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New forms of drug use: An overview

Una aproximación al panorama actual de las nuevas formas de consumo de drogas

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Drug use is deeply rooted in Western 'culture' and its use is related to traditions, celebrations or leisure space. However, such use is not free of risks that depend on the amount, frequency and pattern of consumption, as well as the characteristics of the consumer such as age, sex and some health conditions. Despite mounting scientific evidence proving the toxicity of drugs, their supply and demand for them continues to grow, mainly due to the appearance or rediscovery of new psychoactive substances and the 'attractiveness' of new forms or patterns of use. Paradoxically, although concern aroused by these new consumption patterns is rising, very few studies have been carried out in Spain that analyze this issue.

While we know that adolescence is usually a time of searching and experimentation, and that many young people try substances without necessarily implying that they have an addiction problem, the available evidence points to the appearance of addictive behaviours at increasingly younger ages (Rial, Golpe, Barreiro, Gómez & Isorna, 2020). Although the latest Spanish national survey on drug use in secondary education (Encuesta Estatal sobre uso de Drogas en Enseñanza Secundaria, ESTUDES, 2021) shows that the consumption of all psychoactive substances in general is decreasing slightly, alcohol and cannabis use among the young Spanish population is higher than the European average (ESPAD, 2019), and other forms of consumption such as electronic cigarettes (EC) continue to gain popularity. Our aim was therefore to review these new forms and patterns of use and their possible social health implications, especially for the youngest.

ALCOHOL

According to the ESTUDES survey (Plan Nacional sobre Drogas, 2021), 311,200 students (boys: 152,500, girls: 158,000) started drinking alcohol during the last year, a number slightly lower than that obtained in the two previous reports. In addition, approximately 6 out of 10 students drank alcohol in the last 30 days, and 40% of students said they got drunk in the last 12 months, while 23.2% did so in the last month, with more girls reporting getting drunk than boys, and 27.9% doing 'binge drinking', i.e., having five or more alcoholic beverages in an interval of approximately two hours. This phenomenon has been aggravated in recent years with the proliferation of macro-festivals (approximately 900 a year in Spain), which are mostly financed by the alcohol industry (Torres, 2020). It must be stressed that large amounts of alcohol are drunk before, during and after them, so much so that for this reason many festivals often use a variety of methods to prevent minors from drinking; an example is the use

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of bracelets to differentiate between older and younger festival goers (Adán, 2018).

In addition to binge drinking, other new forms of consumption have emerged, mainly in an attempt to reduce the price of getting drunk as well as the time needed to reach drunkenness; most are imported from the UK and USA, and use other mucosal surfaces of the body than the digestive tract. We can highlight among them:

1. **Eyeballing**: this involves the direct application of alcohol on the ocular mucosa. The alcoholic effect thus achieved is probably low, but as this is generally practised after significant amounts of alcohol have already been drunk, users speak of a greater 'high'. This practice presents a high risk of serious corneal injuries with eventual blindness (Bersani et al., 2015).
2. **Alcohol without liquid** or AWOL: alcohol is ingested in nebulizer devices alongside oxygen, as in bronchodilator treatments. This presents a greater surface area for absorption and speed of action by bypassing the liver filter. This practice could give rise to or worsen pulmonary pathologies. In 2011, the Balearic Islands Public Health Office banned such dispensers of inhaled alcohol shots on the grounds of possible health risks (Saenz, 2011).
3. **Vodka tampon**, also known in Spain as 'tampodka' or 'tampax on the rocks': this consists of the application in the vagina or the anus of tampons previously soaked in alcohol, generally vodka. It produces very rapid absorption and initially avoids alcohol breath, which is why it seems to be popular among adolescents to circumvent parental control. The practice causes an increased incidence of lesions and infections in the mucous membranes. Although considered to be an urban myth (Caudevilla, 2015), cases of this have been recorded in Spain (Fonseca, 2013).
4. Another common practice among young people is to mix **alcohol with energy drinks** (high in caffeine, taurine and guarana). This mixture can lead to more alcohol being consumed due to the false sense of 'control', risks being taken while driving and alcohol dependence being favoured in the medium term (Arria et al., 2011). Because users underestimate their state of intoxication, they tend to stay up later, thereby increasing consumption and engaging in risky behaviour (Burillo-Putze, Hernández & Echeverría, 2012; Oteri, Salvo, Caputi & Calapai, 2007). Using this type of energy drink can cause anxiety, nervousness, insomnia, palpitations, and even atrial fibrillation, seizures and myocarditis (Baez-Ferrer et al., 2020; Izquierdo et al., 2012). For these reasons, the US Food and Drug Administration has initiated a process to outlaw existing caffeinated alcoholic beverages, such as the popular Four Loko, which takes its name from the four types of stimulants it uses: caffeine, taurine, guarana and wormwood (absinthe) and has an alcohol content of 12% (O'Brien, McCoy, Rhodes, Wagoner & Wolfson, 2008; Rehm, Shield, Joharchi & Schuper, 2012). In Spain, the Jägerbomb has been very successful among young people since 2014. This is a fashionable mixture among young Spaniards, particularly at botellones (drinking in public spaces) and combines the German liqueur Jägermeister (35% alcohol) with energy drinks (mainly Red Bull). After reaching Spain as a 'cool shot', the cocktail has become very popular on social networks for some time and its notoriety is growing.

Another form of consumption that can be highlighted are alcoholic jellies or 'drunk gummy bears', basically consisting of pouring the alcoholic beverage into a container full of gummy bears (or another type of gummy bear with similar characteristics), covering it with plastic wrap and leaving it in the fridge for 24 hours. After absorbing the liquid, the gummies are ready to eat, with approximately 17 gummies equalling one drink). This formula has been so successful that its sale and distribution has been industrialized (https://ositosconalcohol.com/).

Another substance incorporated into leisure environments by young people looking for a 'high' is **purple drank** (also called 'lean', 'sizzurp' or 'purple syrup'), a term that refers to a mixture of 'cough syrup' (promethazine hydrochloride), soda (usually Sprite) and/or alcohol, plus Jolly Ranchers for flavour (Agnich, Stogner, Miller & Marcum, 2013; Elwood, 2001; Hart, Agnich, Stogner & Miller, 2014; Miuli et al., 2020). Users without access to promethazine syrup sometimes use another cough syrup containing codeine (Chiappini, Schifano, Corkery & Guirguis, 2021). The Spanish Agency for Medicines and Health Products (2016) recommends special attention to the use of dextromethorphan due to its adverse effects and possible hallucinogenic effects in high doses (Lessenger & Feinberg, 2008). Promethazine abuse has been linked to deafness (Blakley & Schilling, 2008) and even death (Chiappini, Schifano, Corkery & Guirguis, 2021; Hart et al., 2014).

Possibly with the aim of attracting young people, the industry has created a series of drinks in the last decade called **'alcopops'**, 'designer drinks' or 'flavoured alcoholic beverages' (FABs), also known as ready-to-drink beverages (RTD). Globally, the most popular FABs are products such as Bacardi Breezer, Smirnoff Ice, Mike's Hard Lemonade, Ron Cacique Mojito and Two Dogs (Buglass, 2011; Manzoni, 2014). What really sets them apart is not so much their alcoholic content (ranging from 3.5% to 20%) but the associated innovation, design and marketing, as well as the style of presentation (packaging). Characters are used suggesting cartoons, comic strips, juvenile symbols, attractive sexual connotations, special containers that cannot remain upright alone (similar to a laboratory 'test-

tube') and need to be hand held, sweet flavours simulating children's tastes and masking the taste of alcohol, strong and sometimes luminous colours; in short, all elements that make this type of drink very attractive to young people (Buglass, 2011). Many years ago, Pascual (2002) already pointed out how young people, especially aged 14-15, were becoming familiarized with this type of drink, a process particularly noticeable among girls.

Another worrying pattern of alcohol consumption has arisen alongside binge drinking, mainly in young women: **drunkorexia** or **ebriorexia**, a term used for the first time in the The New York Times (Kershaw, 2008), describes the behaviour of young people who restrict the intake of foods with high caloric value in order to drink alcoholic beverages in excess. People exhibiting these behaviours generally know the energy content of alcoholic drinks and try to balance their food intake accordingly to avoid increasing their body weight. Unfortunately, maintaining this 'balance' leads them to stop eating drastically in order to drink excessively (Chambers, 2008). The usual pattern of drunkorexia includes counting the calories of the food and drink to be ingested, not eating for hours or entire days before drinking, and then increasing physical activity to burn off the excessive calories consumed (Martínez, López-Espinoza, Navarro Meza, López-Uriarte & Salazar Estrada, 2014). This seems more common among college women between the ages of 18 and 24 with body image distortion (Pietrabissa et al., 2018). Drunkorexia can have serious physical and psychological consequences (Villarino, 2012).

TOBACCO

According to ESTUDES (2021), just over 169,600 secondary school students began smoking during 2021 in Spain, more of them girls than boys (95,100 and 74,500, respectively). After alcohol, tobacco is the second most widespread drug among students aged 14-18 years. Regarding forms of consumption, 49.2% declared consuming both pack cigarettes and rolling tobacco or 'roll-your-own' (RYO) in the last 30 days, with 22.5% already using only RYO, which is almost double the 2019 figure of 14.1%. The belief among smokers that RYO represents a lower health risk, contains fewer additives and is less harmful, or the ritual involved in its preparation are the main reasons for this increase (Brown et al., 2015). Some studies, however, have found higher concentrations of nicotine, tar, and carbon monoxide (Laugesen, Epton, Frampton, Glover & Lea, 2009). Moreover, RYO smokers show a higher risk of cancers of the mouth, larynx, pharynx, and lung than smokers of conventional cigarettes (Rolke, Bakke & Gallefoss, 2009; Young et al., 2012). The false belief that RYO is less harmful to health is greater in young people, yet the contents of nicotine, tar and carbon monoxide reach values of up to 70%, 85% and 84%, respectively, higher than permitted for conventional cigarettes (Calduch, Jiménez, San Segundo, Valle & Carlos-Roca, 2012). More nicotine means greater addictive power; more tar and carbon monoxide lead to a greater capacity to produce disease. Research has also shown that RYO users tend to be more addicted (Joseph et al., 2018) and younger than traditional cigarette smokers, as well as belonging to low-income social groups (Young et al., 2012).

At the same time, **vaping** has been normalized in recent years through **electronic cigarettes (EC)** as a substitute or complement to traditional cigarettes. Despite being presented as a safe and apparently effective means to achieve cessation of conventional cigarette smoking, they have turned into what has been called a Trojan horse, since their use exposes many adolescents to similar or even higher levels of nicotine than conventional cigarettes (Jackler & Ramamurthi, 2019). Thus, according to ESTUDES (2021), 44.3% of Spanish students between the ages of 14 and 18 have used ECs on some occasion. Consumption among men was 46.9%, and 41.7% in women. It is noteworthy that of every 10 students who have smoked tobacco on some occasion, eight of them have used ECs. The most remarkable thing, however, is that of every ten students who have never smoked tobacco, three have used ECs on some occasion. Among those having smoked ECs, only 8.5% have done so to reduce or quit smoking (with a slightly greater proportion of boys, 9.3%, than girls, 7.6%), although its effectiveness for smoking cessation is being strongly questioned (Córdoba, 2014; El Dib et al., 2017; Signes-Costa et al., 2019). Because these devices produce an aerosol from heating liquids containing solvents (glycerine, propylene glycol), one or more flavouring agents, nicotine, and sometimes cannabis derivatives (mainly THC and CBD), they have been sold as an alternative way of obtaining the effect of nicotine and THC without being exposed to the deleterious effects of the other components of a conventional cigarette or 'joint' (Budney, Sargent & Lee, 2015; Monraz-Pérez, Regalado-Pineda & Pérez-Padilla, 2015). Therefore, there is currently a false sense of security which has favoured the acceptance of CE consumption and great confidence in using them, including the consumption of cannabis derivatives; according to ESTUDES (2021) 5.3% of adolescents (6.7% boys; 3.7% girls) who have used cannabis in the last 30 days have smoked it with this mechanism. In reality, however, ECs do emit volatile carbonyls and metals (nickel, lead, chromium), many of which are toxic to the lung (Gotts, Jordt, McConnell & Tarran, 2019). With an average growth of 25% per year, the number of vapers in Spain stood at over 562,500 in 2018, producing an €88 million turnover for the sector in Spain (Upev, 2019), the market leader of which is JUULpods. In the US, the use of this EC brand is considered a 'youth epidemic'. It is presented with a

USB stick design (and is actually charged by connecting via USB to a computer or socket), into which capsules are inserted with liquid flavours which are very attractive to young people, such as mango, mint, crème brulée, Virginia (original tobacco flavour), cucumber, etc. The liquid contains different chemicals, but the big difference to other electronic cigarettes is that it uses nicotine salts. Vaping an entire capsule (a JuulPod) is equivalent to smoking about 20 cigarettes.

CANNABIS

According to ESTUDES (2021), an estimated 155,800 students started using cannabis in 2018, with slightly more girls (83,200) than boys (72,600). The age of initiation of cannabis use is under 15 years. It is important to highlight that the damage caused is inversely proportional to the age of onset, so that it is four times higher if starting at age 15 (current average age of onset in Spain) than at age 26; it is estimated, for example, that up to 8% of the incidence of schizophrenia in the adult population of smokers could be linked to the use of cannabis in young people (Di Forti et al., 2019; Marconi, Di Forti, Lewis, Murray & Vassos, 2016). It has been shown that even occasional cannabis use can produce structural and cognitive changes in the brain of adolescents (Orr et al., 2019). It is also associated with an increased risk of suffering from behavioural disorders and psychosis, a risk which increases with greater frequency of use and greater potency of cannabis used (Di Forti et al., 2019). Without doubt, the scientific evidence regarding the risks and the organic, psychological and social consequences associated with its use are increasingly robust (Rial et al., 2018; Volkow et al., 2016; WHO, 2016).

Alongside traditional smoking and vaping, **hotboxing** stands out among the new forms of cannabis use. This consists of several consumers inhaling the smoke or aerosol of marijuana, hashish or butane hash oil (BHO) in a small, enclosed space, for example cars, very large motorcycle helmets, pantries, phone booths, tents, or closets. This can be harmful due to the accumulation of CO2 and the increase of other toxins and the transmission of other diseases (Oeltmann et al., 2006). Another practice on the rise is **'Shotgunning'**, the inhalation of illicit drug smoke which is then exhaled directly into another's mouth (Perlman et al., 1997). This is linked to greater addiction severity and riskier behaviours, with users showing little awareness of the risk of transmitting diseases via the respiratory tract (Welsh et al., 2012). Both Hotboxing and Shotgunning are forms of social use and have been associated with the transmission of infectious diseases such as tuberculosis (French et al., 2019; Oeltmann et al., 2006).

Cooking/baking (cookies, cakes, brownies) is the most popular method among young people after smoking, with 1.4% ingesting THC through one of these products in the last 30 days (2% of boys and 0.7% of girls). Because absorption is slower, effects have delayed onset (with a mean peak plasma concentration 1 to 2 hours after ingestion, in contrast to 5 to 10 minutes for peak plasma concentrations when smoked), but the intoxication lasts longer (Hazekamp, Ware, Muller-Vahl, Abrams & Grotenhermen, 2013). Due to this delayed effect of edibles, it is possible to consume several servings in a row before the 'high' from the initial serving is felt. Consuming a large dose of THC can thus lead to a higher concentration of THC, greater intoxication and a higher risk of adverse effects (Hancock-Allen, Barker, VanDyke & Holmes, 2015).

Dabbing is a way of consuming a cannabis concentrate in the form of oil, also called 'budder', 'dab', 'shatter' or 'BHO (butane hash oil)'. Its extraction requires a very dangerous and complex process involving highly flammable chemicals such as butane gas or carbon dioxide. The resulting sticky oil, or 'dab', can reach up to 80% THC compared to 5-20% in traditional cannabis derivatives (Stogner & Miller, 2015). The 'dab' is added to the dabbing device, heated, and then nebulized into an aerosol that is inhaled deeply in a single breath and held in the lungs for several seconds (Anderson & Zechar, 2019; Raber, Elzinga & Kaplan, 2015). Due to its high THC concentration, the risks of dependence and intoxication are very high (Stephens, Patel, Angelo & Frunzi, 2020).

It is important to consider the route of administration of cannabis because the psychotropic effects after inhalation by smoking occur within minutes and last 2 to 4 hours, while the effects of oral consumption generally occur within 30 to 60 minutes and last up to 12 hours (Goldsmith et al., 2015; Monte, Zane & Heard, 2015).

Other forms of consumption known among cannabis users are: cannabis soaked in alcohol, which basically consists of obtaining an alcohol-based cannabis oil tincture, cannabis infusions, or creams or suppositories for transdermal use (Isorna, Villanueva, Veiga & Otero, 2020; Ramos, 2017).

With its street label of 'synthetic marijuana' and the confusion created in many consumers, younger users of synthetic cannabinoids (also known as 'Spice', or 'herbal incense') are more and more frequently found in addiction care. These substances are used because they can be easily and cheaply acquired, and are difficult to trace in toxicological control since they are not detected in police cannabis checks nor in ordinary urine or blood tests. They are preparations of various dry herbs smeared with synthetic cannabinoids, the vast majority of them from the JWH family (JWH-018, CP-47,497, CP-47,497-C8 and HU-210), which are smoked, although in principle no tobacco or marijuana is involved. These compounds comprise more than 100 substances with different chemical structures that have in common their action on the CB1 cannabinoid receptor but, unlike THC, a partial

agonist, they are usually full agonists and much more powerful than THC, which means psychoactive effects are more potent but of shorter duration, so redosing and overdosing are more likely (Su, Seely, Moran & Hoffman, 2015). They are advertised as natural herbs with the intention of minimizing the sense of danger (Dolengevich-Segal, Gómez-Arnau, Rodríguez-Salgado, Rabito-Alcón & Correas-Lauffer, 2014). There are other Spice-type products that contain vegetable preparations, such as Zen, Skunk or K2, differing in name, labelling, and the type of cannabinoids they contain. Names and presentations are constantly evolving to evade legal control. Prices range from €9 to €12 per gram, which makes it a very cheap drug. Its psychoactive effects are similar to those of cannabis, but with more adverse effects since they can act on other receptors, and kidney, heart, digestive and neurological problems have been described which do not occur with cannabis (Tung, Chiang & Lam, 2012). Some cases of toxic schizophreniform psychosis have been described (Müller et al., 2010), and there is talk in user forums of transient psychotic symptoms, although the influence of this substance on sustained psychotic symptoms has also recently been reported (Durand, Delgado, Parra-Pellot & Nichols-Vinueza, 2015; Papanti et al., 2013). Exacerbation of psychoses, induced psychoses and persistent psychoses have been described with these substances, giving rise to the proposed term 'spiceophrenia' (Papanti et al., 2013).

Waterpipe smoking, a very harmful new trend

According to the EMCDDA (2020), slightly more than 47% of students have smoked tobacco using waterpipes, with no significant gender differences being observed. This practice is considered to be a new threat in the global fight against tobacco and its consequences (Maziak et al., 2015; WHO Study Group on Tobacco Product Regulation, 2015). Similarly, with regard to how cannabis is used, the joint or spliff is the most widespread form (91.4% of student users), followed by 'waterpipes' 'hookahs' or 'shishas' (10.3% of users, of which boys 14.3%, girls 5.8%) (PNSD, 2021). The rise in the number of users is based on a series of myths such as that smoking a waterpipe is healthier because the smoke is believed to cool before entering the lungs, that the water that is part of the mechanism that filters the toxic substances in tobacco, that waterpipe smoke is less irritating to the throat and respiratory tract, or that fruit-flavoured tobacco is less harmful, beliefs that are false. In addition to tobacco smoke, waterpipe smokers inhale the smoke from the charcoal tablets used to light the tobacco, thereby inhaling the gas produced by the combustion of coal, which contains heavy metals that pose a significant health risk (Pratiti & Mukherjee, 2019).

With several people sharing a pipe, waterpipe smoking is an eminently social practice, i.e., everyone inhales through the same mouthpiece that passes from mouth to mouth, thereby representing a source of infectious disease transmission (Sterling & Mermelstein, 2011). In addition, more and more adolescents and young people are mixing tobacco with cannabis derivatives (marijuana and/or hashish) and substituting water with alcoholic beverages, thus undoubtedly making this practice even more dangerous.

While the water filter may lead smokers to believe that waterpipe smoking is harmless or less harmful than direct cigarette or joint smoking, the smoke thus inhaled contains, in addition to nicotine and THC, toxic compounds such as carbon monoxide, formaldehyde, polyaromatic hydrocarbons, arsenic and lead (Albisser, Schmidlin, Schindler, Tamm & Stolz, 2013) Risks are therefore multiplied exponentially, since, in addition to the known risks of tobacco and cannabis, other new derivatives of coal burning are incorporated. Primack et al. (2016) compared smoking tobacco in a waterpipe session with smoking a single cigarette and showed that waterpipe use meant inhaling 56 times more smoke, 25 times more tar, 2.5 times more nicotine and 10 times more carbon monoxide. Some experts have calculated that a single waterpipe session amounts to smoking between 25 and 50 cigarettes (Cobb, Schihadeh, Weaver & Eissenberg, 2011).

We must emphasize that waterpipe tobacco smoking is on the increase and affects the youngest above all. Permissive social attitudes favour its use among adolescents, and this is undoubtedly a factor in initiating the smoking of cigarettes and perhaps other substances such as cannabis and its derivatives.

From hypnosedatives (with or without a prescription) to pharming

In clinical toxicology, 'pharming' is the misuse of prescription drugs for 'recreational' purposes, generally by someone other than the patient for whom they were prescribed, and with a dose other than indicated as therapeutic, to seek some of their psychoactive effects (Burillo-Putze et al., 2013). While this is a widespread phenomenon among adolescents and young people in the United States, the practice in recreational and nightlife contexts is also increasing in Europe (United Nations Office on Drugs and Crime, 2011). There are few data on the phenomenon of 'pharming' in Spain, where it began to be studied in the form of tranquilizer and sleeping pill use with or without a prescription in the 2005 EDADES survey. Between 2005 and 2018, there was a significant increase in the prevalence of lifetime use, from 5.1% in 2005 to 19.6% in 2018 (ESTUDES, 2021). This type of substance use is more widespread among girls.

Being perceived as safe without the supervision of a health professional, 'pharming' has become a common

practice among young people (Schifano & Chiappini, 2018), with a series of factors influencing its growing popularity: the drugs are easily accessible both in the home medicine cabinet and through direct prescription-free acquisition in pharmacies or through the Internet (Burillo-Putze et al., 2013); the substances are legal and the perception is that, being medicines, they are safe products and much less dangerous than street drugs; parents or other relatives or acquaintances do not perceive their use to be a type of drug use. In addition to the inherent danger of abusive consumption itself, the risk is increased when several drugs are used together, often mixed with alcohol or other drugs (Burillo-Putze et al., 2012). As an example, the so-called 'trail mix' has been observed among young Americans. In this group phenomenon, each participant brings a collection of drugs from their home medicine cabinet; the drugs are then all mixed in a container for random consumption (Prosser & Nelson, 2012). Another aspect to take into account with pharming is the possibility that it serves as a gateway to the consumption of other illegal drugs, as is the case with 'cheese', a mixture of heroin and anti-flu medicine (mainly diphenhydramine and acetaminophen), which causes euphoria and hallucinations on inhalation and has become known as 'starter heroin' (Maxwell, Coleman, Feng, Goto & Tirado, 2012). Resources and suggestions for possible substance combinations to increase the euphoric effect of loperamide are also easily accessible on the internet (e.g., http://www.bluelight.ru; http://www.drugs-forum.com).

The European Medicines Agency (Schifano & Chiappini, 2018) has observed an increase in recent years both in the prescription and in the availability of second-generation antipsychotics (SGA) such as quetiapine. Another example is **loperamide**, which when used at low doses is a potent mu-opioid receptor agonist and when consumed in large quantities (more than 50 mg) produces euphoric effects, central nervous system depression, possibly stronger initial euphoria followed by CNS depression and cardiotoxicity (Eggleston, Clark & Marraffa, 2017; Schifano & Chiappini, 2018). It is also known as 'poor man's methadone' (Stanciu & Gnanasegaram, 2017).

Finally, consideration of the phenomenon of 'pharming', should not only focus on its use in leisure or recreational spaces, but should also take into account the use of medications to sleep or rest, and also to stay awake, among those people who have to work at night or study during exam times or to combat the effect of medications or drugs that prevent them from falling asleep (Alfaro & Hernández, 2019; Bennett & Holloway, 2017).

Conclusions

The data presented by the PNSD and the EMCDDA reveal how widespread drug use is in today's society, reflecting a change both in the substances themselves and in their patterns of use and even in the epidemiological profile of consumers. This implies the need to update knowledge on how to approach possible medical and psychopathological complications. We find ourselves up against a new, changing panorama and with scarce empirical data, which is a challenge for professionals dealing with these new forms of drug use and their consequences. New substances and hitherto unknown channels of access, sale and distribution of drugs call into question current methods of surveillance, detection and prevention. The anonymity offered by the internet, the simplicity of online ordering, the low prices and, occasionally, the absence of a legal framework, broaden their use among the youngest.

The use of drugs and new forms of use is a major problem affecting the personal, work and family life of many people and leads to another type of consumption that, until recently, was scarcely valued: that of health system resources. As Nogué, Amigó and Galicia (2014) suggest, substance use is no longer an individual problem; it is by rights something that affects all of society. Drug users should be aware that their final destination may be an emergency service or, on other occasions, a Medico-Legal Institute.

Conflict of interests

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Smoking in hospitalized patients. A great opportunity

Tabaquismo en pacientes hospitalizados. Una gran oportunidad

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Abstract

The objective of this study is to describe the characteristics of smokers admitted to different medical and surgical services in a university hospital and the perception of patients regarding the need for a specialized intervention. The sample comprises a total of 307 patients (mean age of 59.4 years), being 40% (n = 123) non-smokers, 42.7% (n = 131) ex-smokers, and 17.3% (n = 53) smokers. The average consumption of smokers was 22.2 cigarettes / day and the severity of nicotine dependence evaluated with the Fagerström test exceeded 5 points in more than half of the sample. On the other hand, 77.7% had made at least one previous attempt to quit tobacco use. Almost the entire sample (89.9%) of smokers and ex-smokers considered it necessary to develop tobacco treatment programs during hospitalization. Finally, the importance of the hospital context is argued as an opportunity to address the cessation of smoking. The data obtained in this study will allow focusing more appropriately on the management of these patients and optimizing resources.

Keywords: Characteristics of smoking; hospital care; treatment of smoking; inpatients smokers; smoking cessation.

Resumen

El objetivo de este estudio es conocer las características de los fumadores ingresados en diferentes servicios médicos y quirúrgicos en un hospital universitario y la percepción de los pacientes respecto a la necesidad de una intervención especializada. La muestra comprende un total de 307 pacientes (edad media de 59,4 años), siendo un 40% (n = 123) no fumadores, 42,7% (n = 131) exfumadores, y un 17,3% (n = 53) fumadores. El consumo medio de los fumadores era de 22,2 cigarrillos/día y la gravedad de la dependencia a la nicotina evaluado con el test de Fagerström sobrepasaba los 5 puntos en más de la mitad de la muestra. Por otra parte, el 77,7% había realizado al menos un intento previo de abandono del consumo de tabaco. Casi la totalidad de la muestra (89,9%) de los fumadores y ex fumadores consideraba necesario desarrollar programas de tratamiento del tabaquismo en la hospitalización. Finalmente se argumenta la importancia del contexto hospitalario como oportunidad para abordar la cesación del hábito tabáquico. Los datos obtenidos en el presente estudio permitirán enfocar más adecuadamente el manejo de estos pacientes y optimizar los recursos.

