda de tratamiento ha aumentado en todos los países europeos. Ello ha motivado el desarrollo de intervenciones preventivas que requieren instrumentos para el cribado de la población en riesgo y la evaluación de la prevención. La Teoría de la Acción Planificada (TAP), ampliamente utilizada para predecir las intenciones conductuales, ha mostrado una buena capacidad predictiva en el campo de las adicciones. El objetivo del presente trabajo es diseñar y validar un Cuestionario de Intención de Consumo de Cannabis (CUIQ, *Cannabis Use Intention Questionnaire*) basado en la TAP. 1011 adolescentes completaron una batería de cuestionarios que se compone de cuatro subescalas: actitud hacia el consumo, norma subjetiva, autoeficacia hacia la abstinencia e intención de consumo. El Cuestionario CUIQ obtuvo buenas características psicométricas. Las ecuaciones estructurales confirmaron el modelo predictivo sobre la intención de consumo en adolescentes españoles (consumidores y no consumidores), llegando a explicar el 40% de la varianza. El CUIQ tiene como objetivo una mejor comprensión del proceso psicológico que conduce al consumo de cannabis y permitir la evaluación de programas. Esto puede ser especialmente útil para mejorar el diseño e implementación de programas de prevención selectiva.

Palabras clave: Cannabis; Intención; Validación de cuestionario; Actitudes; Autoeficacia; Teoría acción planificada.

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Cannabis is the illicit drug with the highest prevalence of use and is currently on the rise (UNODC, 2016). In fact 11.2% of young Europeans (aged 15-34) report having consumed it in the previous 12 months, and prevalence is even higher (13.9%) in the 15-24 age range. Among adolescents, 3% of European students aged 15 to 16 years have used cannabis more than 10 times in the previous month (Hibell et al., 2012). The National Survey on the Use of Drugs in Secondary Education in Spain (ESTUDES) reveals that one in four young people aged 14 to 18 used it in the previous year and 16.1% of them presented hazardous consumption, defined as scoring four points or higher on the CAST scale (*Cannabis Abuse Screening Test*) (OEDT, 2014). The data show that cannabis use is widespread among the younger population, despite the negative consequences its use can have, such as problems of emotional control (Crean, Crane, & Mason, 2011), psychotic experiences (Fonseca-Pedrero, Ortuño-Sierra, Paino & Muñiz, 2016), or risk of psychotic disorders (Chadwick, Miller, & Hurd, 2013; Hall & Degenhardt, 2009; Rubino, Zamberletti, & Parolaro, 2012). This trend is reflected in the increased demand for treatment across European countries (EMCDDA, 2016) and warns of the need to step up efforts in specific preventive interventions against cannabis use. The European CAPPYC (Cannabis Abuse Prevention Program for Young Consumers) project was developed to this end in the period 2014-2016 in four European countries (Spain, Italy, Portugal and Romania), and has also made the present study possible.

In recent years, several tools have been developed to assess the risk factors associated with initiating and maintaining drug use in general. However, the use of cannabis in particular has some characteristics that differentiate it from other substances; personality traits have been found, for example, which have a specific influence on cannabis use (Garcia-Sánchez, Mataly, Martín-Fernández, et al., 2016; González, Espada, Guillon-Riquelme, Secades & Orgilés, 2016). There are also specific beliefs related to cannabis, such as the beliefs that it is not as addictive or dangerous as other drugs (Menghrajani, Klaue, Dubois-Arber & Michaud, 2005), that it provides beneficial relaxing effects (Boys, Marsden & Strang, 2001), that consumption can be controlled, that it is "good" for some diseases and for having fun and forgetting one's problems (Morales-Manrique, Bueno-Cañigral, Aleixandre-Benavent & Valderrama-Zurián, 2011); and there is even the belief that it heightens creativity (Plancherel et al., 2005). Such widely held views regarding cannabis make it advisable to use specific questionnaires.

Some specific assessment questionnaires on the use and abuse of cannabis, associated factors and motivations (see Table 1) can currently be found. However, these instruments, despite their use in detecting problems of cannabis consumption and risk groups, do not allow the assessment of programs since they do not measure factors associated with consumption that may be modifiable through preventive interventions.

Among the different models that attempt to explain cannabis use, this study is based on the Theory of Planned Behaviour (TPB), proposed by Ajzen (1991) as a model rooted in social psychology (Armitage & Conner, 2001) which takes into account the interaction between personal and social factors to explain behaviour. From this psychosocial perspective, TPB proposes that intention is shaped by attitude towards the behaviour, subjective norms (SN) and perceived behavioural control (PBC).

TPB has been extensively used in the field of prevention (Rodríguez Marín, 1998) and has proven predictive capacity in relation to addictions (McMillan & Conner, 2003; Rodríguez-Kuri, Diaz-Negrete, Gracia-Gutiérrez de Velasco, Guerrero-Huesca & Gómez-Maqueo, 2007; Saiz Galdós, 2009; Topa & Moriano, 2010). Specifically, with respect to cannabis, several studies have found that intention significantly predicted cannabis use and, in turn, intention was predicted by attitudes and PBC, while SN did not appear to have a decisive influence (Armitage, Conner, Loach & Willetts, 1999; McMillan & Conner, 2002, 2003).

Table 1. *Scales of cannabis use and abuse.*

Acronym	Name	Year	Author	Measurement areas
CAST	*Cannabis Abuse Screening Test*	2007	Legleye, Karila, Beck & Reynaud	Problematic use of cannabis. Assesses the previous 12 months
CUPIT	*Cannabis Use Problems Identification Test*	2010	Bashford, Flett & Copeland	Problems associated with cannabis use
CUDIT	*Cannabis Use Disorders Identification Test*	2003	Adamson & Sellman	Symptoms of abuse, current and over previous 6 months
CPQ-A	*Adolescent Cannabis Problems Questionnaire*	2006	Martin, Copeland, Gilmour, Gates & Swift	Problems associated with use: psychosocial consequences, physical consequences, severe effects
MEEQ	*Marijuana Effect Expectancy Questionnaire*	1991	Schafer & Brown	Expectations about consequences of cannabis use (adolescents)
CMMQ	*Comprehensive Marijuana Motives Questionnaire*	2009	Lee, Neighbors, Hendershot & Grossbard	Motives for cannabis use

In Spain, Olivar and Carrero (2007) developed a specific cannabis questionnaire based on TPB but, as the authors themselves point out, this measures its factors indirectly and subtly, not following the considerations of Ajzen (2002). In addition, the instrument was used with a small sample of 214 students aged 15 to 21 from a single school in Madrid.

Given the applicability of TPB to cannabis use, the present study aims to meet the need for an assessment tool composed of different factors which: a) explains both the initiation and maintenance of cannabis use from a broad and robust theoretical approach, and b) can be used to assess the effectiveness of preventive interventions. The goal of this study is thus to construct and validate a questionnaire, the CUIQ (Cannabis Use Intention Questionnaire), aimed at evaluating the risk of cannabis use in adolescents within the theoretical framework of TPB (Ajzen, 1991). Since the CUIQ is designed for use primarily in the classroom, efforts have been made to create an instrument with a reduced number of items which is easy to administer and complete, but at the same time reliable and valid in terms of the scores obtained, an essential requirement for a good assessment and screening tool. Therefore, the specific objectives of the study are as follows: 1) to analyse the structure, reliability, and validity of the scores on the CUIQ questionnaire scales, 2) to analyse the differential functioning of the test scales scores according to sex, 3) to determine the sensitivity and specificity in detecting cannabis use and problems associated with it. The working hypotheses are therefore as follows:

Hypothesis 1. The scales that compose the CUIQ will present adequate reliability and validity.

Hypothesis 2. The TPB predictive model will be equivalent across groups of boys and girls.

Hypothesis 3. The scores on the CUIQ scales will enable the detection of cannabis use and the risk of problems due to cannabis use.

Method

Participants

First, a preliminary pilot study was carried out in the province of Alicante in which 73 secondary school students took part, with a mean age of 15.18 years (SD = 0.961, range 13-17 years of age) of which 43.8% were boys. The questionnaire was then applied to a group of 1011 students with a mean age of 16.09 (SD = 0.95, range 15-18), 52.8% boys. Participants were recruited in 16 public schools and 5 private schools in the provinces of Albacete, Alicante, Badajoz, Cuenca, Madrid and Valencia. The percentage of cannabis use in the previous month was 16.9%. By sex, 12.7% of girls and 21.1% of boys admitted using cannabis at least once in the previous month, a difference which proved to be significant (chi-square = 12.34, p-value < .01).

Instruments

The Cannabis Use Intention Questionnaire (CUIQ) we have developed consists of the following scales in accordance with the recommendations proposed by Ajzen (2002): attitude toward cannabis use, subjective norm, self-efficacy towards non-use and intention of use. Furthermore, two criterion variables were included: a) cannabis use in the previous 30 days, an item adapted from the European School Survey Project on Alcohol and Other Drugs, ESPAD (Hibell et al., 2012), and b) the problematic use scale *Cannabis Abuse Screening Test* - CAST (Fernández-Artamendi, Fernández-Hermida, Muñiz-Fernández, Secades-Villa & García-Fernández, 2012; Klempova et al., 2009; Legleye et al., 2007).

