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Intervention strategies in the prevention of suicidal behavior in substance use disorders patients in times of COVID-19

Estrategias de intervención en la prevención de comportamiento suicida en pacientes con trastorno por consumo de sustancias en tiempos de COVID-19

Ashkan Espandian*, Gerardo Flórez**,***, Luisa F. Peleteiro****, María Tajes****, Pilar A. Sáiz***,*****,******,*******, Rocío Villa******,*******, Julio Bobes*** ,*****,******,*******.

* Servicio de Psiquiatría. Complejo Hospitalario del Bierzo. Ponferrada.
** Unidad de Conductas Adictivas, Complejo Hospitalario Universitario de Ourense, España.
*** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), España.
**** Servizo de Saúde Mental. Dirección de Asistencia Sanitaria SERGAS.
***** Área de Psiquiatría, Universidad de Oviedo, España.
****** Servicio de Salud del Principado de Asturias (SESPA), España.
******* Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), España.

Suicide represents a serious public health problem, due both to its current high prevalence and the lack of implementation of adequate preventive strategies in many countries, including Spain (Sáiz & Bobes, 2014).

It has been estimated that the number of suicide attempts (SA) is approximately 10-20 times higher than that of completed suicides. However, the real size of the problem is underestimated given the underreporting that tends to occur in most countries worldwide (Giner & Guija, 2014).

Having a history of SA is still the best predictor of later completed suicide (Wang, Huang, Lee, Wu & Chen, 2014). The presence of mental disorders is a further key risk factor, with uni- and bipolar depressive disorders and alcohol use disorders the most prevalent in relation to suicidal behaviour (Gómez-Durán, Forti-Buratti, Gutiérrez-López, Belmonte-Ibáñez & Martín-Fumadó, 2016; Zalsman et al., 2016).

The main tool for obtaining a clinical impression of the suicidal risk present at a given moment in a patient is the clinical interview, as recommended by the most up-to-date clinical guidelines, which indicates that screening instruments do not have sufficient predictive power (Working Group on the Review of Clinical Practice Guidelines for the Prevention and Treatment of Suicidal Behaviour, 2020; Jacobs et al., 2010; Inagaki, Kawashima, Yonemoto & Yamada, 2019; Mann et al., 2005).

The clinical interview aims to detect suicidal risk factors, while contrasting them with protective factors relevant at the time of assessment. Clear knowledge about and identification of such factors are essential in determining the level of risk, remembering that some have a more specific weight than others and that in combination they considerably increase the risk (Hawton & van Heeringen, 2009; Kraemer & Clarke, 1990).

As a consultation and support tool for the clinician, table 1 presents the main risk factors and table 2 the protective factors.

Substance use and suicidal behaviour

Suicide is the main cause of death in people with substance use disorder (Wilcox, Conner & Caine, 2004). It has been estimated that the risk of death by suicide is 10 times higher for alcohol use disorder and 14 times higher for addicts to other substances compared to the general population (Yuodelis-Flores & Ries, 2015).

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Send correspondence to: Gerardo Flórez. Unidad de Conductas Adictivas, Hospital Santa María Nai, Complejo Hospitalario Universitario de Orense, Ramón Puga 52-56, 32005, Ourense, España.
E-mail: gerardof9672@gmail.com

Table 1. *Main risk factors associated with suicidal behaviour.*

Severe risk		**Moderate risk**	
Sex, age and residence		Sex, age and residence	
Male Rural environment › 65 years old		Female Urban environment › 65 years old	
Mental disorder		Mental disorder	
Major depression	Severe High anxiety Low behavioural inhibition No psychomotor retardation With psychotic features	Major depression	Moderate
		Bipolar disorder	Moderate depressive episode Manic/hypomanic episode Others
		Psychotic disorder	
Bipolar disorder	Episode of major depression With psychotic features Mixed characteristics	Personality disorder	Borderline Antisocial
		Anxiety disorder	Phobias Panic attacks
Psychotic disorder	Acute episode Linked to depression First years of diagnosis Poor treatment adherence	Eating disoders	Anorexia nervosa
		Obsessive-compulsive disorder	
Substance use		Other mental disorders	
Alcohol use disorder	Severe Currently active Linked to mental illness Linked to use of other intoxicants	Substance use	
		Severe substance use disorder	Cannabis Hallucinogens Opioids
			Stimulants (cocaine, amphetamines) Sedatives/hypnotics/ anxiolytics Linked to mental illness
Previous suicide attempt		Previous suicide attempt	
Number	3 or more	When	6 to 12 months
When	Last 6 months	Method	Medium lethality
Method	High lethality	Suicidal ideation	
Planned	Yes	Weekly frequency	
Suicidal ideation		Socioeconomic/work/education-related	
Daily frequency Linked to suicide attempt		Unemployed/retired Low level of education and culture Depressed social status	
Current suicide attempt		Marital status	
High-lethality method Planned Farewell letter Steps to prevent rescue		Divorced Widower	
Disabling physical illness		Life Events (Precipitating Factors)	
Chronic pain Disease with poor prognosis Loss of mobility		Loss of loved ones Somatic diseases Gender violence Sexual abuse Legal problems	
History		Psychological factors	
Suicide in first-degree relative		Hopelessness Impulsivity	
		History	
		Suicide in second-degree relative	

Table 2. *Main protective factors against suicidal behaviour.*

Personal or specific to subject	Social and environmental
• Individual's own attitudes and values	• Having a good family and social support
• Conflict resolution or problem-solving skills	• Social integration
• Presence of cognitive flexibility	• Accessibility to health facilities
• Having self-confidence	• Comprehensive, permanent and long-term treatment for patients with mental disorders
• Skills for personal and interpersonal relationships	• Control when acquiring potentially lethal weapons or medications
• Religious beliefs disapproving of suicide	
• Self-control of impulsivityand anger management	

Suicide was attempted by 3.4% of men and 4.4% of women with substance use in the 30 days before incorporation into a treatment program (Tiet, Ilgen, Byrnes & Moos, 2006). The presence of a high prevalence of both suicidal ideation and AS at the start of treatment seems to be linked to periods when consumption is out of control, to the presence of social problems in the environment (work, marital, legal, etc.) and with the onset or exacerbation of mental illness (Ross et al., 2005).

Regarding sex, the risk of both AS and completed suicide has been found to be higher in women, unlike the pattern established in the general population where suicide is clearly predominant in men. The psychiatric comorbidities and social maladjustment involved in substance use are considered relevant factors with regard to increased risk in women (Wilcox et al., 2004).

Alcohol use disorders play a prominent role in suicidal behaviour. Not only as a risk but also as a precipitating factor due to the disinhibition and executive dysfunction caused by alcohol intoxication (World Report on Violence and Health, 2002). It has been estimated that alcohol was drunk in 37% of completed suicides, rising to 40% in non-lethal attempts (Wilcox et al., 2004). This represents a 15-fold increase in risk compared to the general population (Beautrais, Collings, Ehrhardt & Henare, 2005).