Palabras clave: Características del tabaquismo; atención hospitalaria; tratamiento del tabaquismo; pacientes hospitalizados fumadores; cesación tabáquica.

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Smoking is responsible for serious ilnesses, causing millions of smokers to be hospitalized every year for tobacco-related diseases (Thomsen, Villebro & Moller, 2014). These admissions could be an opportunity to implement smoking cessation programs. Indeed, treating hospitalized patients who smoke not only helps restore health, it also improves the social atmosphere and compliance with legislation, which since 1988 (RD 192/88) prohibits smoking in health centers (Royal Decree 192/1988, Law 28/2005.

Containing tobacco use is one of the criteria for hospital accreditation by the *Joint Commission on Accreditation of Healthcare Organizations (JCAHO)* and one of WHO's priorities for Europe (Fiore, Goplerud & Schroeder, 2012). The analysis of tobacco consumption trends in Spain suggests that efforts in smoking prevention and control policies should not be reduced (Leal-Lopez, Sanchez-Queija & Moreno, 2019) since the implementation of measures such as law 42/2010 have led to a reduction in smoking (Rodriguez Munoz, Carmona Torres, Hidalgo Lopezosa, Cobo Cuenca & Rodriguez Borrego, 2019).

A hospital stay could be an optimal time to quit smoking. We currently have data that indicate better withdrawal rates when treatment is initiated in patients during hospital admission (Rigotti, Clair, Munafo & Stead, 2012). With regard to the efficiency of interventions to help hospitalized patients to quit smoking, a hospital intervention consisting of advice on admission to quit smoking, pharmacological treatment plus post-discharge follow-up has a cost per year of life gained, adjusted for quality (QALY), of 1,386 Canadian dollars. It has been estimated that the provision of this type of treatment for 15,326 hospitalized smokers would cause 4,689 of them to quit and serve to avoid 116 rehospitalizations, 923 days of hospital stay and 119 deaths (Mullen et al., 2015).

According to Spanish National Institute for Statistics (INE) data, in 2013 there were 4,637,427 hospital admissions in Spain. Cardiovascular diseases, which accounted for 13.3% of the total, and those of the respiratory system, 10.9%, are frequently caused by smoking. Between 15 and 27% of patients admitted to Spanish hospitals are smokers (Alonso-Colmenero, Diez de, Alvarez & de Oteyza, 2010; Nieto Garcia, Abdel-Kader Martin, Rosado Martin, Carriazo Perez de Guzman & Arias Jimenez, 2003) and 20.6% of hospitalized COPD cases are active smokers (Pozo-Rodriguez et al., 2010). In other countries, a prevalence of smoking in asthmatic patients of 36% has been documented (Bittner et al., 2016) and up to 54.5% in those with HIV (Fitzgerald et al., 2016). The higher prevalence of smoking in the HIV/AIDS population than in the general population affects its prognosis, and it has been recommended to start smoking treatment during hospital stays (Mussulman et al., 2018). In the area of mental health, it has been observed that patients with severe mental disorder or with affective disorders have higher smoking prevalence than the general population and a life expectancy up to 10 years lower than that of the general population (Bobes, Arango, Garcia-Garcia & Rejas, 2010; Jimenez-Trevino et al., 2019).

The scientific literature clearly indicates the pernicious effects of tobacco use on the most vulnerable people. Thus, heart patients experience more relapses of their disease if they continue smoking (Jimenez-Trevino et al., 2019; Mohiuddin et al., 2007). There is also recognition of the relationship between smoking and the possibility of developing postoperative pulmonary complications, which double in smokers with respect to ex-smokers and non-smokers (Bluman, Mosca, Newman & Simon, 1998; Borglykke, Pisinger, Jorgensen & Ibsen, 2008; Moller, Villebro, Pedersen & Tonnesen, 2002; Regan, Viana, Reyen & Rigotti, 2012; Taylor, Houston-Miller, Killen & DeBusk, 1990). Unfortunately, concrete actions in this regard have so far been minimal (Emmons & Goldstein, 1992; France, Glasgow & Marcus, 2001), although their effectiveness and efficiency are well documented in the literature (Lightwood & Glantz, 1997; Mullen et al., 2015; Sarramea et al., 2019a).

There are enough data in the international literature to recommend starting smoking treatment on admission to hospital and its follow-up after discharge (Jimenez Ruiz et al., 2017). The paucity of studies carried out in Spain is an important limitation when adapting the recommendations to our environment (Alonso, 2001; Jimenez Ruiz et al., 2017; Ortega et al., 2011; Roig Cutillas et al., 2001). In this regard, the recently published SEPAR Regulations (Jimenez Ruiz et al., 2017) features a literature search of studies related to aiding smoking cessation and, based on the results, indicates recommendations for the treatment of smoking in hospitalized patients. Since then the subject continues to be treated in international publications (Campos et al., 2018; Feterik et al., 2019; Vander Weg et al., 2017; Warner et al., 2016; Ylioja et al., 2017) although information regarding the Spanish population is still lacking.

The objective of the present study was to reveal the characteristics of smokers admitted to different medical and surgical services in a university hospital, as well as to assess the perception of patients regarding the need for specialized intervention, information which could be of interest in matching recommendations to the Spanish context.

Method

Descriptive cross-sectional study of a sample of patients admitted to the University Hospital of Valencia. The study variables referred to the smoking behavior of smokers and ex-smokers. The smoking questionnaire, administered by

a single interviewer, was complemented with information on epidemiological and clinical characteristics of patients.

Participants

The study sample was obtained incidentally: all patients admitted to various medical and/or surgical departments of the hospital (Cardiology, Thoracic Surgery and General and Digestive Surgery) with acute organic pathology were consecutively included for a period of time, 9 months, between January 1 and September 30, 2007. The selection of these hospital services was carried out for convenience based on their accessibility to the researchers and the agreement of the corresponding heads of department.

Sample size (n = 307) was calculated by applying the formula for estimating sample size when population size is unknown: $n = Z_{\alpha}^{2} \times p \times q/d^2$

Where:

$Z_{\alpha}^{2} = 1.96^2$ (given a desired confidence interval of 95%)

p = expected proportion (in this case 15%)

q = 1-p (in this case 1-0.15 = 0.85)

d = precision (in this case 4%)

Procedure

Interviews with smokers were conducted by a medical specialist in pulmonology, in the same room on the ward to which the patient had been admitted. An ad hoc questionnaire was used to record data and inform the patient of the type of help that could be offered to stop smoking. Depending on their stage of quitting smoking, they were given information specifying the risks of smoking and the benefits of giving up, and provided with a guide to quitting and helped to decide which day they would stop smoking. In each case the following methodology was followed.

Variables

The most relevant aspects of smoking behavior were investigated (age of onset, number of cigarettes smoked daily, whether or not they had a partner who smoked, previous attempts to quit smoking and reasons for failure), as well as other characteristics of the patient (profession and pathological background). For the purpose of this study, an "attempt to quit smoking" corresponds to "more than one day without smoking."

The assessment of the degree of physical dependence on nicotine was performed using the modified Fagerström nicotine dependence test (Jimenez Ruiz et al., 2017). Scores equal to or greater than 6 indicate a high degree of dependence.

Statistical analysis

The appendix contains the data collection sheet (an ad hoc questionnaire), as well as the codes assigned to the variables. As can be seen, the data were scored according to their nature, so that in the case of quantitative variables, real values were obtained, while categorical values were given in the case of qualitative variables. The results are expressed in relative frequencies.

For the descriptive analysis, the mean, standard deviation (SD) and range were calculated in the case of quantitative variables, while in the case of qualitative variables the number and percentage of subjects in each class were determined. In order to assess the existence of differences in the characteristics of smoking depending on the department in which the smoker had been hospitalized or on the main diagnostic categories (ischemic heart disease or cancer), the Kruskal-Wallis H test was performed. This is a non-parametric comparison test of three or more independent groups which allows us to decide if we can accept the hypothesis that k independent samples come from the same population or from identical populations with the same median. For statistical analysis and data exploration, a database was configured using the SPSS 18.0 program. A value of $p < 0.05$ was accepted for statistical significance.

Results

Among the 307 subjects included in the study, there were 123 non-smokers (40%), 53 smokers (17.3%) and 131 former smokers (42.7%), with a mean age of 59.4 years (SD 16.54 years, ranging from 16 to 88). All patients who were asked agreed voluntarily to answer the questionnaire. If they were not in their rooms, the researcher would come back later. Seventy percent had diseases associated with those that caused their admission, among them respiratory diseases in 17.2% and cardiovascular diseases in 27% of cases.

With regard to *employment*, 19.3% were homemakers, 3.6% public officials, 17.7% salaried employees, 6.6% business owners/self-employed persons, and 51.8% had other employment. The vast majority, 297, were of Spanish origin (97.4%), while 2.6% were immigrants or tourists.

Characteristics of smoking among smokers and ex-smokers

The *average consumption of tobacco* amounted to 22.2 cigarettes/day, SD 14.4, range 2-60 cigarettes/day. Only 16.7% of respondents smoked fewer than 10 cigarettes/day, while 66.1% smoked 20 or more cigarettes per day (Table 1). The *average age of smoking onset* was 16.1 years, SD 4.3, range 9-40 years (Table 1), and among the 290 who had a partner, 86 (28.2%) had a *partner who smoked*, while in 49 (16%) of cases the partner was an ex-smoker, and a non-smoker in 153 (50.2%).

With respect to the smoker's *process of change phase*, 37.3% were at the precontemplation stage, 28.8% at the contemplation stage, 1.7% at the stage of preparation for

Table 1. *Characteristics of the smoking habit in smokers and ex-smokers of the study.*

	Mean	Standard deviation	Limits
Tobacco use (cigarettes/day)	22.2	14.4	2-60
Age of onset (years)	16.1	4.3	9-40
Fagerström Test (score)	3.9	2.9	0-10

change and 32.2% in the action phase. The *physical dependence on nicotine, measured by the Fagerström test*, yielded an average score 3.9 points, SD 2.9 and showed that 49% of smokers had 4 points or fewer (low physical dependence on nicotine), 34% had 5-6 points (moderate physical dependence on nicotine) and the remaining 17% scored 7 or more points (high physical dependence on nicotine) (Table 1).

Evolution of smoking habit after diagnosis of illness.

At least one attempt to quit smoking was made by 77.7% of smokers and ex-smokers, while the remaining 22.2% did not remember making attempts to quit. In case of those who made unsuccessful attempts to quit, the causes of failure were the following: anxiety-nervousness 59.6%, social causes 12.8%, weight gain 23.4% and other reasons 4.3%.

In this regard, it should be noted that only 89 patients (48.4%) remembered that their doctor had advised them to quit smoking. Among the rest, 35 (18.6%) remembered the recommendation of family members or friends, while 34 patients (18.5%) did not remember any recommendation to quit smoking.

Perception of patients regarding smoking.

The vast majority (90.9%) of smokers and ex-smokers considered that smoking was very harmful to health, and 81.5% of them believed that smoking was very harmful to the health of people around them at home or in the workplace. Only 6.2% believed that it was not harmful to the health of household members or workplace colleagues. It is thus unsurprising that 89.9% of smokers and ex-smokers considered it necessary to develop smoking treatment programs, especially aimed at hospitalized patients who smoke.

The distributions of age ($p = 0.033$), national, immigrant or tourist origin ($p = 0.009$) and the perception of the need for a specific smoking program in hospitalized patients ($p = 0.007$) differed depending on the diagnostic category (ischemic heart disease, cancer or other diagnoses). In fact, patients in the diagnostic category "cancer" were the most likely to consider the implementation of smoking treatment programs during hospitalization, compared to those in the "ischemic heart disease" diagnostic category.

Stage of change and importance of smoking cessation

While 90.9% of smokers and ex-smokers believed that smoking is very harmful to health, 89.9% thought that it was necessary to implement smoking treatment programs during hospitalization. Those in the diagnostic category "cancer" were the most frequent supporters of this recommendation compared to those in the "ischemic heart disease" diagnostic category. The chronicity of the underlying pathology could have contributed to these differences.

In addition, it is worth highlighting that only 33.9% of smokers were in preparation or action phases, while the rest were not be willing to attempt to quit smoking in the short term, that is, during their hospital stay.

Discussion

The high prevalence of smokers found in this study, with data comparable to others published (Rigotti et al., 2000; Regan et al., 2012), demonstrates the expediency of starting smoking treatment during hospitalization, a time in which prevention and treatment of nicotine withdrawal must necessarily be confronted. In the same vein, it has been pointed out that smoking interventions in patients admitted to *Veterans Affairs Hospitals* require substantial changes in the behavior of doctors and improve follow-up after discharge (Ortega et al., 2011). Therefore, helping smokers to quit is one of the greatest prevention efforts in which hospitals can engage, although it is true that there are some barriers. The lack of expectations due to the absence of treatment resources, for example, and the cognitive impairment associated with certain pathological conditions (Sarramea et al., 2019b) could have contributed to these results in many cases. In order to accelerate the process of change phase of pre-contemplators and contemplators, it is necessary to provide information regarding the consequences of smoking, the benefits of quitting smoking in the particular prognosis and the existence of effective therapeutic alternatives (Jaen-Moreno et al., 2019). Likewise, the difficulties and heavy workloads facing the professionals themselves, in addition to the lack of training in the use of therapeutic instruments such as motivational interviewing, are some of the main obstacles to be overcome (Jimenez-Ruiz et al., 2013; Muquebil Ali Al Shaban Rodriguez et al., 2017). It has been pointed out that most hospitals avoid implementing the set of tobacco cessation measures because they require greater effort and resources (intensive identification, treatment, follow-up of all smokers) than other sets of hospital measures

(Fiore et al., 2012). To improve this situation, new forms of intervention and more training have been studied which also contemplate the use of computer systems to improve results (Jaen-Moreno et al., 2019; Muquebil Ali Al Shaban Rodriguez et al., 2017; Ylioja et al., 2017).

Among the smoking cessation interventions for hospitalized patients, health advice to stop smoking and drug treatment, or a combination of both, have been considered. The effectiveness of advice provided in the hospital by different health professionals when prolonged for at least one month after the hospital stay is greater than the standard treatment of the disease which motivated admission without specifically differentiated anti-smoking advice. With regard to drug treatments, a meta-analysis indicates that the effectiveness of intensive health advice (counseling during hospitalization which lasts at least one month after discharge) is significantly increased when treatment with nicotine supplements is added (RR 1.54; 95% CI 1.34-1.79) (Rodriguez Munoz et al., 2019). Counseling interventions during hospitalization which include a follow-up of at least one month after discharge increase abstinence rates. No significant effects of lower intensity interventions have been documented, i.e. those implemented only during hospitalization or for less than one month.

In spite of the limitations of our study, among which we highlight the small sample size, the absence of co-oximetry measurements and the time elapsed since the completion of the field work, the data highlight the existence of smokers with serious diseases associated with smoking who frequently enter hospitals without routinely receiving specialized care to treat smoking. These data are still valid today, largely due to the absence of more recent studies in Spain.

Fortunately, the vast majority of patients are aware of the harmful effects of smoking on their health and on the health of people around them, and would consider it very appropriate to participate in smoking treatment programs aimed at hospitalized patients. Therefore, we recommend the implementation of intervention programs for smokers who need to be hospitalized for various reasons. The aim would be to take advantage of hospitalization to facilitate the diagnosis and treatment of smoking, leading to better prognoses for patients and a reduction in health care costs.

In short, hospitalization is a unique opportunity to address the problem of smoking, during which diagnostic and treatment processes could begin. The data obtained in this study will allow us to focus more adequately on the management of these patients and optimize resources.

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Conflict of interests

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

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Appendix. Data collection sheet

Department 1. General and digestive surgery; 2. Thoracic surgery; 3. Cardiology
Diagnosis DIAGNOSTIC CATEGORY
1. Ischemic heart disease; 2. Others; 3. Cancer

NAME TEL.
CLINICAL HISTORY No
DAY AGE

EMPLOYMENT
1. Unemployed
2. Homemaker
3. Public official
4. Salaried employee
5. Business owner/Self-employed
6. Other

OTHER PATHOLOGICAL BACKGROUND
1. None
2. Respiratory diseases
3. Cardiovascular diseases
4. Depression
5. Other

ORIGEN
1. Spanish
2. Immigrant (…)
3. Other (tourist, etc.)

PARTNER WHO SMOKES
1. Yes
2. Yes, but quit
3. No
4. No partner

If you have never been a smoker, TICK HERE ___

If you are or have been a smoker,
COMPLETE THE FOLLOWING PAGES:

HOW OLD WERE YOU WHEN YOU STARTED TO SMOKE?

HOW MANY CIGARETTES DO YOU SMOKE PER DAY?

Since you were diagnosed with your illness,
HOW HAS YOUR SMOKING HABIT CHANGED?
1. I stopped smoking completely
2. I cut down on smoking
3. No change
4. I smoked more
5. I didn't smoke

Since your illness was diagnosed, HAS ANYONE RECOMMENDED STOPPING SMOKING COMPLETELY?
1. No
2. Yes, my physician or specialist
3. Yes, my spouse or other relative
4. Yes, my friends

Since you were diagnosed with your illness,
HAVE YOU MADE ANY ATTEMPT TO QUIT SMOKING?
1. No
2. Yes

If yes, WERE YOU GIVEN ANY MEDICATION TO HELP YOU QUIT SMOKING?
1. No
2. Yes, nicotine gum
3. Yes, nicotine patches
4. Yes, Zyntabac ®
5. Yes, Champix ®

If yes, WHO RECOMMENDED THIS TREATMENT?
1. The chemist
2. My physician
3. A doctor at the Addictive Behavior Unit (ABU)
4. The pulmonologist
5. Other doctor or specialist
6. The patient him/herself

If yes, WHY DO YOU THINK YOU DIDN'T MANAGE TO QUIT?
1. Anxiety-nervousness
2. Social reason
3. Greater weight gain than desired
4. Other reasons (…)

DO YOU BELIEVE THAT SMOKING IS HARMFUL TO PATIENTS?
1. Yes, greatly
2. Yes, a little
3. No
4. Don't know

DO YOU BELIEVE THAT SMOKING IS HARMFUL TO THOSE WHO YOU LIVE OR WORK WITH?
1. Yes, greatly
2. Yes, a little
3. No
4. Don't know

DO YOU THINK IT IS NECESSARY TO IMPLEMENT SMOKING TREATMENT PROGRAMS FOR HOSPITALIZED PATIENTS?
1. Yes
2. No
3. Don't know

Diagnosis of quitting stage

If you are currently a smoker,

ARE YOU PLANNING TO QUIT WITHIN THE NEXT SIX MONTHS?
1. Yes
2. No

ARE YOU PLANNING TO QUIT WITHIN THE NEXT MONTH?
1. Yes
2. No

ARE YOU PLANNING TO QUIT NOW?
1. Yes
2. Yes, but I will need medical help
3. No

Fagerström Test

HOW MANY CIGARETTES DO YOU SMOKE DAILY?
0. Fewer than 10 cigarettes
1. Between 11 and 20 cigarettes
2. Between 21 and 30 cigarettes
3. More than 30 cigarettes

HOW LONG AFTER YOU GET UP DO YOU SMOKE YOUR FIRST CIGARETTE?
0. Más de 60 minutos
1. More than 60 minutes
2. Between 31 and 60 minutes
3. Between 6 and 30 minutes
4. Less than 6 minutes

WHICH OF ALL THE CIGARETTES YOU SMOKE DURING THE DAY IS THE ONE YOU NEED MOST?
0. None in particular
1. The first of the morning

DO YOU SMOKE MORE DURING THE FIRST HOURS OF THE MORNING THAN DURING THE RESTO OF THE DAY?
0. No
1. Yes

DO YOU FIND IT DIFFICULT NOT TO SMOKE IN PLACES WHERE IT IS PROHIBITED (HOSPITAL, CINEMA, LIBRARY, TRAIN...)?
0. No
1. Yes

DO YOU SMOKE EVEN THOUGH YOU ARE SO ILL THAT YOU HAVE TO STAY IN BED MOST OF THE DAY?
0. No
1. Yes

Availability and promotion of alcohol across different outlets typologies and under different area-level socio-economic status

Disponibilidad y promoción de alcohol según la tipología de los locales y las condiciones socioeconómicas del área

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Abstract

We aimed to characterise the availability and promotion of alcohol at alcohol outlets in Madrid and to compare them according to type of outlet and area-level socioeconomic status. We used the OHCITIES instrument to characterize the alcohol outlets in 42 census tracts of Madrid in 2016. We specified alcohol availability as the density of alcohol outlets and the number of alcohol outlets with extended opening hours (12 or more). We registered any type of promotion associated to alcohol outlets that could be perceived from outside the outlet. We calculated and compared proportions of availability and promotion by alcohol outlet (on- and off-premise) using chi-squared and Fisher Exact tests. We estimated the availability and promotion of alcohol densities per census tract according to area-level socioeconomic status. To assess statistical significance, we used Kruskal-Wallis tests. We recorded 324 alcohol outlets, 241 on-premise and 83 off-premise. Most of the outlets had extended opening hours (73.77%) and at least one sign promoting alcohol (89.51%). More on-premise outlets had extended opening hours and higher presence of alcohol promotion than off-premise (p values<0.001). Higher density of alcohol outlets, extended opening hours and presence of alcohol promotion were found in higher socioeconomic areas (all p values<0.001). These results were also observed for on-premise alcohol outlets. Alcohol availability and promotion were associated with alcohol outlets in Madrid. Future alcohol policies regulating the availability and promotion of alcohol should consider outlet types and area-level socioeconomic status.

Key Words: Alcohol availability; alcohol outlet; alcohol promotion; socioeconomic status; inequalities.

Resumen

El objetivo es caracterizar la disponibilidad y promoción de alcohol asociados a los locales de venta y consumo de alcohol en Madrid, así como explorar las diferencias en su distribución en función de la tipología del local y las características socioeconómicas del área. Se utilizó el instrumento OHCITIES para caracterizar locales situados en 42 secciones censales de Madrid durante 2016. Se registró la densidad de locales y el número de locales con amplios horarios de apertura (12 o más horas). Se registró cualquier tipo de promoción asociada al local visible desde el exterior. Se comparó los porcentajes de características de disponibilidad y promoción asociada a los locales de consumo y venta de alcohol utilizando el test de chi cuadrado y la prueba exacta de Fisher. Se estimó la densidad de disponibilidad y promoción por sección censal y se exploró su distribución en función de las características socioeconómicas del área mediante el test de Kruskal-Wallis. Se registraron 324 locales, 241 de consumo y 83 de venta. La mayoría tenía un horario amplio de apertura (73,77%) y algún elemento promocional (89,51%). Los locales de consumo tenían horarios más amplios de apertura y más elementos promocionales que los de venta (valor p<0,001). Se encontró mayor densidad de locales, amplitud de horarios y elementos promocionales en áreas de nivel socioeconómico alto (todos p<0,001). La disponibilidad y promoción estuvieron asociadas con los locales de venta y consumo de alcohol en Madrid. Futuras políticas cuyo objetivo sea el control del consumo de alcohol deben tener en cuenta la influencia de los tipos de locales y las características socioeconómicas del área en la distribución de la disponibilidad y promoción de alcohol.

Palabras clave: Disponibilidad de alcohol; locales de venta de alcohol; promoción de alcohol; nivel socioeconómico; desigualdades.

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Alcohol is one of the leading factors associated with disability and death worldwide (World Health Organization, 2018). Harmful use of alcohol has been associated with adverse health effects (Galán, Valencia-Martín, Guallar-Castillón & Rodríguez-Artalejo, 2014; Griswold et al., 2018), socioeconomic disadvantages (Waller & Iritani, 2013) and social problems (Cunradi, 2010; Mair, Gruenewald, Ponicki & Remer, 2013). Worldwide, alcohol-related problems have increased during the last twenty years (World Health Organization, 2018).

In Spain, alcohol consumption is accepted as part of the culture (Sureda, Villalbí, Espelt & Franco, 2017a). Although the prevalence of heavy daily drinking and alcohol attributable mortality have declined, the prevalence rate of binge drinking remained high among men between 25 and 29 years old (30%) and women between 20 and 24 years old (20%), according to data obtained in 2017 (National Drugs Plan, 2017).

Features of the physical environment, such as alcohol availability and alcohol promotion, have been described as part of urban settings and may influence alcohol consumption (Bryden, Roberts, Petticrew & McKee, 2013; Sureda et al., 2018a). Alcohol availability have been usually specified as the density of or proximity to alcohol outlets (Popova, Giesbrecht, Bekmuradov & Patra, 2009). Some studies have demonstrated positive associations between the availability of alcohol outlets and alcohol consumption (Sherk et al., 2018). For instance, one study conducted in Australia on adolescent found a 17% of increase in alcohol use per 10% of increase in overall density of alcohol outlets (Rowland et al., 2016). Alcohol outlets have been usually classified into on-premise (such as bars and restaurants) and off-premise (including supermarkets or convenience stores) (Rowland et al., 2014; Shortt et al., 2015). Studies that compared on- and off- premise alcohol outlets availability found different effects on alcohol behaviours (Giesbrecht et al., 2015; Young, Macdonald & Ellaway, 2013). For example, a study exploring the associations in on- and off-premise outlets availability on adolescent alcohol consumption found an increase of 5.30% risk for every 10% of off-premise outlets density, but only an increase of 1.68% for on-premise alcohol outlets (Rowland et al., 2014). Other studies have also reported stronger associations between the density of off-premise alcohol outlets and hazard drinking patterns, as binge drinking, in young people than in on-premise alcohol outlets (Halonen et al., 2013; Young et al., 2013).

Similarly, higher availability of alcohol outlets may increase the opportunities for alcohol promotion (Bryden et al., 2013; Sureda et al., 2017b). Previous studies had mainly focused on alcohol advertisements and its role on sponsorship (Anderson, De Bruijn, Angus, Gordon & Hastings, 2009a; Westberg, Stavros, Smith, Munro & Argus, 2018). However, other promotion elements typically located on alcohol outlets have been overlooked. Therefore, alcohol promotion might have been underestimated in the existing literature. Despite the lightly approach of alcohol promotion, previous studies have suggested hazardous alcohol drinking patterns associated with it, especially in children and young people (Bosque-Prous et al., 2014; Esser, Waters, Smart & Jernigan, 2016).

In addition to alcohol outlet types, area-level socioeconomic status (SES) may influence the distribution of availability and promotion of alcohol within the city (Bryden et al., 2013; Morrison, Gruenewald & Ponicki, 2015). Evidence suggests that there is greater availability of alcohol outlets in lower SES areas than in high SES ones (Hay, Whigham, Kypri & Langley, 2009; Major et al., 2014; Sudhinaraset, Wigglesworth & Takeuchi, 2015). However, this relation is less clear when considering alcohol outlets types (Angus et al., 2017; Rhew, Kosterman & Lee, 2017). The distribution of alcohol promotion according the SES have been less explored. However, few studies have found more alcohol promotion in SES deprived areas than in less deprived ones (Gentry et al., 2018; Hackbarth, Silvestri & Cosper, 1995; Lee & Callcott, 1994).

Different methodologies have been used to describe alcohol availability and promotion of alcohol in urban environment settings. Some of the studies have used secondary databases (Richardson, Hill, Mitchell, Pearce & Shortt, 2015; Shortt et al., 2015) while others have relied on self-reported information (Scribner, Cohen & Fisher, 2000; Wechsler, Lee, Hall, Wagenaar & Lee, 2002). However, both approaches provide limited information for availability and promotion and are not exempt of biases. For this study, we proposed the use of the instrument OHCITIES, based on on-street social systematic observation (Sureda et al., 2017b). This methodology would allow us to define characteristics of the neighbourhoods at street view through direct observation (Costa et al., 2017; Raudenbush & Sampson, 1999) that would be difficult or even impossible to capture using other methodologies. Therefore, and using this instrument, we aim to characterize alcohol availability and promotion at alcohol outlets in the city of Madrid, Spain. Moreover, we compare the differences in alcohol availability and promotion according to outlet type (on- and off-premise outlets) and area-level SES.