Attitude to cannabis use. Attitudes are measured by four items about beliefs regarding the consequences of consuming and their assessment. This scale has two dimensions: a) the items in the first block measure to what extent marijuana or hashish is considered to influence a set of beliefs (e.g, "helps you relax"), with a Likert-type response scale of 5 points from 1 (*unlikely*) to 5 (*very likely*), and b) since attitudes depend not only on beliefs but also on the person's assessment of each of those beliefs, a second block of items measures how important the aspects listed in the first block are to each person, with a 5-point response scale from 1 (*not important*) to 5 (*very important*). Thus, two people can believe with the same strength that cannabis helps to relax, but one of them may value such relaxation very positively, while for the other it may be undesirable. These two dimensions are combined in a multiplicative fashion to obtain a unique score as follows (*a* denotes the items of the beliefs dimension and *b* the items of the valuation dimension):

$$Attitude = \frac{\sum_1^n Attitude_N}{n.items} = \frac{(a_1 \times b_1)/_5 + \ldots + (a_n \times b_n)/_5}{n.items}$$

Subjective norm. This is the most social component of the model and reflects the influence of the subject's immediate environment on his/her behaviour, that is to say, to what extent the subject's main reference groups would agree or not were he/she to use cannabis. It consists of two dimensions: a) normative beliefs regarding significant others or referents (close friends, person I like and companions) are operationalized with three items that denote the degree to which the closest people would agree if cannabis were used on a 5-point Likert response scale, from 1 (*strongly disagree*) to 5 (*strongly agree*); and b) the motivation to go along with the significant others or referents, with three items measuring how the opinion of these people in relation to the use of marijuana or hashish on a response scale from 1 (*not important*) to 5 (*very important*). These two dimensions are also combined in a multiplicative way to obtain a unique

score as follows (a denotes the beliefs dimension items, and b the items of the dimension measuring the motivation to accommodate the referents):

$$Subjetive\ norm\ = \frac{\sum_1^n NS_N}{n.items} = \frac{(a_1 \times b_1)/_5 + \ \ldots + \ (a_n \times b_n)/_5}{n.items}$$

Self-efficacy. Perceived behavioural control has been operationalized as a measure of self-efficacy, since both concepts refer to the perceived ability to perform a particular behaviour (Bandura, 1982). This scale gathers a series of beliefs about the extent to which the individual feels capable of not using cannabis in different situations (for example, being able to "be with friends without smoking joints"). These beliefs can form part of one's own experience of past behaviour or vicarious information about behaviour from family and friends, as well as depending on other factors that increase or reduce perceived difficulty in engaging in behaviour. The five items are measured with a 5-point Likert response scale, from 1 (*not capable*) to 5 (*fully capable*).

Intention to use. This consists of three items on "the intention to consume marijuana or hashish," "planning to consume marijuana or hashish soon," and "wanting to consume marijuana or hashish if the opportunity presents itself." The response scale is a 5-point Likert-type measure, from 1 (*definitely not*) to 5 (*definitely yes*).

Procedure

In order to meet the objective proposed in this research, these phases were followed: 1) review of the main scales and questionnaires available focusing on the consumption of cannabis and associated problems (see Table 1); 2) questionnaire item development following guidelines for questionnaire creation within the TPB framework (Ajzen, 2002), 3) review and cleaning up of the item bank by a panel of 14 independent expert judges who evaluated comprehension and content with regard to the relevance and adequacy of the items for evaluating TPB dimensions, with the aim of guaranteeing evidence of content validity, 4) implementation of a pilot study using a semi-structured questionnaire that included open-ended questions about other benefits/negative effects of cannabis use (attitudinal beliefs) and identification of other relevant people (subjective norm), after which some items were eliminated whose score correlated poorly with the other items of its scale, while no new aspects to be included were identified in the responses to the open questions, and 5) application of the final questionnaire to a group of 1011 students.

In all cases, the questionnaires were administered in the classroom by experts, who explained the instructions and purpose of the study. The students responded to the paper questionnaire anonymously in the classrooms of their secondary schools in the provinces of Albacete, Alicante, Cuenca, Madrid, Badajoz and Valencia. Parental consent was obtained as well as that of school management.

Data analysis

An initial exploratory analysis of the data was carried out which included checking the distribution of variables and for the existence of extreme data through stem-and-leaf plots, and their suitability for parametric analysis was assessed. Next, item analysis was performed by calculating the mean, standard deviation, asymmetry, and kurtosis. Due to the non-normality of the distribution of the variables it was decided to use robust methods (Brown, 2015; Satorra & Bentler, 1994). The missing values were treated using the listwise deletion method (Bentler, 2004), where the records in which missing data appeared were excluded. Due to the ordinal nature of the variables, alpha ordinal and omega reliability indices (Zumbo, Gadermann and Zeisser, 2007; Elosua and Zumbo, 2008) were calculated. To study sources of validity in relation to the internal structure of the test, confirmatory factor analysis was performed with structural equations based on the four-dimensional structure of TPB and in comparison with the one-dimensional model in order to analyse potential common method bias (Podsakoff, MacKenzie, Jeong-Yeon and Podsakoff, 2003). For the estimation of the models, the polychoric correlation matrices were used in accordance with the ordinal nature of the variables (Bentler, 2004). Model fit was evaluated using the chi-square index, Bentler-Bonett Non-Normed Fit Index (NNFI), Comparative Fit Index (CFI), and the root mean-square error of approximation (RMSEA) with 90% confidence interval. The chi-square index analysis has been widely used, although it has been considered too strict, especially with studies of large sample sizes, in which in most cases it is significant. Therefore, alternative fit indices have been proposed, such as the NNFI, which is based on the index developed by Tucker and Lewis (1973) and has the advantage of adequately reflecting the fit in samples of different size. Having said that, however, it also has the disadvantage of not being a good estimator for noncentral parameters (Bentler, 2004). The robust CFI index was thus proposed, which is a better estimator of noncentral parameters (Bentler, 2004). In addition, absolute adjustment indices based on the non-centrality of parameters, such as RMSEA with 90% confidence interval, were used. The main advantage of the latter is that it is one of the indices least affected by sample size (Browne and Cudeck, 1992; Jöreskog and Sörbom, 1993). Due to the differences in consumption between the participants, a factorial invariance analysis by sex was also carried out following the procedure presented by Dimitrov (2010) with the purpose of analysing the internal consistency of the test in the groups of boys and girls. To study validity evidence in relation to other criterion variables, Spearman correlations be-

Table 2. *Item analysis and score reliability.*

	Mean	SD	Asymmetry	Kurtosis	λ	*p*	Communality	α	ω	AVE
Attitude_1	2.56	1.39	0.30	-0.92	0.60	0.98	0.36	0.68	0.68	0.34
Attitude _2	2.36	1.33	0.44	-0.79	0.57	0.98	0.33			
Attitude _3	1.82	1.30	1.02	0.18	0.58	0.98	0.33			
Attitude _4	1.14	1.19	1.94	3.14	0.60	0.98	0.36			
SN_1	1.62	0.94	1.44	2.08	0.66	0.97	0.44	0.58	0.58	0.32
SN_2	1.33	0.76	1.51	4.08	0.51	0.97	0.26			
SN_3	1.42	0.91	1.90	3.76	0.52	0.97	0.27			
SETNU_1	4.53	1.05	-2.35	4.45	0.66	0.98	0.44	0.79	0.79	0.43
SETNU _2	4.56	1.01	-2.46	5.08	0.68	0.99	0.46			
SETNU _3	4.24	1.13	-1.44	1.13	0.61	0.98	0.37			
SETNU _4	4.62	0.94	-2.73	6.78	0.67	0.99	0.44			
SETNU _5	4.46	1.10	-2.05	3.12	0.65	0.98	0.42			
Intention_1	1.70	1.20	1.64	1.50	0.68	0.99	0.46	0.77	0.77	0.47
Intention_2	1.59	1.17	1.98	2.68	0.70	0.99	0.49			
Intention_3	1.69	1.19	1.68	1.66	0.68	0.99	0.46			

Note. SD Standard Deviation; λ completely standardised weigthing; p associated p value; α ordinal alpha coefficient; ω omega coefficient; AVE average variance extracted.

tween the proposed TPB model variables and cannabis use in the previous month and the CAST questionnaire scores were calculated. The TPB predictive model was also put to the test in relation to cannabis use through the application of path analysis. Finally, the ROC curve analysis with the criteria of having used cannabis in the previous 30 days and a cut score 3 of CAST (Legleye et al., 2015) allowed cut-off points to be established for the risk of cannabis use and the risk of problems arising from its use, respectively. Statistical packages used were SPSS © Version 22 and EQS © Version 6.3.

Results

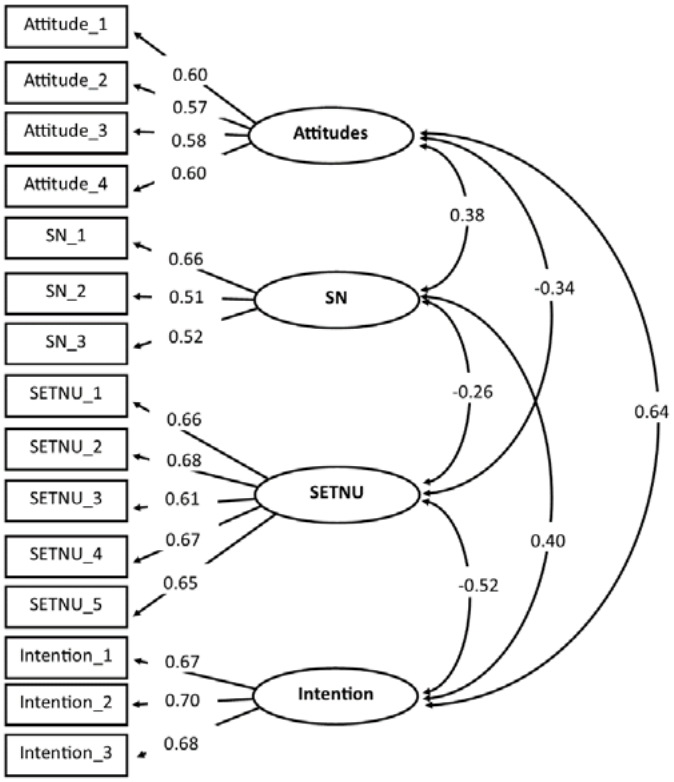
Item analysis and reliability

Positive asymmetries are shown in the item scores on the attitudes, subjective norm and intention scales, whereas the scale for self-efficacy towards non-use shows negative asymmetries, which takes into account the reverse direction of the self-efficacy towards non-use scale in comparison to the other constructs presented in the proposed model. Kurtosis varies widely from -0.92 to 6.78. The items presented moderate standardized factor loads for the attitudes and subjective norm scales, varying from 0.51 to 0.66, while standardized factor loads were higher on the self-efficacy towards non-use and intention scales (between 0.61 and 0.70). On the scales of attitudes, self-efficacy towards non-use and intention, reliability coefficient scores were above 0.70, the level recommended for reliability analyses (Nunnally & Bernstein, 1995), while for the subjective norm scale a value of 0.58 was obtained.