The use of other substances similarly increases the risk of suicidal behaviour. Compared to the general population, the risk of suicide has been estimated to be 14 to 17 times higher and associated mainly with cognitive impairment, social maladjustment and psychiatric comorbidity (Price, Hemmingsson, Lewis, Zammit & Allebeck, 2009; Tiet et al., 2006; Wilcox et al., 2004).

Moreover, polydrug use naturally increases the risk of suicide. A history of suicide attempts is found in 58% of polydrug patients, and their risk is 17 times greater than that of the general population; in addition, the lethality of overdose, the most frequent suicide method in the addicted population, is on the increase (Wilcox et al., 2004).

The severity of drug use, as well as the number of substances consumed, represent a risk factor of greater impact in the link to AS than the type of substance consumed (Ilgen, Harris, Moos & Tiet, 2007).

In terms of psychiatric comorbidity, the risk increases considerably when another mental disorder is linked to substance use. Depressive disorder stands out as the most harmful association, followed by personality disorder and impulse control disorder (Artenie et al., 2015; Wilcox et al. 2004).

Intervention in patients with substance use disorder as a prevention method

Current evidence clearly highlights the high prevalence of suicidal behaviour in patients with substance use. The challenge of applying prevention strategies is greater with this patient profile as it is not yet clear which strategy is best suited to reducing the rate of suicide deaths in this population (Goldstone, Bantjes & Dannatt, 2018).

Of the currently available strategies in relation to the prevention of suicidal behaviour, few can show sufficient evidence of ensuring a reduction in the incidence of suicide in the general population. The main strategies demonstrating evidence in prevention at the level of public health and health care were published in 2017 (Zalsman et al., 2017).

Although work is in progress on implementing prevention strategies in the different risk groups, there is a lack of studies on interventions developed in the population of substance-using patients (Goldstone et al., 2018). It would be very useful to have information that can tell us which intervention measures are best applied in this population, or reaffirm that general population strategies are equally efficacious in this profile of patients at risk.

To date, two pilot projects investigating the efficacy of two different interventions in the substance-using population have published results (Esposito-Smythers, Spirito, Uth & LaChance, 2006; Voss et al., 2013). The results show that the benefits of the interventions for this patient profile are fundamentally based on improving adherence, reducing suicidal ideation and facilitating greater capacity for managing moments of anxiety by increasing the ability to seek help. The programs provide the patient with copious information regarding the association of substance use with suicidal behaviours, equipping them with a better

attitude towards such situations and the ability to manage them. Unfortunately, these programs do not appear to be effective in preventing repeated AS.

We therefore find favourable data pointing us towards a feasible and viable model to apply as a prevention strategy, and strongly indicated in this patient profile. Nevertheless, it should be noted that these results must be interpreted with caution since they represent pilot studies with multiple limitations, such as small sample size, the use of unspecific and inadequate psychometric tests recommended for improvement in future studies, and the lack of a control group for comparison. The paucity of studies on the subject invites further analysis and the search for new strategies in this patient profile.

Prevention strategies at three levels (universal, selective and indicated) obtain excellent results in combination, when patients with a substance use diagnosis are placed in the at-risk population group and indicated for intervention. It would be very useful to have resources for use in improving standard treatment in this group of patients, mainly in training health professionals in the three levels of intervention, these being: treatment of substance use, psychiatric comorbidity and prevention of suicidal behaviour. Such treatment would offer a more specific and non-generic intervention (Goldstone et al., 2018).

A considerable proportion of personnel working in addictive behaviour units acknowledge their lack of training regarding intervention with patients at risk of suicide. Adequate training would provide the therapist with knowledge and confidence in working with such patients, leading to improved treatment adherence; on their own, years of experience working in addictive behaviour treatment units do not equate to the capacity to manage the suicidal risk patient (Fruhbauerova & Comtois, 2019).

Interview and intervention in patients with suicide risk and substance use disorder

All intervention must be based on the following psychotherapeutic principles: empathy, collaboration and honesty. In other words, healthcare professionals do not position themselves as guardians of their patient's physical integrity, but rather as professionals concerned about their suffering; while wanting the patient to continue living, they also understand their difficulties and respect the patient's point of view and their decisions, offering help to improve the situation and overcome crises. The healthcare professional must remember that in most cases there will be an ambivalence towards life and death that needs exploring in order to discover and be able to intervene in the factors that determine this ambivalence.

It is advisable to work within clearly established time periods. It is essential that the therapist inform the patient about the legal and care framework in which the intervention takes place and what their obligations are within this framework.

Next, strategies to be used during the psychotherapeutic intervention are outlined:

Decisional balance

A very useful activity to carry out with the patient is a decisional balance on the reasons for living versus the reasons for dying. It must be done collaboratively and honestly without the therapist clearly positioning himself in favour of reasons to live.

Crisis stabilization/intervention plan

The crisis stabilization/intervention plan is drawn up in consultation with the patient, who should always carry it with them in the form of a card or on the mobile phone. The elements of the plan should be simple and easy to apply. At the very least, it should include the following items:

- warning signs to activate the plan
- ways to reduce access to lethal means
- distraction and self-regulation activities for periods of crisis
- people to contact during periods of crisis: they must be available and know that they have been assigned this role in order to respond empathically to the patient's call
- emergency telephone numbers to contact

Increase activities that involve experiencing positive emotions

Increasing the level of activity and directing it towards emotionally positive experiences is a fundamental behavioural technique to be applied with this type of patient.

Improve emotional regulation strategies

Training the patient in relaxation techniques, meditation/mindfulness, imagery, and encouraging positive strategies already used by the patient to self-regulate emotionally is a task of great importance.

Increase the patient's social support

Drawing up a list of people who can be supportive outside the therapeutic framework to a greater or lesser degree is another highly recommended strategy.

Increase support from other health and social services by improving adherence to them

The previously mentioned risk factors may be addressed and mitigated by other health and social services. A list of possible help resources should be established collaboratively with the patient and strategies to improve adherence to these resources should be proposed.

Improve the ability to handle problematic thoughts or ideas

Preparing notes or messages on the mobile phone with thoughts that counteract the suicidal ideation of the patient is very useful. Such notes must be simple and easily accessible.

Impact of the COVID-19 pandemic on substance use

We are currently in a pandemic situation due to COVID-19. Multiple publications have made negative forecasts and warn the health authorities of the possible increase in both the rates of SA and completed suicides due to the increase in risk factors such as unemployment, the economic crisis, social conflicts, the increase in anxiety and depression levels, reluctance to seek help in health centres given difficulties in accessing them, the increase in alcohol use and finally the ease of access to lethal means (bleach, disinfectants) (Gunnell et al., 2020).

Data obtained in previous natural disasters and pandemics show a reduction in the momentary suicide rate followed by an immediate increase after the event, which supports the forecasts and warnings (Wasserman, Iosue, Wuestefeld & Carli, 2020).