Materials and Methods

Study design and sample size

This cross-sectional and observational study was conducted in Madrid, Spain, during 2016. Madrid is divided in 21 districts and further sub-divided in 128 neighborhoods and 2,412 census tracts. Census tract were considered for this study. Census tracts are the smallest administrative areas, with a median population of 1,500 inhabitants and defined by limits easily identifiable.

We used a multistage sampling design to select the study areas for observation and ensure the representativeness of the social characteristics of the whole city. First, two neighbourhoods were selected using a non-probabilistic sampling design for each district (42 neighborhoods in total) representing the following socio-economic characteristics: unemployment, precarious work, occupational class, educational level and immigration. Second, we selected the median census tract in each neighborhood (n=42) based on population density, business density, education level, immigration, and population aging. The procedure to select the census tracts has been described elsewhere (Sureda et al., 2018b).

Social systematic observation: alcohol availability and promotion associated with on-premise and off-premise outlets

OHCITIES instrument and data collection procedure

We used the OHCITIES instrument, a valid and reliable tool to capture systematically alcohol elements in the environment (Sureda et al., 2017b) as the availability and promotion of alcohol. The instrument psychometric showed more than 80% for percent-agreement values for variables of alcohol exposure related to on- and off- premise alcohol outlets as well as greater than 0.80 inter-rater and test-retest reliability values (Sureda et al., 2017b). We characterized all on- and off-premise alcohol outlets within the 42 selected census tracts using social systematic observation.

On-premise alcohol outlets were classified in: 1) bars or similar (including cafes, breweries or bodegas (where mostly unbranded wine is served); 2) restaurants (including sit-in, take-away and fast food); 3) night clubs (including musical pub, cocktail bars, night clubs or discotheques) and 4) other types of on-premise outlets (book-stores, wine-tasting establishment, etc.). *Off-premise alcohol outlets* were classified into: 1) supermarkets; 2) convenience or small grocery stores; 3) specialty food stores (including greengrocers, butchers, fishmongers, and bakeries); and 4) wine or liquor stores.

Data collection was carried out by three trained observers between May and November 2016, on weekdays between 4PM to 9PM to capture all alcohol outlets opened (on- and off-premise). They completed the OHCITIES questionnaire walking along all sides of the street located within the chosen census tract. The route in each census tract was previously defined using a map that the observer followed the day of the data collection. Each census tract was completed by one observer. The observer registered all the on-premise and off-premise alcohol outlets within each selected census tract.

Alcohol environment variables

The variables related to the availability of alcohol included the absolute number of alcohol outlets per census tract and the number of alcohol outlets with extended opening hours. Outlet opening hours were derived from signage outside each outlet. For outlets that this information was not visible, we inputted the mode of the hours of sales of the outlets within the same census tract for the same type of outlets. Based on those data we divided outlet into two categories: (1) outlets opening 12 hours or less; (2) outlets opening more than 12 hours.

To assess the distribution of availability according to types of alcohol outlets, we computed the percent of outlets opened more than 12 hours. Besides, we estimated the absolute number of alcohol outlets and the number of alcohol outlets opened more than 12 hours per 10,000 population for each census tract to explore the distribution according to area SES.

Variables related to alcohol promotion included the presence of: i) advertisements and sponsorship in shop windows or visible windows; ii) structural elements such as awnings, label, and/or specific alcohol beverage menu associated with alcohol products or an alcoholic brand; iii) furnitures such as barrels, alcohol boxes, tables, chairs, umbrellas, napkin holder or ashtray associated with alcohol products or an alcoholic brand (this variable applies to on-premise alcohol outlets); iv) the presence of alcohol products (alcohol bottles, cans, and beer, cider or wine tap) inside the venue that could be perceived from outdoors; and v) presence of alcohol bottles and/or cans exhibited in shop windows. We derived a promotion overall variable by considering the presence of at least one sign of alcohol promotion mentioned above.

To assess the distribution of promotion according to types of alcohol outlets, we computed the percent of outlets with signs. We also estimated the number of alcohol outlets with at least one sign of alcohol promotion per 10,000 population for each census tract to explore the distribution according to area SES.

Socioeconomic status

We used a composite SES index (Gullón et al., 2017) based on 7 indicators obtained by several databases. Madrid municipal registry of population (Padrón), a continuous and universal census collected for administrative purposes (http://www-2.munimadrid.es/CSE6/jsps/menu BancoDatos.jsp), was used to obtain the data on: (1) low education (defined as percent of people above 25 years of age with primary studies or below) and (2) high education (defined as percent of people above 25 years of age with university education or above). Social security registry (http://www.seg-social.es/Internet_1/Estadistica/Est/index.htm) was used to obtain the data about: (3) part-time employment (percent of workers in part-time jobs), (4) temporary employment (percent of workers in temporary jobs), (5) manual occupational class (percent of workers in manual or unqualified jobs). Finally, 'Idealista' (https://www.idealista.com/informes-precio-

vivienda), a report from a large real-estate corporation in Spain on housing, and employment service registry (http://www.sepe.es/contenidos/que_es_el_sepe/estadisticas/datos_estadisticos/empleo/index.html) was used to obtain the indicators of (6) the average housing prices (per sq. m) and (7) the unemployment rate, respectively. Data for all the indicators were obtained at census tract level for the year 2015.

The SES index was operationalized as tertiles (low, medium and high) based on all census tracts in Madrid.

Statistical analysis

Descriptive statistics were calculated for alcohol availability and promotion in the environment according to on- and off-premise alcohol outlets. We compared alcohol availability and promotion associated to on-premise outlets using chi-square test while for off-premise outlets we used Fisher´s exact test due to this small sample. Kruskal-Wallis test for non-normally distributed continuous data was used to examine the densities of alcohol related variables (availability and promotion) differences between on- and off-premise among area SES tertiles. These tests were used with a significance level of 95%. The analyses were conducted using STATA v.12.0 software.

Results

Description of the sample

A total of 324 alcohol outlets (241 on-premises and 83 off-premises alcohol outlets) were observed within the 42 census tracts (Table 1). Cafes and bars were the most prevalent type of alcohol outlet (74.38%) followed by convenience stores (19.14%). The number of on-premise alcohol outlets ranged from 0 to 37 per census tract while for off-premise alcohol outlets the range was from 0 to 7 per census tract. Most on-premise (75.93%) and off-premise (85.54%) alcohol outlets were open at time of the data collection.

Table 1. *Description of the study sample by type of alcohol outlets in 42 census tracts in the city of Madrid, 2016.*

Types of alcohol outlets within 42 census tracts sampled	N	%
ALCOHOL OUTLETS	**324**	
On-premise	**241**	**74.38**
Bar or similar	176	54.32
Restaurant	50	15.43
Night clubs	13	4.01
Others on-premise outlets	2	0.62
Off-premise	**83**	**25.62**
Supermarkets	11	3.39
Convenience stores	62	19.14
Specialty stores	8	2.47
Wine or liquor stores	2	0.62

Alcohol-related variables associated to alcohol outlets

Table 2 shows alcohol exposure characteristics related with availability and promotion of alcohol associated with on- and off-premise alcohol outlets. Overall, 73.77% of the alcohol outlets had extended opening hours (more than 12 hours), and 89.51% had at least one sign of alcohol promotion associated to the outlet.

For alcohol promotion, 32.41% of alcohol outlets had advertisements and/or sponsorship in shop windows or

Table 2. *Alcohol-related variables associated to on and off-premise alcohol outlet in 42 census tracts in the city of Madrid, 2016.*

	ALCOHOL OUTLET TYPOLOGY				
	Overall (n=324 outlets)		On premise (n = 241)	Off premise (n = 83)	*p*-value *
	N	%	%	%	
AVAILABILITY					
Hours of sale					**<0.001**
More than 12 hours	239	73.77	78.84	59.04	
PROMOTION					**<0.001**
With promotion	290	89.51	92.95	79.52	
Advertisements and sponsorship in shop window or visible windows					0.053
Present	105	32.41	29.46	40.96	
Structural elements associated with alcohol products					**<0.001**
Present	119	36.73	47.72	4.82	
Bottles and/or cans in shop windows					**0.039**
Yes	35	10.80	8.71	16.87	
Bottles, cans and/or alcohol taps inside the venue					0.155
None	87	26.85	28.22	22.89	
Between 1 to 15	67	20.68	22.41	15.66	
More than 16	170	52.47	49.38	61.45	

Note. * *p*-value were estimated with chi-square test between on- and off-premise outlets.

a)

Note. Panel a) Bar (on-premise alcohol outlet) where they promoted different types of drinks and alcohol brands in shop windows. Alcohol products (bottles and alcohol taps) inside the venue were visible from outdoors.

b)

Note. Panel b) Convenience store (off-premise alcohol outlet) where the owners exhibited alcohol products in the shop window (there were more than 16 alcohol beverages visible from outdoors).

Figure 1. Examples of availability and promotion associated to alcohol retail outlets in Madrid, 2016. Photographs: Victor G. Carreño.

visible windows; 36.73% had at least one structural element associated with alcohol products or an alcoholic brand; 10.80% had alcohol bottles and/or cans in shop windows; and 50.47% exhibited more than sixteen alcoholic beverages (bottles, cans or alcohol taps) inside the outlet but visible from outdoors. When compared with off-premise, on-premise alcohol outlets were more likely to have extended opening hours (p<0.001); at least one sign of alcohol promotion associated to the outlet (p = 0.001); and at least one structural element associated with alcohol products or an alcoholic brand (p<0.001). More -off-premise alcohol outlets had bottles and/or cans exhibited in shop windows (p = 0.039); and advertisements and/or sponsorship in shop window than on-premise ones. Presence of alcohol products inside the venue visible from outside did not differ between on- and off-premise alcohol outlets. In Figure 1, we show some examples of alcohol exposure associated to on- and off-premise alcohol outlets.

We explored differences in alcohol exposure according to types of on-premise alcohol outlets (Table 3). We

Table 3. *Alcohol-related variables by typology of on-premise alcohol outlet (bars, restaurants or night clubs) in 42 census tracts in the city of Madrid, 2016.*

	ON-PREMISE ALCOHOL OUTLETS					
	Overall (n=239 on-premise)		Bars (n = 176)	Restaurants (n = 50)	Night Club (n = 13)	*p*-value*
	N	%	%	%	%	
AVAILABILITY						
Hours of sale						**<0.001**
More than 12 hours	188	78.66	88.64	44.00	76.92	
PROMOTION						**<0.001**
With promotion	222	92.89	96.59	90.00	53.85	
Advertisements and sponsorship in shop window or visible windows						0.200
Present	71	29.71	30.68	32.00	7.69	
Structural elements associated with alcohol products						**0.001**
Present	113	47.28	54.55	24.00	38.46	
Furniture elements associated with alcohol products						**0.003**
Present	76	31.80	37.50	20.00	–	
Bottles and/or cans in shop windows						0.384
Yes	21	8.79	8.52	12.00	–	
Bottles, cans and/or alcohol taps inside the venue						**<0.001**
None	68	28.45	20.45	40.00	92.31	
Between 1 to 15	54	22.59	24.43	22.00	–	
More than 16	117	48.95	55.11	38.00	7.69	

Note. **p*-value were estimated with chi-square test between bars or similar, restaurants and night clubs of on-premise outlets.

excluded "other type of on-premise alcohol outlets" from the analysis because we recorded only two outlets in that category (one library, and one tasting establishment). Finally, we explored 239 on-premise outlets. More bars than restaurants and night clubs had extended opening hours (p<0.001); had at least one sign of alcohol promotion associated to the outlet (p<0.001); at least one structural element associated with alcohol products or an alcoholic brand (p<0.001); at least one furniture element associated with alcohol products or an alcoholic brand (p = 0.003); and more alcohol products inside the venue that could be perceived from outdoors (p<0.001). The presence of advertisement or sponsorship in shop windows or visible windows, and bottles and/or cans in shop window did not vary significantly for type of on-premise alcohol outlets.

When we compared differences between types of off-premise alcohol outlets (including supermarkets and conveniences stores), we did not find differences in alcohol exposure characteristics related to availability and promotion of alcohol (Table 4).

Table 4. *Alcohol- related variables by typology of off-premise alcohol outlet (supermarkets and convenience stores) in 42 census tracts in the city of Madrid, 2016.*

	OFF-PREMISE ALCOHOL OUTLETS				
	Overall (n=73 off-premise)		Supermarkets (n=11)	Convenience stores (n=62)	*p*-value*
	N	%	%	%	
AVAILABILITY					0.562
More than 12 hours	48	65.75	63.64	66.13	
PROMOTION					0.353
With presence	59	80.82	72.73	82.26	

Note. **p*-value were estimated with Fisher´s exact test between supermarkets and convenience stores of off-premise outlets.

Alcohol exposure associated to alcohol outlets by socioeconomic characteristics of the area

Overall, the median density of alcohol outlet within the 42 census tracts was 56.17 alcohol outlets per 10,000 population (including both on- and off-premise). When we explored its distribution according to area-level SES (Table 5), the median density of alcohol outlets per 10,000 population increased from 64.01 in areas with low SES to 94.11 in areas with high SES (p<0.001). Similar pattern was observed for the rest of the alcohol exposure variables. The density of outlets with extended opening hours was higher in areas with medium and high SES than in areas with low SES (p<0.001). The highest density of outlets with at least one signs of promotion was observed in areas with the highest SES (p<0.001).

Table 5. *Alcohol-related variables per 10,000 population associated to alcohol outlets according to area-level socioeconomic status in 42 census tracts in the city of Madrid, 2016.*

	Socioeconomic Status						
	Low (n=77)		Medium (n = 138)		High (n=109)		*p*-value*
	Median	Range	Median	Range	Median	Range	
TOTAL ALCOHOL OUTLETS	64.01	41.39-73.91	88.44	51.81-319.30	94.11	72.78-140.85	**<0.001**
AVAILABILITY							
Hours of sale							
More than 12 hours	38.58	25.44-62.53	68.03	45.78-203.19	60.31	43.67-92.20	**<0.001**
PROMOTION							
With presence	62.54	22.83-66.15	82.19	51.81-253.99	94.12	72.78-133.43	**<0.001**
Advertisements and sponsorship in shop window or visible window							
Present	16.54	16.54-17.06	43.84	20.06-145.14	30.67	14.56-59.30	**<0.001**
Structural elements associated with alcohol products							
Present	18.28	17.06-33.08	30.09	22.21-87.08	32.89	14.56-51.89	**<0.001**
Bottles and/or cans in shop windows							
Yes	0.00	0.00-11.03	5.02	0.00-43.54	30.67	7.28-37.06	**<0.001**
Bottles, cans and/or alcohol taps inside the venue							
More than 16	18.28	9.13-44.10	38.36	31.81-181.42	49.34	35.29-81.54	**<0.001**

Note. * *p*-value were estimated with Kruskal-Wallis tests for continuous data.

Table 6. *Alcohol-related variables per 10,000 population associated to on-premise outlets according to area-level socioeconomic status in 42 census tracts in the city of Madrid, 2016.*

	Socioeconomic Status						
	Low (n = 50)		Medium (n = 105)		High (n = 86)		*p*-value*
	Median	Range	Median	Range	Median	Range	
TOTAL ON-PREMISE ALCOHOL OUTLETS	44.10	22.83-56.85	93.15	49.65-268.51	82.35	49.34-118.60	**<0.001**
AVAILABILITY							
Hours of sale							
More than 12 hours	34.32	22.83-45.48	71.23	49.65-174.17	58.82	32.89-92.02	**<0.001**
PROMOTION							
With presence	37.17	22.83-51.17	76.71	49.65-210.45	82.35	49.34-111.19	**<0.001**

Note. * *p*-value were estimated with Kruskal-Wallis tests for continuous data.

Table 7. *Alcohol-related variables per 10,000 population associated to off-premise outlets according to area-level socioeconomic status in 42 census tracts in the city of Madrid, 2016.*

	Socioeconomic Status						
	Low (n = 27)		Medium (n =33)		High (n = 23)		*p*-value*
	Median	Range	Median	Range	Median	Range	
TOTAL OFF-PREMISE ALCOHOL OUTLETS	25.87	17.06-28.45	25.07	15.58-29.61	22.24	15.34-32.89	0.776
AVAILABILITY							
Hours of sale							
More than 12 hours	8.48	5.17-21.34	10.03	6.80-29.03	7.41	6.22-27.41	0.448
PROMOTION							
With presence	16.96	7.53-28.45	20.41	9.16-29.61	22.24	12.35-27.41	0.726

Note. * *p*-value were estimated with Kruskal-Wallis tests for continuous data.

The median density of on-premise alcohol outlets per 10,000 population were higher in areas with medium and high SES than in more deprived areas (93.15 and 82.35 vs 44.10 on-premise outlets per 10,000 population, respectively, p<0.001). The same patterns were observed for density of on-premise outlets with extended opening hours and with any type of promotion (p<0.001; Table 6). In contrast, we did not observe differences in the distribution of off-premise alcohol outlets according to area-level SES (p = 0.776; Table 7). Similarly, there was not variation in the density of off-premise alcohol outlets with extended opening hours and with any type of promotion according to area-level SES (p = 0.448 and 0.726, respectively).

Discussion

In this study, we investigated the availability and promotion of alcohol at alcohol outlets in the city of Madrid, Spain. Our findings showed differences in their distribution according to types of alcohol outlets and area-level SES. Specifically, we found that 1) more on-premise outlets had extended opening hours and higher presence of alcohol promotion than off-premise; and 2) higher density of alcohol outlets, extended hours of sale and presence of alcohol promotion were found in higher SES areas.

Alcohol exposure associated to on- and off-premise alcohol outlets

Our findings showed high availability of alcohol in the city of Madrid. The median alcohol outlet density in Madrid (56.17 alcohol outlets per 10,000 population) was higher than those obtained in other places as Scotland, UK (Shortt et al., 2015), Victoria, Australia (Livingston, 2012) or Tallinn, Estonia (Orro, Martens, Lepane, Josing & Reinman, 2017). However, it was lower than the density of alcohol outlets obtained in a study conducted in the city of Barcelona (Spain) that used the same instrument explained in this study (Villalbí et al., 2019).

We also found that most alcohol outlets in Madrid had extended opening hours (more than 12 hours), especially on-premise outlets. Among on-premises, bars or similar had the most extended opening hours. Recently, an European Union Directive liberalized the opening hours of outlets (Anderson & Room, 2011; Villalbí, Bosque-Prous, Gili-Miner, Espelt & Brugal, 2014), thereby other countries

such as Austria or Finland have extended their opening hours (World Health Organisation, 2014). This policy should be reconsidered since easier access to alcohol, including extended alcohol sales hours, stimulate alcohol consumption (Lu, Zhang, Holt, Kanny & Croft, 2018; Trapp, Knuiman, Hooper & Foster, 2018). The regulations of alcohol availability are the most cost-effective to control alcohol consumption (Anderson, Chisholm & Fuhr, 2009b). Thus, certain interventions should be considered for the alcohol control agenda, such as define minimum distances between alcohol outlets (proximity between outlets); limit the number of licenses of alcohol outlets or restrict the access of alcohol to exclusive stores (Valiente et al., 2018); increase alcohol taxes; or decrease the opening hours.

Additionally, we observed that most alcohol outlets had at least one sign of promotion. Specifically, on-premise alcohol outlets were the ones with more presence, specifically the bars. High density of advertisement had been associated with an increase in the consumption of the promoted alcohol brand (Kwate & Meyer, 2009; Sillero-Rejon, Maynard & Ibáñez-Zapata, 2020; Westberg et al., 2018), and identified women and young people as the most vulnerable population (Kypri, Maclennan, Cousins & Connor, 2018; Ross et al., 2014). European Union policies regulate alcohol promotion in specific supports (i.e. TV, printed media, cinema, billboard, internet and social media) (European Alcohol Policy Alliance, 2016). However, the alcohol industry circumvents these policies using alcohol outlets to promote its brands. This alcohol promotion at alcohol outlets is unnoticed for many people and has been incorporated as another urban element in cities (Sureda et al., 2017a). The continuous visibility of alcohol beverages may increase the acceptance and normalisation of alcohol consumption (Petticrew et al., 2017) promoting hazard alcohol patterns, especially among young people (Barry et al., 2016). The World Health Organization had identified social acceptance as one of the new challenges for alcohol-control (World Health Organization, 2018), because this acceptance is related with alcohol patterns such as binge drinking or alcohol consumption initiation among young people (Jernigan, Noel, Landon, Thornton & Lobstein, 2017; Lobstein, Landon, Thornton & Jernigan, 2017). There is enough evidence to support the enforcement and extension of current alcohol promotion regulations. One alternative to improve the effectiveness of these regulations could be implementing interventions to control the content of the alcohol promotion (usually related with success, sports or musical events), or the place of the alcohol promotion prohibiting any type of promotion that could be seen or perceived from street view (Burton et al., 2017; Chambers et al., 2019).

Previous studies found differences in how on- and off-premise alcohol outlets influence on alcohol-related outcomes (Rossheim, Thombs & Suzuki, 2016; Sherk et al., 2018). Our findings showed different distribution of alcohol promotion features according to alcohol outlet typologies that may explain the difference found in their effects on alcohol consumption patterns. Future studies should examine how these features relate to alcohol outcomes and acceptance of alcohol consumption among those who are exposed. Evidence from such studies may provide some hints for future interventions in countries with analogous policy framework and with similar typologies of alcohol outlets.

Alcohol exposure associated to alcohol outlets by socioeconomic characteristics of the area

Previous studies examining how alcohol outlets density differ according to the area-level SES found higher availability of alcohol outlets in areas of greater socioeconomic deprivation (Angus et al., 2017; Rhew et al., 2017). In our study, we found opposite results. Overall, higher density of alcohol outlets and extended opening hours were found in areas with high SES than in low SES areas. These differences could be explained by the land use distribution around the city. In compact cities such as Madrid, the areas with high SES are usually used by population from other neighbourhoods who commute to such areas for work, shopping or leisure, being crowded central places with a high number of alcohol outlets. Moreover, outlets located in high area-level SES are related with more expensive products which may influence on the location of the alcohol outlets, where the purchase power and alcohol demand of population ensure the feasibility of the alcohol-related business (Schneider & Gruber, 2013). In addition, these areas often match the touristic areas (Veal, 2006). Surrounding the touristic sites in the city exist a great demand for leisure activities that may increase the number of alcohol outlets, especially on-premise alcohol outlets.

In contrast, off-premise alcohol outlets were equally distributed according to area-level SES. The high availability of off-premise alcohol outlets have been related with hazard patterns of alcohol consumption among young population (Shih et al., 2015; Young et al., 2013). Moreover, alcohol beverages in these outlets are cheaper than in on-premise outlets. The easier access of alcohol makes it more appealing not only to young people but also to low-income communities. The higher availability of off-premise alcohol outlets has been also related with an increase of the signs of alcohol consumption (Forsyth & Davidson, 2010a). These signs of consumption were described as the presence of litter related to alcohol and the presence of people drinking alcohol in public spaces, sometimes near off-premise outlets (Forsyth & Davidson, 2010a; Galloway, Forsyth & Shewan, 2007; Sureda et al., 2017a). The effects of the visibility of signs of alcohol consumption on alcohol behaviours are similar to the

effects of alcohol promotion (Forsyth & Davidson, 2010b; Villalbí et al., 2019). We did not include this element on the analysis since the source of exposure in our study was the alcohol outlets. However, future studies may include this aspect of urban environment in their explorations.

The distribution of alcohol promotion associated to all alcohol outlets and on-premise alcohol outlets (when considering any type of promotion) also differed according to the area-level SES. Density of alcohol outlets and on-premise alcohol outlets with promotion were higher in medium and high area-level SES. These results could be also explained by the land use of these areas, and by the higher density of alcohol outlets, especially on-premise outlets, that facilitates alcohol promotion opportunities.

These findings taken together suggest evidence of social inequalities in the availability of alcohol outlets and its promotion. The unequal distribution of the alcohol availability and promotion may influence alcohol behaviours among individuals who are exposed. Previous studies found higher prevalence of alcohol daily intake in areas with high area-level SES in comparison with deprived areas (Grittner, Kuntsche, Gmel & Bloomfield, 2013; Pabst, Auwera, Piontek, Baumeister & Kraus, 2019) However, hazardous alcohol patterns as heavy episodic or binge drinking had higher prevalence in more deprived areas (Bellis et al., 2016; Pabst et al., 2019). Reducing alcohol availability though licensing and zoning regulations have proven to be a good option to reduce and prevent these inequalities (Hippensteel, Sadler, Milam, Nelson & Furr-Holden, 2018; Jennings et al., 2013) These regulations identify the zones with overprovision of alcohol outlets, and redistribute them by guaranteeing minimum distances between them. Future policies should consider these types of initiatives to protect those who are more exposed and more vulnerable to the harmful use of alcohol.

Strengths and limitations

All measurements were conducted between 4 and 9 PM. These times were chosen to ensure that most on- and off- premises would be open during the data collection. However, some pubs and nightclubs were closed at the time of the observation. Future analysis could include an entire 24-hour period to capture outlets open at different times. Although we could not include information of all alcohol outlets within the city of Madrid, we registered all alcohol outlets distributed within 42 census sections scattered around the city and representative in terms of sociodemographic and socioeconomic characteristics. Three observers collected all data. However, they were trained by the principal investigator before conducting the fieldwork to avoid inter-observer variability. Our study also presents some strengths. Most of studies examining the alcohol environment focused on the alcohol availability measured as density or proximity of alcohol outlets, and most of them were located in America or Australia (Burton et al., 2017; Lu et al., 2018; Trapp et al., 2018). Moreover, the approaches to measure exposure to alcohol promotion did not include the promotion associated to alcohol outlets underestimating the real exposure (Burton et al., 2017; Gentry et al., 2018). This is the first study to explore comprehensively the alcohol availability and promotion associated to on- and off-premise alcohol outlets, and to compare differences between them, and its distribution according to area-level socioeconomic characteristics. The differences found according to the types of alcohol outlets and social inequalities in its distribution reaffirm and support the need of considering this type of analysis in future studies and further examining their association with drinking behaviours.

This study is part of the 'Heart Healthy Hoods' (HHH) project, aiming to understand how physical and social characteristics of the urban environment may affect the cardiovascular health. The HHH project includes a cohort of adult residents in Madrid, and we are currently collecting data on drinking behaviours among those residents. Future studies will use this information to understand how alcohol exposure on outlets may be associated to alcohol drinking behaviors.

Conclusions

To our knowledge, this is the first study describing the availability and promotion of alcohol in both on- and off-premises alcohol outlets in a representative sample of census tracts in a large city like Madrid. Our findings showed different distribution in the availability and promotion of alcohol according the different types of alcohol outlets and area-level SES. The availability and promotion of alcohol at alcohol outlets were high, especially at on-premise. Moreover, we found different distribution on alcohol outlets availability and promotion according to area-level SES. Alcohol outlets were more available and had more associated promotion in higher area-level SES than in areas of low SES.

Future steps should be taken to strengthen regulations on the availability, and promotion of alcohol at on- and off-premise alcohol outlets considering socioeconomic inequalities in the city.