Analysis of the internal structure of the test

The four-dimensional model based on TPB presented an adequate fit (Figure 1). The goodness of fit indices exceed those recommended (Mulaik, et al., 1989; MacCallum, Browne & Sugawara, 1996). As for the comparison of the four-dimensional model with the one-dimensional model, the difference was significant ($\Delta SB\chi 2 = 571.94$, $\Delta gl = 6$, $p < 0.01$) and the one-dimensional model obtained worse goodness of fit indices (CFI = 0.775 ; NNFI = 0.738; RMSEA = 0.165; 10% CI RMSEA = 0.159-0.170), which shows that the data support the proposed four-dimensional model. The mean extracted variance from the self-efficacy and intention factors did not exceed the 0.50 cut-off point proposed by Fornell and Larcker (1981), only the attitudes and intention scales coming close with an average variance extracted of 0.43 and 0.47, respectively.

Factor invariance analysis of the measurement model (Table 4) indicated strict measurement invariance with respect to boys and girls, according to the classification proposed by Dimitrov (2010). Multi-group comparison indicated the equivalence of factorial loads (Model 1), the equivalence of intercepts with the exception of item Attitude_4 (Model2PA), and the equivalence of residual variances except for items Attitudes_3 and Attitudes_4 (Model3PB). Even with the proposed exceptions, Dimitrov (2010) recognizes that partial invariance of up to 20% of the items would be acceptable. Moreover, although in this case an acceptable partial invariance of the residual variances was obtained, it has been recognized that tests of strict metric invariance or invariant item uniqueness are excessively restrictive (Bentler, 2004; Byrne, 1988). Therefore, based on the re-



SBχ2	DF	SBχ2 /DF	P-value	R-CFI	NNFI	RMSEA	RMSEA (90% CI)
209.20	84	2.49	< 0.01	0.988	0.985	0.040	0.033 - 0.047

Fig. 1. Measurement model fit.

Note. Bχ2 Satorra-Bentler chi-square; DF degrees of freedom; R-CFI Robust Comparative Fit Index; NNFI Non-Normed Fit Index; RMSEA Root Mean-Square Error of Aproximation.

Table 3. *Factorial invariance analysis by sex.*

Model	SBx2	DF	R-CFI	RMSEA(90% IC)	ΔSBx2	ΔDF	p
Model0	17.86	160	1	0	-	-	-
Model1	366.72	175	0.945	0.048(0.041-0.055)	0.013	15	1
Model2	423.47	190	0.948	0.049(0.042-0.056)	65.59	15	‹0.01
Model2PA	371.18	189	0.958	0.044(0.037-0.056)	17.21	14	0.245
Model3	419.60	204	0.952	0.047(0.041-0.054)	44.03	15	‹0.01
Model3PA	402.22	203	0.956	0.045(0.038-0.054)	29.87	14	0.008
Model3PB	375.37	202	0.962	0.043(0.036-0.049)	16.47	13	0.225
Model4	508.39	199	0.925	0.057(0.051-0.064)	85.73	14	‹0.01

Note. Model_0: Unconstrained; Model_1: fixed and equal factor loadings; Model_2: Model_1 with fixed and equal item intercepts; Model_2PA partially invariant with free intercept of Attitude 4; Model_3: Model_2 with fixed and equal residual variances/covariances; Model_3PA: Model_3 partially invariant with fixed and equal residual variances/covariances of Attitude _4 and Attitude _3 free; Model_3PB: partially invariant with fixed and equal residual variances/covariances of Attitude _4 and Attitude _3 free; Model_4: Model_2 with fixed and equal factorial variances/covariances; SBx2 Satorra-Bentler chi-square; DF degrees of freedom; R-CFI robust comparative fit index; RMSEA root mean-square error of aproximation; ΔSBx2 scaled difference of SBx2.

Table 4. *Spearman correlations, scores on CUIQ scales and cannabis use and CAST.*

	Attitudes	Social Norm	Self-efficacy towards non-use	Intention
Cannabis use	0.38**	0.32**	-0.35**	0.65**
CAST	0.38**	0.33**	-0.34**	0.58**

Note. **correlations significant at 0.01.

sults obtained, mean factor scores could be compared between both groups as could correlations between factors and other external variables since the change in one would also be equivalent in both groups. These results substantiate the good fit of the items to the dimensionality proposed by TPB.

Association of test scores with other variables

The attitude, subjective norm and intention variables showed significant and positive correlations with cannabis use in the previous month, as well as with CAST scores (Table 5). In line with expectations, self-efficacy towards non-use presented a negative correlation with the two measures of use: in the previous month (r = -0.35, p < 0.01) and CAST (r = -0.34, p < 0.01). According to TPB, the intention to perform a given behaviour is the best predictor of the effective performance of said behaviour, which in this study is evidenced by the high correlations between the intention variable and the two measures of use, with said correlations varying between 0.59 and 0.65 depending on the sample (p < 0.01).

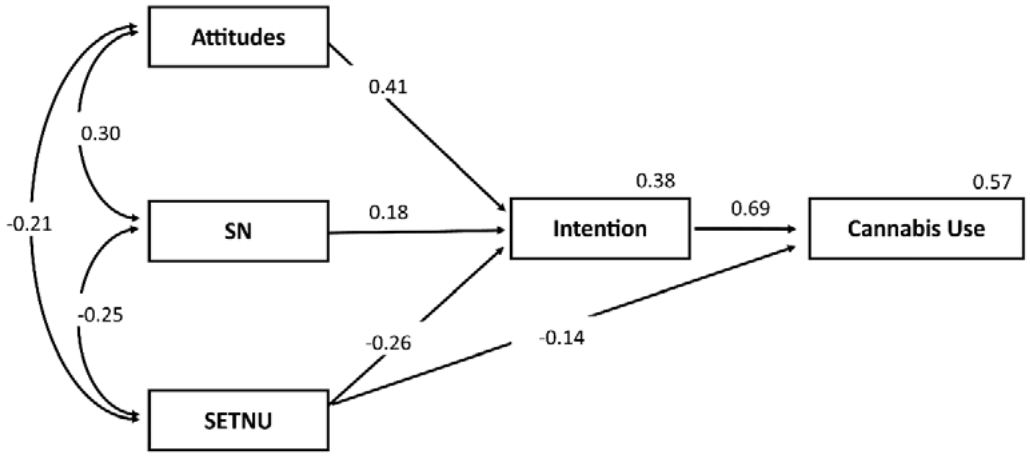
The path analysis of the proposed model revealed a good fit (Figure 2). The effect of attitudes and subjective norm on cannabis use was mediated by intention, whereas self-efficacy towards non-use also showed a direct effect on consumption. The predictor variables explained 38% of the variance in intention, and, in turn, intention together with self-efficacy explained 57% of the variance in cannabis use.

Previous 30 day use ROC curve and CAST

Analyses of ROC curves (Table 6, Figures 3 and 4) indicate that intention is the factor that best classified both cannabis use and risk of problems due to use, measured as cut-off point 3 in CAST (Legleye et al., 2015). Areas under the intention curve were high (0.93 for cannabis use and 0.87 for risk measured with CAST). The cut-off point of 1.83 in intention adequately classified 87% of users and 87% of non-users, while the cut-off point of 2.17 in intention for risk of problems due to cannabis use adequately classified 82% of participants at risk and 82% in non-risk situations. The cut-off points of attitudes, subjective norm and self-efficacy had lower sensitivity and specificity than intention.

Discussion

The objective of this study was to construct and validate a questionnaire for the purpose of evaluating the intention to use cannabis and its predictors among adolescents. The design was based on the conceptual framework of TPB, which claims that intention is the main predictor of behaviour, while attitudes, subjective norm and self-efficacy are the antecedents of intention. Based on the results obtained, it can be concluded that the scores of the CUIQ scales have good psychometric properties. The reliability statistics of each subscale were adequate, with the exception of subjective norm, which yielded slightly lower results. These results are in line with those obtained by other authors,



SBχ2	DF	SBχ2 /DF	P-valor	R-CFI	NNFI	RMSEA	RMSEA (90% IC)
0.15	2	0.08	0.930	1	1	0	0 - 0.019

Fig. 2. Standardised coefficients of the TPB predictive model

Note. SBχ2 Satorra-Bentler chi-square; DF degrees of freedom; R-CFI Robust Comparative Fit Index; NNFI Non-Normed Fit Index; RMSEA Root Mean-Square Error of Aproximation..

Table 5. *ROC curve: consumption previous 30 days and CAST.*

		AUC	Cut score	Susceptibility	Specificity
Cannabis 30 days	*Attitudes*	0.79	2.28	0.71	0.75
	SN	0.74	1.50	0.71	0.70
	Self-efficacy (*)	0.74	4.78	0.71	0.68
	Intention	0.93	1.83	0.87	0.87
CAST	*Attitudes*	0.82	2.63	0.73	0.79
	SN	0.70	1.72	0.62	0.73
	Self-efficacy (*)	0.76	3.90	0.56	0.86
	Intention	0.87	2.17	0.82	0.82

Note. AUC area under the curve; * Inverted.