The population with substance use disorders represents a vulnerable group at risk of infection due to clinical, psychopathological and psychosocial conditions (Ornell et al., 2020). It is expected that quarantine and social isolation may have negative effects in terms of increased consumption and a higher relapse rate in individuals with long periods of abstinence, focusing mainly on alcohol use (Kahil et al., 2021). On the other hand, there are data that show how drinking and/or smoking are strategies used by the general population in trying to cope with the consequences of the pandemic (Martínez-Cao et al., 2021).

There is a bidirectional interaction between COVID-19 and addictions that carries a threat and a greater impact on public health. Government and legislative bodies must act to guarantee social security in this group of patients, maintaining availability and access to all treatment options, linked to the provision of clear, accessible and easily understood information in relation to preventive measures against COVID-19 in these patient groups (Dubey et al., 2020; García-Álvarez, Fuente-Tomás, Sáiz, García-Portilla & Bobes, 2020; Mallet, Dubertret & Le Strat, 2021). Strengthening mental health is recommended as a priority in order to manage the after-effects of the pandemic.

Conclusions

While work is being done on the prevention of SA in the general population and in mental health patients, efforts in the population with substance use disorder have been little promoted. The evidence clearly shows the high prevalence of suicidal behaviour in these patients, with substance use being considered an indirect alarm signal requiring patient monitoring.

The creation of intervention protocols in patients attending health care units is therefore recommended, beginning with systematic screening to assess the risk of suicidal behaviour and the development of intervention strategies in these patients in order to achieve reductions in the rates of both SA and completed suicide, with a key focus on highlighting and evaluating the level of social exclusion, psychiatric comorbidities and levels of hopelessness presented by the patient.

General therapeutic interventions for the treatment of suicidal behaviour may be suitable for this population, although research proving their effectiveness has been limited to date. It is recommended that healthcare personnel who care for patients with substance use disorders be familiar with and possess the ability to identify patients at risk; it is essential to detect risk factors and warning signs in the patients they treat. It is worth underlining the importance of the treatment of psychiatric comorbidity as a therapeutic tool in reducing suicide risk in these patients.

This is not intended to downplay the role of suicidal behaviour intervention units, which are greatly needed, but to stress and highlight the fundamental contribution that addiction treatment units can make in reducing the prevalence of such behaviours.

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Conflict of interests

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Cocaine and depressive disorders: When standard clinical diagnosis is insufficient

Trastorno por uso de cocaína y depresión: Cuando el diagnóstico clínico no es suficiente

María Alías-Ferri[1], *, **, Nuria García-Marchena[1], *, ***, Joan Ignasi Mestre-Pintó*,*****, Pedro Araos***,*****, Esperanza Vergara-Moragues******, Francina Fonseca*,*******,********, Francisco González-Saiz*********, Fernando Rodríguez de Fonseca***, Marta Torrens*,*******,******** and NEURODEP Group**********.

* Grup de Recerca en Addiccions, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
** Departament de Psiquiatria I Medicina Forense. Universitat Autònoma de Barcelona, Cerdanyola del Valles. Barcelona, Spain
*** Unidad Gestión Clínica de Salud Mental. Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Regional Universitario de Málaga. Málaga, Spain
**** Universitat Pompeu Fabra. Departament de Ciències Experimentals i de la Salut (CEXS) Barcelona, Spain
***** Departamento de Psicobiología y Metodología de las Ciencias del Comportamiento, Instituto de Investigación Biomédica de Málaga (IBIMA), Facultad de Psicología, Universidad de Málaga, Spain
****** Departamento de Psicobiología y Metodología en Ciencias del Comportamiento, Universidad Complutense de Madrid (UCM), Madrid, Spain
******* Universitat Autònoma de Barcelona, Cerdanyola del Valles. Barcelona, Spain
******** Institut de Neuropsiquiatria i Addiccions (INAD), Hospital del Mar, Barcelona, Spain
********* Área de Psiquiatría. Departamento de Neurociencias (Universidad de Cádiz). Hospital Universitario de Jerez. Cádiz, Spain
********** NEURODEP Group: Mateus, J., Papaseit, E., Pérez-Mañá, C., Rodríguez-Minguela, R., Rossi, P., Tamarit, C., Vallecillo, G.

Abstract

Background: Cocaine use is a growing global health problem and patients with cocaine use disorders (CUD) present several complications, including high rates of major depression. There are two types of major depressive disorder (MDD) in these subjects: primary major depressive disorder (P-MDD) and cocaine-induced major depressive disorder (CI-MDD). To improve treatment, it is necessary to distinguish between both types. The aim of this study was to assess the differences in depressive symptomatology criteria (P-MDD vs CI-MDD) in CUD patients. *Methods:* Secondary data analysis was carried out with a cross-sectional sample of 160 patients presenting CUD and MDD. Clinical assessment was performed using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). A differential diagnosis was obtained between P-MDD and CI-MDD. *Results:* Men represented 80% of the sample, the mean age was 38.61 years, and 64.5% had elementary studies. CI-MDD diagnosis (61.3%) was more frequent than P-MDD (38.7%). There was a younger age of CUD onset in CI-MDD patients. In addition, 79.4% of the patients had another substance use disorder diagnosed. The criterion *"Changes in weight or appetite"* was more prevalent (57.1%) in P-MDD group. *Conclusions:* We found differences in the criterion *"Changes in weight or appetite"*. Further research is needed in this field in order to establish a differential diagnosis and thus provide better treatment for CUD individuals.
Keywords: Dual diagnosis; cocaine use disorder; cocaine-related disorders; depressive disorder; induced depression.

Resumen

Antecedentes: El consumo de cocaína es un creciente problema de salud en todo el mundo y los pacientes con trastorno por consumo de cocaína (TCC) presentan una alta comorbilidad con el trastorno depresivo mayor (TDM). Existen dos tipos de TDM: trastorno depresivo mayor primario (TDM-P) y trastorno depresivo mayor inducido por cocaína (TDM-IC). El objetivo de este estudio es evaluar las diferencias en la sintomatología depresiva (TDM-P vs. TDM- IC) en los pacientes con TCC para mejorar su tratamiento. *Métodos:* Se llevó a cabo un análisis secundario en una muestra transversal de 160 pacientes que presentaban TCC y TDM. La evaluación clínica, así como el diagnóstico diferencial entre TDM-P y TDM-IC se realizó utilizando la entrevista PRISM. *Resultados:* Los hombres representaron el 80% de la muestra con una edad media de 38,61 años y el 64,5% sólo tenía estudios elementales. El diagnóstico de TDM-IC (61,3%) fue más frecuente que el de TDM-P (38,7%). Los pacientes con TDM-IC mostraron una edad de aparición más temprana para el TCC. El 79,4% de los pacientes cumplían criterios para otro trastorno por consumo de sustancias. Únicamente el criterio *"Cambios en el peso o en el apetito"* fue estadísticamente más frecuente (57,1%) en los pacientes con TDM-P. *Conclusiones:* Existen diferencias en el criterio *"Cambios en el peso o apetito"* entre TDM-P y TDM-IC. Se necesita más investigación a fin de obtener un diagnóstico diferencial entre los dos tipos de depresión y proporcionar un mejor tratamiento para los pacientes con TCC.
Palabras clave: Patología dual; trastorno por uso de cocaína; trastornos relacionados con el uso de cocaína; trastorno depresivo; trastorno depresivo inducido.