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X.S. and A.P. conceive the original idea. X.S. supervised the data collection. A.P. prepared the databases and analysed the data with the advice of X.S. and A.E. A.P. and X.S. drafted the manuscript. All authors contributed substantially to the interpretation of the data, the manuscript review and approved its final version. X.S. and

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Substance use in sexual context among Spanish resident men who have sex with men

Consumo sexualizado de drogas entre hombres que tienen sexo con hombres residentes en España

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Abstract

We analysed patterns of sexualized drug use (SDU) and pinpointed the one with the highest risk for the acquisition/transmission of HIV/Sexually Transmitted Infections (STIs) in a sample of men who have sex with men (MSM) residing in Spain. Additionally, we also identified the most affected subpopulations by highest risk SDU pattern. In 2016, we promoted an online survey in gay dating apps. We estimated the prevalence of several HIV/STI risk indicators for each identified SDU pattern. We built two different Poisson regression models identifying factors associated to the pattern associated with the highest risk. All analyses were carried out by HIV status. Of 2,883 MSM, 21.9% self-reported SDU in the last 12 months. All patterns of SDU were more frequent in HIV+ MSM. Of the four SDU patterns identified (*chemsex*, recreational drugs, sexual performance enhancing drugs, and cannabinoids), the most frequent was *chemsex* (21.9% in HIV+ vs 6.6% in HIV-). It also comprised the highest risk profile for HIV/STI. Among HIV-, *chemsex* was associated with living in a city of > 1,000,000 inhabitants, living sexuality in an open way and having been paid for sex, having had unprotected anal intercourse (UAI) in the

Resumen

Analizar los patrones de consumo sexualizado de drogas (CSD) e identificar cual es el de mayor riesgo para la adquisición/transmisión del VIH y de otras infecciones de transmisión sexual (ITS) en una muestra de hombres que tienen sexo con hombres (HSH) residentes en España. Adicionalmente, también se identifican las subpoblaciones más afectadas por el patrón de CSD de mayor riesgo. En 2016, se realizó una encuesta online en app de contacto gay. Se identificaron los patrones de CSD y se estimaron las prevalencias de varios indicadores de riesgo para el VIH/ITS para cada uno. Se construyeron dos modelos multivariantes de Poisson identificando factores asociados al patrón de mayor riesgo. Todos los análisis se realizaron en función del estado serológico frente al VIH. De 2883 HSH, el 21,9% refirió CSD en los últimos 12 meses. Todos los patrones de CSD fueron más frecuentes en los VIH+. De los cuatro patrones identificados (*chemsex*, drogas recreacionales, drogas para mejorar el rendimiento sexual y cannabinoides) el más prevalente y de mayor riesgo, fue el *chemsex* (21,9% en VIH+ vs. 6,6% en VIH-). En los VIH- el *chemsex* se asoció con: ciudad de residencia > 1 000 000 habitantes, vivir la sexualidad abiertamente, haber cobrado por tener sexo, haber

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last 12 months and having ever received an STI diagnosis. Among HIV+, it was associated with being 30-49 years old, having paid for sex, having had UAI and having been diagnosed with an STI in the last 12 months. Given its high prevalence, especially among HIV positive individuals, and its association with subpopulations with high-risk behaviour, *chemsex* could be playing a relevant role in the acquisition/transmission of HIV and other STIs.
Keywords: Men who have sex with men; *chemsex*; drug use; HIV; STI.

mantenido relaciones anales desprotegidas (RAD) en el último año y haber sido diagnosticado de una ITS. En los VIH+ se asoció con: tener 30-49 años, haber pagado por tener relaciones sexuales, haber tenido RAD y haber sido diagnosticado de ITS en el último año. Dada su elevada prevalencia especialmente en VIH+ y a que se observa fundamentalmente en poblaciones con perfiles de alto riesgo, el *chemsex* podría estar jugando un papel relevante en la adquisición y/o transmisión del VIH y otras ITS.
Palabas clave: Hombres que tienen sexo con hombres; *chemsex*; consumo de drogas; VIH; ITS.

In some Western countries, the use of illicit drugs has been reported to be higher among men who have sex with men (MSM) and other sexual minority populations than that reported by the general population (Caputi, Smith, Strathdee & Ayers, 2018; Gómez-Gil et al., 2019; Lawn, Aldridge, Xia & Winstock, 2019) and is a recognized concern especially when it occurs in sexual contexts because it could be a driver of riskier sexual risk behaviour.

Drugs have been taken in sexual contexts for centuries but half a decade ago, "chemsex" rose as a phenomenon that has since caught the attention of both the community and the academia. This phenomenon grew in parallel with geo spatial networking apps that facilitate access to sexual activities involving chemsex drugs as well as the acquisition drugs easily and on demand (Dolengevich-Segal, Rodriguez-Salgado, Bellesteros-Lopez & Molina-Prado, 2017; Winstock, 2015). Although definitions vary, there is certain consensus that chemsex involves the use of mephedrone, GHB/GBL (Gamma hydroxybutyrate/Gamma butyrolactone) and/or methamphetamine (Abdulrahim, Whiteley, Moncrieff & Bowden-Jones, 2016; Edmundson et al., 2018; Redondo-Dominguez, Picazo, Docavo-Barrenechea-Moxo & Gonzalez Del Castillo, 2018). These drugs enhance and prolong sexual encounters by increasing arousal, stamina and pleasure (Frankis & Clutterbuck, 2017).

A number of studies have associated chemsex with high risk sexual behaviours (Daskalopoulou et al., 2014; Glynn et al., 2018; Gonzalez-Baeza et al., 2018; Hammoud et al., 2018; Ottaway et al., 2017; Pufall et al., 2018; Sewell et al., 2017; Weatherburn, Hickson, Reid, Torres-Rueda & Bourne, 2017), diagnosis of sexually transmitted infections (STI) (Carey et al., 2009; Glynn et al., 2018; Gonzalez-Baeza et al., 2018; Hegazi et al., 2017; Ottaway et al., 2017; Pakianathan et al., 2018; Pufall et al., 2018; Rosinska et al., 2018; Sewell et al., 2017; Tomkins, George & Kliner, 2018), injecting drug use (Hegazi et al., 2017; Pakianathan et al., 2018; Rosinska et al., 2018) and has been reported to be especially common among HIV positive individuals (Carey et al., 2009; Daskalopoulou et al., 2014; Edmundson et al., 2018; Hammoud et al., 2018; Melendez-Torres et al., 2018; Pakianathan et al., 2018; Rosinska et al., 2018; Schmidt et al., 2016). Some authors have also suggested that chemsex could interfere with patients' adherence to highly active antiretroviral therapy among those who live with HIV (Bracchi et al., 2015). This could also be the case for those taking pre-exposure prophylaxis. As a consequence of all the above, it could be an important driver of the HIV and other STIs epidemics (McCall, Adams, Mason & Willis, 2015). Additional negative outcomes include increased risk of overdose deaths by GHB/GBL (Corkery, Loi, Claridge, Goodair & Schifano, 2018; Hockenhull, Murphy & Paterson, 2017), and mental health problems (Gonzalez-Baeza et al., 2018; Hirshfield et al., 2015; Kirby & Thornbern-Dunwell, 2013; Pakianathan, Lee, Kelly & Hegazi, 2016; Prestage et al., 2018; Pufall et al., 2018). In Europe, most of the studies about chemsex have been carried out in the UK but, in other European countries it is largely under-researched. The few studies we have found are focused on populations recruited in very large urban areas and in clinical settings (Glynn et al., 2018; Gonzalez-Baeza et al., 2018; Rosinska et al., 2018).

Additionally, the assessment of Sexualized Drug Use (SDU) has mostly been restricted to chemsex. The use that MSM make of other illicit drugs in sexual contexts is unknown (Knight, 2018). There are very few studies that have assessed the particular configurations of sexualized substance use other than chemsex. Thus, the existence and the magnitude of other SDU patterns remains unknown and we also do not know if they have distinct behavioural risk profiles.

In the present study, we identify the different patterns of SDU reported by a sample of online recruited MSM resident in Spain, quantify their size by HIV serostatus and describe the prevalence of several sexual risk behaviours, HIV infection and history of STI diagnosis. We also perform two multivariate analysis in MSM HIV positive and of HIV negative or unknown serostatus to identify subpopulations more affected by chemsex.

Methods

Between April and December 2016, we performed an online cross-sectional survey in 8 European countries (Belgium, Denmark, Germany, Greece, Portugal, Romania,

Slovenia and Spain). The analysis of the present paper is restricted to participants recruited in Spain.

Data collection instrument

We designed an online questionnaire that included sections assessing sociodemography, sexual risk behaviours, testing history for HIV, HIV serostatus, STI history and SDU. The latter included our main outcome that was assessed with the following question: *In the LAST 12 MONTHS, have you taken recreational drugs immediately preceding and/or during sex?* Those who answered "yes" were asked to select the drugs used from a list of drugs that included: Mephedrone/Methylone, Methamphetamine, Cocaine, Ecstasy/MDMA, Ketamine, GHB/GBL, Amphetamines, Poppers, Viagra, and Cannabis. We also included an open ended "other drugs" category where participants were able to specify what drug they used if they felt it was not included in the list provided.

The survey was anonymous and confidential. No variables allowing personal identification were collected. The study was approved by the Researchs Ethics Committee of the Institute of Health Carlos III (CEI PI52_2015-v2) and the Hospital Germans Trias i Pujol (CEI PI-14-106).

Recruitment procedures and inclusion/exclusion criteria

Participants were invited to participate through mailing lists, personal messages and promotional banners distributed mainly through gay dating websites but also in gay oriented websites and Facebook events. Those who decided to click on the study banner or link were directed to a screen where they were informed about the aim and content of the survey. To participate, the participants needed to click on the "I have read and understood the above information, in the country I live in I am old enough to legally have sex and I want to participate" box. No retribution was offered to participants in exchange for participation. More details of the questionnaire and the recruitment procedures can be found elsewhere (Hoyos et al., 2017).

Initially, we included MSM who were male at birth, >=18 years of age and who reported having lived in Spain for most of the last 12 months (N=4,123). For the present analysis, we excluded 1,240 who did not answer the question assessing our main outcome (main characteristics can be found as additional information). Thus, our final sample was comprised by 2,883 MSM.

Statistical analysis

We first performed a descriptive analysis of the main characteristics of our sample stratifying it in three groups according to their self-reported HIV serostatus and previous testing history: never tested, last HIV test with a negative result (hereafter HIV negative) and HIV positive.

Table 1. Additional information. *General characteristics of excluded participants due to missing data in the question assessing Sexualised Drug Use (N=1,240).*

	N = 1240	
	n	%
Age		
‹ 29	415	33.5
30-39	350	28.2
40-49	303	24.4
› 50	172	13.9
Place of birth		
Spain	1085	87.5
Latin America	46	3.7
Europe and other countries	94	7.6
Number of inhabitants in place of residence		
≥ 1 000 000	435	35.1
500.000-999.000	123	9.9
50.000-499.999	406	32.7
‹ 50 000	267	21.5
Education		
No university education	605	49.0
University education	629	51.0
Lives sex life with men...		
Openly	450	36.3
Not openly	789	63.6
Sex of sex partners (ever)		
Only men	704	56.8
Mainly men	293	23.6
Equally or less with men	243	19.6
HIV Serostatus/ Testing history		
Never tested	374	30.2
Last HIV test negative › 12 months	264	21.3
Last HIV test negative ≤ 12 months	410	33.1
HIV positive	41	3.3

Differences were assessed using the chi-square test for categorical variables.

Secondly, we described the different patterns of SDU. To do so, substances were categorized into 3 groups: 1) sexual performance enhancing drugs: poppers (amyl nitrites) and erectile dysfunction medications, 2) party drugs: ecstasy, cocaine, amphetamine and ketamine 3) chemsex drugs: mephedrone, methamphetamine, GHB/GBL. Cannabis was treated independently.

Based on these 3 groups and the use of cannabis, we created a 5 mutually-exclusive category variable to reflect relevant patterns of SDU: 1) No drugs, 2) ONLY cannabis, 3) Sex performance enhancing drugs and/or cannabis use, 4) Presence of party drugs but no chemsex drugs (with or without cannabis or sex performance enhancing drugs use), 5) Presence of chemsex drugs (with or without the presence of the rest of drugs).

For each pattern we estimated the prevalence of several sexual risk indicators during the last 12 months: having given money or any kind of goods for sex (has paid for sex hereafter), having received money or other goods in exchange for sex (has been paid for sex hereafter), having received an STI diagnosis and having had ≥ 5 unprotected anal intercourses (UAI). This analysis was stratified by testing history/HIV serostatus: 1) participants with a self-reported HIV positive serostatus and 2) HIV negative/never tested individuals.

Two multivariable Poisson robust variance regression models were built to identify engagement in chemsex: one for HIV negative/never tested individuals and the other one for HIV positive. For each model, we calculated both crude and adjusted Prevalence Ratios (cPR and aPR) and 95% Confidence Intervals (CI95%). Variables with a significance level of <0.20 in the single variable analysis were introduced in each multivariable model. We used the Akaike information criteria values to perform model comparisons and select the optimal model.

Results

Main characteristics of the sample

The main characteristics of the participants by testing history and HIV serostatus can be found in table 2.

Of the 2,883 MSM included in the analysis, 22.8% had never been tested for HIV, 64.7% reported that their last test was negative and 12.5% that it was positive. Some 61.3% were under 40 years of age (76.7% among never tested MSM (p<0.001)). Some 87.6% had been born in Spain although among HIV+ participants we observed a higher proportion of Latin Americans (13.1%; p<0.001) (table 2).

Some 32.4% lived in cities ≥ 1.000.000 inhabitants, with never testers presenting a lower proportion (21.5%). Over half had finished university studies (57.1%) and had a comfortable economic situation (59.1%). Among HIV positive individuals, 61.1% reported living their sexuality openly vs. 47.9% among HIV negative individuals and 23.9% in never testers (p<0.001). Some 61.3% reported having ever had sex exclusively with men (table 2).

Regarding sexual risk behaviours, HIV positive MSM reported more frequently having paid (p <0.001) or being paid for sex (p<0.002) than the other two groups. The proportion of HIV positive participants that reported having had >5 UAI in the last 12 months (30.3%) was also higher than in the other two groups (p<0.001); as well as having been diagnosed with an STI (26.7%; p<0.001) (table 2).

Overall, the proportion of SDU in the previous 12 months was of 21.9% and was higher among HIV positive MSM (45.1%) than in HIV negative (21.9%) or never testers (9.1%) (p<0.001). The most frequent pattern of SDU was the one comprised by chemsex associated substances (7.5%) which was higher among HIV positive (21.9%) than among HIV negative (6.6%) and never tested (2.1%). In fact, in the other two groups, the most frequent SDU pattern was the one comprised by sexual performance enhancing drugs (table 2).

Prevalence of drug use in the last 12 months by type of SDU pattern

Poppers were the commonest substance (17.1%) and it was used by almost all those included in the sex performance enhancing drugs pattern (98.1%); those who reported using party drugs but no chemsex drugs (68.6%) and those using chemsex drugs (85.7%). Of all party drugs, cocaine was the most frequently reported substance (9.1%). It was used by 79.7% of those who used party drugs but no chemsex drugs and by 64.8% of those included in the chemsex pattern. Finally, GHB/GBL was the commonest chemsex drug (5.6%) and it was reported by 74.1% of those included in the chemsex pattern (table 3).

Sexual risk behaviours and STI diagnosis by SDU pattern and HIV serostatus

The prevalence of all three sexual risk behaviours assessed (having been paid for sex, having paid for sex and ≥ 5 UAI) as well as of STI diagnosis in the last 12 months, was higher among HIV positive (Figure 1). The pattern was very similar in both serostatus groups; with comparable prevalence of all indicators assessed among those reporting no SDU and cannabis users which gradually grew peaking in the chemsex group (p<0.001) (Figure 1).

Factors associated with chemsex

In the multivariable analysis for HIV negative/never tested individuals, chemsex was independently associated with living in a city of ≥1,000,000 inhabitants (aPR 1.6; CI95% 1.2-2.3), living sex life openly (aPR 1.5; CI95% 1.1-2.1), having been paid for sex in the last 12 months (aPR 3.5; CI95% 2.3-5.2), having had 1-4 (aPR 1.7; CI95% 1.1-2.6) or ≥ 5 UAI (aPR 4.5; CI95% 2.7-7.6) in the last 12 months and having been diagnosed with an STI >12 months or <12 months ago (aPR 2.1; CI95% 1.5-3.1; aPR 2.1; CI95% 1.3-3.3, respectively). Among HIV positive MSM chemsex was associated with being between 30-39 years of age (aPR 2.3; CI95% 1.2-4.5) or 40-49 (aPR 2.2; CI95% 1.1-4.2); having

Table 2. *General characteristics of the study participants by sexualized drug use, during last 12 months, in Spain.*

	Never tested		HIV negative		HIV positive		Total		chi square *p*-value
	N = 657 22.8%		N = 1865 64.7%		N = 361 12.5%		N = 2883 100%		
	n	%	n	%	n	%	n	%	
Age									‹ .001
‹ 29	351	53.4	498	26.7	65	18.0	914	31.7	
30-39	153	23.3	579	31.0	121	33.5	853	29.6	
40-49	95	14.5	497	26.6	98	27.1	690	23.9	
› 50	58	8.8	291	15.6	77	21.3	426	14.8	
Place of birth									‹ .001
Spain	611	93.3	1609	87.1	284	79.3	2504	87.6	
Latin America	26	4.0	146	7.9	47	13.1	219	7.7	
Europe and other countries	18	2.8	92	5.0	27	7.5	137	4.8	
Number of inhabitants in place of residence									‹ .001
≥ 1 000 000	141	21.5	652	35.0	140	38.8	933	32.4	
500.000-999.000	60	9.1	211	11.3	44	12.2	315	10.9	
50.000-499.999	249	37.9	625	33.6	104	28.8	978	34.0	
‹ 50 000	207	31.5	374	20.1	73	20.2	654	22.7	
Education									‹ .001
No university education	345	52.7	712	38.2	176	48,9	1233	42.9	
University education	310	47.3	1150	61.8	184	51.1	1644	57.1	
Economic status									.012
Comfortable	370	57.5	1115	60.8	184	52.7	1669	59.1	
Uncomfortable	273	42.5	718	39.2	165	47.3	1156	40.9	
Lives sex life with men...									‹ .001
Openly	157	23.9	892	47.9	220	61.1	1269	44.0	
Not openly	500	76.1	972	52.1	140	38.9	1612	56.0	
Gender of sex partners (ever)									‹ .001
Only men	393	59.8	1136	60.9	237	65.7	1766	61.3	
Mainly men	105	16.0	567	30.4	113	31.3	785	27.2	
Equally or less with men than women	159	24.2	162	8.7	11	3.1	332	11.5	
Has paid or given any kind of goods in exchange for sex (last 12 months)	31	4.7	162	8.7	38	10,6	231	8.0	‹ .001
Has received money or other goods in exchange for sex (last 12 months)	31	4.7	110	5.9	36	10.1	177	6.2	.002
Number of unprotected anal intercourses (last 12 months)									‹ .001
None	312	47.8	687	37.2	121	34.0	1120	39.2	
1	205	31.4	604	32.7	59	16.6	868	30.4	
2-4	97	14.9	370	20.0	68	19.1	535	18.7	
≥ 5	39	6.0	188	10.2	108	30.3	335	11.7	
History of sexually transmitted infections diagnosis (ever)									‹ .001
No STI diagnosis	580	89.6	1036	56.1	98	27.8	1714	60.2	
STI diagnosis › 12 months ago	53	8.2	607	32.9	160	45.5	820	28.8	
STI diagnosis in the last 12 months	14	2.2	204	11.0	94	26.7	312	11.0	
HIV serostatus/ testing history									
Never tested	657	100.0					657	22.8	
Last HIV test negative › 12 months			666	35.8			666	23.1	
Last HIV test negative ≤ 12 months			1194	64.2			1194	41.5	
HIV positive					361	100.0	361	12.5	

Table 2 (cont.). *General characteristics of the study participants by sexualized drug use, during last 12 months, in Spain.*

	Never tested		HIV negative		HIV positive		Total		chi square *p*-value
	N = 657		N = 1865		N = 361		N = 2883		
	22.8%		64.7%		12.5%		100%		
	n	%	n	%	n	%	n	%	
Time since HIV diagnosis									
≤ 3 months					136	37.8			
4-6 months					66	18.3			
7-12 months					30	8.3			
1-2 years ago					34	9.4			
2-5 years ago					33	9.2			
›5 years ago					61	16.9			
Pattern of sexualized drug use									‹ .001
No drugs	597	90.9	1457	78.1	198	54.9	2252	78.1	
ONLY cannabis	10	1.5	36	1.9	10	2.8	56	1.9	
Sex performance enhancing drugs (1)*	19	2.9	140	7.5	47	13.0	206	7.2	
Party drugs (2) but NO chemsex drugs (3)**	17	2.6	109	5.8	27	7.5	153	5.3	
Chemsex drugs with or without party drugs**	14	2.1	123	6.6	79	21.9	216	7.5	

Note.
(1) Sex performance enhancing drugs: poppers, erectile dysfunction medications.
(2) Party drugs: ecstasy, cocaine, amphetamine, ketamine.
(3) Chemsex drugs: mephedrone, methamphetamine, GHB/GBL.
*Independently if they have used cannabis.
**Independently if they have used cannabis, poppers or erectile dysfunction medications.

Table 3 . *Prevalence and kind of drugs used for sex in the last 12 months, by pattern of sexualized drug use, in Spain.*

	TOTAL	ONLY cannabis	ONLY Sex performance enhancing drugs (1)*	Party drugs (2) but NO chemsex drugs (3)**	Chemsex drugs with or without party drugs**
		1.9%	7.2%	5.3%	7.5%
	N = 2883	N = 56	N = 206	N = 153	N = 216
	(%)	(%)	(%)	(%)	(%)
Cánnabis	10.7	100.0	38.4	48.4	46.3
Sexual performance enhancing drug	17.7				
Poppers	17.1		98.1	68.6	85.7
Erectile dysfunction medications	7.1		15.1	26.1	62.0
Party drugs	11.0				
Ecstasy	3.9			22.9	35.2
Cocaine	9.1			79.7	64.8
Amphetamine	3.2			20.3	28.7
Ketamine	2.3			8.5	24.1
Chemsex drugs	7.5				
Mephedrone	3.4				45.8
Methamphetamine	3.0				40.3
GHB/GBL	5.6				74.1

Note.
(1) Sex performance enhancing drugs: poppers, erectile dysfunction medications.
(2) Party drugs: ecstasy, cocaine, amphetamine, ketamine.
(3) Chemsex drugs: mephedrone, methamphetamine, GHB/GBL.
* Independently if they have used cannabis.
** Independently if they have used cannabis, poppers or erectile dysfunction medications.

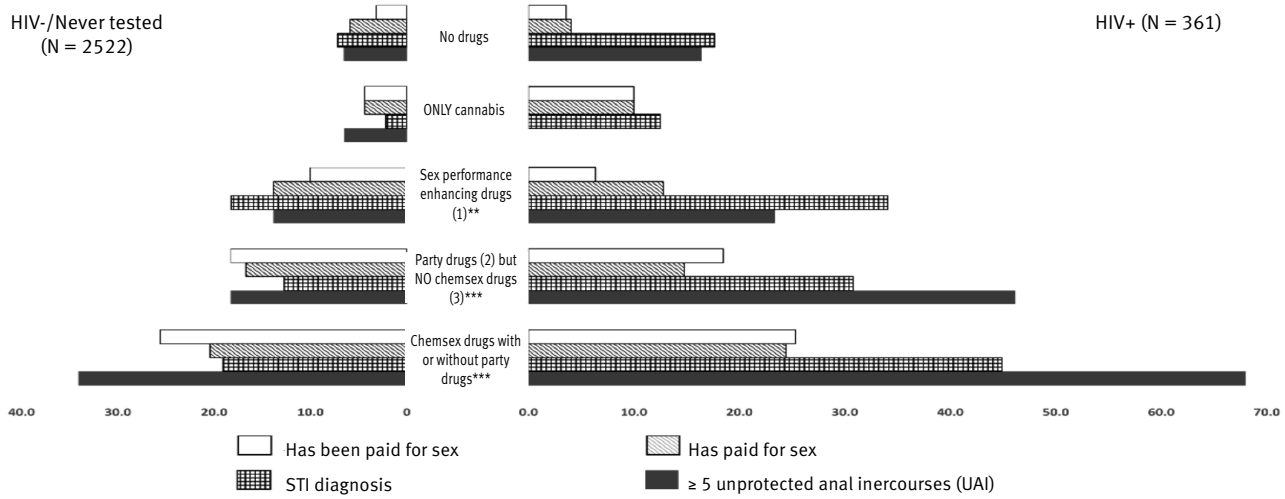

Figure 1. Prevalence of sexual risk indicators* and diagnosis of sexually transmitted infections (STI)* by type of sexualized drug use pattern* in HIV-/never tested and HIV+ MSM.

Note.
* In the last 12 months.
Chi square test for linear trend in both groups: has been paid for sex p ‹ 0,001; has paid for sex p ‹ 0,001; diagnosis of STI p ‹ 0,001; ≥ 5 UAI p ‹ 0,001.
(1) Sex performance enhancing drugs: poppers, erectile dysfunction medications. (2) Party drugs: ecstasy, cocaine, amphetamine, ketamine (3) Chemsex drugs: mephedrone, methamphetamine, GHB/GBL.
** Indedendent of cannabis use.
*** Independently if they have used cannabis, poppers or erectile dysfunction medications.

Table 4. *Use of chemsex drugs in the last 12 months in Spain by sociodemographic, behavioural and clinical correlates. Crude and adjusted Poisson analysis.*

	Chemsex drugs* in last HIV test negative and never tested MSM (N = 2522)					**Chemsex drugs* in HIV positive MSM (N = 361)**				
	%	cPR[a]	(95% CI[b])	aPR[c]	(95% CI[b])	%	cPR[a]	(95%CI[b])	aPR[c]	(95% CI[b])
Age										
‹ 29	4.8	1.1	.6-2.0	1.3	.7-2.3	16.9	1.4	.6-3.3	1.9	.9-4.1
30-39	6.2	1.4	.8-2.5	1.5	.9-2.6	24.8	2.1	1.1-4.2	2.3	1.2-4.5
40-49	6.1	1.4	.8-2.5	1.4	.8-2.4	29.6	2.5	1.3-5.0	2.2	1.1-4.2
› 50	4.3	1.0		1.0		11.7	1.0		1.0	
Place of birth										
Spain	5.5	1.0				20.8	1.0			
Other country	5.3	1.0	.6-1.6			25.7	1.2	.8-1.9		
Number of inhabitants in place of residence										
≥ 1 000 000	8.3	1.9	1.3-2.7	1.6	1.2-2.3	27.1	1.7	1.1-2.6		
50.000-999.999	4.5	1.0		1.0		16.2	1.0			
100-49.999	3.4	.8	.5-1.3	.8	.5-1.4	23.3	1.4	.8-2.5		
Education										
University education	4.9	1.0				20.7	1.0			
No university education	6.2	1.3	.9-1.8			23.3	1.1	.8-1.7		
Economic status										
Comfortable	4.7	1.0				17.4	1.0			
Uncomfortable	6.6	1.4	1.0-2.0			27.9	1.6	1.1-2.4		
Lives sex life with men...										
No openly	3.8	1.0		1.0		17.1	1.0			
Openly	7.7	2.0	1.5-2.8	1.5	1.1-2.1	25.0	1.5	.9-2.2		
Sex of sex partners (ever)										
Only men	6.0	1.0				19.0	1.0			
Men and women	5.6	.9	.6-1.2			27.4	1.4	1.0-2.1		

Tabla 4 (cont.). *Use of chemsex drugs in the last 12 months in Spain by sociodemographic, behavioural and clinical correlates. Crude and adjusted Poisson analysis.*

	Chemsex drugs* in last HIV test negative and never tested MSM (N = 2522)					Chemsex drugs* in HIV positive MSM (N = 361)				
	%	cPRa	(95% ICb)	aPRc	(95% ICb)	%	cPRa	(95% ICb)	aPRc	(95% ICb)
Has pad or given any kind of goods in exchange for sex (last 12 months)										
No	4.7	1.0				18.3	1.0		1.0	
Yes	14.5	3.1	2.1-4.6			50.0	2.7	1.8-4.0	1.9	1.3-2.8
Has received money or other goods in exchange for sex (last 12 months)										
No	4.3	1.0		1.0		18.4	1.0			
Yes	24.8	5.8	4.1-8.2	3.5	2.3-5.2	55.6	3.0	2.1-4.4		
Number of unprotected anal intercourses (last 12 months)										
None	2.5	1.0		1.0		5.0	1.0		1.0	
1-4	5.0	2.0	1.3-3.2	1.7	1.1-2.6	15.0	3.0	1.2-7.3	2.7	1.1-6.3
≥ 5	20.3	8.1	5.1-12.9	4.5	2.7-7.6	49.1	9.9	4.4-22.1	6.6	2.8-15.5
History of sexually transmitted infections diagnosis (ever)										
No STI diagnosis	3.0	1.0		1.0		7.1	1.0		1.0	
STI diagnosis › 12 months ago	9.2	3.0	2.1-4.4	2.1	1.5-3.1	22.5	3.1	1.5-6.8	2.0	.9-4.2
STI diagnosis in the last 12 months	11.9	3.9	2.5-6.2	2.1	1.3-3.3	37.2	5.2	2.4-11.2	2.6	1.2-5.8
Time since last test HIV										
Never tested	2.1	.6	.2-1.8							
≤ 3 months	10.7	3.1	1.1-8.3							
4-6 months	5.6	1.6	.6-4.6							
7-12 months	4.1	1.2	.4-3.5							
1-2 years	6.6	1.9	.7-5.3							
2-5 years	5.1	1.4	.5-4.4							
› 5 years	3.5	1.0								
Time since HIV diagnosis										
≤ 3 months						23.5	1.0	.6-1.8		
4-6 months						22.7	1.0	.5-1.9		
7-12 months						16.7	.7	.3-1.8		
1-2 years						23.5	1.0	.5-2.2		
2-5 years						15.2	.7	.3-1.7		
› 5 years						23.0	1.0			

Note. (a) cPR, crude prevalence ratio; (b) CI, confidence interval; (c) aPR, adjusted prevalence ratio.
*Mephedrone, methamphetamine or GHB/GBL. Independently if they have used the rest of drugs.

paid for sex (aPR 1.9; CI95% 1.3-2.8), having had 1-4 (aPR 2.7; CI95% 1.1-6.3) or ≥ 5 UAI (aPR 6.6; CI95% 2.8-15.5) and having been diagnosed with an STI in the last 12 months (aPR 2.6; CI95% 1.2-5.8) (table 4).