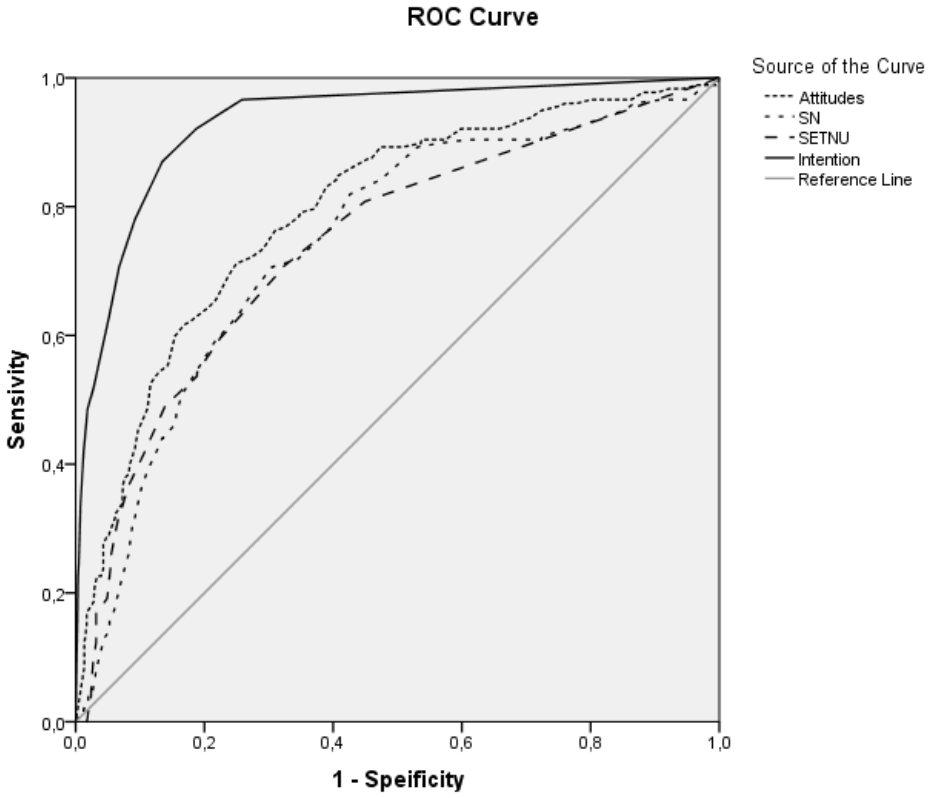


Fig. 3. 30 day use ROC curve

who also found a lower predictive capacity of subjective norm (Armitage & Conner, 2001; McMillan & Conner, 2003). Once the sampling was performed, analysis of the internal structure of the test and the factorial invariance with respect to gender suggest high generalizability of the questionnaire in the population of Spanish adolescents. The proposed predictive model, and in particular the variable intention to use, point to adequate evidence of validity in relation to cannabis use and to the probability of experiencing problems related to use, as reflected in the CAST score.

Having a validated questionnaire to measure the intention to use cannabis during adolescence is useful for monitoring populations, detecting early intervention needs and evaluating preventive interventions, all the more so when considering that most of the instruments available in Spanish are aimed at the adult population, which may present differences to the adolescent population, in particular as regards the understanding of the questions or the capacity for sustained attention required for the completion of a questionnaire. The CUIQ has therefore been specifically designed to be a brief questionnaire, easily understood by

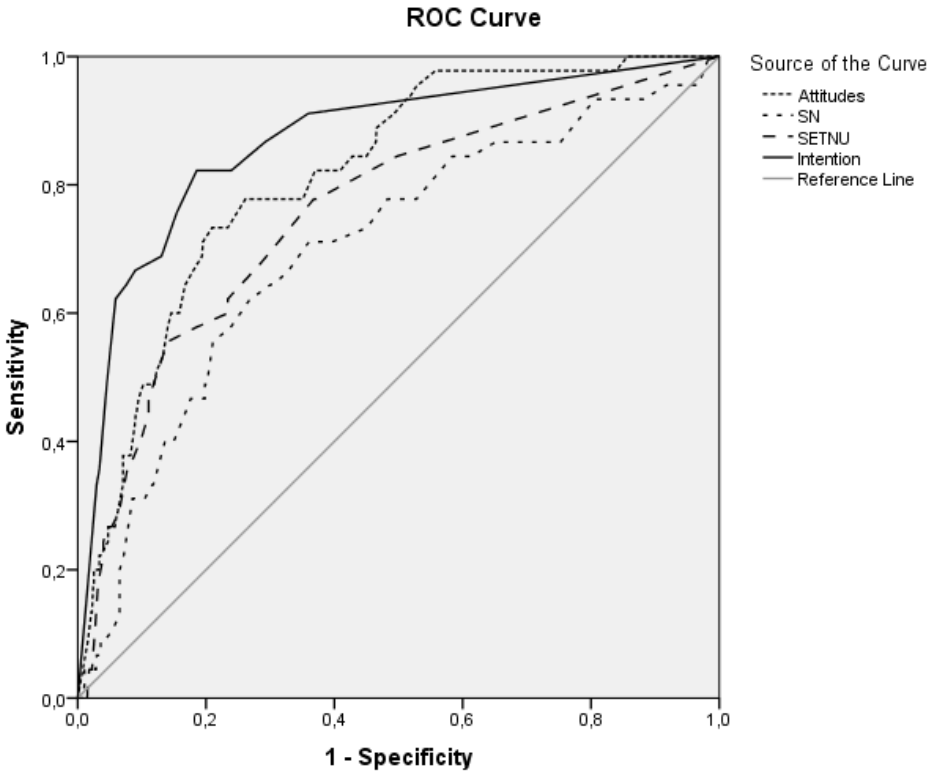


Fig. 4. CAST ROC curve

minors, which can be administered individually or in group in a simple way by teachers or other professionals working with adolescents, such as psychologists or social workers. For this purpose, a manual and an Excel spreadsheet for scoring have been developed alongside the questionnaire, aiming to facilitate its use especially in the educational field. Its application in the CAPPYC prevention project has demonstrated its usefulness in evaluating a program to prevent cannabis abuse among younger consumers.

The CUIQ presents some differences compared to other questionnaires such as CPQ-A, validated in Spain by Fernández-Artamendi et al. (2012), such as the lower number of items and the use of 5-point Likert scales (instead of dichotomous yes/no answers). In addition, it was developed within the TPB (Ajzen, 1991) framework. Compared to other scales, the CUIQ measures factors linked to cannabis use which are susceptible to change through preventive interventions and, therefore, enables pre- and post-intervention measures to be compared. However, as with any self-report measure, it is not without limitations, such as the potential lack of honesty if the anonymity of the questionnaire is doubted, or if the estimate of use is too low. Nevertheless, self-report measures are widely used for the screening of problematic substance use as well as for other types of addictive behaviour. This new questionnaire should on no account be taken for a diagnostic tool, since it aims to be a useful instrument for prevention, in combination with programs specially designed for this purpose, by identifying intervention needs and evaluating the impact of such programs.

This study paves the way for future lines of research. Firstly, validation is considered necessary in other cultural contexts. Secondly, a longitudinal study would deepen the analysis of the evidence regarding predictive validity. Similarly, expanding the target population in further studies with slightly older subjects, in early adulthood for example or adults, would confirm its generalizability. It is important that this new questionnaire is not restricted to occasional administrations, but is accompanied by an intervention that focuses on a reduction or total elimination of cannabis use.

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ropean Commission (JUST Programme/2013/Action Grants). More information on the CAPPYC project, which provides the framework for this study, as well as the downloadable CUIQ questionnaire and scoring manual can be found at the following link: http://cappyc.eu/en/

Conflict of interests

The authors have no conflicts of interest to report.

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Dual diagnosis in Depression: treatment recommendations

Patología dual en Depresión: recomendaciones en el tratamiento

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Abstract

Comorbidity between substance use disorders (SUD) and major depression (MD) is the most common dual pathology in the field of addiction to substances and has prevalence rates ranging between 12% and 80%, which complicates the response to treatment and worsens the prognosis of patients.

Differentiating between diagnoses of induced depressive episodes and primary depressive episodes concurrent to substance use is especially relevant for therapeutic management.

This article presents the state of the art of the currently available pharmacologic treatments of comorbid depression in patients with SUD, taking into account the safety and risk of abuse of antidepressant drugs.

Due to the fact that comorbidity of MD and SUD is frequent and presents greater psychopathological and medical severity, as well as worse social functioning, it is crucial to treat MD and SUD simultaneously using the integrated treatment model and not to treat both conditions separately.

Keywords: Depression; Dual pathology; Comorbidity; Treatment; Recommendations.

Resumen

La comorbilidad entre los trastornos por uso de sustancias (SUD) y la depresión mayor (DM) es la patología dual más común en el campo de las adicciones a sustancias, con prevalencias que oscilan entre el 12 y el 80% complicando la respuesta al tratamiento y empeorando el pronóstico de los pacientes. Diferenciar entre el diagnóstico de episodios depresivos inducidos y episodios depresivos primarios concurrentes al uso de sustancias es especialmente relevante para el manejo terapéutico.

En este artículo se presenta el estado actual de los tratamientos farmacológicos disponibles hasta el momento para la depresión comórbida en pacientes con SUD, teniendo en cuenta la seguridad y el potencial de abuso de los fármacos antidepresivos.

Debido a que la comorbilidad de DM y SUD es frecuente y a que estos pacientes presentan mayor gravedad psicopatológica y peor funcionamiento social, es crucial un modelo de tratamiento integrado y no abordar el tratamiento por separado.

Palabras clave: Depresión; Patología dual; Comorbilidad; Tratamiento; Recomendaciones.

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Mood disorders and anxiety disorders are the mental disorders most frequently associated with substance use disorders (SUD) (San, Arranz, & Grupo de Expertos de la Guía de Práctica Clínica de Patología Dual, 2016). In this review we present an update of what is known about the comorbidity of depression and SUD, and resulting treatment recommendations. To indicate the simultaneous presence of an episode of MD and an SUD, the terms dual depression, comorbid depression with SUD, or MD + SUD are used interchangeably in this paper.

The prevalence of this combination varies between 12% and 80% across the different studies. According to Torrens and Rossi (2015), several factors explain this wide range. The factors to consider include: the main substance consumed (tobacco, alcohol, cocaine, opiates, hypnosedatives, etc.); whether the study was conducted among the general population or with a sample of substance users - and in the latter case, whether they were recruited in addiction treatment centers, in mental health care facilities or in other populations (prison, the homeless), or methodological aspects such as diagnostic criteria (DSM or ICD, in their different versions), and the diagnostic tools used (diagnostic interviews such as PRISM, SCID or SCAN, or screening tools such as DDSI).