[1] These authors contributed equally to this work.

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Send correspondence to: Dr. Joan Ignasi Mestre.
Addiction Research Group, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM). C/ Dr. Aiguader, 88, 08003 Barcelona. Spain. Tel. +34933160697
E-mail: jmestre@imim.es (JIM)

Globally, cocaine is one of the most widely used illicit stimulant and represents an increasing health problem. Its annual prevalence for use in Europe is early 1% (United Nations Office on Drugs and Crime (UNODC), 2016a) and among persons treated for drug use, 8.4% receive treatment for cocaine as main drug (United Nations Office on Drugs and Crime (UNODC), 2016b).

Patients diagnosed with cocaine use disorder (CUD) experience several complications including medical problems, family and social impairment, unemployment, and physical and sexual trauma. These issues are particularly marked in high risk populations such as women, older adults, and polysubstance users (John & Wu, 2017). Moreover, a number of studies in CUD populations have reported an elevated prevalence, over 40%, of comorbid psychiatric disorders (Araos et al., 2014; Herrero, Domingo-Salvany, Brugal, Torrens & Itinere Investigators, 2011; Herrero, Domingo-Salvany, Torrens, Brugal & ITINERE Investigators, 2008). The most frequent are mood disorders, including major depressive disorders (MDD), followed by anxiety and psychotic disorders (Araos et al., 2017; Lai, Cleary, Sitharthan & Hunt, 2015).

Comorbid depression in CUD patients presents more severe clinical features than those found in patients with a single diagnosis. They include: poorer course of both pathologies (Magidson, Wang, Lejuez, Iza & Blanco, 2013), earlier age of onset of depression, greater number of depressive symptoms and elevated functional impairment (Cohn et al., 2011), augmented social and personal impairment, and higher risk of suicide and other psychiatric conditions (Davis, Uezato, Newell & Frazier, 2008).

Contingency management has been proved as a highly effective treatment for substance use disorders with or without mood disorders (Garcia-Fernandez, Secades-Villa, Garcia-Rodríguez, Peña-Suarez & Sanchez-Hervas, 2013). At present, the relevance of differentiating between induced and primary depression among substance users, has been highlighted and among antidepressant drugs, only Desipramine has demonstrated its efficacy improving depressive symptoms in cocaine users (Tirado-Muñoz, Farré, Mestre-Pintó, Szerman & Torrens, 2018).

The accurate diagnosis of comorbid depression is hindered by the overlapping of symptoms. Nowadays, emphasis is placed on nosological decision-making supported by evidence and the translational vision of research in both main classifications (ICD and DSM) (Bobes, Flórez, Seijo & Bobes, 2019). According to DSM-IV-TR (American Psychiatric Association (APA), 2000) and DSM-5 (American Psychiatric Association (APA), 2013) criteria, two different conditions are considered for the diagnosis of comorbid disorders: primary disorder when is not substance or medically induced and substance-induced disorder when the symptoms are considered unreasonable, due to their severity or characteristics, with respect to those that appear as a result of intoxication or withdrawal. Furthermore, the expected effects are symptoms that appear as a result of the intoxication/withdrawal of a given substance and are considered physiological in relation to the pharmacological prospective of the substance and must be considered. In order to achieve an accurate diagnosis, clinicians should collect current and past history of substance consumption, all lifetime pathological symptoms and their clinical and temporal course.

There is increasing literature describing the differences and clinical relevance between primary and induced depression in substance use disorder (SUD) populations. In general terms, individuals with a SUD and induced depression exhibit greater consumption (Cohn et al., 2011; Davis et al., 2008) and poorer prognosis (Magidson et al., 2013; Tirado-Muñoz, Farré, Mestre-Pintó, Szerman & Torrens, 2017). Moreover, such patients present higher impairment including risk of suicide (Conner et al., 2014), more hospitalizations, and have been prescribed more medication throughout life (Schuckit et al., 1997). In the case of alcohol, each type of depressive episode can be considered as two different diseases since P-MDD patients' present greater familial risk to develop a primary episode, while this association is not present for the induced episodes (Raimo and Schuckit, 1998).

These two types of depressive episodes are also found in CUD population: primary major depressive disorder (P-MDD) and cocaine-induced depressive disorder (CI-MDD). Leventhal, Mooney, DeLaune y Schmitz (2006) found that CUD patients with a P-MDD diagnosis reported affective impairment more frequently than those with CI-MDD. It is thus crucial to distinguish between the two types of episodes due to implications in prognosis and treatment which must be adapted accordingly (Foulds et al., 2015; Tirado Muñoz et al., 2017). The prevalence of each type of depressive episode is unclear. In a systematic review comparing both types among patients with varying SUD, those with a CUD diagnosis showed more induced episodes than primary ones (Dakwar et al., 2011). Some studies have found a relationship between duration of use, frequency and age of consumption onset, and the probability of developing a cocaine-induced depressive episode (Herrero et al., 2008). With regard to treatment outcomes, a CI-MDD diagnosis has been observed to increase the risk of relapse with less time from discharge to relapse (Samet et al., 2013).

The aim of the study is to emphasize in the specific clinical characteristics including the depressive criteria that characterize each type of depressive episode, primary and induced, in patients with a CUD diagnosis to improve the diagnostic accuracy.

Material and Methods

Participants and recruitment

The present work is a secondary data analysis composed of a cross-sectional sample of 160 CUD individuals. Pa-

tients were recruited from out treatment facilities located in Barcelona and Málaga and in public therapeutic communities located in Andalucía in order to evaluate psychiatric comorbidities and search for biomarkers of cocaine addiction. The distribution of the participants, according to the medical service where they were recruited, was 103 (64.4%) outpatients and 57 (35.6%) from the therapeutic community.

Participation in the study was voluntary and subjects were required to meet eligibility criteria. The inclusion criteria for these studies were to be over 18 years old and seeking treatment for cocaine use. Exclusion criteria were language barriers or cognitive impairment to complete the clinical assessments. Patients who presented both types of depression (primary and induced) throughout their lives were also excluded.

Ethics statement

Written informed consent was obtained from each participant after a complete description of the study and responses to any queries provided. The study and protocols for recruitment were approved by the Ethics Committee from each participating center.