Discussion

SDU was reported by a relevant proportion of the study participants, especially among those who self-reported being HIV positive. The most prevalent pattern of SDU

was chemsex, mainly due to the high rates reported by HIV positive individuals. The chemsex pattern presented higher prevalence of sexual risk behaviours and previous STI history than two of the other SDU patterns assessed: "Only sexual performance enhancing drugs" and "Party drugs but no chemsex drugs". Nevertheless, those pertaining to any of these two patterns also presented significantly higher rates of all risk indicators than participants who did not report SDU or only consumed cannabis. Having received an STI diagnosis, reporting having paid or having been paid for sex and reporting UAI in the last 12 months increased the probabilities of reporting chemsex in both HIV positive and non-positive participants. Among HIV positive individuals, chemsex was especially prevalent among those between 30 and 49 years of age and in non-HIV positive individuals, among those living in large urban areas and those living their sex life with other men openly.

Comparing overall self-reported SDU with other published studies is difficult because definitions vary depending on the drugs included in the different data collection instruments and the time reference used. We did find a study that assessed overall SDU in an online recruited sample of UK-resident MSM which included the same list of drugs and the same time reference (last 12 months) as we did (Hibbert, Brett, Porcellato & Hope, 2019). In this sense, SDU in our study was less than half than that reported by this study. Overall SDU was also assessed in a study that recruited their sample of MSM from a London sexual health clinic and differences were even higher in this case, especially if we take into account that they assessed SDU in the last 3 months (vs.12 months) (Rana et al., 2019).

To our knowledge, no one in Europe has assessed sexual risk behaviours and STI acquisition among individuals involved in SDU other than chemsex. In our study, we identified 3 different patterns outside of drugs related to chemsex and all of them were consistently more frequent among HIV positive individuals than among never tested or HIV negative participants. In two of these three patterns (sex performance drugs and party drugs but no chemsex drugs), the prevalence of all sexual behaviours and of previous STI acquisition was higher than among participants who reported not having used drugs immediately before or during sex. The only exception was observed among those who only used cannabis. They comprised the smallest group and presented similar or even lower percentages of sexual risk behaviours and past STI diagnosis than those who reported not using drugs. Although cannabis has been associated to several health problems (Degenhardt et al., 2013) it appears that, in our sample, its role in the transmission of HIV and other STIs could be very limited. Things, however, begin to change when we focus on those who conformed the other two SDU patterns. Those who reported only using sexual performance enhancing drugs conformed the second most frequent drug pattern. It has been described that sexual performance enhancing drugs are commonly used among MSM in Europe (Daskalopoulou et al., 2014; Hibbert et al., 2019; Rosinska et al., 2018) but until now we did not know whether using them alone without other drugs could also be associated with sexual risk behaviours and STI acquisition as appears to be the case in this study. Thus, our results are in line with cohort studies conducted in the US that present strong associations between the use of amyl nitrites and erectile dysfunction drugs with increased risk of unprotected anal intercourse and higher seroconversion rates among those using these substances (Dutta et al., 2017; Swartz & McCarty-Caplan, 2018). The next pattern in the "risk ladder" was the one comprised by what has been called "party drugs". Individuals pertaining to this group presented an even higher prevalence of risk indicators than participants of the "sex performance enhancing drugs" category. However, the same did not happen with STI acquisition and those in the "party drugs" category presented a lower self-reported pervious STI history than those in the "sex performance enhancing drugs "category. Very few studies have assessed the use of party drugs immediately before or during sex among MSM (Hibbert et al., 2019; Rosinska et al., 2018) but as far as we know this is the first time that persons that only use these drugs (and not chemsex) have been characterized in terms of sexual risk behaviours and STI prevalence. In this sense, the sole use of substances of this nature appears to be strongly associated with sexual risk behaviours and STI acquisition.

Nevertheless, the most frequent pattern and the one that had the highest proportion of all three sexual risk behaviours and STI prevalence for both HIV positive and negative/never tested individuals was the one comprised by chemsex associated drugs. The prevalence of chemsex reported by our participants was substantially lower than that reported by several studies carried out in the UK (Rana et al., 2019; Sewell et al., 2019; Sewell et al., 2017). In fact, three studies used "last 3 months" as a reference period (vs. "last 12 months") which makes differences even more striking. Another study conducted in a sexual health clinic in Amsterdam (Druckler, van Rooijen & de Vries, 2018) also found a higher prevalence of chemsex than the one reported by our participants. Part of the difference is probably derived from the fact that their samples were recruited in sexual health clinics based in London, Brighton and Amsterdam, where the use chemsex substances has been reported to be especially high (Schmidt et al., 2016). In our case, more than half of the sample we recruited pertained to small-very small

municipalities which has been a factor traditionally associated with lower chemsex frequency (EMIS Network, 2013). This is a strength of our study which included a sample not exclusively comprised by MSM from urban settings and probably more representative of the overall MSM population. When we compare our data to studies similar to ours in terms of recruitment strategy, differences level out and present similar figures (Hibbert et al., 2019).

In our study, the number of UAI and having been diagnosed with an STI was associated with chemsex among both HIV positive and HIV negative/never tested MSMs. This is in line with previous studies who also reported more frequent UAI and higher rates of STI among those involved in chemsex (Glynn et al., 2018; Gonzalez-Baeza et al., 2018; Pufall et al., 2018; Rosinska et al., 2018). Additionally, among HIV positive individuals, chemsex was found to be independently associated with being between 30-49 years of age and having been paid for sex. The latter association has never been described before as far as we know and could suggest that the use of chemsex drugs is especially present at contexts where transactional sex is occurring. The association between chemsex and having been paid for sex among HIV negative/never tested participants also points toward this direction. Also, among HIV negative never tested individuals, chemsex was significantly higher in residents of cities of ≥ 1,000,000 inhabitants reflecting the concentration of chemsex in very large urban areas (Frankis & Clutterbuck, 2017). Similarly, the increased rates of chemsex among those who lived their sex life with other men openly could also be related to the fact that they have access to larger networks where the use of chemsex drugs is more common.

The results of this study need to be interpreted in light of several limitations. There was a high number of participants that could not be included in the analysis due to non-response of the question assessing SDU. This question was introduced towards the end of a long questionnaire and is probably the reason or the high number of missing values. Our rate of missing data is actually very similar to the rates of a large scale international online survey among MSM (EMIS Network, 2013). In this study, seven of ten of participants made it to the last page of the questionnaire. Non-response was probably due to "response fatigue" and virtually all that made it to the question assessing SDU had answered the other questions used in our analysis. The questionnaire was totally anonymous and confidential. No IP or cookies were collected and therefore we were not able to ascertain the existence of participants answering the survey more than one time. However, given the length of the questionnaire and that fact that no retribution was given in exchange for participation, the occurrence of "double participation" is highly unlikely.

Although we were able to recruit a large sample, the results do not necessarily represent the overall MSM population. Geospatial apps and online dating sites are widespread among MSM but certain subpopulations might not be included in the study because they choose not to use these methods to meet new partners. Due to the cross-sectional nature of the study, we could not assess the causal directionality of sexual risk behaviours, STI acquisition and the different patterns of SDU. This is also relevant for HIV positive participants as we cannot establish whether substance use occurred before or after seroconversion.

In this online sample of Spanish resident MSM, we found that all forms of SDU were a minority. However, given the high prevalence of sexual risk behaviours and high presence of STI especially among HIV positive individuals involved in SDU, preventive efforts need to be considered in order to control the possible negative effects that SDU can have in this population. This is especially true with chemsex which, not only was the most prevalent pattern, but also the one with the highest risk profile. In this sense, geospatial network apps and gay dating represent an ideal opportunity to conduct preventive and informative interventions focused on MSM who are taking illicit drugs in sexual contexts.

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Conflict of interests

The authors declare that they have no conflict of interest.

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Role of drug-associated environmental stimuli in the development of cross-tolerance to the tachycardic effects of nicotine and alcohol in humans

Papel de los estímulos ambientales asociados a la droga en el desarrollo de tolerancia cruzada a los efectos de taquicardia de la nicotina y el alcohol en humanos

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Abstract

According to the Pavlovian conditioning model, drug tolerance is modulated by drug-associated environmental cues. This study evaluated the contribution of drug-associated cues in the development of cross-tolerance to the tachycardic effects of nicotine from tobacco and alcohol in human subjects. Forty undergraduate students were recruited for this experiment, and each student was randomly assigned to one of two experimental conditions. Twenty students smoked nicotine-containing cigarettes in context A and placebo cigarettes in context B, and twenty students smoked nicotine-containing cigarettes in context B and placebo cigarettes in context A. A cross-tolerance test was carried out by dividing the subjects in each condition into two subgroups (n = 10). Each subgroup consumed alcohol in both contexts (A and B). The results of this experiment showed that cross-tolerance between nicotine and alcohol was exhibited only if the cross-tolerance test was carried out in the same context where tolerance had developed to the nicotine from tobacco. These results support the hypothesis that drug-associated environmental stimuli play a modulatory role in the development of cross-tolerance between nicotine from tobacco and alcohol.

Keywords: Cross-tolerance; classical conditioning; tobacco; nicotine; alcohol; heart rate response.

Resumen

De acuerdo con el modelo de condicionamiento pavloviano, las claves ambientales asociadas a la droga modulan la tolerancia a las drogas. Este estudio evaluó la contribución de las claves asociadas a la droga en el desarrollo de tolerancia cruzada a los efectos taquicárdicos de la nicotina de tabaco y el alcohol en sujetos humanos. En este experimento participaron cuarenta estudiantes universitarios. Cada estudiante fue asignado aleatoriamente a una de dos condiciones experimentales. Veinte estudiantes fumaron cigarros con nicotina en el Contexto A y placebo en el Contexto B y veinte estudiantes fumaron cigarros con nicotina en el Contexto B y placebo en el Contexto A. La prueba de tolerancia cruzada fue llevada a cabo dividiendo a los participantes de cada condición en dos subgrupos (n = 10), cada subgrupo consumió alcohol en cada uno de los contextos (A y B). Los resultados de este experimento muestran que la tolerancia cruzada entre nicotina y alcohol se presentó únicamente cuando la prueba de tolerancia cruzada se realizó en el mismo contexto donde se desarrolló la tolerancia a la nicotina del tabaco. Estos resultados concuerdan con la hipótesis de que los estímulos ambientales asociados a la droga juegan un papel modulador en el desarrollo de la tolerancia cruzada entre la nicotina del tabaco y el alcohol.

Palabras clave: Tolerancia cruzada; condicionamiento clásico; tabaco; nicotina; alcohol; frecuencia cardíaca.

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There is a strong relationship between drinking alcohol or ethanol and smoking nicotine-containing cigarettes. Clinical studies have provided the best evidence of this association, suggesting that it is common to find patients diagnosed with alcohol dependence and diagnosed with tobacco/nicotine dependence (Abburi et al., 2016; Abreu-Villaça, Manhaes, Krahe, Filgueiras & Ribeiro-Carvalho, 2017; Drobes, 2002; Funk, Marinelli & Lê, 2006; Oliver et al., 2013). In fact, it has been estimated that 80-90% of alcoholic individuals often also smoke nicotine-containing cigarettes (Taslim, Soderstrom & Saeed, 2011). Similarly, consumption of alcohol is higher in smokers than in nonsmokers (Abburi et al., 2016; Oliver et al., 2013), and it seems that consumption of both nicotine from tobacco and alcohol can enhance or reinforce the effects of each drug (Chi & De Wit, 2003; Enggasser & Wit, 2001; Oliver et al., 2013). A study with human subjects revealed that the interaction of the pharmacological effects of nicotine and low doses of alcohol plays an important role in the motivation for consuming both substances, and this phenomenon contributes to the development of cross-reinforcement and cross-tolerance, as well as dependence on both drugs (Oliver et al., 2013).

In this regard, several studies have reported evidence that alcohol and nicotine can interact in several ways. Some studies that have explored the long-term behavioral effects of nicotine and alcohol have revealed that chronic use of one drug induces tolerance to the behavioral and physiological effects of the other drug, which increases the potential for coabuse (Taslim et al., 2011). Another study in which mice were chronically treated with different doses of alcohol found that the animals also developed tolerance to the hypothermic effects of an acute dose of nicotine (Majchrzak & Dilsaver, 1992). In vitro studies have also shown that chronic exposure to alcohol decreased nicotine-induced dopamine (DA) release (Dohrman & Reiter, 2003).

Cross-tolerance occurs when the development of tolerance to one drug produces tolerance to a second drug, and the development of cross-tolerance between nicotine and alcohol could explain the increased use of both drugs and contribute to coabuse. Although it is difficult to assess the development of cross-tolerance between nicotine and alcohol in human subjects because both drugs are commonly used and abused, cross-tolerance between nicotine and alcohol is well documented in animal models. For example, alcohol and nicotine produce hyperthermic and tachycardic effects. Studies with mice have shown that chronic administration of alcohol through a liquid diet, which induced tolerance to various effects of alcohol, also produces cross-tolerance to the hyperthermic and tachycardic effects of nicotine (Collins, Burch, De Fiebre & Marks, 1988).

The neurobiological perspective on the cross-tolerance between nicotine and alcohol has suggested at least four possible mechanisms based on the overlapping sites of action for tobacco and alcohol or the neuronal pathways where both substances exert their rewarding effects, particularly in the mesolimbic DA system. The first suggested mechanism is that both substances can modulate the nicotinic acetylcholine receptor. It is clear that nicotinic acetylcholine receptors are the principal site of action for nicotine (Adams, 2017); however, it has been suggested that ethanol can directly or indirectly interact with these receptors, and perhaps this is because ethanol stabilizes open channel states. Some authors have suggested that ethanol and nicotine could desensitize the nicotinic receptors in the central nervous system (CNS) (Adams, 2017; Collins et al., 1988). The second overlapping mechanism between nicotine and ethanol is their ability to increase the release of neurotransmitters such as DA, serotonin, glutamate, and GABA. A third neurobiological explanation of the interaction between nicotine and ethanol is their ability to sensitize corticotropin-releasing factor systems, a component of the stress system (Abreu-Villaça et al., 2017; Funk et al., 2006). The fourth mechanism in which alcohol and nicotine interact is the activation of the brain reward system. Both drugs increase the activity of the mesocorticolimbic DA system, generating a functional interaction between nicotine and ethanol (Adams, 2017). Finally, it is important to note that there are common genetic factors associated with both substances (De Fiebre & Collins, 1993; Madden, Bucholz, Martin & Heath, 2000). It is clear that cross-tolerance between nicotine and alcohol could have a neurobiological explanation. However, this approach does not explain the previously reported influence of environmental stimuli.

There are several ways in which environmental stimuli can influence people's behavior, for example, in the visual discrimination of an alcoholic beverage or its alcoholic content (Sillero-Rejon, Maynard & Ibañez-Zapata, 2020), or inhibitory control levels may vary in real-world alcohol-related settings, where people are surrounded by visual and auditory stimuli associated with alcohol that may affect their ability to control their consumption (Qureshi et al., 2021). From a different perspective, there have been approaches to the behavioral mechanisms involved in drug tolerance. It has been suggested that a Pavlovian conditioning model of tolerance to drugs, originally proposed by Siegel (1977), could explain the cross-tolerance between nicotine and alcohol. This model suggests that the environmental stimuli associated with the administration of a drug acquire the function of the conditioned stimulus (CS), and the pharmacological stimulation acts as the unconditioned stimulus (US). The CS plays a central role in the development of tolerance since it elicits a conditioned compensatory response (CCR) that

attenuates the unconditional effects of a drug, producing tolerance (González, Navarro, Miguez, Betancourt & Laborda, 2016; Ruiz, Vila & Miranda, 2010; Vila, Ruiz, Trejo & Miranda, 2013). In the absence of the CS, the CCR does not occur, and therefore, there is no reduction in the effects of the drug (González et al., 2016; Ruiz et al., 2010; Siegel, 1979; Siegel, Baptista, Kim, McDonald & Weise-Kelly, 2000; Siegel & Ramos, 2002; Vila et al., 2013). A logical consequence of Siegel's model is that if a second drug is administered in the tolerance test in the presence of the stimuli associated with the first drug, it would cause a CCR that would attenuate the unconditional effects of the second drug, producing cross-tolerance.

In line with the above mechanism, some studies have reported that Pavlovian conditioning processes could be involved in cross-tolerance to several drugs (Cappell, Roach & Poulos, 1981). Although several cross-tolerance experiments have been conducted with laboratory animals (Cappell et al., 1981), it has not yet been demonstrated whether these conditioning processes also regulate cross-tolerance in human subjects using two widely used legal drugs, i.e., nicotine and alcohol (Oliver et al., 2013). The investigation of these processes involved in cross-tolerance could help develop a better treatment for addiction to these drugs. Therefore, in this study, we evaluated the participation of Pavlovian conditioning processes in cross-tolerance to the tachycardic effects of nicotine from tobacco and alcohol in human subjects.

Methods

Participants

The sample was composed of forty undergraduate students from Facultad de Estudios Superiores Iztacala, UNAM (23 men and 17 women), whose average age was 21 years. The inclusion criteria were that they smoked 5 to 7 cigarettes per day and drank alcohol 1 to 2 times per month. Participants with little nicotine and alcohol dependence (4 points maximum in the Fagerström test; 5 points maximum in the AUDIT test) were identified. The participants had an average weight between 60 and 70 kg and a height between 1.60 and 1.70 m. The exclusion criteria were the presence of health problems or taking medically prescribed drugs at the beginning of or during the study. Each subject received an explanation of the experimental protocol, and they were informed of the ethical norms and principles for human research in accordance with the ethical code of the psychologist (Sociedad Mexicana de Psicología, 2009; American Psychological Association, 2010). All students participated voluntarily and gave their informed consent before starting the experiment, being free to abandon the task at any point in the process, though that never happened. They were asked to not use cigarettes for three days before and throughout the experiment. This period of time did not cause withdrawal or any change in the cardiovascular response evaluated, still, allows a stable baseline in all the subjects.

Materials

Heart rate responses of subjects were recorded with a photoplethysmograph (HR / BVP IOIT: Thought Technology LTD, Quebec, Canada). In addition, an AIWA 130 recorder, a reggae music CD and recorded instructions to relax were used.

Drugs and placebo

Two types of drugs were used: nicotine-containing cigarettes (Marlboro, with approximately 0.9 mg of nicotine per cigarette) and alcohol (Absolut vodka, with 40° of pure alcohol). The subjects were instructed to drink alcohol in a vodka mixture (0.65 g/kg) in 100 ml of orange juice. The formula to calculate the amount of alcohol was as follows:

$$\text{Grams of alcohol} = \frac{\text{volume (in c.c.)} \times \text{graduation} \times 0.8}{100}$$

For placebo, cigarettes that did not contain nicotine or any substance that could cause an effect on the cardiovascular system were chosen; Reef LiveTM lettuce cigarettes were used.

Experimental situation

Sessions were carried out in two contexts. Context A and B were created in a room illuminated by two white light lamps, with a table (1.7 m x 0.90 m), a chair and an air extractor that remained in operation across all sessions. In the room, there was an additional table in which the computer and the sound recorder were placed. The differences between the contexts were created by the light intensity and music. Context A included a low intensity light (30 W) and music. Context B was illuminated by 100 W, 100 V lamps and had no music.

Procedure

The subjects were randomly assigned to one of the two experimental conditions, context A or context B, in a counterbalanced manner. Twenty subjects smoked nicotine-containing cigarettes in context A and placebo cigarettes in context B; the remaining 20 subjects smoked nicotine-containing cigarettes in context B and placebo cigarettes in context A. Each subject individually participated in a one-hour session. One of the researchers began the session by informing each subject of the smoking procedure. After clarifying any questions, another researcher recorded the heart rate of the subjects. The subjects were then asked to follow the recorded instructions and relax for 10 minutes, and at the end of the relaxation period, their heart rate was recorded again.

Acquisition phase. The order of presentation of the nicotine or placebo trials was counterbalanced. This phase involved four trials in a session. When the session consisted of smoking nicotine-containing cigarettes in context A, the trials were conducted according to the following procedure. Three minutes before subjects took the first puff, a change was made in the ambient light intensity of the room (from normal to low intensity), and music was turned on. Each trial consisted of smoking four puffs, with a 20-second interval between puffs. Each puff consisted of sucking the smoke from the cigarette by mouth for two seconds and keeping the smoke in the lungs for two seconds. Five minutes after the last puff, the heart rate response was recorded. During the interval between trials, a change in light intensity was made (from 30 W to 100 W), and the music was turned off. When smoking nicotine-containing cigarettes in context B, the trials were identical in terms of the administration of the drug, but no change in ambient light or music occurred.

Placebo (lettuce cigarettes) was administered under the same environmental conditions, that is, in context A and in context B.

Tolerance test phase. The tolerance test was carried out in both contexts A and B. The order of presentation of the contexts was counterbalanced. Five minutes after the last acquisition trial, the tolerance test was carried out. In both contexts, all subjects were allowed to smoke nicotine-containing cigarettes; the smoking instructions were identical to those described in the previous phase. Five minutes after the last puff, their heart rate response was recorded.

Cross-tolerance test phase. A cross-tolerance test was conducted as follows. A researcher gave instructions for consuming the alcoholic drink in approximately 3 minutes. The subjects drank alcohol in the two different contexts (A and B), and the order of presentation of the context was counterbalanced. Five minutes after consuming the beverage, a researcher recorded their heart rate response.

Reacquisition phase. This phase was identical to the first acquisition phase. This phase was carried out to eliminate the influence that the previous evaluation could have and stabilize the tolerance for the subsequent test.

CCR test phase. Five minutes after the last reacquisition trial, the CCR test was carried out. For the CCR test, all subjects were allowed to smoke lettuce-containing cigarettes; the smoking instructions were identical to the previous phase; each subject consumed placebo (lettuce cigarettes) in each context.

For a summary of the procedure, see Table 1.

Table 1. *Cross-tolerance development.*

Acquisition	Tolerance Test	Cross Tolerance Test	Reacquisition	CCR Test
A: NIC	A: NIC	A: ALC	A: NIC	A: P
B: P	B: NIC	B: ALC	B: P	B: P
A: P	A: NIC	A: ALC	A: P	A: P
B: NIC	B: NIC	B: ALC	B: NIC	B: P

Note. A=Context A, B=Context B, NIC=Nicotine, ALC=Alcohol, P=Placebo.

Statistical analysis

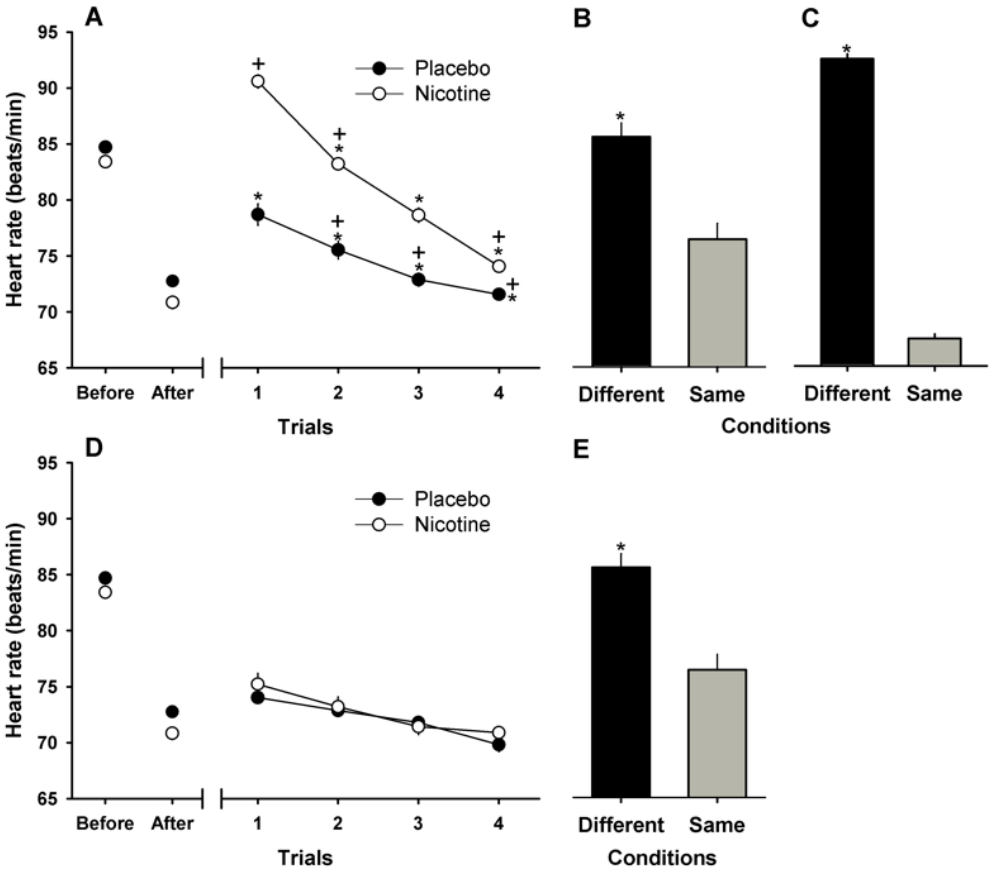
The subject´s heart rate responses were recorded at baseline, during the training, and during the cross-tolerance test. The baseline data were analyzed using two-way ANOVA, with condition (nicotine and placebo conditions) as the first factor and the baseline (before and after relaxation) as the second factor. During the training phase, the data were analyzed using two-way repeated measures ANOVA, with the nicotine and placebo conditions as the first factor and the trial number as the second factor. During the cross-tolerance test, data were analyzed with Student's t-test. Data from the reacquisition phase were analyzed using two-way repeated measures ANOVA, with the nicotine and placebo conditions as the first factor and the trial number as the second factor. For the CCR test, the data were analyzed using Student's t-test. When ANOVAs were significant, multiple comparisons were carried out using Tukey's test. In all tests, the rejection level for type I error was 0.05.