In a systematic review with meta-analysis of epidemiological studies in the general population carried out between 1990 and 2014, the authors confirm the close link between MD and SUD (Lai, Cleary, Sitharthan, & Hunt, 2015). This association is stronger for the use of illegal drugs than for alcohol, and greater for disorders with dependence criteria than for disorders due to abuse, regardless of the temporal criterion for establishing prevalence (during a lifetime or over the previous 12 months). The main results are shown in Table 1.

The prevalence of MD and SUD comorbidity at the European level among clinical populations in different care facilities and among some special populations (e.g. prisoners or the homeless), is available in various publications such as Insight 19 from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2015) and others (Arias et al., 2013; Torrens & Rossi, 2015).

Furthermore, studies performed both in the general population and in the clinical population show that comorbid MD with SUD is more frequent in women than in men, and is twice as frequent as in women of the general population. Women with SUD thus constitute a particularly vulnerable group (Torrens et al., 2011).

Table 1. *SUD-MD prevalence in general population epidemiological surveys (Lai et al., 2015).*

MD with SUD	Alcohol	Abuse OR 1.53, 95% CI 1.20-1.95 Dependence OR 3.09, 95% CI 2.38-4.03
	Other drugs	Abuse OR 3.80, 95% CI 3.02-4.78 Dependence OR 4.83, 95% CI 3.01-7.73

Note. SUD: substance use disorder; MD: major depression; OR: odds ratio; CI: confidence interval.

Etiopathogenesis

Three hypotheses are proposed to explain the frequent concurrence of MD and SUD:

1. SUD and MD share common risk factors, such as stressful life events, psychological trauma, genetic vulnerability and/or previous neurobiological impairments leading to the occurrence of both disorders without a causal relationship between them.
2. Continued use of certain substances of abuse leads to neurobiological changes through neuroadaptive mechanisms that mediate MD.
3. SUD develops to relieve the MD (self-medication hypothesis). In this case, MD increases the risk behaviors linked to consumption.

In both MD and SUDs, genetic and environmental factors play a crucial role in facilitating neurobiological mechanisms related to their psychopathogenesis (Brady & Sinha, 2005; Schuckit, 2006). The major neural and molecular mechanisms involved in the neurobiology of depression include the monoaminergic system, the hypothalamic-pituitary-adrenal axis, the immunological system, neurotrophic factors, the endocannabinoid system, the circadian rhythm, and the system controlling ingestion and metabolism (Belmaker & Agam, 2008; Krishnan & Nestler, 2010; Valverde & Torrens, 2012; Valverde et al., 2009).

Most of these systems are also involved in the development of SUDs (Brady & Sinha, 2005; Gutiérrez-Sacristán et al., 2015; Valverde & Torrens, 2012). Similarly, reward circuits, which are highly relevant to the pathogenesis of addiction (Wise, 1989), are involved in the neurobiology of depressive disorders (Nestler & Carlezon, 2006).

Clinical aspects

The clinical diagnosis of MD in substance users is complex due to different factors. On the one hand, the acute or chronic effects of substance use may mimic depressive symptoms, making it difficult to distinguish between the symptoms of a case of MD independent of symptoms related to consumption or withdrawal. On the other hand, diagnoses of psychiatric disorders such as MD are more syndromic than those of diseases with clear pathophysiology and associated biological markers. This lack of biological markers has forced psychiatrists to develop operative diagnostic criteria, including DSM and ICD, and to design clinical diagnostic interviews to improve the validity and reliability of psychiatric diagnoses. With reference to the diagnosis of other psychiatric disorders among substance users, the criteria used changed over time until they matched those of DSM-IV (American Psychiatric Association, 1994) and were maintained in DSM-IV-TR (American Psy-

chiatric Association, 2002) and DSM-5 (American Psychiatric Association, 2013), with three conditions considered necessary to facilitate a more accurate diagnosis:

- *"Expected effects":* this refers to symptoms considered specific to intoxication or withdrawal from a given substance which should therefore not be taken into account as symptoms for diagnosing depression (e.g. insomnia during acute stimulant poisoning or during a period of opiate withdrawal).
- "*Substance-Induced":* disorders that appear in relation to substance use or withdrawal, but can be considered excessive in relation to the expected effects.
- *"Primary":* mental disorders that are not induced by substances or arising from medical illness, i.e., independent disorders.

Medical professionals tend to bear in mind the concept of primary or independent disorder and that of induced disorder more than the concept of "expected effect", which is, nevertheless, very relevant in order to increase diagnostic validity and reliability.

In clinical practice, the differentiation between primary depressive episodes and those induced by substance use is one of the difficulties in the diagnosis of depressive symptoms when there is co-occurrence of substance use. To help with this issue, different diagnostic interviews are available to establish the diagnosis. Among them, the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996) enables the diagnosis of primary or substance induced depression in a valid and reliable way. This difference may be especially relevant for treatment management. Table 2 shows the main clinical indicators that facilitate the differential diagnosis of induced depressive episodes and primary depressive episodes concurrent with substance use.

Table 2. *Clinical indicators for the diagnosis of a depressive episode concurrent to the use of substances.*

Primary depression	Induced depression
Depressive symptomatology appears during a phase of stable consumption	Appearance of depressive symptomatology during an increase in consumption
Depressive symptomatology persists after a period of abstinence	Appearance of depressive symptomatology during a significant decrease in consumption
History of depressive episodes in the absence of substance use	
History of good response to antidepressant treatments	
Family history of depression	

Table 3. *Principal clinical characteristics of dual depression.*

Clinical characteristics of dual depression
Dual MD is more frequent when SUD severity is moderate-severe than if SUD is mild (DSM-IV criteria show dual MD to be more frequent in dependence disorders than in abuse disorders)
Dual MD is more frequently independent rather than induced (except in the case of alcohol SUD)
The presence of MD (primary or induced) is associated with unfavorable SUD progress
The presence of SUD is associated with unfavorable MD progress
Patients with dual depression have a higher prevalence of attempted/completed suicides
Patients with dual depression have more medical and psychiatric comorbidities (including more SUDs)
Patients with dual depression present greater social problems and increased use of health resources, including more psychiatric admissions

It has been observed in the case of SUDs involving cocaine, opiates or among polydrug users that episodes of MD usually occur more frequently independently of consumption (Torrens, Gilchrist, & Domingo-Salvany, 2011), whereas in the case of alcohol a higher prevalence of association with induced MD has been reported (Schuckit, Smith, & Kalmijn, 2013). However, both types of depression (primary and induced) can be found in the same patient (Langås, Malt, & Opjordsmoen, 2013; Torrens, Gilchrist, & Domingo-Salvany, 2011). It has also been observed that patients with MD are twice as likely to develop a SUD and that patients with SUD are twice as likely to have MD during their lifetimes (Boden & Fergusson, 2011). In addition, the coexistence of both disorders has been linked to an unfavorable course for both pathologies, with worse response to treatment and worse prognosis (Agosti & Levin, 2006; Davis, Uezato, Newell, & Frazier, 2008). Thus, in follow-up studies among samples of substance-dependent patients it has been observed that the presence of major depressive episodes, both primary and induced, has facilitated relapse to substance use (Landheim, Bakken, & Vaglum, 2006; Samet et al. 2013). Indeed, several studies have found that SUD comorbidity in patients with MD increases the clinical severity of these patients, and there is a greater risk of suicidal behavior (Marmorstein, 2011; Szerman et al., 2011). In addition, these patients are more likely to develop other medical comorbidities, making treatment even more difficult. Thereby, and as expected due to their high clinical severity, these dual patients also present considerable psychosocial severity and make greater use of health resources, including emergency services and psychiatric admissions (Martin-Santos et al., 2006; Mueller et al., 1994; Pettinati, O'Brien, & Dundon, 2013; Samet et al., 2013).

Given the available knowledge it can thus be affirmed that induced depressive episodes can be as or more serious than primary or independent ones, both in terms of relapse to substance use and in the severity of depressive symptomatology, including risk of suicide.

Table 3 summarizes the main clinical features of dual depression.

Treatment of dual depression

Since the frequency and clinical and social severity of these dual patients is high, their treatment is important. However, we hardly have any studies on the treatment of dual depression, and most have been carried out on patients with alcohol dependence. The current state of clinical management of patients with MD and SUD is presented below.

General recommendations

1. A depressive episode should be treated even though the patient is actively using substances. The treatment of dual depression should take both disorders into account; depression treatment cannot replace addiction treatment.
2. The addiction should be treated even if the patient is in a depressive episode. Treatment with antidepressants has a limited impact on substance use; specific concomitant treatment should be considered for SUD.
3. Substance use is not a limitation for the treatment of depression.
4. The effects of antidepressants are greater when patients have primary MD.
5. Treatment should consider pharmacological and psychotherapeutic approaches.

Pharmacotherapy

The pharmacological treatment approach for MD with SUD should consider not only the efficacy of different drugs, but also aspects relating to the safety of using antidepressants, their possible interactions with the consumption of different substances and the abuse potential of the different drugs administered for the treatment of dual depression.

The following outlines the most important aspects to be taken into account when prescribing antidepressants.

Efficacy of antidepressant drugs in dual depression

Two systematic reviews of controlled clinical trials analyzed with meta-analysis are currently available (Nunes & Levin, 2004; Torrens, Fonseca, Mateu, & Farré, 2005). The main results were that selective serotonin reuptake inhibitors (SSRIs) yielded worse results than non-SSRI antidepressants in the treatment of dual MD and that antidepressants did not directly affect the improvement in substance use. Other studies were subsequently published on the treatment of dual depression. The following summarizes the seven ensuing studies on the efficacy of antidepressants in the treatment of comorbid MD with alcohol consumption disorder (Table 4), and the six subsequent studies on the efficacy of antidepressants in the treatment of comorbid MD with cocaine use disorder (Table 5).

With regard to the efficacy of antidepressant treatment in comorbid depression with opioid use disorder, it should be noted that following the systematic review with meta-analysist of Torrens (Torrens et al., 2005), only one review of the Cochrane (Pani, Vacca, Trogu, Amato, & Davoli, 2010) was published, which included the same studies. Subsequently and to date, no other study has been published.