Clinical assessments

Participants were evaluated using the Spanish version of the *Psychiatric Research Interview for Substance and Mental Diseases* (PRISM) according to "Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision" (DSMIV-TR) criteria. The PRISM is a semi-structured psychiatric research interview to diagnose psychiatric disorders among substance users that has demonstrated good psychometric properties in terms of test-retest reliability, inter-rater reliability, and validity for primary MDD and substance-induced MDD, with kappa ranging from 0.66 and 0.75 (Hasin et al., 2006; Torrens, Serrano, Astals, Pérez-Domínguez & Martín-Santos, 2004). All the interviews were performed by trained and experienced psychologists. In order to achieve the differential diagnosis in MDD it explores all depressive symptom criteria and consumption history. A time-line of each disorder and their symptoms is recorded to establish the relationship between them and differentiate among a primary disorder, an induced disorder or the expected effects of consumption. The length of each interview administration was between 2 and 3 hours depending of the subject assessed.

Statistical analysis

Descriptive analyses were used to characterize the samples. The estimations of the rates for each variable were described in frequencies and percentages. Group comparisons (P-MDD and CI-MDD) were performed using Student's t-test for continuous variables and the chi-square test for categorical ones. All estimates were performed with the SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) to analyze the data considering a significance level of 95% (p<0.05).

Results

Socio-demographic and clinical characteristics.

A total of 160 participants with CUD (80% men, mean age 38.61 years) were studied. According to the diagnosis of the comorbid lifetime depressive episode, 62 (38.7%) patients presented a P-MDD diagnosis and 98 (61.3%) a CI-MDD one.

Table 1 shows the sociodemographic and clinical description of the sample. The average participant was a 38-year-old, unemployed, male, receiving outpatient treatment. Significant differences were observed between the two groups with respect to the age of onset of CUD (p=0.039) with the CI-MDD group being younger at the time of initiation. No other significant differences were reported between P-MDD and CI-MDD patients.

In addition to these variables, 79.4% of the CUD patients with P-MDD or CI-MDD, were diagnosed with comorbid substance disorders (e.g., alcohol, heroin, cannabis, benzodiazepines, hallucinogens, or other stimulants). Alcohol was the substance with the highest prevalence (55.0%), followed by heroin (37.5%), and cannabis (36.3%).

Depressive diagnosis criteria

The comparison of diagnostic criteria for the worst episode of depression between P-MDD and CI-MDD is shown in Table 2.

No differences were found between groups for the first two criteria; meeting at least one of them was necessary to diagnose a major depression disorder. Prevalence in both groups was high and quite similar: 95.2% P-MDD patients and 98% CI-MDD met criterion 1 *(Depressed mood most of the day, nearly every day)* whilst 95.2% P-MDD and 93.8% CI-MDD met criterion 2 *(Markedly diminished interest or pleasure).*

Although we observed similar criteria between two types of depressive disorder, the statistical analysis revealed differences. For instance, significant ones were found in criterion 3 *(Significant weight or appetite loss/gain)* with a higher prevalence in P-MDD patients (57.1%) than CI-MDD (42.9%) (p=0.008).

Discussion

The purpose of this study was to characterize P-MDD and CI-MDD according the differences in clinical characteristics and depressive symptomatology in CUD patients. Main differences were found in some depressive symptoms and the age of CUD onset.

With respect to symptomatology we observed that criterion 3 (significant weight loss/gain when not dieting or increased/decreased appetite) was more prevalent in

Table 1. *Baseline, sociodemographic, and clinical characteristics of the study sample.*

Variables	Total N = 160	Primary Major Depressive Disorder N = 62 (38.7%)	Cocaine-Induced Depressive Disorder N = 98 (61.3%)	p Value
Sociodemographic Variables				
Age *[mean (SD)]*	38.61 (8.73)	39.24 (8.69)	38.20 (8.77)	0.465
Sex *[N (%)]*				
Women	32 (20)	15 (24.2)	17 (17.3)	0.292
Men	128 (80)	47 (75.8)	81 (82.7)	
Educational Level*[N (%)]*				
Elementary	103 (64.4)	40 (64.5)	63 (64.3)	0.968
Secondary	43 (26.9)	17 (27.4)	26 (26.5)	
University	14 (8.8)	5 (8.1)	9 (9.2)	
Work Status *[N (%)]*				
Employed	52 (32.5)	22 (35.5)	30 (30.6)	
Unemployed	78 (48.8)	25 (40.3)	53 (54.1)	0.291
Pensioner	27 (16.9)	14 (22.6)	13 (13.3)	
Hospice	3 (1.9)	1 (1.6)	2 (2)	
Criminal Record *[N (%)]*				
No	81 (50.6)	33 (53.2)	48 (49)	0.601
Yes	79 (49.4)	29 (46.8)	50 (51)	
Clinical Variables				
Depression Age of onset** *[mean (SD)]*	30.29 (12.5)	32.74 (11.52)	28.44 (13.04)	0.171
Number of depressive episodes** *[mean (SD)]*	3.14 (2.46)	2.57 (2.1)	3.6 (2.65)	0.099
Cocaine Use Disorder Age of onset *[mean (SD)]*	25.09 (8.16)	26.24 (8.63)	24.04 (7.71)	0.039
Length of CUD *[mean (SD)]*	13.52 (8.42)	12.47 (8.46)	14.16 (8.37)	0.220
Another Substance Use Disorder *[N (%)]*	127 (79.4)	48 (77.4)	79 (80.6)	0.690
Alcohol	88 (55)	34 (38.6)	54 (61.4)	0.974
Cannabis	58 (36.3)	20 (34.5)	38 (65.5)	0.403
Hallucinogens	18 (11.3)	7 (38.9)	11 (61.1)	0.990
Sedatives	36 (22.5)	12 (33.3)	24 (66.7)	0.449
Stimulants	17 (10.6)	8 (47.1)	9 (52.9)	0.457
Opioids	2 (1.3)	2 (100)	-	0.074
Heroin	60 (37.5)	19 (31.7)	41 (68.3)	0.154

Note. [a] p-value from Student's t-test; [b]p-value from Fisher's exact test or chi-square test.
**Primary Major Depressive Disorder (N=27); Cocaine-Induced Depressive Disorder (N=36).

P-MDD patients. This finding does not always concur with the limited literature: Some authors have reported that P-MDD patients showed frequently changes in weight/appetite (Cohn et al., 2011) whilst others have found the contrary, a greater prevalence in CI-MDD patients (Schuckit et al., 2007)

Regarding sociodemographic variables, P-MDD and CI-MDD patients have similar characteristics. Nevertheless, the age of CUD onset is lower in the CI-MDD, a finding which can be of use to clinicians for an accurate diagnosis. In SUD studies younger onset age has been correlated with long-term consequences (Grant & Dawson, 1998), and is a crucial factor in the development of this disorder (Jordan & Andersen, 2017). Due to our non-representative sample size we did not observe gender differences, nevertheless, some authors have reported a greater prevalence of P-MDD in women, and substance-induced depressive episodes in men (Dakwar et al., 2011).

With respect to prognosis, differences were found in the literature between P-MDD and CI-MDD. There is some evidence referring to greater severity, frequency, and risk of relapse in substance-induced depressive episodes compared to primary depressive ones (Samet et al., 2013; Schuckit et al., 2007).