Results

Acquisition phase

The results of the baseline (before and after *relaxation*) are shown on the left side of Figure 1-A. Two-way ANOVA indicated that there were no differences between the nicotine condition (84.8 beats per minute) and placebo condition (83.4 beats per minute) before relaxation. Although there was a significant decrease in heart rate response after relaxation in both conditions, there were no differences between the nicotine (72.8 beats per minute) and placebo (70.9 beats per minute) conditions after relaxation ($F\ [1, 39]=0.357$, $p>0.05$; $F\ [1, 39]=107.601$, $p<0.05$; respectively). Additionally, the test revealed that there were no differences between the after and before conditions based on the nicotine and placebo conditions (i.e., no interaction) ($F\ [1, 39]=1.040$, $p>0.05$). In summary, after relaxation, all subjects started the experiment with a constant heart rate of approximately 70-72 beats per minute.

Different heart rate responses across the four tolerance acquisition trials are shown on the right of Figure 1-A. The data showed that the initial effect of nicotine was to increase the heart rate response. Two-way repeated measures



Note. The results are represented as the mean of the subject's heart rate response ± SEM. A. Development of nicotine tolerance. The first two points represent before and after the relaxation period. It is also shown the development of conditioned tolerance to the tachycardic effects; open circles show the effects after successive smoked nicotine-contained cigarettes, while closed circles show the effect obtained after smoked placebo cigarettes. Asterisk (*) indicates significant differences with respect to the first nicotine trial. The cross (+) indicates significant differences with respect to the first placebo trial. B. Tolerance test. Heart rate of the subjects that smoked nicotine in the Different or the Same context. Asterisk (*) indicates significant differences with respect to the Same context. C. Cross-tolerance test. Results obtained when subjects drank alcohol in the Different and Same context. Asterisk (*) indicates significant differences with respect to the Same context. D. Reacquisition phase. Shows the reacquisition of the tolerance; open circles show the effect of nicotine, while closed circles show the effect obtained after smoked placebo. E. CCR test. Results obtained when subjects smoked placebo in the Different and Same context. Asterisk (*) indicates significant differences with respect to the Same context.

Figure 1. Role of drug-associated cues in the development of cross-tolerance to the tachycardic effects of the nicotine from tobacco and alcohol.

ANOVA indicated that there were differences between the nicotine and placebo conditions ($F [1, 38]=19,204$, $p<0.05$), between trials ($F [5, 90]=36.779$, $p<0.05$) and in the condition-trial interaction ($F [5, 90]=10.541$, $p<0.05$). As shown on the right of Figure 1A, the effect on the heart rate response decreased depending on the number of exposures to the drug. Tukey's test indicated that in the case of the nicotine condition, there was an important decrease ($p<0.05$) from the second trial onwards. On the other hand, although an increase in trial 1 was observed with respect to the baseline in the placebo condition, the mean heart rate response was significantly lower than that observed in trial 1 in the nicotine condition ($p<0.05$).

In the placebo condition, the trials did not present significant differences among themselves, compared to trial 4 of the nicotine condition, or compared to after *relaxation.*

Tolerance test phase

Results from the tolerance test phase showed that when subjects smoked nicotine-containing cigarettes in the context associated with the consumption of the drug, they exhibited a decrease in the heart rate response (bar indicated by "Same" in Figure 1B), whereas when the subjects smoked nicotine-containing cigarettes in the absence of the environmental stimuli associated with the drug, their heart rate response increased (bar indicated by "Different" in Figure 1B). Related Student's t-test confirmed a significant difference between the responses in these two conditions ($t [38] =3.707$, $p< 0.05$).

Cross-tolerance test phase

Results of the cross-tolerance test are shown in Figure 1C. When the subjects drank alcohol in the environment associated with smoking nicotine-containing cigarettes, the subjects exhibited a decrease in the heart rate response (bar indicated by "Same" in Figure 1C), while when the subjects drank alcohol in the absence of environmental stimuli associated with smoking nicotine-containing cigarettes, the heart rate response increased (bar designated as "Different" in Figure 1C). Related Student's t-test indicated a difference between the responses in these two conditions ($t\ [38] = 15.036$, $p<0.05$).

Reacquisition phase

The changes in heart rate responses across the four tolerance reacquisition trials are shown in Figure 1D. The data from this phase showed that the initial effect of smoking nicotine-containing cigarettes did not produce an increase in the heart rate response compared to the baseline response. As can be observed, this effect was maintained over the course of the trials and became less pronounced in comparison with the trials in the placebo condition. A two-way repeated measures ANOVA revealed that there were no significant differences between the groups ($F\ [1, 38] = 2.01$, $p>0.05$). The results also showed that there were no significant differences between the trials ($F\ [5, 70] = 0.248$, $p>0.05$), and there was no condition-trials interaction ($F\ [3, 114] = 0.391$, $p>0.05$).

CCR test phase

The results of the CCR test in the reacquisition phase showed that when subjects smoked lettuce-containing cigarettes in the context associated with the consumption of the drug, they exhibited a decrease in the heart rate response (bar indicated by "Same" in Figure 1E); whereas, when the subjects smoked lettuce-containing cigarettes in the absence of the environmental stimuli associated with the drug, the heart rate response increased (bar indicated by "Different" in Figure 1E). Related Student's t-test confirmed a significant difference between the response in the two conditions ($t\ [19] = 6.688$, $p<0.05$).

Discussion

The purpose of this study was to evaluate the contribution of drug-associated cues in the development of cross-tolerance to the tachycardic effects of nicotine from tobacco and alcohol in human subjects. In addition, the expression of the CCR as a possible mechanism that underlies the cross-tolerance between nicotine and alcohol on the tachycardic effects was evaluated. We found that the development of tolerance to the tachycardic effects of nicotine can be modulated by the environmental signals associated with its consumption. The data also showed cross-tolerance between nicotine and alcohol on heart rate responses, and this effect was only observed if the cross-tolerance test was carried out in the same context in which tolerance to the first drug was developed; when, the cross-tolerance test was carried out in the different context, the cross-tolerance was reversed and an increase in the heart rate response was observed. An additional finding was evidence of a CCR when the subjects consumed placebo in the presence of environmental stimuli associated with nicotine consumption by presenting a decrease in heart rate compared to that in the subjects who consumed placebo in the absence of such stimuli; the results suggest that a CCR could be the mechanism underlying cross-tolerance.

The behavioral results described above are consistent with those of existing studies demonstrating the influence of the context-specificity of tolerance using different procedures with rats and using different drugs including nicotine (Field & Duka, 2001; McDermut & Haaga, 1998; Mucha, Pauli & Angrilli, 1998; Naqvi & Bechara, 2006) and alcohol (Duncan, Alici & Woodward, 2000; Le, Poulos & Cappell, 1979; White, Roberts & Best, 2002).

With regard to the modulatory role of the environmental context on cross-tolerance, the present results are the first evidence that shows the contribution of the drug-associated cues in the development of cross-tolerance between the effects of nicotine from tobacco and the effects of alcohol in human subjects and suggest that the tolerance that develops to a particular drug effect in a specific context may contribute to the expression of tolerance to the effects of a second drug that has not been previously used by the subjects if the second drug is consumed in the same environment where the first drug was consumed. Therefore, it can be suggested that the Pavlovian conditioning processes that contributed to the expression of the cross-tolerance between nicotine and alcohol corresponded to the effects reported in previous studies carried out using different procedures with animals and could be used as evidence regarding the knowledge of the phenomena that contribute to the development and maintenance of drug addiction since the development of cross-tolerance can be an important component in the progression or increase in consumption and the development of dependence on drugs of abuse (Cappell et al., 1981; Carmona-Perera, Sumarroca-Hernández, Santolaria-Rossell, Pérez-García & Reyes del Paso, 2019; Collins et al., 1988; De Fiebre & Collins, 1993; Oliver et al., 2013).

An initial explanation of the results of our investigation involves the study of the mechanisms that underlie the development of nicotine and alcohol addiction and dependence, which have been widely evaluated (Little, 2000). The neurobiological mechanisms constitute a first set of factors that has provided an explanation of not only these phenomena but also the cross-tolerance between

nicotine and alcohol. In this case, the explanation has focused on the indirect actions that these drugs have on the reward system. Nicotine increases DA concentrations in the nucleus accumbens (nAcc) by three different mechanisms (De Kloet, Mansvelder & De Vries, 2015): activation of ventral tegmental area (VTA) neurons through nicotinic receptors with α4, α6, α7 and β2 subunits; activation of DAergic neurons by cholinergic activation from the pedunculopontine nucleus; and inhibition of GABAergic interneurons in the VTA by desensitization of nicotinic receptors with β2 subunits. On the other hand, alcohol also increases DA concentrations and acts on GABAA receptors on the GABAergic interneurons in the VTA. GABAA activation produces a decrease in the release of GABA in the VTA and consequently increases DA release in the nAcc (Leggio, Kenna & Swift, 2008). Additionally, it is known that alcohol and nicotine can produce differential effects on different behavioral and physiological variables that could be the same depending on the dose of drug consumed, and it has even been suggested that both drugs share at least one genetic component that could produce a predisposition to the use or abuse of these drugs (Funk et al., 2006). Based on the similarity in the mechanisms, it has been proposed that nicotine pharmacological stimulation of specific sites generates plastic changes in neurons. Since these changes do not disappear and are the same site of action of the second drug, when alcohol is consumed for the first time, the phenomenon of tolerance occurs, even in the absence of previous experience. This pharmacological explanation seems to explain the cross-tolerance phenomenon; however, it does not explain the environmental specificity of the cross-tolerance. That is, it does not explain why cross-tolerance occurred only in the context where tolerance had developed and did not occur when the context was different. Thus, cross-tolerance can be studied as a pharmacological phenomenon or as a learning phenomenon; however, pharmacological theories are silent in terms of the role of environmental stimuli associated with the administration of a drug in the development of cross-tolerance or with respect to the incentive value of a drug. Therefore, understanding how the development of tolerance to a drug can modulate tolerance to a second drug requires an appreciation of both learning principles and pharmacological principles.

Another factor that could contribute to the explanation of the development of cross-tolerance is the role of environmental stimuli associated with the administration of the drug. The drug tolerance conditioning model proposed by Siegel (1977) predicts that the development of tolerance is influenced by environmental variables, particularly the history of association of environmental stimuli with the administration of a drug. Thus, the development of tolerance occurs because the conditioned stimuli cause a CR that is opposite to the effects of the drug, and this antagonistic CR attenuates the unconditional effects of the drug (Dafters & Anderson, 1982; Duncan et al., 2000; Newlin, 1986; Siegel, 1977, 1979).

In addition to contextual specificity providing an empirical basis for the participation of Pavlovian conditioning in tolerance, the model indicates that the production of a CCR is fundamental in the explanation of tolerance. The CCR can usually be evidenced in subjects who have undergone a process of acquisition and development of tolerance to a drug, and in a subsequent phase, a placebo is administered in the presence of the environmental stimuli associated with the chronic administration of the drug (Newlin, 1986; Ruiz et al., 2010). One example is previous research that we conducted in our laboratory showing that environmental stimuli are an important component in the explanation of tolerance; stimuli that produced the CCR attenuated the unconditional effects of the drug, but the absence of these stimuli did not cause the CCR, and therefore, reduced drug effects were not observed (Ruiz et al., 2010).

In this way, the model could suggest an additional explanation of the cross-tolerance between nicotine and alcohol observed in the present experiment. Environmental stimuli associated with smoking nicotine-containing cigarettes could have produced a CCR that was able to add to the acute effects of alcohol (Cappell et al., 1981; González et al., 2016; Ruiz et al., 2010; Vila et al., 2013). In other words, in the cross-tolerance test, the contextual stimuli caused a decrease in the heart rate response in the subjects. This effect was algebraically added to the increase in the heart rate caused by alcohol consumption. The result that we observed was a decrease in the acute effects of alcohol on the heart rate compared with the effects observed in absence of the contextual stimuli, which allows us to suppose that the CCR also underlies the cross-tolerance observed in this experiment. In this way, our results support the hypothesis proposed by several researchers that contextual cues are an important component in the explanation of the cross-tolerance between nicotine and alcohol, assigning a central role to Pavlovian associative processes (Ruiz et al., 2010; Siegel, 1979, Siegel et al., 2000; Siegel & Ramos, 2002; Vila et al. 2013). Although these results could not be reduced to pharmacological mechanisms, we could state that both mechanisms (pharmacological and conditioning) are complementary.

The clinical significance of our results lies in the pertinence of conditioned cross-tolerance in human nicotine and alcohol abuse based on Siegel's demonstration that the lethality of a drug dose can be greatly influenced by the presence of drug-related stimuli. In a nondrug-related environment, the absence of drug-opposite conditioned responses and thus the absence of conditioned cross-tolerance results in an increase in drug

potency, thereby increasing the potential for overdose. Because of the potentially lethal consequences for the active drug abuser, further research is needed to more comprehensively determine the incidence of conditioned cross-tolerance in the natural environment and the extent to which it is involved in accidental overdose. At the applied level, these findings are particularly relevant for clinicians, considering that treatments for drug-related disorders have not been very effective. The results presented here could help improve therapy in the clinical environment by implementing techniques that have been shown to reduce the influence of environmental stimuli associated with the use of a drug.

Another aim of treatment programs is the prevention of resumption of excessive drug use. Typically, following a period of detoxification, the patient will no longer display withdrawal distress and no longer report craving. Therefore, when patients are released and return to environments where they previously used drugs, they display withdrawal distress, report craving, and relapse. The factors contributing to relapse may be that the capacity of drug-associated stimuli to elicit craving and withdrawal distress has not been reduced during treatment.

These results require future research since a full discussion of the potential mechanisms that explain the development of cross-tolerance to heart rate responses produced by nicotine and alcohol requires incorporating an analysis of the symmetric effects of the two drugs used, so it would be important to evaluate whether cross-tolerance develops when the order of presentation of the drugs is reversed; that is, first administering alcohol for the development of tolerance and then nicotine to observe cross-tolerance. Additionally, it would be important to evaluate whether cross-tolerance can be observed with different effects produced by these drugs.

Conclusions

The results of this investigation showed that the cross-tolerance between nicotine and alcohol was modulated by the environmental stimuli associated with the administration of the first drug and the resulting CCR. Our results have important implications in the study of the mechanisms of addiction and drug dependence. The interaction of conditioning factors, such as the control of environmental stimuli in tolerance and cross-tolerance, could play an important role in drug abuse and dependence.

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Conflict of interest

No conflict of interest to report.

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Changes in alcohol consumption in Spain between 1990 and 2019

Cambios en el consumo de alcohol en España de 1990 a 2019

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Abstract

Spain is one of the countries of the European Union in which alcohol consumption has decreased in the past decades. The aim of this paper is to distinguish different phases of the level of alcohol consumption in Spain since 1990. Adult alcohol consumption *per capita* data between 1990 and 2019 were analysed for temporal trends using the Joinpoint regression model. An additional analysis using interrupted time-series between 1962 and 2016 was performed using data from Global Information System on Alcohol and Health. Data from the survey on alcohol and other drugs in Spain were collected and a narrative review was conducted to identify possible reasons for the trends found. Five point changes were identified on the timeline between 1990 and 2019, including: a decrease of 3.2% per year from 1990 to 1995, an increase of 1.1% per year from 1995 to 2000, a period of stability from 2000 to 2006, a decrease of 4.5% per year from 2006 to 2011, and a period of stability from 2011 onwards. These changes can largely be explained by the different public health measures carried out by the Spanish government, as well as the change in the pattern of consumption in society, which shifted its alcoholic beverage preference from wine to beer, and increased its binge-drinking behaviour. Further studies such as interrupted time-series analyses should test if indeed the hypothesized measures on public health have been effective; this could inform future policies in Spain and in other countries.

Key Words: Alcohol; Spain; Public health; policies; temporal analysis.

Resumen

España es uno de los países de la Unión Europea donde el consumo de alcohol disminuyó en las últimas décadas. Este estudio tuvo como objetivo identificar las diferentes fases de consumo de alcohol desde 1990. Los datos de consumo de alcohol per cápita en adultos entre 1990 y 2019 se analizaron para determinar las tendencias temporales utilizando el modelo de regresión Joinpoint. Se realizó un análisis adicional utilizando series temporales interrumpidas entre 1962 y 2016 con datos del Sistema de Información Global sobre Alcohol y Salud. Además, se recopilaron datos de la encuesta sobre el alcohol y otras drogas en España y se realizó una revisión narrativa para identificar las posibles razones que expliquen los cambios de tendencia encontrados. Cinco puntos de cambio fueron identificados: disminución del 3,2% por año de 1990 a 1995, aumento del 1,1% por año de 1995 a 2000, período de estabilidad de 2000 a 2006, disminución del 4,5% por año de 2006 a 2011 y período de estabilidad a partir del 2011. Este cambio en la tendencia puede explicarse por las diferentes medidas en políticas de salud pública implementadas por el gobierno español, así como por el cambio en el patrón de consumo que presentó la sociedad, cambiando las preferencias de las bebidas alcohólicas del vino a la cerveza y aumentando el *binge drinking*. Futuros estudios deberían analizar si las medidas de salud pública han sido efectivas; esto permitiría trabajar con ellas en España y en otros países.

Palabas clave: Alcohol; España; salud pública; políticas; análisis temporal.

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Alcohol use has been identified as a major risk factor for global mortality and burden of disease (Rehm & Imtiaz, 2016). Europe is no exception, and in fact the proportion of alcohol-attributable health burden is highest in this region (World Health Organization, 2018a), due to its high level of consumption (Manthey et al., 2019). Spain is one of the largest countries in Europe, and alcohol consumption is socially very accepted and integrated into daily life (Calafat, 2002). In 2017, 91.2% of the Spanish population between 15 to 64 years of age reported that they have consumed alcohol at least once in their lifetime, 75.2% had had alcohol at least once in the last 12 months, 62.1% at least once in the last month, and 7.4% every day in the last 30 days (Plan Nacional sobre Drogas, 2017). Alcohol and tobacco are the most used drugs in Spain and are the ones that have generated the greatest public health problems (Institute for Health Metrics and Evaluation, 2017). However, as indicated above, for alcohol there are inherent conflicts between public health concerns and the cultural integration of alcohol.

Worldwide, total per capita consumption of alcohol has increased from 5.9 liters (95% CI 5.8-6.1) in 1990 to 6.5 liters (95% CI 6.0-6.9) in 2017 (Manthey et al., 2019). However, in the European Region, it has decreased from 12.2 liters (95% CI 12.0-12.4) in 1990 to 9.8 liters (95% CI 9.3-10.4) in 2017. Spain is one of the European countries where alcohol consumption decreased over the past decades (Galán, González & Valencia-Martín, 2014; Matrai et al., 2014), from 14.2 liters (95% CI 13.8-14.6) in 1990 to 10.0 liters (95% CI 9.1-11.0) in 2017. However, these general trends since 1990 are composed of differing short-term trends of increases or decreases.

It is the aim of this paper to distinguish different phases of level of alcohol consumption since 1990. Moreover, we will try to understand the mechanisms which led to these developments. More specifically, we will try to answer the following questions:

- Which periods for Spain are notable for changes in trends and can be distinguished with respect to level of alcohol use since 1990?
- What characterized the trends of alcohol use within these periods, which factors are responsible for these trends, and which factors for changes in trends, i.e., the transition between periods?

Methods

Data

Adult alcohol consumption *per capita* data between 1990 and 2019 were taken from Manthey et al. (2019). These data are comprised of both recorded and unrecorded consumption, and the time period was selected because comparable data for adult consumption only exists since 1990. The beverage specific adult *per capita* data and total recorded were taken from Matrai et al. (2014) up to 1989, and then from the Global Information System on Alcohol and Health (GISAH) (World Health Organization, 2016). Manthey and colleagues also based their estimates on this report from the WHO. Data from the annual survey on alcohol and other drugs in Spain (EDADES) (Plan Nacional sobre Drogas, 2017), carried out since 1995, was collected. This survey is an initiative by the Government Delegation for the National Drug Plan and is conducted every two years. It targets those between 15 and 64 years of age, living in household, with the aim of understanding the trends regarding drug use. The results are representative for the general population.

Data on alcohol control policy and other determinants were obtained from the National Drug Plan, a government initiative created in 1985 with the aim of coordinating and strengthening policies in the area of legal and illegal drugs, and carried out by the different governmental agencies and social entities in Spain (available at http://www.pnsd.mscbs.gob.es/pnsd/Introduccion/home.htm).

Methodology for determining periods

The temporal trend was evaluated using the Joinpoint regression model, a statistical modelling technique useful in identifying and describing the occurrence of temporary changes and providing a clearer picture of the trend over long periods of time (Fay, Kim, Feuer & Midthune, 2000; Rea et al. 2017). This model identifies the time points where a given trend changes, called "Joinpoints". The final number of Joinpoints given is established based on a set of a statistical criteria. Using a Monte Carlo Permutation method, the p-value under the null hypothesis is calculated. The annual percentage of change within the period studied is also obtained.

Sensitivity analyses for determining periods

We tried to cross-validate the analyses of Joinpoint with more traditional interrupted time-series analyses for the time between 1962 and 2016 (the last year in GISAH (World Health Organization, 2016) without estimated values). Moreover, we used only adult recorded consumption to check to what degree shifts in beverage preference were responsible for the changes in overall level in consumption, and whether the periods in the main analyses were mainly determined by unrecorded alcohol consumption. Finally, we tested WHO data against the detailed data from Sordo and colleagues (Sordo et al., 2016) for the period between 2001 and 2011; these data have been considered the gold standard for Spanish consumption.

We first examined the distribution of the main dependent variable —adult recorded *per capita* consumption—both visually and with Q-Q plots, and found that the assumption

of a normal distribution could not be refuted. Second, we fitted simple models to account for autocorrelation, as recommended by Beard and colleagues (Beard et al., 2019). We used general additive models from the 'mgcv' package of R (Wood, 2006), of normalized residuals to identify possible autocorrelation in the time series. If present, autocorrelation was corrected for by adding AR and MA terms in the correlation structure of the model. The best-fitting model was selected using likelihood-ratio tests comparing models adjusted for autocorrelation with non-adjusted models.

We evaluated level (immediate effects) and slope (sustained effects) changes of six distinct periods, which were defined *a priori* based on the joinpoint analysis. The models included both "level change" and "slope change" variables. The "level change" variable was entered as a dummy variable, coded with 1 within and with 0 outside the respective period. For the "slope change" variable, each month was coded with 0 if it fell outside the respective period, and with increasing integers if it fell within the respective period. These models included also a covariate for cumulative years since 1962.

As for the comparison with the data from Sordo and colleagues (Sordo et al., 2016), we conducted formal analyses for correlation and rank correlation, as well as compared the overall level with a paired t-test.

Methodology for determining factor underlying trends and changes in trends

A narrative review was conducted to identify possible reasons for the trends found. The search terms used were: alcohol AND (public policy OR regulation) AND Spain, adding the year in which a point of change in the trend was identified. The search was performed in Spanish and English language and conducted through MEDLINE (PubMed), Web of Science and Google general index. For the Google general index, the search was continued until it reached 100 hits or relevancy for our analysis.

Software used

All statistical analyses were performed using Joinpoint v4.5.0.1 (National Cancer Institute, Bethesda, USA) and R v3.6.0 (University of Auckland, New Zealand) computer software programs.

Results

Determined periods

The Joinpoint model (Figure 1) showed that there were five different trends: a decrease of 3.2% per year from 1990 to 1995, an increase of 1.1% per year from 1995 to 2000, a period of stability from 2000 to 2006, a decrease of 4.5% per year from 2006 to 2011 and from 2011 onwards a period of stability. Sensitivity analyses corroborated the identified periods using a different methodology (see Figure A1 and Table A1, Appendix 1). Using this additional analysis we identified that the first trend on the Joinpoint model started in 1976. Finally, we assessed that data used (Manthey et al. 2019), based on WHO data, were highly correlated with the data of Sordo and colleagues (Sordo et al., 2016), both with respect to level (Pearson correlation of 0.913; 95% CI: 0.693-0.978; t=6.72; df=10; p<0.001) and

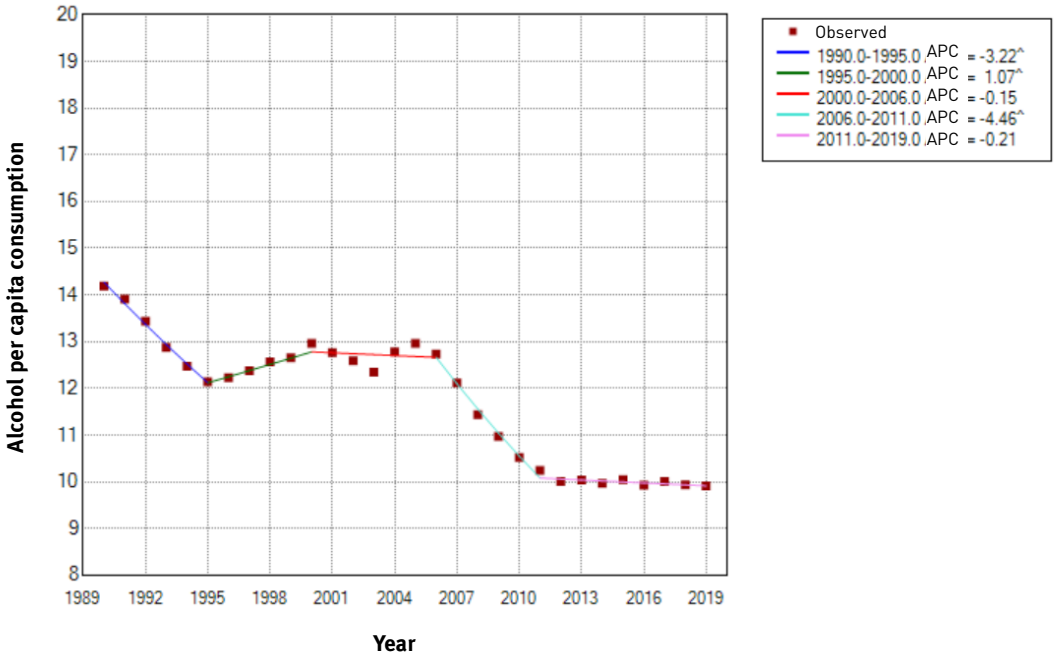

Figure 1. Alcohol per capita consumption in Spain between 1990 and 2019 plotted using a Joinpoint regression model.
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the Alpha = 0.05 level.

rank (Spearman correlation of 0.852; 95% CI: 0.398-1.000; p<0.05). The WHO data were on average 1 liter higher, due to different estimates for unrecorded, i.e., not registered, alcohol (difference: 0.964; t=7.74; df= 10; p<0.001). Both sets of data also showed a more pronounced decline starting 2006.

Results of search

The narrative search resulted in a total of 1,222 articles in MEDLINE (PubMed), 58 articles in Web of Science and 60,800,000 results in Google's general index.