As for the treatment of MD and cannabis dependence disorder, only a single randomized, placebo-controlled trial in 103 patients with cannabis and MD or dysthymia disorder is available, which compared the effect of delayed release venlafaxine with placebo for 12 weeks. In addition, all patients received concomitant treatment with weekly sessions of individual cognitive-behavioral therapy. No significant differences were found in terms of clinical depression and an increase in cannabis use was observed in patients in the delayed-release venlafaxine group (Levin et al., 2013).

The review of the available literature on the pharmacological treatment of dual depression thus allows us to assert that:

1. SSRIs are the most commonly used antidepressants in the studies and have in no case demonstrated efficacy in the treatment of depression comorbid with alcohol, cocaine or opiate use disorders.
2. There are few studies with other non-SSRI antidepressant drugs, and in this case evidence indicates that: a) imipramine and desipramine are effective in improving depression in patients with MD and alcohol use disorder, and desipramine in MD and cocaine use disorder; b) other antidepressants studied, such as venlafaxine, mirtazapine and nefazodone, have not proved efficacious in improving dual depression.
3. No antidepressant has been shown to be effective in reducing substance use.

The safety of antidepressant drugs in dual depression

An especially relevant aspect in the pharmacological treatment of dual depression is the possibility of pharmacological interactions between antidepressants and the substances of abuse themselves, the drugs used for the treatment of SUD, or the drugs used for the treatment of other medical comorbidities that the patient may suffer (e.g. human immunodeficiency virus infection or hepatitis C virus). It is notable that methadone is the second most frequent cause of drug arrhythmia after dofetilide (Kao et al., 2013), according to the adverse event reporting system of the Food and Drug Administration (FDA). Because methadone is one of the most widely used drugs in the treatment of opioid use disorder, a review of Chou's (2014) methadone interactions is recommended. Table 6 summarizes the most relevant interactions that should be taken into account in the clinical management of dual depression. Special caution should be exercised with monoamine oxidase inhibitors (MAOIs) due to their interaction with fatal results with tyramine in some foods or alcoholic beverages, with the consumption of stimulants (cocaine, amphetamines, methamphetamine, MDMA) also totally contraindicated.

Table 4. *Double blind and controlled clinical trials on MD and alcohol consumption disorder included and not included in previous meta-analyzes.*

Authors	Study type	Medication	N	Duration	Concomitant treatment	Efficacy on depression	Efficacy on substance use
Altamura 1990*	PC-RCT	Viloxazine	27	12 wks	4 weeks hospital followed by outpatient treatment	Yes. Decreased depressive symptomatology with significant differences between both groups	Both groups improved alcohol consumption without significant differences between groups
Mc Grath 1996*	PC-RCT	Imipramine	56	12 wks	Individual BCT and relapse prevention	Yes. Decreased depressive symptomatology with significant differences between both groups	No effect
Mason 1996*	PC-RCT	Desipramine	22	24 wks	Alcoholics Anonymous	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with significant differences between both groups
Cornelius 1997*	PC-RCT	Fluoxetine	51	12 wks	Support psychotherapy	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with significant differences between both groups
Roy 1998*	PC-RCT	Sertraline	15	6 wks	Inpatient treatment followed by intensive day hospital	Yes. Decreased depressive symptomatology with significant differences between both groups	Not assessed
Roy-Byrne 2000*	PC-RCT	Nefazodone	31	12 wks	Group CBT	Yes. Decreased depressive symptomatology with significant differences between both groups	Decreased consumption with no differences between both groups
Pettinati 2001*	PC-RCT	Sertraline	29	14 wks	12-Step Therapy	No. No differences between both groups	No differences between both groups
Gual 2003*	PC-RCT	Sertraline	46	24 wks	2 weeks of abstinence after detoxification	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Moak 2003*	PC-RCT	Sertraline	82	12 wks	Individual CBT for alcohol and depression	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Hernández-Àvila 2004*	PC-RCT	Nefazodone	41	10 wks	Support psychotherapy	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Kranzler 2006	PC-RCT	Sertraline	328	10 wks	No	No. Decreased depressive symptomatology without significant differences between both groups	No
Altintoprak 2008	RCT	Amitriptiline vs Mirtazapine	44	8 wks	No	No. Decreased depressive symptoms without differences between the two drugs. Better mirtazapine tolerance	No Both reduced alcohol craving
Muhonene 2008	RCT	Memantine vs Escitalopram	80	2 años	No	No. Both drugs decreased depressive symptoms without differences	Not assessed
Cornelius 2009	PC-RCT	Fluoxetine	40	12 wks	Standard CBT motivational therapy	No. Both drugs decreased depressive symptoms without differences	No Both decreased consumption
Petinatti 2010	PC-RCT	Setraline vs Naltrexone vs Sertraline + Naltrexone vs placebo	170	14 wks	Placebo group standard CBT relapse prevention	No. Sertraline + naltrexone improved depression at the end of the study compared to other groups, with no significance	Sertraline + naltrexone improve abstinence and lengthen time to relapse
Adamson 2015	PC-RCT	Natrexone + Citalopram vs Natrexone + Placebo	138	12 wks	No	No. Decreased depressive symptomatology without significant differences between both groups	Decreased consumption with no differences between both groups
Foulds 2015	PC-RCT	Natrexone + Citalopram Vs Natrexone + Placebo	138	12 wks	No	No. Improvement on the induced depression scales, although without being able to determine a significant effect of the treatment in relation to decrease in consumption	Greater decrease of consumption in induced than independent depression

Note. PC-RCT: Placebo-controlled, Randomized Clinical Trial. RCT: Randomized Clinical Trial. No: no efficacy. SSRI: Selective serotonin reuptake inhibitors. CBT: Cognitive Behavioral Therapy. AD: Antidepressant. * Studies included in previous metaanalysis.

Table 5. *Double-blind and controlled clinical trials on MD and cocaine use disorder included and not included in previous meta-analyzes.*

Authors	Study type	Medication studied	N	Duration	Concomitant treatment	Efficacy on depression	Efficacy on substance use
Ziedonis 1991*	RCT	Desipramine or Amantadine	14	12	PMM	Decreased depressive symptomatology	Yes. Decreased consumption with differences between both groups
Nunes 1995*	RCT	Imipramine	69	12	Individual counseling	No. No effect	No. Decreased consumption without differences between both groups
Cornelius 1998*	RCT	Fluoxetine	17	12	Support therapy	No. Decreased depressive symptomatology without differences between both groups	No
Schmitz 2001*	RCT	Fluoxetine	68	12	CBT and relapse prevention	No. Decreased depressive symptomatology without differences between both groups	No
Gonzalez 2003*	RCT	Desipramine	56	12	Contingency management	No. No significant differences	No
MacDowell 2005	RCT	Desipramine	111	12 wks	Standard CBT and relapse prevention	Yes. Clinical improvement in patients in the desimipramine group	No
Ciraulo 2005	RCT	Nefazodone	69	8 wks	1 hour counseling sessions	No. Both groups improve without differences	No
Afshar 2012	RCT	Mirtazapine	24	12 wks	Manual-guided relapse prevention therapy	No. Decreased clinical depression in both groups	No
Oliveto 2012	RCT	Sertraline	86	12 wks	Standard CBT and relapse prevention	No. No significant differences	No
Mancino 2014	RCT	Sertraline vs Sertraline + Gabapentine	99	12 wks	Standard CBT and relapse prevention	No. Improvement in all groups	Group with sertraline increased time to relapse
Raby 2014	RCT	Venlafaxine	130	8 wks	Manual-guided relapse prevention therapy	No	No

Note. PC-RCT: placebo-controlled randomized clinical trial. CBT: cognitive behavioral treatment. *Studies included in previous meta-analyses.

Abuse liability of antidepressant drugs

Since the 1970s, case series have been described which suggest that some antidepressants may have potential for abuse, with those with stimulant or sedative properties being the most risky. The antidepressants with the highest risk and with which special care should be taken in patients with SUDs (Evans & Sullivan, 2014; Haddad, 1999; Jasinski, Faries, Moore, Schuh & Allen, 2008; Reeves, Ladner, Perry, Burke, & Laizer, 2015; Volkow et al., 2005) are outlined below.

- MAOIs: Tranylcypromine and phenelzine have been involved in oral abuse due to their amphetamine-like structure; series of cases have been reported in particular with tranylcypromine.
- Tricyclics: Especially those with sedative and anticholinergic properties have been reported in oral abuse. Cases have been described where amitriptyline and dothiepin (the analogue of amitriptyline used in Europe) have been used to get a feeling of euphoria.
- Bupropion: Intranasal abuse with cocaine-like effects has been described. Isolated cases of intravenous abuse have also been reported.
- SSRIs: There are studies indicating that fluoxetine has been used orally to give amphetamine-like effects in combination with alcohol or MDMA.
- SNRIs: A case of venlafaxine abuse has been reported with withdrawal symptoms and requiring admission for detoxification.

- Tianeptine: This is an antidepressant approved in France and recently in Spain. Cases of oral abuse have been reported to provide a psychostimulant effect.
- Amineptine: Oral abuse has stimulant-like effects.

Psychological treatments

Treatment of dual depression with cognitive-behavioral therapy (CBT) is well recognized. However, it is still not routinely applied in clinical practice despite available data on its efficacy.

There are currently several combined treatments for MD and SUD, including psychotherapeutic treatments as adjuvants or alternatives to pharmacological treatment. A recent systematic review with meta-analysis has assessed the efficacy of CBT and motivational intervention on MD in patients with alcohol-induced SUD vs usual treatment (Riper et al., 2014). The authors observed that in both cases the interventions yielded a slight clinically significant effect both in the reduction of depressive symptoms and in the decrease in alcohol consumption, although the effect size was lower compared to that obtained with the pharmacological treatments. Furthermore, the BRIGHT project (Building Recovery by Improving Goals, Habits, and Thoughts), which compared residential SUD treatment with residential SUD treatment and CBT together, yielded better clinical results with greater treatment adherence and greater improvement of depressive symptoms in patients who also received CBT (Watkins et al., 2011).