Although the present symptomatology is insufficient for accurate differential diagnosis, and there is a lack of knowledge regarding depressive stratification, studies in alcohol and other substance use disorders have shown differences in prevalence, risk factors, and treatment outcomes for P-MDD and CI-MDD (Langås, Malt & Opjordsmoen, 2013; Nunes, Liu, Samet, Matseoane & Hasin, 2006; Samet et al., 2013). Moreover, there is evidence that suggests that

Table 2. *Comparison between primary mayor depressive disorder and substance-induced depressive disorder (DSM-IV-TR) diagnostic criteria in the worst depressive episode criteria.*

Diagnosis according DSM-IV-TR criteria			
Criteria	**Primary Major Depressive Disorder N = 62**	**Cocaine-Induced Depressive Disorder N = 98**	**p Value**
Depressed mood most of the day, nearly every day (› 2 weeks)	59 (95.2)	96 (98.0)	0.322
Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day	59 (95.2)	92 (93.9)	0.731
Significant weight loss/gain when not dieting or decreased appetite	46 (57.1)	52 (42.9)	0.008
Insomnia or hypersomnia nearly every day	45 (72.6)	64 (65.3)	0.336
Psychomotor agitation/retardation nearly every day	40 (64.5)	54 (55.1)	0.239
Fatigue or loss of energy nearly every day	45 (72.6)	73 (74.5)	0.789
Feelings of worthlessness or excessive inappropriate guilt nearly every day	53 (85.5)	84 (85.7)	0.968
Diminished ability to think or concentrate, or indecisiveness nearly every day	43 (69.4)	60 (61.2)	0.295
Recurrent thoughts of death, recurrent suicidal ideation or suicide attempt	37 (59.7)	58 (59.2)	0.951

P-MDD and CI-MDD are distinct conditions (Samet et al., 2013; Torrens Mèlich, 2008).

In addition, differences in biological mediators have been reported with specific changes in the serotonin and tryptophan profiles between P-MDD and CI-MDD (Keller et al., 2017). Despite the lack of information regarding their neurological pathways, clinicians treat the symptomatology profiles with either dopaminergic or serotoninergic pharmacotherapy (Saltiel & Silvershein, 2015). The genetic component has also been shown to be fundamental in research on substance use disorders (Yang, Han, Kranzler, Farrer & Gelernter, 2011).

Due to their high prevalence, comorbid mental disorders have been extensively studied, specifically mood disorders in CUD. Our study underlines the importance of identifying the differences between P-MDD and CI-MDD in order to accurately diagnosis both types of depression.

Our study has some limitations. The first is the sample size which was relatively small for the detection of significant differences among variables. Moreover, women were under-represented as few of them seek treatment for substance use. Gender differences will need to be addressed in further research. Furthermore, the influence of other clinical variables such as body mass index or tobacco use could be explored. Finally, other environmental factors also could influence our data. Future investigation should take into account these limitations.

Our main strength is that the diagnostic procedures were performed with the PRISM interview which has demonstrated good reliability and validity for drug dependence and MDD diagnoses.

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Conflict of interests

The authors have no conflicts of interest.

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Evaluation of the efficacy of WhatsApp through a harm reduction intervention group for injecting drug users

Evaluación de la eficacia de WhatsApp en un programa grupal de reducción de daños asociados al consumo inyectado de drogas

Fran Calvo*,**, Oriol Turró-Garriga***, Xavier Carbonell****.

* Departament de Pedagogia, Institut de Recerca sobre Qualitat de Vida, Universitat de Girona.
** Grupo de Investigación en Salud Mental y Adicciones, Instituto de Investigación Biomédica de Girona [IdIBGi], Institut d'Assistència Sanitària, Girona.
*** Grupo de Investigación en Envejecimiento, Discapacidad y Salud [IdIBGi], Girona.
**** FPCEE Blanquerna, Universitat Ramon Llull, Barcelona.

Abstract

This study aims to analyse the use of an instant messaging app (WhatsApp®) as a means of communication for reaching people who inject drugs. An eight-week prospective longitudinal and observational study with three observations was designed for five addiction centres in Catalonia. The participants were 105 people who inject drugs, distributed in five intervention groups. The results of the Risk Assessment Battery (RAB) were compared in the three levels of analysis pre-test, post intervention and one month after the intervention. The main results indicate a significative reduction in RAB scores after the intervention. The main conclusion was that the WhatsApp® intervention has great potential for developing harm reduction interventions and to reduce the HIV contagion risk.

Keywords: Needle exchange program; street drugs; drug dependence; eHealth; harm reduction; homeless persons; WhatsApp®; online social networking.

Resumen

El presente estudio analiza el uso de una aplicación de mensajería instantánea (WhatsApp®) como canal de acceso a personas que se inyectan drogas. Se diseñó un estudio observacional longitudinal prospectivo de ocho semanas y tres observaciones en cinco centros de adicciones en Cataluña. Participaron 105 personas que consumían drogas por vía parenteral, distribuidas en cinco grupos de intervención grupal. Se compararon los resultados de la escala Risk Assessment Battery (RAB) (después de ser traducida al español y analizada su consistencia interna) en las tres fases de análisis pre test, post intervención y un mes después de la intervención. Los resultados indican una disminución significativa de las puntuaciones RAB tras la intervención a través de WhatsApp®. Se concluye que la intervención grupal a través de WhatsApp presenta grandes potencialidades para realizar intervenciones en reducción de daños y reducir el riesgo de contagio del VIH.

Palabras clave: Programa de intercambio de jeringuillas; drogas en la calle; dependencia de drogas; eSalud; reducción de daños; personas sin-hogar; WhatsApp®; mensajería instantánea; redes sociales en línea.

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Send correspondence to:
Fran Calvo. CAS Gironès, Institut d'Assistència Sanitària. C/ Baldiri Reixac 50, bajos. 17003 Girona. Phone + 34 617238344
E-mail: fran.calvo@ias.cat / fran.calvo@udg.edu

Introduction

The concept of harm reduction (HR) refers to interventions, programs and policies with the aim of minimising the harmful effects of drug use (Martínez-Luna et al., 2018; Mira, Llinás, Lorenzo & Aibar, 2009). It is one of the four pillars of drug addiction care alongside supply control policies, prevention and treatment of addictive behaviours. HR is an alternative to the more demanding models of specialized care based on abstinence, the necessary commitment to which cannot be met by some patients and which mostly require the retention of injection drug users (IDUs) in health centres (Erickson, 1995).