1990-1995

The first period identified (the decrease from 1990 to 1995) started back in 1976 and was due to a change in drinking preferences from wine to beer (see Figure A1, Appendix 1). Several factors can explain this shift: the emergence of new beverages (colas, sodas, light and low alcohol beer) changed the status of wine as the only drink on the market and there was more invested in advertising them. Spirits and beer had better marketing strategies due to the multi-national enterprises behind them, while wine was only occasionally advertised and its market was mainly comprised of small producers. The price of wine in Spain increased by 23% from 1985 to 1992 while the price of beer only increased by 14%. As far as the public was concerned, beer was considered to be less dangerous than drinking wine or spirits. Finally, the role of lunch as a family meal was lost which also reduced the wine consumption in households (Galán et al., 2014; Gual & Colom, 1997; Matrai et al., 2014).

Another factor that may have influenced this decrease were the public health measures taken due to the epidemic of heroin use in the 80s (Sánchez-Niubò et al., 2009). Drug use became one of the main concerns for Spain, and the government created legislation to regulate alcohol consumption as well, especially among young people (Gual, 2006). In 1982, the minimum age to purchase alcoholic beverages was legislated to be 16 years old (Real Decreto 2816, 1982). The advertising of alcoholic beverages with more than 20% alcohol by volume was banned in 1988 (Ley 34, 1988) and the sale of alcoholic beverages was prohibited in public education centers in 1989 (Orden de 7 de noviembre, 1989) and at sport events in 1990 (Real Decreto 1045, 1990).

Up to 40% of traffic accidents were associated with the consumption of alcoholic beverages in the 90s (Del río, 2002; Pascual Pastor, 2002) which led to some measures related to road safety. In 1992, the minimum level of Blood Alcohol Concentration (BAC) was settled upon for the first time, at 0.8 g/l for drivers of motor vehicles, 0.5 g/l for transporters of goods and 0.3 g/l for transporters of passengers or hazardous material (Ley Orgánica 1, 1992).

Spain controls alcohol taxes by a set of indirect taxes called "the special taxes" regulated by Law 38 (1992). The tax rate applicable to alcohol beverages increased by 10% in 1993, by 5.9% in 1994 and by 3.5% in 1995 (Secretaría de Estado de Hacienda, 2013).

1995-2000 and period of stability

Between the end of 1992 and the end of 1993 there was a severe economic crisis in Spain («España sufrió en 1993 la peor recesión económica registrada en los últimos 30 años», 1994), but in late 1994, the economy began to recover with an increase of 2.4% of GDP, the creation of

Table 1. *Evolution of alcohol consumption in the Spanish population aged 15-65 (1995-2017).*

	1995	1997	1999	2001	2003	2005	2007	2009	2011	2013	2015	2017
Sample size	8888	12 304	12 234	14 113	12 033	27 934	23 715	20 109	22 128	23 136	22 541	21 249
Mean age to start drinking	NA	16.8	16.9	16.9	16.7	16.7	16.8	16.7	16.7	16.7	16.6	16.6
Life-time alcohol consumption* (percentage)	NA	90.6	87.3	89.0	88.6	93.7	88.0	94.2	90.9	93.1	93.5	91.2
Alcohol consumption in the last 12 months* (percentage)	68.5	78.5	75.2	78.1	76.6	76.7	72.9	78.7	76.7	78.3	77.6	75.2
Alcohol consumption. last 30 days* (percentage)	NA	64.0	61.8	63.7	64.1	64.6	60.0	63.3	62.3	64.4	62.1	62.7
Daily alcohol consumption, last 30 days* (percentage)	18.4	12.7	13.7	15.7	14.1	14.9	10.2	11.0	10.2	9.8	9.3	7.4
Binge drinking**, last 30 days (percentage)	NA	NA	NA	NA	5.3	4.9	12.6	14.9	15.2	15.5	17.9	15.1
Individuals that perceive risks associated with alcohol consumption (percentage)												
Having 5-6 drinks daily	NA	89.2	90.7	86.1	83.3	87.3	89.2	91.4	91.7	90.7	90.0	90.0
Having 5-6 drinks on weekend	NA	45.6	49.2	44.2	41.8	43.6	46.6	45.0	49.3	43.5	45.8	49.1

*Note.**at least one drink; **5 or more drinks for men, 4 or more drinks for women.
Source: OEDA Survey on Alcohol and Drugs in Spain (EDADES).

nearly 400,000 jobs and a decline in unemployment rates from 22.4% to 22%. This economic improvement might explain the point change in 1995 in our Joinpoint model.

Among the safety road traffic measures, BAC was modified in 1998, reducing the amount allowed to 0.5 g/l for drivers of motor vehicles and 0.3 g/l for transporters of goods, passengers or hazardous material (Real Decreto 116, 1998).

Another tax increase by 3.5% at the beginning of 1996 and by 25.58% at the end of July of that year occurred, and remained stable until January 1, 2002, when it increased by 8%. In 2005, there are two increases: the first of 2%, in effect until September 16th, and the second of 10% in effect since September 17th (Secretaría de Estado de Hacienda, 2013).

2006-2011

In December 2005, tobacco-control legislation was approved and enacted in January 2006, which regulated the sale and place of its consumption (Ley 28, 2005). In September 2006 a proposal to regulate alcohol consumption was presented to the Council of Ministers whose relevant aspects were two: regulation of the sale (banning street sales, regulation of the license to sell in stores, time limit of sale and limitation of age for purchase) and limitation of advertising (in press, television and radio from 6h to 22h) (Ministerio de Sanidad y Consumo, 2006). This unleashed a major media and social debate against the proposed law. The non-supporters were the political opposition and also some Ministries and Autonomous Governments of the government itself, organizations of farmers and winemakers, along with other organizations (Villalbí, Granero & Brugal, 2008). In February of 2007, the Minister of Health announced the withdrawal of the proposed law. But among the supporters of the law were scientific societies, consumer organizations, parents and mothers' organizations, and associations representing alcohol victims or their families. This debate may have triggered widespread public awareness and account for the decrease in alcohol consumption that began in 2006.

Also, between 2005 and 2007, an increase of 7.7% in reports of binge drinking in the past 30 days (4.9% in 2005 vs 12.6% in 2007) was identified by EDADES (Table 1). In Spain, a phenomenon called "botellón", which is defined as a group of mostly young people consuming alcohol in open public places, became widespread and it has been associated with binge drinking (Soler-Vila et al., 2014; Teixidó-Compañó et at., 2019). Between the years mentioned there were massive gatherings of more than 25,000 people in several cities in Spain, mostly in the southern part of the country, to participate in the so-called "macrobotellones" («Más de 25.000 jóvenes se reúnen en el "macrobotellón" de Granada», 2006). In response to this problem, the Autonomic Government of Andalucia approved a law that regulated this phenomenon (Ley 7, 2006). The law banned the gathering of people who consuming drinks in open public places, except in those areas predetermined by municipalities. It also banned the sale of alcoholic beverages after 10pm and the ban on hotel and nightlife establishments serving drinks for consumption outside the premises, including the authorized spaces (i.e., terraces).

The slope was maintained by the economic crisis that began in 2007-2008. In times of economic recession, it was observed that people gave priority to other expenses over alcohol beverages, as alcohol is a dispensable product (Blázquez-Fernández, Canterero-Prieto & Perez, 2019; de Goeij et al., 2015; Martin Bassols & Vall Castelló, 2016). In the United States and Eastern Europe another mechanism was suggested where drinking problems increased due to psychological distress often triggered by income reductions and unemployment (de Goeij et al., 2015). In the case of Spain and in most countries in the European Union, the first mechanism produced the decrease in alcohol consumption during the economic crisis: a regular pattern of heavy drinking decreased (maybe related with less available income) but a pattern of binge drinking increased (perhaps to cope with emotional distress related to unemployment and financial hardship) (Catalano, 1997).

Additional measures and final period of stability

Since the creation of the National Drug Plan different strategies have been approved by the Council of Ministers with the aim of establishing the framework for action for public health policies in Spain, as well as the lines of general execution. Campaigns for moderate consumption, education on drug consumption targeted to young people, policies on drinking and driving, detection and treatment of alcohol abuse and dependence, among others, have been some of the action plans gathered in the agenda (Plan Nacional sobre Drogas, 2015). Also the Autonomic Governments and municipalities have enacted regulations and norms towards the use and availability of alcohol and specific campaigns to reduce its consumption (Plan Nacional sobre Drogas, 2019).

And finally, in June 2013, taxes were raised by 10% and in 2016 there was another increase in tax of 5% (Secretaría de Estado de Hacienda, 2013).

Discussion

Alcohol consumption in Spain has varied over the years, presenting different trends and an overall decrease over the past three decades. Our main findings showed that Spain is a country in transition, where beer has replaced wine as the preferred alcohol beverage and binge drinking among younger people is replacing daily alcohol consumption still seen in adults. Our results are in line with other studies that analyzed epidemiologic aspects of alcohol consumption

(Galán et al., 2014; Gual, 2006; Sordo et al., 2016; Villalbí & Brugal, 2012).

This change in the trend can be explained by the different public health measures carried out by the Spanish government as well as the change in the pattern of consumption. Some of the policies mentioned in the results have been effective, such as increasing the minimum alcohol purchase age, advertising regulations, and the ban on the sale of alcoholic beverages in public education centers and at sporting events (Matrai et al., 2014).

The attempts by the government to legislate stricter control over alcohol sales and advertising in 2006 was a massive failure due to the strong influence of industry and others interested in its consumption, including the Spanish Wine Federation (FEV), Brewers of Spain and the Spanish Federation of Spirits (FEBE), which form part of the Spanish Confederation of Business Organizations (CEOE) through the Spanish Federation of Food Industries and Beverages (FIAB) (Villalbí et al., 2008; Villalbí & Pérez, 2006). These entities together form a strong alliance with well-defined strategies which are widely believed to encourage alcohol consumption. As in tobacco-control policies, it is necessary to define a strategy and priorities that regulate it (Villalbí, Rodríguez-Martos, Jansà & Guix, 2006). There are some effective measures like increase on taxes, restrictions on availability, control over advertising, interventions to prevent driving under the influence, and offering interventions in primary care (the first three are recommended as "best buys" as they are highly cost-effective and easy to implement (Chisholm et al., 2018); all five measures are subsumed in the SAFER initiative of WHO (World Health Organization, 2018b)). It is crucial to generate favorable public policies to prevent psychoactive substance use and reduce the burden they generate (Brugal, Rodríguez-Martos & Villalbí, 2006; Robledo de Dios, 2002; Villalbí, Bosque-Prous, Gili-Miner, Espelt & Brugal, 2014).

Previous studies have shown an association between binge drinking and the "botellón" phenomenon described above (Romo-Avilés, Marcos-Marcos, Marquina-Márquez & Gil-García, 2016; Soler-Vila et al. 2014; Tomás, Tort, del Río & Iñíguez, 2010). Some reasons that explain this association involve peer pressure, accessibility to cheap alcoholic beverages, the "positive" effects of alcohol consumption including the enhancement of social relationships and gaining admiration from other colleagues when drinking large amounts of alcohol (Espejo, Cortés, del Río, Giménez & Gómez, 2012). Public policies related to alcohol consumption should consider this emerging phenomenon and target interventions that control them, as in the case of Autonomous Community of Andalucia which enacted a law regulating it. "Botellon"-control should be widespread at a national level, focusing on legislating the accessibility and availability of alcohol by young people (Dolz del Castelar & Martín Castro, 2010; Teixidó-Compañó et al., 2019).

In regard to the economic crisis, the recession has been associated with less alcohol consumption, which was noted in Spain which supported the pro-cyclical theory of alcohol consumption (Martin Bassols et al., 2016). This theory claims that due to their reduced budget, people invest less money in alcoholic beverages, which explains the decrease in daily alcohol consumption, but may bring about an increase in binge drinking. This phenomenon has been observed and analyzed in other countries as well (Bosque-Prous, Kunst, Brugal & Espelt, 2017; Colell, Sánchez-Niubò, Delclos, Benavides & Domingo-Salvany, 2015; de Goeij et al., 2015; Pacula, 2011). Some vulnerable groups with a predisposition to increasing their alcohol consumption —such as the unemployed— were identified (Blázquez-Fernández et al., 2019; Bosque-Prous et al., 2015; Dom et al., 2016). Economic fluctuation and instability are triggers to mental health disorders such as alcohol dependence and alcohol abuse in determinate subgroups (Gili, García Campayo & Roca, 2014; Gili, Basu, McKee & Stuckler, 2013). Therefore some public health policies should be directed at these subgroups in order to prevent and treat alcohol-related problems.

Even though there have been several increases on alcohol taxes through the years studied, Spain is still the country with the lowest taxes in all ranges of alcoholic beverages among the European Union. For example, in contrast to there being a tax exemption on wine in Spain, there is one in the United Kingdom of more than 2 Euros per liter (Antoñanzas Villar, Martínez-Zárate & Pradas Velasco, 2008). It has been shown, that heavy drinkers and people with alcohol use disorders as well as young people tend to consume cheaper alcoholic beverages (Meier, Purshouse & Brennan, 2010; Purshouse, Meier, Brennan, Taylor & Rafia, 2010). Pricing policies should take such factors into account as a way to reduce alcohol consumption (Wagenaar, Salois & Komro, 2009).

A limitation of this study is that we did not perform an analysis to verify if our possible explanations represent causation, but we refer to them as correlations in the results. We also cannot exclude other influencing factors, such as other contextual factors and long-term social and economic trends as illustrated by Allamani and colleagues for Italy (Allamani et al., 2014), a country with partly similar trends. Another limitation is that the interpretations above refer to the use of EDADES, a survey with the weakness of any general population survey in the fields of alcohol: considerable degree of non-response, under-coverage, and potential biases due to self-report (Rehm, Klotshe & Patra, 2007; Shield & Rehm, 2012; Sordo et al., 2016). Despite these limitations, the strength of this study lies in following: a homogeneous, continuous and standardized methodology over time that allows us to study the temporal

trend on alcohol consumption over a span of almost 30 years. Several hypothesis explaining why this decrease happened in the past years have arisen in this article, and further studies should analyze these possible reasons to see if the measures taken have been effective and, if so, then be used to set an example for other countries.

In conclusion, Spain is a country in transition where the trend on alcohol consumption has changed. The alcohol policy measures undertaken, the change in the lifestyle, the rise in beer consumption and binge drinking may explain the decrease observed and so far there has been an improvement on reducing consumption, but stricter public health policies and legislation should be taken into account in regulating alcohol consumption even more.

Conflict of interests

The authors declare no conflicts of interest.

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Appendix 1

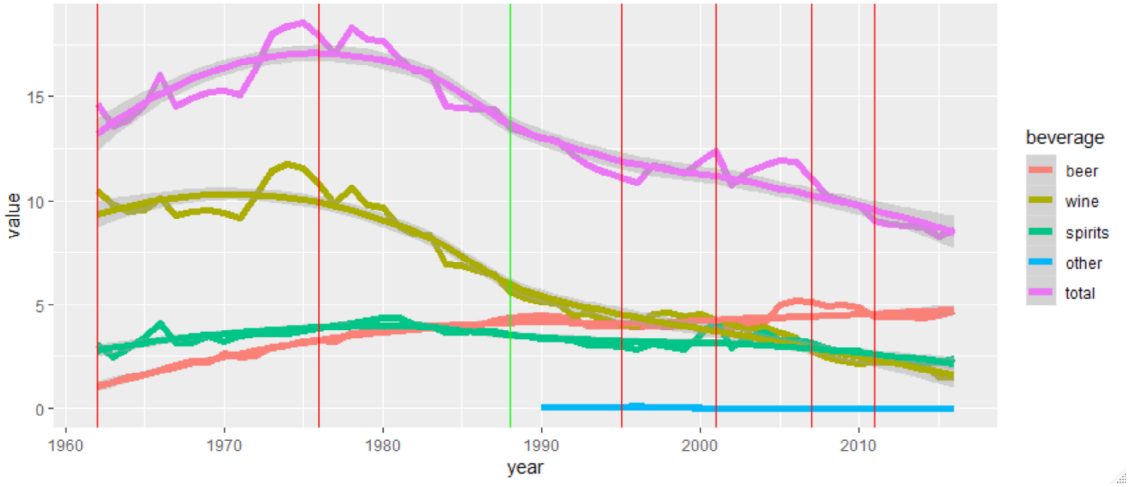

Figure A1. Alcoholic beverage trends and periods of changes identified by sensitive analysis.

Table A1. *Data on alcohol per capita consumption by year, type of alcoholic beverage and source.*

Year	Wine	Beer	Spirits	Other	Total	Source
1962	10.49	1.05	3.10		14.64	Matrai
1963	9.81	1.27	2.48		13.56	Matrai
1964	9.50	1.49	2.89		13.88	Matrai
1965	9.54	1.61	3.44		14.59	Matrai
1966	10.08	1.82	4.13		16.03	Matrai
1967	9.26	2.10	3.18		14.54	Matrai
1968	9.45	2.28	3.18		14.91	Matrai
1969	9.53	2.22	3.47		15.22	Matrai
1970	9.39	2.67	3.19		15.25	Matrai
1971	9.16	2.48	3.47		15.11	Matrai
1972	10.22	2.50	3.61		16.33	Matrai
1973	11.43	2.95	3.60		17.98	Matrai
1974	11.72	3.06	3.60		18.38	Matrai
1975	11.55	3.25	3.73		18.53	Matrai
1976	10.77	3.30	3.86		17.93	Matrai
1977	9.85	3.23	3.99		17.07	Matrai
1978	10.58	3.58	4.12		18.28	Matrai
1979	9.79	3.68	4.24		17.71	Matrai
1980	9.69	3.64	4.36		17.69	Matrai
1981	8.78	3.73	4.33		16.84	Matrai
1982	8.40	3.81	4.02		16.23	Matrai
1983	8.32	3.88	3.98		16.18	Matrai
1984	6.94	3.87	3.68		14.49	Matrai
1985	6.86	3.97	3.64		14.47	Matrai
1986	6.65	3.99	3.73		14.37	Matrai
1987	6.45	4.26	3.70		14.41	Matrai
1988	5.64	4.34	3.54		13.52	Matrai
1989	5.33	4.45	3.50		13.28	Matrai
1990	5.10	4.46	3.35	0.07	14.18	GISAH
1991	5.07	4.39	3.34	0.08	13.91	GISAH
1992	4.49	4.32	3.31	0.07	13.43	GISAH
1993	4.56	4.00	3.04	0.07	12.88	GISAH
1994	4.27	3.99	3.02	0.08	12.47	GISAH
1995	4.03	3.99	2.99	0.08	12.14	GISAH
1996	3.97	3.93	2.86	0.10	12.23	GISAH
1997	4.57	3.95	3.08	0.09	12.38	GISAH
1998	4.62	3.94	2.95	0.07	12.57	GISAH
1999	4.39	4.06	2.82	0.06	12.66	GISAH
2000	4.53	3.79	3.52		12.96	GISAH
2001	4.20	3.91	4.23		12.77	GISAH
2002	4.02	3.83	2.89		12.59	GISAH
2003	3.82	4.11	3.42		12.35	GISAH
2004	3.89	4.10	3.69		12.78	GISAH
2005	3.67	4.98	3.27		12.96	GISAH
2006	3.43	5.15	3.28		12.73	GISAH
2007	2.78	5.09	3.18		12.12	GISAH
2008	2.44	4.92	2.88		11.43	GISAH
2009	2.28	4.98	2.73		10.97	GISAH
2010	2.15	4.87	2.76		10.52	GISAH
2011	2.20	4.40	2.42		10.24	GISAH
2012	2.21	4.41	2.20		10.01	GISAH
2013	2.15	4.42	2.20		10.04	GISAH
2014	2.16	4.35	2.18		9.97	GISAH
2015	1.55	4.51	2.21		10.04	GISAH
2016	1.55	4.64	2.39		9.93	GISAH
2017					10.00	Manthey
2018					9.93	Manthey
2019					9.91	Manthey

An estimation of the social cost of illicit drug consumption in Catalonia

Estimación del coste social del consumo de drogas ilegales en Catalunya

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Abstract

Worldwide, as well as in Spain, the use of illegal drugs is among the major contributors to the global burden of disease. Quantifying the costs that illegal drugs impose on society is key in terms of decision-making. The objective of this paper is to estimate the social cost of illicit drug consumption in Catalonia for a specific year, and to establish a methodology to be able to replicate such estimations regularly and monitor properly the impact of national plans. To do that, a cost of illness study was performed. For the estimation of mortality and morbidity costs, we relied on the Attributable Fraction approach. Only public sector costs were included: healthcare and non-healthcare costs. The cost of illegal drug consumption in Catalonia in 2011 was estimated at €326.39 million (0.16% of the Catalan GDP in 2011; 0.15% in 2018). Of the total cost, 82% corresponded to direct costs. Among direct costs, 30.32% corresponded to the penal system, 15.99% to hospitalizations, 13.48% to the police force, 17.19% to pharmacy, 8.34% to treatment in specialized centres, and 5.74% to therapeutic communities, among others. Indirect costs represented 18% of total costs, mostly lost income due to drug-related death. This study has been an opportunity to systematically collect data and think about the potential economic returns that could be achieved from effective policies and programs aimed at reducing the consumption of illegal drugs.

Key Words: Illegal drugs; cost of illness; social cost; policy; national plans.

Resumen

Mundialmente, así como en España, el consumo de drogas ilegales es uno los principales contribuyentes a la carga mundial de morbilidad. Cuantificar los costes que las drogas ilegales imponen a la sociedad es clave para la toma de decisiones. El objetivo de este trabajo es estimar el coste social del consumo de drogas ilegales en Cataluña para un año específico y establecer una metodología para poder replicar dichas estimaciones regularmente y monitorear el impacto de los planes nacionales. Se ha realizado un estudio de coste de la enfermedad. Para la estimación de los costes de mortalidad y morbilidad se ha utilizado el enfoque de la fracción atribuible. Solo se incluyeron los costes del sector público, sanitarios y no sanitarios. El coste del consumo de drogas ilegales en Cataluña en 2011 se estimó en 326,39 millones de € (0,16% del PIB catalán en 2011; 0,15% en 2018). El 82% del coste total correspondió a costes directos; de estos, el 30,32% correspondió al sistema penal, 15,99% a hospitalizaciones, 13,48% a la policía, 17,19% a farmacia, 8,34% a tratamiento en centros especializados y 5,74% a comunidades terapéuticas, entre otros. Los costes indirectos representaron el 18% de los costes totales, principalmente pérdidas de productividad debidas a muertes por el consumo de drogas. Este estudio ha sido una oportunidad para recopilar datos de forma sistemática y pensar en los posibles rendimientos económicos que podrían obtenerse de políticas y programas efectivos destinados a reducir el consumo de drogas ilegales.

Palabas clave: Drogas ilegales; coste de la enfermedad; costes sociales; política; planes nacionales.

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Worldwide, substance use disorders are among the major contributors to the global burden of disease. Actually, in 2015, they contributed to 111 million of global disability-adjusted life years (DALY). Global risk exposure to drugs for both sexes combined has increased significantly over the past 25 years. As the fifth-leading risk for men, substance use disorders were associated with 6.6% of disease burden; for women, they were the 12th leading risk factor with 2% (IHME, 2016).

Global estimated annual prevalence of illicit drug use was highest for cannabis (3.8% of adults aged 15-64 years), followed by amphetamines (0.77%), opioids (including prescription opioids and opiates; 0.37%) and cocaine (0.35%) (UNODC, 2017). It was also estimated that 0.25% of the adult population aged 15-64 years reported injecting drug use in 2015, equating to 11.8 million people. Cannabis and opioid dependence were the most common types of illicit drug dependence, with 19.8 and 16.8 million cases, respectively. Amphetamine and cocaine dependence were less prevalent, with 6.6 million and 3.9 million cases, respectively (Peacock et al., 2018). Globally, the age-standardized rates of mortality were 6.9 deaths per 100,000 people in 2015 for illicit drugs (Peacock et al., 2018). Illicit drug attributable burden was concentrated in drug use disorders (16.9 million), of which 12.9 were opioid use disorders-attributable, cirrhosis (4.7 million), HIV infection (3.0 million) and liver cancer (1.8 million) (IHME, 2016). Harm to others caused by the use of illegal drugs, as families, communities and the society as a whole, is also large and wide, ranging from violence to production losses (Nutt, King & Phillips, 2010).

In Spain, illegal drug use is, together with alcohol use, in the 6th position among the risk factors in terms of burden of disease – DALYs- (IHME, 2016). Spain is ranked among the countries with higher illegal drugs consumption (European Monitoring Centre for Drugs and Drug Addiction, 2016). Drugs are far less prevalent, but up to 2% of Spaniards refers daily cannabis consumption, and 7%, daily use of sedatives (Observatorio Español de la Droga y las Toxicomanías, 2016). Policonsumption is usual and in 95% of the occasions associated with alcohol and in 60% with cannabis, being "tobacco-daily tobacco-cannabis-cocaine" the most frequent pathway (Sánchez-Niubò, 2020). Particularly, Catalonia is the region of Spain with the highest prevalence (up 50%) of Hepatitis C, related to the consumption of intravenous drugs (Saludes et al., 2019). Spain is also one of the leading countries in drug seizures in Europe, mainly in cannabis and heroine (Observatorio Europeo de las Drogas y las Toxicomanías, 2016).

However, to undertake these studies, the available information on public expenditure on social cost of illegal drug abuse in Europe remains scarce and heterogeneous, both at local and national level. Several contributions suggest that these costs are high, but there is still a lot of controversy and there is not yet consensus on how to calculate the costs of such complex phenomenon (Barrio, Reynolds & García-Altés, 2017). Recent review of guidelines undertaken in the context of the LEADER project has resulted in a proposal of two frameworks (minimum and ideal) to guide estimation of social costs for future research (Vella, García-Altés, Segura García, Ibáñez Martínez & Colom Farran, 2018), together with and a guidance document on methods for their estimation (LEADER, 2017). Having a standardized social estimation approach can also facilitate analysing the economic impact of introducing national drug strategies, as Portugal did recently, where social costs of drugs decreased by 18% in the eleven-year period following the approval of Portuguese Strategy for the fight against drugs (Gonçalves, Lourenço & Nogueira da Silva, 2015).

The drug-related public spending among the 18 countries that have developed estimates over the past 10 years is estimated at between 0.01 and 0.5 per cent of gross domestic product, with health interventions between 15% and 53% of that figure, differing considerably from one country to another (Observatorio Europeo de las Drogas y las Toxicomanías, 2016).

In Spain, major efforts have been made over the last decades to counteract the effects of drug consumption in individuals and society at large. In this sense, various policies at national and regional level have been implemented, coordinated and monitored. Among these efforts there were the attempts to estimate the social cost of illegal drug use abuse (García-Altés, Ollé, Antoñanzas & Colom, 2002; Rivera, Casal & Currais, 2017). The authors estimated that in 1997 minimum costs of illegal drug consumption in Spain reached about in 0.07% of GDP, while for Galicia it amounted to 0.12% of GDP in 2008 (Portella et al., 2003).

As part of an effort to improve the planning tools in the context of the evaluation of the Catalan Plan on Drugs, the objective of this research is to estimate the social cost of illicit drug consumption in Catalonia in 2011.

Methods

Healthcare in Catalonia (a region in Spain) is organized as a National Health System, funded by taxes. All residents (7,348,275 as of 2017) are granted universal public healthcare coverage by law. Public healthcare spending represents 5.4% of Catalan GDP.

We performed a cost of illness (COI) study, which has been extensively implemented for the calculation of social costs of substance abuse (García-Altés et al., 2002; Godgrey, Eaton, McDougall & Culyer, 2002; Kopp, 2001; Rehm et al., 2006; Rivera et al., 2017). As in any cost-of-illness study, the counterpoint of the analysis is that the costs are being calculated against the hypothetical alternative of the

absence of the condition of interest, in our case the non-existence of illegal drug use.