Table 6. *Main interactions in the clinical management of dual depression.*

Substance/medication	Antidepressant	Effect
Benzodiazepines	Tricyclics	↑ plasma concentrations of *desipramine* and *imipramine*
	SSRI	*Fluoxetine and fluvoxamine* ↑ plasma concentrations of *alprazolam* and *diazepam*
Disulfiram	Tricyclics	↑ plasma concentrations of *desipramine* and *amitriptiline* via metabolism ⚓ and increased neurotoxicity of the combination
	MAOI	*Tranylcypromine,* Confusional psychosis in combination
Opioids	Tricyclics	*Methadone:* ↑ risk of QTc interval prolongation ↑ risk of death with overdose ↑ plasma concentrations of methadone if co-administered with *desipramine*: *Morphine:* ↑ bioavailability and analgesic effect *Doxepine* may induce delirium during OWS
	SSRI	*Methadone and buprenorphine* ↑ risk of serotonin syndrome ↑ plasma concentrations of methadone through ⚓ elimination with *Fluvoxamine*
	MAOI/RIMA	*Moclobemide:* ↑ effects of morphine, fentanyl and methadone
	Other antidepressants	*Mirtazapine* ↑ Risk of prolonging the QTc interval with *methadone*
Alcohol	Tricyclics	↑ alcohol toxicity ↓ cognitive function risk of convulsions (*maprotiline*)
	SSRI	↑ sedation (*fluvoxamine*)
	MAOI	↑ effects of alcohol Hypertensive crisis through ↑ release of catecholamines
	Other antidepressants	↑ sedation (*trazodone and mirtazapine*)
Stimulants (Cocaine/amphetamine)	Tricyclics & SSRIs	↓ craving, and convulsive threshold ↑ of heart rate and diastolic pressure by 20-30%, increased risk of arrhythmia
	MAOIs	Absolute contraindication

Note. OWS: opiate withdrawal syndrome; MAOIs: monoamine oxidase inhibitors; SSRIs : selective serotonin reuptake inhibitors; RIMA: reversible MAO-A inhibitor.

Intervention protocol

Diagnostic assessment

Since antidepressant drugs have been shown to be more effective in independent than in induced disorders, one of the key points for treatment is a good diagnostic approach, as discussed previously. The medical literature indicates that structured interviews are the best tool to establish these diagnoses and that the PRISM (Psychiatric Research Interview for Substance and Mental Disorders) is the most appropriate for this. In addition to this, it is also important to assess the intensity of the episode in order to consider the possibility of starting treatment with antidepressants.

Scope of treatment

In an outpatient setting it is not always possible to keep patients abstinent nor to guide them to a significant reduction in consumption. To stabilize the patient, hospital admission, whether urgent or scheduled, should be considered even in patients with moderate depressive symptomatology, regardless of whether it is induced or primary.

SUD treatment

Despite the presence a depressive symptomatology, the treatment of SUD should not be neglected and psychosocial and pharmacological interventions must be initiated to reduce substance use (e.g. naltrexone or nalmefene for alcohol dependence, methadone or buprenorphine-naloxone for the treatment of opioid dependence). To reduce the risk of long-term relapse for those dependent on alcohol and other drugs it is important to assess and treat major depression.

Pharmacological treatment of depression

Treatment with non-SSRI antidepressants should be considered for patients. Adding a more dopaminergic and noradrenergic profile or mixed mechanisms of action appears to be more effective. Figure 1 shows a therapeutic algorithm for the treatment of MD-SUD dual pathology.

Finally, it is necessary to emphasize that despite the high prevalence of MD in patients with SUD, the available evidence regarding the best treatment is scarce. Future research should propose controlled trials to analyze the efficacy, safety and interactions profile of the new antidepressants available.

Parallel, sequential or integrated treatment

It is important to note that in most countries there are two separate networks for the treatment of mental illness and for the treatment of SUD. This implies that patients with dual pathology are very frequently treated in two facilities (parallel treatment model): a mental health care center and a center for addiction. In addition, substance abstinence is a fundamental prerequisite in many cases for the treatment of depression (sequential treatment model). Currently, it is recommended that these models of treatment are replaced by the so-called integrated model, which involves a simultaneous and coordinated approach to both addictive and affective disorders in order to improve the adherence and effectiveness of treatment (Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens, & Bulbena, 2012).

Conclusions

The comorbidity of MD and SUD is frequent and all patients affected by a dual disorder present greater psychopathological and medical severity, as well as worse social functioning. It is very important that MD and SUD are treated simultaneously on the basis of the integrated model and not approached via the treatment of both pathologies separately or sequentially. It is also of the highest priority to

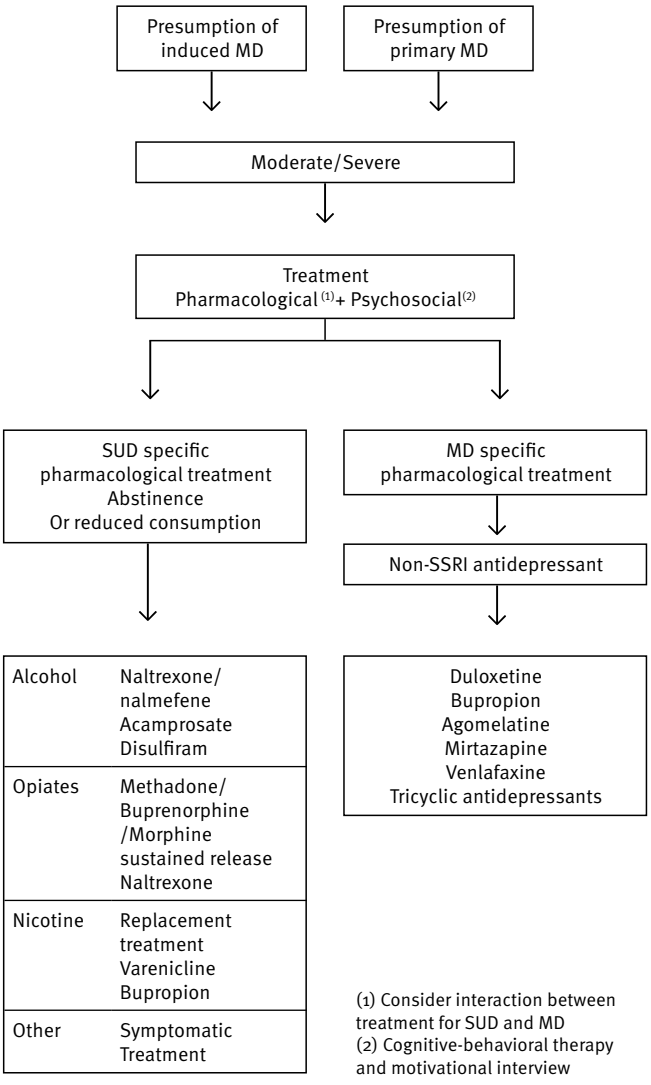

Figure 1. Therapeutic algorithm for the treatment of major depression and substance use disorder.

further investigate the neurobiology of the mechanisms of action involved in dual disorders in order to develop more effective prevention strategies and treatments.

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Conflicts of Interest

All authors declare that they have no conflict of interest.

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Confidence Intervals for Omega Coefficient: Proposal for Calculus

Intervalos de confianza para coeficiente Omega: Propuesta para el cálculo

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Measuring instruments are today widely used when conducting scientific research. It is therefore important to verify two properties of such instruments: (a) validity evidence and (b) score reliability. The latter has a direct impact on accuracy and measurement error (Martínez, Hernández & Hernández, 2014), which makes calculating and reporting it in scientific studies advisable.

Reliability is understood to be the ability, based on the instrument scores, to consistently differentiate between that which has a large amount of what is being measured and that which has little of it (Norman, 2014). In its classical form, it is the proportion of true variance explained by the indicators (Morales, 2013), a definition that reveals its connection to measurement instrument scores (Muñiz, 1996), and makes it reporting it on the basis of the sample examined essential for any study (Wilkinson, 1999).

Advances in the measurement of reliability have led to the creation of a variety of coefficients. Among these we find the coefficient β, coefficient H and the Ordinal Alpha coefficient, a suitable estimator for the demands of health scales which frequently use Likert-type response formats (Zumbo et al., 2007). The present letter, however, focuses on the Omega coefficient (ω), which is a relatively new estimator of reliability used in factorial models (Ventura-León & Caycho, 2017).

The Omega coefficient (ω) is an internal consistency estimator based on factorial loads which indicates the proportion of variance attributed to the totality of common variance (McDonald, 1999). Its greater sensitivity compared to other estimators (Zinbarg, Revelle, Yovel & Li, 2005), its robustness when sampling heterogeneous populations, and the reduced risk of overestimating reliability (Waller, 2008) makes ω preferable. Furthermore, ω does not require tau-equivalence nor the absence of correlated errors, which are limitations of Cronbach's alpha (Dunn et al., 2014). Given these factors, the omega may surpass the alpha coefficient and over time become one of the options of choice for the calculation of reliability (Zinbarg et al., 2005).

The interest in discussing confidence intervals (CI) for ω arises from the recent publication of two articles in the journal *Adicciones* in which this coefficient is used (Irles, Morell-Gomis, Laguía, & Moriano, in print; Merino-Soto & Blas, in print), thus making it a necessary complement to be included in future studies in the journal. The CI is understood as a range of values with a normal distribution and a high probability of finding the real value of a given variable (Candia & Caiozzi, 2005). It is nevertheless necessary to clarify that the CI is interpreted as the probability of finding the true value in 95 of 100 intervals produced by taking random samples under the same study conditions (Clark, 2004). Consequently, the resulting CI is highly likely to contain the true value of the variable.