In Spain, HR has managed to reduce IDU mortality linked to the problems of injected heroin use, the increase in human immunodeficiency virus (HIV) infections and the mortality associated with acquired immune deficiency syndrome (AIDS) (Barrio et al., 2012). Despite this positive impact, IDUs in Spain have the highest rates of HIV infection and hepatitis C virus (HCV) in Western Europe (30.6% and 79.6% respectively) (Stone, 2014 and 2016). Although far from the dramatic figures of HIV-associated mortality among young people in the mid-1990s, 15.4% of IDUs are currently dying as a result of HIV and HCV infection, with coinfection being one of the main risk factors (Lozano, Domeque, Perálvarez, Torrellas & Gonzalo, 2019). Risk practices related to drug injection, whether direct (sharing used needles) or indirect (sharing injection paraphernalia such as filters, containers, water or loading the syringes with shared dissolved doses) are frequent, especially in the young population (Folch et al., 2016). The exposure to risk factors of contagion through sexual intercourse among IDUs is very high, and 34% have unprotected sexual intercourse, claiming to be aware of the risks and taking them anyway because of a dislike of using condoms (Calvo-García, Turró-Garriga & Giralt-Vázquez, 2014). Extreme social exclusion and homelessness are among the main risk factors for initiating injected drug use among young people (Calvo, Carbonell & Badia, 2018; Folch et al., 2016). Consequently, many authors raise both the need to revitalize HR programs and to incorporate new approaches which complement those already in operation (Bosque-Prous & Brugal, 2016; Fuente et al., 2006; Trujols et al., 2010).

One of the most significant changes in the organization of health care in recent years is the progressive incorporation of information and communication technologies (ICTs). EHealth, defined as the use of ICTs for the development of health and mHealth, defined as health care supported by the incorporation of mobile devices such as smartphones, tablets and other devices, form a growing part of the health care options available in European Union member states (World Health Organization, 2011).

Online social networks (OSNs) are included in eHealth and mHealth because they are Internet-based utilities which allow the creation and exchange of multimedia content generated by the users themselves (Kaplan & Haenlein, 2010). Their applicability to health is based on the Web 2.0 philosophy, the main potential of which lies in how it contributes to collaborative and open health models, offering the patient more capacity to manage their own process, thus empowering them in dealing with their own health (Armayones et al., 2015). The use of OSNs in eHealth has proven effective in promoting the use of condoms among homeless drug users (Rice, 2010), in reducing direct harm related to the consumption of alcohol and other drugs (Rice, Milburn & Monro, 2011) and in facilitating the acceptance of harm reduction and prevention programs (Rice, Tulbert, Cederbaum, Barman Adhikari & Milburn, 2012). Psychoeducational interventions aimed at showing people in situations of social exclusion how to use them have already had psychological benefits in themselves (Calvo & Carbonell, 2018).

Taking into account the importance of psychosocial interventions to improve the quality of life of patients injecting drugs (Fernández, González, Saiz, Gutiérrez & Bobes, 1999), this research aims to analyse the potential usefulness of using a mobile instant messaging service (WhatsApp®) as a complementary communication channel in the organization of discussion groups for harm reduction.

Method

Design

Prospective longitudinal observational study.

Population

Active injection drug users treated in harm reduction centres, addiction treatment centres or specific centres for homeless people.

Sample

Convenience sample from five centres (two addiction treatment centres, two harm reduction centres and a centre for the care of the homeless). Given the estimated number of IDUs in the five participating centres (n = 300) and assuming the principle of maximum indetermination, p = q = 50, with a margin of error of 8% and a confidence level of 95%, the sample size requirement was set at 101 participants.

The inclusion criteria for participants were having injected drugs in the last year and possessing a smartphone. During participant recruitment, the supervisor in each of the centres asked potential candidates whether they would be interested in participating. If the inclusion criteria were met, they were put on the list and at the start of the inter-

vention itself, it was confirmed that they were still interested and that they still met the inclusion criteria. They then received printed information about the objectives of the study, its methodology and possible results, and their right to abandon at any time was also explained. They subsequently signed the informed consent. Exclusion criteria were expressly stating that they did not wish to continue in the study, voluntarily abandoning the WhatsApp® group and refusing to complete the test at any of the three assessment points.

Procedure

After analysing the use of mobile devices and smartphones by people in situations of extreme social exclusion and injected drug use (Calvo, Carbonell, Turró & Giralt, 2018; Genz et al., 2015), an eight-week group intervention was designed with the aim of reducing the impact of the harm associated with injected drug use based on harm reduction treatment, which prioritizes keeping patients in the intervention program as the key element for facilitating change (Little, Hodari, Lavender & Berg, 2008). The participants were distributed across seven WhatsApp groups with the aim of facilitating discussion, as in face-to-face groups. The intervention featured a weekly thematic proposal based on some of the issues most relevant to reducing the risk of HIV infection. In the WhatsApp groups, participants interacted with each other or addressed professionals directly by asking questions, making suggestions, explaining experiences, clarifying doubts among themselves, and interacting. Researchers intervened minimally in an attempt to have the group mediate in answering questions and taking advantage of the described potential regarding peer support in discussion groups, following the usual procedure for managing groups of this type. The intervention was designed in the form of a discussion group, the effectiveness of which has been widely demonstrated (Calvo, Pérez, Sacristán & Paricio, 2009; Cheung et al., 2015). An in-depth analysis of this content and the proposed group intervention methodology has been described previously (Calvo, Carbonell, Giralt, Lloberas & Turró, 2017).

The research was approved by the CEI-Girona Research Ethics Committee, code *XSO_2017,* June7, 2017.

Study variables and evaluation instruments

An ad hoc questionnaire was used to determine age, sex, HIV infection, homelessness, participation or not in a methadone maintenance program -MMP- and the main drug injected in the last month.

Dependent variable: Data on drug use typology and HIV risk practices were obtained with the Risk Assessment Battery (RAB) (Navaline et al., 1994), which consists of 29 items, 17 of them scoreable with a score range from 0 to 40 points (ratio 0-1). The remaining items provide descriptive information about drug use, sexual activity, the level of concern regarding the possibility of HIV infection and patients' level of knowledge about their most recent analysis and serological status. The scale yielded internal consistency of 0.82 in its standard version and 0.86 in its electronic version (Navaline et al., 1994). The scale underwent translation and back-translation into Spanish and was adapted to the Spanish population with internal consistency of 0.81 calculated on the total observations of the participants (105 participants x 3 observations = 315). The original scale does not present specific data on factorial structure, cut-off points or sensitivity and specificity. Appendix 1 shows the original scale which was translated into Spanish for the study.

Finally, for additional qualitative information, participants were asked at the end of the eight weeks of intervention about the possibility of answering three open questions as feedback on the intervention: i) evaluation of the information proposed in the intervention groups; ii) evaluation of WhatsApp as a communication channel for people who inject drugs; and iii) evaluation of the use of groups as part of the treatment or harm reduction process that they were following during the program.

Statistical analysis

For the description of the data, measures of central tendency and dispersion, and the analysis of absolute and relative frequencies was used for quantitative and qualitative data respectively. Pearson correlations were used for comparing quantitative variables, and statistics comparing the means of quantitative variables between groups according to normality criteria, and contingency tables for the comparison of qualitative variables. Observations were carried out at the beginning of the training (T^1), at the end of the program (T^2) and one month afterwards (T^3). Student's t was used for related samples to analyse the difference in means in intra-group scores. The index of intra-group score differences between T^1 and T^3 $[(T^1 - T^3/T^1)*100]$ was calculated, and this was used as a dependent variable in the adjusted linear regression model in order to determine the variables associated with the greatest difference. A mixed linear regression model was adjusted to determine whether this difference in the score was attributable or not to the centre or the specific individual variables.