For the estimation of mortality and morbidity costs, we relied on the Attributable Fraction approach (AF) (Rehm et al., 2006). AF represents the share of a disease that are consequent to the exposure of a specific risk factor, in our case illicit drug consumption. AFs are calculated according to the following formula (Rehm et al., 2006):

$$AF = \frac{\left[\sum_{i=1}^{k} P_i\,(RR_i - 1)\right]}{\left[\sum_{i=1}^{k} P_i\,(RR_i - 1) + 1\right]}$$

Where:

- i is the exposure category. The baseline (no exposure) is i=o;
- RR(i) indicates the relative risk at exposure level i compared with no consumption of drugs;
- P(i) indicates the prevalence of the ith category of exposure.

Direct costs from the public sector perspective were included, as well as indirect costs, while private and intangible costs were excluded (Kopp, 2001). The matrix of cost of reference that was adopted is comparable to two of the most recent studies in the field focusing on European countries (Gonçalves et al., 2015; Rivera et al., 2017). These contributions are consistent with classical references (Kopp, 2001; Single et al., 2003) in terms of the definition of social cost and the categorisation of the items. Estimated categories are presented in Table 1.

All the not publicly available data was provided by entities of the Catalan Health or Justice systems. Each source of data is identified throughout the document when presented, together with the assumption adopted for the estimation.

Health-related direct costs

Treatment costs were broken up in the following components: pharmacy, which includes all cost of drugs provided to treat health consequences of illicit drug consumption, visits to primary care centres, treatment in specialized centres, and treatment of addiction in prisons (Gerència d'Atenció Farmacèutica i Prestacions Complementàries. Àrea Sanitària. Servei Català de la Salut). Five main prescription drugs were identified as relevant in the treatment of illegal drug users: methadone (8,055 people were in opioid substitution therapy), buprenorphine (4,189 people), naltrexone (2,263 people), benzodiazepines, and retroviral therapy for HIV (4,484 people). The first three were considered as 100% dedicated to the treatment of illicit drug users. For benzodiazepines, only 1% for male and 0.5% for female was attributed to the treatment of drug users. These were applied to the population of users aged between 18 and 65, in order to exclude cases of consumption not related to illicit drugs. To estimate antiretroviral cost for HIV, the total 2011 cost on these drugs in Catalonia was identified, totalling €152,092,275. To this budget, we applied the corresponding AF (Rehm et al., 2006) (21%) to obtain the part of the budget related to the treatment of illicit drug users (€32,851,931.40). Despite that, between 60% and 80% of drug users are estimated to be infected with hepatitis C, antiviral cost was excluded, because back in 2011 very few drug addicts were treated given the adverse effects and poor effectiveness of the treatment with interferon and ribavirin.

Visits to primary care centres related to illicit drug consumption treatment were identified on the primary care minimum data set (Servei Català de la Salut), using the ICD 10 codes of addiction to cocaine and opioids. Then, it was possible to identify the number of doctors, nurses or social services' visits, and apply them the cost of each type of visit (Vela, Clèries, Vella, Adroher & García-Altés, 2019).

To calculate treatment costs in specialized centres, we applied the proportion of patients consulting due to drug addiction (49.4% of the total) to the total budget expended on that services (CatSalut, 2012) (€20,510,803.39). The cost of detoxication units (€1,746,359.13) was added on top.

Cost of treatment for addiction to illicit drugs provided in correctional facilities was estimated from data provided

Table 1. *Cost matrix.*

Type of cost	Direct cost	Indirect cost
Health-related	Treatment costs	Lost income due to drug-related death
	Hospitalisation	Lost productivity due to treatment and/or hospitalisation
	Research and prevention	
	Support programs against addiction	
Non-health-related	Justice	
	Police	
	Penal system	

by the Catalan Department of Health and other non-governmental organizations. The cost of treating 3,980 addicted inmates in Catalan prisons amounted a total of €5,062,116.66.

Hospitalisation cost was furtherly divided in the following categories: morbidity cost for in-patient treatment costs; emergency costs, and ambulance service costs.

Registries of hospitalisations due to illicit drug consumption were retrieved from the hospital discharge database (Registro de Actividad de Atención Especializada. RAE-CMBD). Each DRG-related cost was multiplied by the corresponding AF (Rehm et al., 2006).

The basis for the calculation on "emergency" were data on emergency visits provided by three hospitals in Barcelona. The mean number of visits of emergency visits was calculated for these hospitals, taking into consideration their total population of reference. The result of this calculation was then applied to the total 2011 Catalan population. Unit cost for emergency visits was calculated as the weighted mean between the reimbursement tariff of two categories of hospitals, general and specialized, using relative frequencies of use in 2011 as weights.

Number of ambulance services specific for illicit drug related-emergencies was obtained from the Catalan emergency medical system (Sistema d'Emergències Mèdiques), and a unit cost was applied through a weighted average of the price of a basic service and an advance service ambulance (Orden de 17/11/2014, 2014).

Expenditure on research related to illicit drug consumption was calculated as the sum of total funding from the three main research calls on the topic: The National Plan on Drugs (Plan Nacional sobre Drogas, 2011), the Network of Addictive Disorders (Red de Trastornos Adictivos - RETOX) and the Agency for Management of University and Research Grants (Agència de Gestió d'Ajuts Universitaris i de Recerca - AGAUR).

Prevention expenditures were calculated accounting for total governmental resources dedicated to prevention coming from the budget of the Catalan Department of Health, and specific funding coming from the National Plan on Drugs from the Spanish government. Only those directed toward Catalonia and its population, or only the share of national programs focusing on Catalonia were included.

Regarding rehabilitation and social inclusion costs, estimation of cost associated with therapeutic communities and similar rehabilitation services was performed taking into account the number of individuals benefiting from them (Catalan Department of Health and Catalan Department of Welfare and Family). We also included the cost of the addiction hotline "Linea Verda" as reported by the service itself.

Non-health related direct costs

For justice costs, the number of judicial procedures related to illegal drug trafficking in Catalonia for the year 2011 was obtained (Observatorio Español de la Droga y las Toxicomanías, 2013), and an estimated cost of €415 for each procedure was applied (Rivera et al., 2017).

Police cost data was provided by the Catalan autonomic police force, including drug driving controls, scientific police, and public security, data provided by Plan Nacional de Drogas regarding drug trafficking control, and by the Dirección General de Tráfico regarding police drug test among drivers in cars with and without road traffic collisions.

Penal system cost was calculated applying a mean cost of €20,340, corresponding to the maintenance cost of inmates in prison (Rivera et al., 2017), to the 3,980 addicted inmates treated in Catalan penitentiaries.

Health-related indirect costs

Productivity losses. To estimate the cost generated by deaths related to illicit drugs consumption, we applied AF (Rehm et al., 2006). Potential annual income generated was identified using Catalonia's 2011 per capita average annual salary (assumed equal for both men and women) (Idescat, 2017). Future yearly income was updated using a typical net present value approach, using a 3% discount rate. The formula used for calculating lost income is presented below:

$$Lost\ income = N_t^{DRD} \cdot \left[\frac{R_t(1-(1+r)^{-m_t}}{r}\right]$$

where N_t^{DRD} is the number of illicit drugs-related deaths; represent average annual salary; R_t is the difference in years between the retirement age (which was set at 65 for both males and females) and the age at the time of death. In other words, lost income is the actualized value of drug-related deaths' forgone salary. Deaths are calculated by grouping individuals by age group. This was consistent with the main contributions in the literature (Rehm et al., 2006). Only individuals who are still in their working life were considered, therefore those deaths incurred in the 70-79 and 80+ age groups were excluded.

Income losses were estimated with an approach based on the gross value added (GVA) net of salaries method (Gonçalves et al., 2015). GVA per day (Idescat, 2018) was applied to the number of days of hospitalisation associated with morbidity data used for estimating hospitalisation costs (see the previous sections). As for productivity losses, AF were applied to data on hospitalisation days. GVA per day was estimated as equal to €95.93.

Results

As can be seen in Table 2, the cost of illegal drug consumption in Catalonia in 2011 was estimated at €326.39 million. 82% of the total cost corresponded to direct costs, distributed quite evenly between health and non-health related. Among direct costs, 44.37% corresponded to the non-health related costs (justice, police and penal system), 15.99% to hospitalizations, 17.19% to pharmacy, 8.34% to treatment in specialized centers, and 5.74% to therapeutic communities and other aid programs, among others. Indirect costs represented 18% of total costs, mostly lost income due to drug-related death (Figure 1).

Health-related direct costs

Pharmacy costs' estimations account to €45,886,505.83. Of these, the vast majority was generated by HIV treatment (71.59%). Treatment in specialized centres, including detoxification units and outpatient drug treatment centres, accounts to €22,257,162.52; primary care centres visits, €3,515,452.00, and treatment in correctional facilities, €5,062,116.66 (Table I Online annex).

A total of 8,385 cases of hospitalisation related to illicit use were identified, that represented €42,696,460.35 hospitalization costs. Male patients generated the 86.56% of total costs, of which HIV and hepatitis C represented 16% and 24%, respectively. Illnesses that generated the higher use of resources for women were pregnancy complications and hepatitis C, 37% and 25% respectively. The contribution provided by each illness is provided in Table II Online annex.

Emergency visits accounted for a total of estimation of €5,352,194.97, generated by 31,858 visits associated to illicit drugs consumption. A total number of ambulance service cases of 12,283 (men: 54%; women: 44%; sex not reported: 2%) was estimated, with total cost accounting to €5,968,429.79.

Research represented 0.36% of direct costs. The contribution of each research centre is presented in Table III Online annex.

Prevention costs amounted to a total of €1,952,888.55. Among support programs against addiction, rehabilitation and social inclusion stand-off, accounting to €15,332,085.96€. The existing addiction hotline had a cost of €45,399.84.

Non-health related direct costs

In 2011, 3,980 trials were identified as related to illicit drugs, representing a cost of €1,509,355.00 (0.56% of direct costs).

Police force is involved in the fight against illicit drug consumption and trafficking in different ways. The most relevant activities are included in Table IV Online annex, which estimates the contribution of each components to

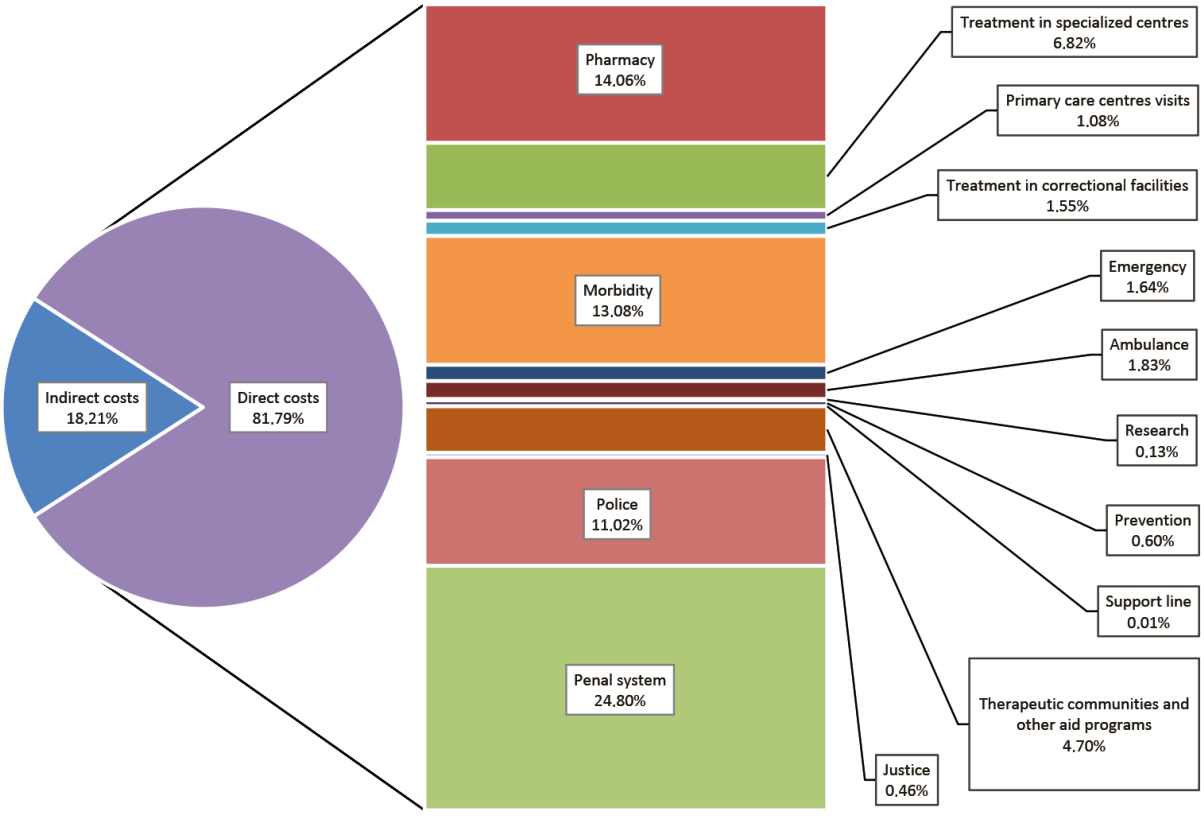

Figure 1. Distribution of direct and indirect costs. Catalonia, 2011.

Table 2. *Cost of illegal drug consumption by type of cost. Catalonia, 2011.*

Type of cost		Item	Amount
Direct costs			
Health-related	Treatment costs	Pharmacy	€ 45,886,505.83
		Treatment in specialized centres	€ 22,257,162.52
		Primary care centers visits	€ 3,515,452.00
		Treatment in correctional facilities	€ 5,062,116.66
	Hospitalization	Morbidity	€ 42,696,460.35
		Emergency	€ 5,352,194.97
		Ambulance	€ 5,968,429.79
	Research and prevention	Research	€ 436,568.75
		Prevention	€ 1,952,888.55
	Support programs against addiction	Addiction hotline	€ 45,399.84
		Therapeutic communities and other rehabilitation and social inclusion programs	€ 15,332,085.96
Non-health-related	Justice		€ 1,509,355.00
	Police		€ 35,977,463.81
	Penal system		€ 80,953,200.00
Indirect costs			
Health-related	Lost income due to drug-related death		€ 57,405,516.65
	Lost productivity due to treatment and/or hospitalisation		€ 2,039,622.66
Total direct costs	Health-related		€ 148,505,265.22
	Non-health-related		€ 118,440,018.81
Total			€ 266,945,284.03
Total indirect costs			€ 59,445,139.30
Total social cost			€ 326,390,423.33

the total €35,977,463.81, where drug trafficking control activities and Intelligence Centre Against Organized Crime (CICO) represented 41.64% of it. A total of 3,980 inmates were incarcerated for felonies related to illicit drugs that generated a total of €80,953,200.00 (30.32% of direct costs).

Health-related indirect costs

A total of 151.85 deaths associated with illegal drugs occurred in 2011, representing a loss of future income equal to €57,405,516.65 (94.45% of indirect costs) (Table V Online annex). Men accounted for 71.20% of the total. The illness inducing the highest number of deaths was HIV (indicated as B20-B24 in the table), followed by suicide (X60-X84, Y87.0).

Regarding productivity losses, the total of 21,274.11 days of work lost generated a total of €2,039,622.66 of costs (Table VI Online annex).

Discussion

This study estimated that the minimum social cost of illegal drug consumption in Catalonia in 2011 was €326.39 million (€349.56 million in 2018). Just to put these figures into context, the social cost of illegal drug consumption represented 0.16% of the Catalan GDP in 2011 (0.15% in 2018). Also, this gross figure could be compared with €1.27 million invested in prevention programmes during the same year. Previous estimations referred to Spain: 1,436 million euros in 2012 (0.14% of Spanish GDP) (Rivera et al., 2017), and 88,800 million PTA in 1997 (around €836.30 million nowadays) (García-Altés et al., 2002).

We adopted the COI framework, which have been extensively implemented for the calculation of social cost of substance abuse (Godgrey et al., 2002; Kopp, 2001; Rehm et al., 2006), also for the case of Spain (García-Altés et al., 2002; Rivera et al., 2017). Advantages and limitations of COI have been thoroughly analysed, both from a general point of view and in relation to our area of

interest (Collins & Lapsley, 2002; Single et al., 2003). This has encouraged the development of a variety of alternative approaches and specific solutions to COI's limits when applied to illicit drugs (Portella et al., 2003; Rehm et al., 2006; Single et al., 2003). Additionally, alternative methods for the estimation of indirect costs have been suggested (Koopmanschap, Rutten, van Ineveld & van Roijen, 1995). The adopted framework in our study relies on COI and takes into account posterior improvements (Gonçalves et al., 2015; Kopp, 2001; Rehm et al., 2006).

However, the estimates generated through this study are higher than those coming from similar studies. We hypothesise that the higher estimation is determined by 1) the innovative approach used and the effort to include as much local level data as possible; 2) the inclusion of the majority of the categories from Rehm et al. (2006) in the framework including those with higher impact on social costs, as productivity losses; 3) the inclusion of all categories of illnesses in the analysis of the mortality and morbidity costs.

One of the main issues related to the estimation of drugs' social cost during a specific time period consists in defining the analysis' counterfactual. The most common option in the literature is to assume no past, present and future substance use as counterfactual (Gonçalves et al., 2015; Kopp, 2001; Rivera et al., 2017). Though commonly adopted, this approach received criticism (Collins et al., 2002; Single et al., 2003). Critics advocate for considering only part of total costs in the estimation, i.e., the one that it is amenable by public policies. These are defined as avoidable costs. Total costs, instead, include expenditures which can't be influenced by today's policies, for example, those related to either past use of drugs or those generated by cases of past consumption which will continue in the future (Collins et al., 2002; Single et al., 2003). By adopting the case of zero-consumption as counterfactual, these costs are automatically included in the estimation of social costs. Hence the criticism to this approach. Therefore, they should be considered as unavoidable and not included in the calculation of social costs (Single et al., 2003). Despite of these criticism, currently there is no alternative available that can allow for a precise calculation of those unavoidable costs (Collins et al., 2002). The approach adopted for this paper relies on the zero-consumption case as counterfactual.

The matrix of cost of reference that was adopted is comparable to previous ones (Gonçalves et al., 2015; Rivera et al., 2017), which represent two of the most recent studies in the field focusing on European countries, that are consistent with classical texts, in terms of the definition of social cost and the categorisation of the items (Kopp, 2001; Single et al., 2003). Due to absence of data regarding some items of the matrix of cost, it was possible to estimate only a subset of categories included in the matrix of reference. Moreover, intangible costs were not estimated, due to the limitations inherent in the available methodologies. Specific costs that could not be included are prevention costs by local administrations, and social inclusion costs paid by the Labour Department. Similarly, some estimations are based on means and extrapolations, as is the case of emergency visits, average salary for men and women or judicial procedures.

Data used for the estimation were both public and private, mainly not-for-profit organizations. The decision of using both types of source has two main reasons. First, it allowed us to rely on the authors' vast network of contacts in the Catalan system of entities that provide different types of service related to illicit drug consumption. This includes, among others, costs for drugs used in treating addiction, programs in scientific research, and support programs (as hotlines) for addicts. Second, by presenting data from entities that generally do not appear in official calculation of social cost of illicit drug consumption, it allowed for all these entities to emerge as a network of providers. Anyway, the study presented here is easily replicable, so estimations can be regularly redone, allowing for properly monitoring the impact of national plans. At the same time, it has been extremely valuable to stablish relationships with other Governmental departments, and to raise awareness on drug addiction problem, a public health problem where "health in all policies" is totally relevant.

Already 8 years have passed since 2011, when we collected all these drug-related costs. Interestingly, in 2012, due to the severe economic crisis, the prevention budget was dramatically reduced in approximately 1 million euros and evenly-matched again in 2014 and sustained ever since. A brief review of the changes occurred between 2011 and the most recent data available in the majority of the indicators tells us, regardless of some fluctuation in the data, that drug-related costs might not have increased significantly except for the costs on pharmacological treatment. The advent of the new antivirals of direct action in 2015 have resulted in a significant increase in the number of PWID that are treated for their infection for hepatitis C. Bearing in mind that the average treatment cost is €6,500 per person and that at least 50% of the PWID have been treated (7,482 people in 2017), the increase amounts to approximately €24,316,500 (7,7% of the drug-related costs back in 2011).

Nowadays several typologies of governance of addiction coexist in Europe. There are countries that introduced innovative harm reduction strategies; others still rely on a more traditional approach (Anderson et al., 2017). Regardless of the governance approach, quantifying prevalence use and associated burden of disease and mortality at country level and accompanying this with the

analysis of the economic direct and indirect costs that illegal drugs impose on society is key and should inform policy planning and evaluation and service provision (Degenhardt et al., 2012).

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

Una vez aceptado el artículo, se enviará a los autores las pruebas de imprenta para que las corrijan. Los autores son totalmente responsables de la versión final que se publique. Los autores pueden hacer el uso que crean pertinente para la difusión del artículo, siempre que quede clara toda la información necesaria acerca de la revista donde ha sido publicado.

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MIRANDO *al* FUTURO

PLAN TREVICTA®

DIARIO[1,2]
ORALES
RISPERIDONA/
PALIPERIDONA

MENSUAL[3]
XEPLION®
PALMITATO DE
PALIPERIDONA

4 AL AÑO[4]
TREVICTA®
PALMITATO DE
PALIPERIDONA

CP-146909-04-2020

Janssen Neuroscience

PHARMACEUTICAL COMPANIES OF Johnson&Johnson

BIBLIOGRAFÍA: 1. Ficha técnica Risperdal®. **2.** Ficha técnica Invega®. **3.** Ficha técnica XEPLION®. **4.** Ficha técnica TREVICTA®.

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. CÓMPOSICION 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 equivaleptes 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 la inyección trimestral de palmitato de paliperidona. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

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

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

No se ha estudiado la dosis de TREVICTA equivalente a la dosis de 25 mg de palmitato de paliperidona inyectable mensual. Después de la dosis inicial de TREVICTA, este medicamento se administrará mediante inyección intramuscular una vez cada 3 meses (± 2 semanas, ver también la sección Dosis omitidas). Si es necesario, se puede ajustar la dosis de TREVICTA cada 3 meses en incrementos dentro del intervalo de 175 a 525 mg en función de la tolerabilidad del paciente y/o de la eficacia. Debido a la acción prolongada de TREVICTA, la respuesta del paciente al ajuste de la dosis puede no ser evidente hasta que han transcurrido varios meses (ver sección 5.2). Si el paciente sigue presentando síntomas, se le tratará conforme a la práctica clínica. *Cambio desde otros medicamentos antipsicóticos.* No se debe cambiar a los pacientes directamente desde otros antipsicóticos dado que el inyectable trimestral de palmitato de paliperidona solo se debe iniciar después de que el paciente esté estabilizado con el inyectable mensual de palmitato de paliperidona. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se deben tener en cuenta sus características de liberación prolongada. *Cambio desde TREVICTA a palmitato de paliperidona inyectable mensual.* Para cambiar desde TREVICTA a palmitato de paliperidona inyectable mensual, este se administrará en el momento en que se 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 en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides (y viceversa) en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se facilitan en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se facilitan en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos o profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso <90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dada la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones**. Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo**. Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos $<1 \times 10^9$/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. Excipientes. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis; esto es, esencialmente "exento de sodio". **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiacinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vitro ni in vivo de que esas isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de $C_{máx}$ y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP a la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de $C_{máx}$ y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, difícultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. No se debe utilizar TREVICTA durante el embarazo a menos que sea claramente necesario. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas**. La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es 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[d], hiperinsulinemia, aumento del apetito, anorexia, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnia[a]	agitación, depresión, ansiedad	trastornos del sueño, manía, disminución de la líbido, nerviosismo, pesadillas	catatonía, estado de confusión, sonambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[c], acatisia[c], sedación/somnolencia, distonía[c], mareo, discinesias[c], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotriz, mareo postural, trastornos de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, falta de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones[c], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

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

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP).* En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y miodistonía), distonía (incluye distonía, espasmo cervical, empurstótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetanía, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurotótonos, espasmo lingual y trismus) y temblor. *Aumento de peso.* En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de +0,94 kg y -1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia.* Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de +7,48 ng/ml para las mujeres (frente a -32,93 ng/ml en el grupo placebo). Una mujer (2,4%) del grupo de TREVICTA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguna mujer del grupo placebo. No hubo reacciones adversas potencialmente relacionadas con la prolactina en ninguno de los grupos de varones. Efecto de clase. Con el uso de antipsicóticos pueden aparecer prolongación del intervalo QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicada, paro 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 las monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratadas adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o al final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

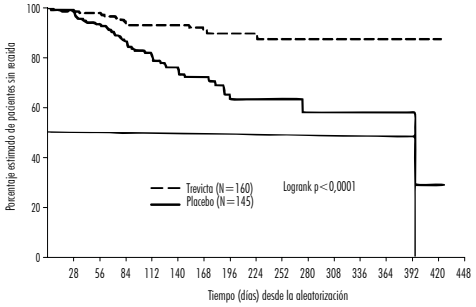


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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

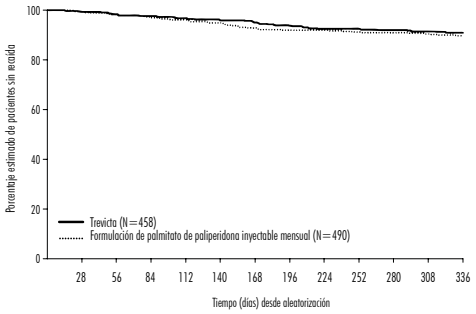


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{max}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas in vivo, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_∞) 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: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACION.**

Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/ RENOVACIÓN DE LA AUTORIZACION.** Fecha de la primera autorización: 5 de diciembre de 2014. Fecha de la última renovación: 14 noviembre 2019. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 11/2019. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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

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

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

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

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

Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queilitis	obstrucción del intestino, íleo
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción debida al medicamento, hiperqueratosis, caspa	angioedema, decoloración de la piel, dermatitis seborreica
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda, artralgia	aumento de la creatina fosfoquinasa en sangre, espasmos musculares, rigidez en las articulaciones, debilidad muscular, dolor de cuello	rabdomiólisis, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales					síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastorno de la eyaculación, trastornos menstruales[2], 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[4], 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		

[1]La frecuencia de estas reacciones adversas se clasifica como "no conocidos" porque no fueron observadas en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. [2]Referido a "Hiperprolactinemia" a continuación. [3]Referido a "Síntomas extrapiramidales" a continuación. [4]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. [5]**Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia post-comercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basada en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3 con Xeplion. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poco frecuente) y nódulos (raro). *Síntomas extrapiramidales (SEP).* SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano, reflejo de la glabella anormal y temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y miocloníа), distonía (incluye distonía, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefaroespasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonia, 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. *Hiperprolactinemia.* En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado Torsades de pointes y fibrilación ventricular en un paciente en relación con la sobredosis de paliperidona oral. En caso de sobredosis aguda, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. Administración: Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. *Tratamiento agudo de la esquizofrenia.* La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Los 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. Las resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

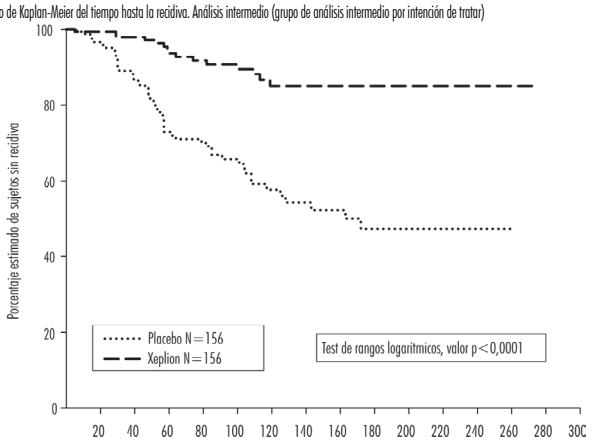
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



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

MIRANDO *al* FUTURO

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