Calculating the CI for a reliability coefficient is not an unknown procedure due to its development in connection with Cronbach's alpha (Domínguez-Lara & Merino, 2015) as well as being recommended by editorial policies (Fan & Thompson, 2001). However, obtaining a CI for ω requires the use of computational methods. For this purpose, this letter presents R codes (R Development Core Team, 2007)

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specifically for the "MBESS" library (Kelley & Lai, 2017), which uses the bootstrap method of estimating the CI for the ω coefficient. The following is an example of how this is estimated:

First, the "MBESS" library must be installed and loaded using the following code in the statistical program R:

```
install.packages("MBESS", dependencies = TRUE)
library(MBESS)
```

Second, you must enable the ci.reliability () function, which contains several arguments:

```
ci.reliability(data=happiness, type="omega", conf.level = 0.95, interval.
type="bca", B=1000)
```

In this example, ω is calculated for a scale of happiness. The results of the calculations are shown below (this usually take a few minutes):

```
$est
[1] 0.9098134
$se
[1] 0.00645999
$ci.lower
[1] 0.8962767
$ci.upper
[1] 0.9221084
```

As can be seen from the results shown above, the program enables the calculation of the ω coefficient, standard error, and the confidence interval's lower and upper limit. It should be noted that in the data argument an array of correlations can be loaded and an omega for each of the models to be tested can be extracted.

Based on these results, the CI for ω is reported thus: the happiness scale has an internal consistency of .909 as measured by the omega coefficient. It therefore follows that, according to the level of confidence, there is a 95% probability of the true value of omega being found in the resulting interval [.896, .922].

Finally, it is timely to offer a method for the estimation of a confidence interval for ω due to its use in this journal and its potential increase in scientific studies (Zinbarg et al., 2005). Given that many professionals are not experts in statistics, a great advantage of the estimation method outlined in this letter is also the ease and user-friendliness with which the calculation is performed. This makes it a useful tool for researchers writing for *Adicciones*, thus helping to increase measurement accuracy in future studies.

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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.

Papel. La revista Adicciones está impresa en papel estucado fabricado con pastas libres de cloro (TCF).

Conflictos de intereses. La política de la revista es que en todos los artículos y editoriales conste expresamente la existencia o no de conflicto de intereses en el apartado correspondiente. Todos los conflictos de interés son importantes, pero especial cuidado hay que poner en el caso de haber recibido para el estudio financiación de la industria farmacéutica, alcoholera, tabaquera, etc. La revista Adicciones sigue en este tema las recomendaciones de ISAJE (International Society of Addiction Journals Editors). Tener conflicto de intereses no significa no poder publicar el artículo. En caso de duda sobre esta cuestión se debe contactar con el editor.

Autoría. Es muy importante que únicamente se consideren autores aquellos que han hecho sustanciales contribuciones: 1) a la concepción y diseño, adquisición de datos, o el análisis e interpretación de datos; 2) a la redacción del artículo o a su revisión crítica; y 3) que ha dado su aprobación de la versión que se publicará. Los autores deben asegurarse de que partes significativas del material aportado no ha sido publicado con anterioridad. En caso de que puedan tener dudas sobre el cumplimiento de esta norma, deberán presentar copias de lo publicado o de lo presentado para publicación a otras revistas antes de poder ser considerado el artículo para su revisión. En caso de dudas sobre alguno de los aspectos anteriores los autores deben consultar el acuerdo de Farmington al que está adherida la revista Adicciones (Anexo 1), las normas de "Sponshorship, authorship, and accountability" del International Committee of Medical Journal Editors (www.icmje.org/sponsor.htm) o las normas de publicación de la American Psychological Association, 6ª edición (2010) (www.apastyle.org). El editor de la revista puede dirigirse a los autores del artículo para que especifiquen cual ha sido la contribución de cada uno de ellos.

Preparación de manuscritos. Los autores deben seguir exclusivamente para la presentación de sus manuscritos las Normas de Publicación de la American Psychological Association (6ª edición, 2010; http://www.apastyle.org). Las excepciones a esta regla son mínimas y dependen sólo de las diferencias que puede haber en el uso del español y del inglés. Por ejemplo, los ingleses utilizan en la bibliografía el signo '&' antes del último autor, mientras que en español dicho signo se corresponde exactamente con la 'y' (por tanto los artículos en español utilizarán solo la 'y'); otra diferencia puede ser en los títulos de los artículos, puesto que en inglés se pone en mayúscula la primera letra de muchas de las palabras, mientras que en español sólo ponemos la primera…

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.

Artículos originales. Serán preferentemente trabajos de investigación clínicos o experimentales sobre el campo de las drogodependencias o las adicciones. Pero también pueden ser aceptados trabajos teóricos o de otro tipo.

Informes breves. En esta sección se considerarán los trabajos de investigación que por sus características especiales (series con número reducido de observaciones, casos clínicos, trabajos de investigación con objetivos y resultados muy concretos, estudios epidemiológicos descriptivos, primeros resultados de un estudio amplio, etc.) pueden ser publicados de forma abreviada y rápida.

Artículos de revisión. Presentarán la actualización de un tema de forma rigurosa y exhaustiva. Deberán regirse normalmente por metodologías sistematizadas. El contenido del artículo podrá llevar los apartados necesarios para la mejor comprensión de los lectores. En su parte final debe aparecer un apartado de discusión o conclusiones. La extensión preferiblemente no debería superar las 5.000 palabras, pero siempre que esté justificado, se admitirían revisiones más largas.

Cartas al Director. Tendrán normalmente un máximo de 800 palabras, 10 referencias y una tabla o figura. Pueden consistir en una presentación breve sobre algo novedoso, una investigación original, o la contestación o matización a un artículo publicado en la revista. Cuando sea éste el caso la carta tendrá que recibirse dentro de las 6 semanas subsiguientes a la publicación del artículo en el número de la revista

PRESENTACIÓN DE LOS TRABAJOS

Envío electrónico. La forma más rápida y preferente de enviar artículos para su revisión editorial es a través de www.adicciones.es. Allí encontrará todas las instrucciones a seguir y la forma de adjuntar el original. Todo el seguimiento del proceso de revisión y editorial se realizará a través de la web (a través de la plataforma de RECYT). Ésta es la única forma prevista para envío de artículos (pero si tiene alguna duda puede comunicarse con secretaria@adicciones.es). Será muy útil para facilitar el proceso de revisión que en el momento del envío del artículo proporcione a través de la misma plataforma información sobre por lo menos dos posibles revisores para su artículo (nombre, institución y correo electrónico). Estos revisores deberán ser expertos en el tema y no estar ligados a la investigación que se desarrolla en el trabajo presentado. Tampoco podrán pertenecer al actual Comité de Redacción o Editorial. La revista se reserva la decisión de utilizar o no dichos revisores propuestos. El editor señalará además normalmente otros revisores. Recordar que el proceso de revisión es anónimo para los autores. Caso de que no fuese posible por alguna razón o tuviese algún problema con el envío del artículo a través de la web, le agradeceremos que se ponga en contacto con secretaria@adicciones.es o al teléfono (+34) 971727434 o a Editor de Adicciones. Rambla, 15, 2ª, 3ª. 07003 Palma de Mallorca.

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

1. En la *primera página* del artículo se indicarán, en el orden que aquí se cita, los siguientes datos:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

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

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

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). *Dosis omitidas. Medidas que evitar la omisión de dosis:* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y 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. *Omisión de la segunda dosis de inicación (> 4 semanas desde la primera inyección):* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección):* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (> 7 semanas desde la primera inyección):* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes o 4 semanas):* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (> 6 semanas o 1 mes):* 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 150 mg:* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg:* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (> 6 meses):* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *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 psicótica 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 cardiaca, 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* 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 períodos 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 alimentarias. 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 faringoalaríngeo, 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[d], 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. Prolactinemia: En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado Torsades de pointes y fibrilación ventricular en un paciente en relación con la sobredosis de paliperidona oral. En caso de sobredosis aguda, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. Administración: Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. Tratamiento agudo de la esquizofrenia: La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de Xeplion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xeplion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xeplion fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xeplion en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

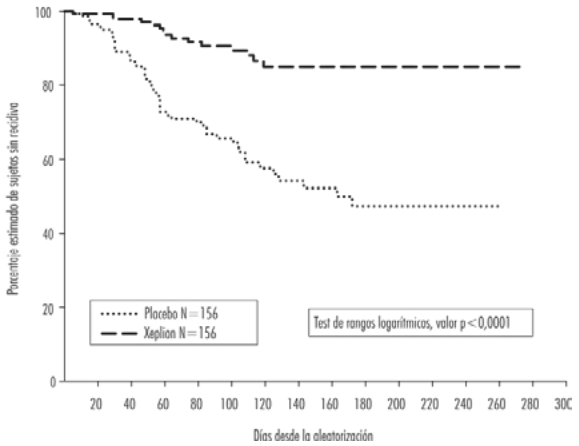
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de el 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 vitro 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 (ClCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (ClCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (ClCl =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{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 cancinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico 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. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada PVL: 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 deba 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 de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥ 90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso < 90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dada la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía. 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 $<1 \times 10^9$/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 libido, nerviosismo, pesadillas	estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[e], acatisia[e], sedación/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 faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía

Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, edema lingual, incontinencia fecal, fecaloma, queilitis	obstrucción intestinal, íleo
Trastornos hepatobiliares		niveles elevados de transaminasas	niveles elevados de gamma-glutamiltransferasa y de enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción farmacológica, hiperqueratosis, caspa	angioedema, trastornos de la pigmentación, dermatitis seborreica
Trastornos osteomusculares y del tejido conjuntivo		dolor osteomuscular, dolor 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%]).

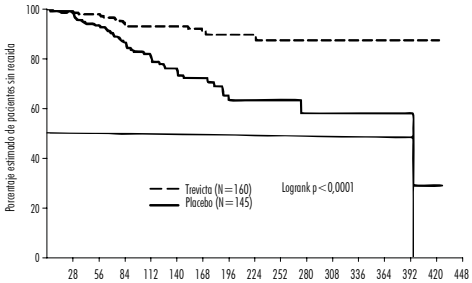


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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.

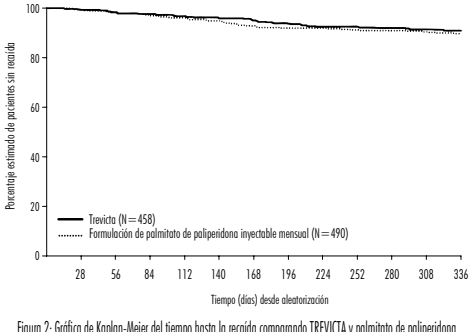


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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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