Results

Sample description

A total of 130 IDUs were recruited, of which 11 were excluded as they lacked a smartphone and 14 left the WhatsApp group; the final sample thus comprised 105 IDUs.

Men made up 86.7% of the participants, with a mean age of 41.3 years (SD = 6.7). All participants had used a drug during the month prior to the intervention, although they reported not having used opioids (apart from meth-

adone), amphetamines, methamphetamine or hallucinogens. Of the sample, 32.4% reported being infected with HIV (n = 34). Of the remaining 71 participants who did not know if they were infected, 88.7% (n = 63) reported some level of concern about the possibility of being infected and 97.2% (n = 69) about the possibility of having been exposed to the virus. Fifty-four of the participants (76.1%) reported having taken a blood test to check for the presence of HIV on average 1.9 times (SD = 2.8) and 1.7 years before the pre-test (SD = 1.7). A large majority (88.6%) of the participants were on an MMP.

Participants who said they were homeless made up 39.6% of the sample. Differences were found between people who were homeless and those who were not, especially in the type of drug use in the previous month. As Table 1 shows, homeless people had higher rates of using cannabis (100% vs. 80.6%), alcohol (100% vs. 89.5%) and cocaine (81.6% vs. 55.2%), especially injected (73.7% vs. 66.1%) and lower rates of injected heroin (42.1% vs. 88.1%) and injected speedball (21.1% vs. 58.2%) use. A greater proportion of the homeless were in MMPs (94.7% vs. 82.1%).

Table 1. *Sample descriptives at pretest.*

Variables, *n (%)*	**Total**	**Homeless**	**Housed**	**Values**		
	(n = 105)	*(n = 38)*	*(n = 67)*	X^2 / *t*	*gl*	*p*
Sex Male	91(86 7)	31 (81.6)	60 (89.6)	1.33	1	0.195
Age, M (SD)	41.3 (6.7)	40.5 (9.2)	41.8 (4.8)	-0.913	103	0.364
Drug use [a]						
Cannabis (smoked)	92 (87.6)	38 (100)	54 (80.6)	8.41	1	0.002
Alcohol (oral)	98 (93.3)	38 (100)	60 (89.5)	11.2	1	0.001
Cocaine [b]	68 (64.8)	31 (81.6)	37 (55.2)	7.38	1	0.005
Snorted	11 (10.5)	3 (7.9)	7 (10.4)	1.21	1	0.292
Smoked	22 (21.0)	7 (18.4)	15 (22.4)	0.97	1	0.576
Injected	51 (48.6)	28 (73.7)	45 (66.1)	7.92	1	0.005
Benzodiazepinas (oral)	42 (40.0)	12 (31.6)	30 (44.8)	9.82	1	0.005
Heroin [b]	63 (60.0)	20 (52.6)	43 (64.2)	1.36	1	0.170
Smoked	12	4 (10.5)	8 (11.9)	0.83	1	0.457
Injected	51	16 (42.1)	59 (88.1)	17.8	q	‹0.001
Speedball (injected)	47 (63.8)	8 (21.1)	39 (58.2)	18.6	1	‹0.001
HIV positive	34 (32.4)	13 (34.2)	21 (31.3)	1.03	1	0.521
In MMP[b]	93 (88.6)	36 (94.7)	55 (82.1)	7.68	1	0.004

Note. [a] In the last month. [b] Any route of administration.

Comparison of intra-group measures

The mean RAB scores at T^1 were 13.35 (SD = 5.42), which decreased to 9.49 (SD = 5.58) at T^2, with a decrease in the mean scores of 3.87 points (SD = 7.89; t = 5.021; gl = 104; p <0.001). At T^3, the average score was 8.70 (SD = 5.01) which, despite not presenting a significant decrease with respect to T^2 (M = 0.79; SD = 4.23; t = 1,915; gl = 104; p = 0,058), does indicate a statistically significant tendency. The difference in mean scores between T^1-T^3 was 4.65 points (SD = 7.25; t = 6.58; gl = 104; p <0.001) (Figure 1). Table 2 shows the score items of the RAB.

Mixed linear

The mixed linear analysis for repeated measures showed the effect of the intervention on the RAB (F = 28.5; df = 2; p <0.001). When adjusted for the pre-test variables (sociodemographic and clinical), significant differences were observed between T^3 and T^1 but not between T^3 and T^2 (Table 3). The matrix of variances and the estimation of covariance parameters showed that only 21.9% of the variance in the RAB score is attributable to the difference between subjects while the intervention accounts for 78.1%.

Participation in WhatsApp® groups

Participants were distributed across seven WhatsApp® groups, with an average of 15.1 participants per group (SD = 1.8). Once the experimental situation began, the participants sent a total of 21,893 communications in the form of text messages, non-text symbols (emoticons), videos or audios between T^1 and T^2.

This represents an average of 3,127.6 (SD = 752, 1) communications per group, an average of 391.0 (SD = 121.8)

Table 2. *Score items of the RAB scale.*

#	Item	Range	Me	MP[a](%)	M	SD	r[b]
1	In the past six months, have you injected drugs?	0-1	1	82.6	.851	.319	-.917
2	In the past six months, have you shared needles or works?	0-3	0	23.6	.623	1.11	.672**
3	With how many different people did you share needles in the past six months?	0-3	0	2.0	.346	.675	.691*
8	In the past six months, how often have you been to a shooting gallery/house or other place where users go to shoot-up?	0-3	0	31.6	1.23	1.42	.532**
9	In the past six months, how often have you been to a Crack House or other place where people go to smoke crack?	0-3	1	01.9	.897	1.66	.593**
12	In the past six months, how often have you shared rinse-water?	0-3	0	8.6	.639	.901	.421*
13	In the past six months, how often have you shared a cooker?	0-3	0	5.1	.498	.873	.396**
14	In the past six months, how often have you shared a cotton?	0-3	0	4.8	.563	.764	.321**
15	In the past six months, how often have you divided or shared drugs with others by using one syringe (yours or someone else's) to squirt or load the drugs into the other syringe(s) (backloading, for example) ?	0-3	0	1.1	.981	.894	.411**
16	How would you describe yourself? (Straight, Gay or Homosexual, Bisexual)	0-3	1	6.4	2.01	.512	-.921
17	With how many men have you had sex in the past six months?	0-3	0	3.0	.609	.743	-.235*
18	With how many women have you had sex in the past six months?	0-3	1	22.8	1.12	.661	.402**
19	In the past six months, how often have you had sex so you could get drugs?	0-3	0	22.6	.574	.802	.097
20	In the past six months, how often have you given drugs to someone so you could have sex with them?	0-3	1	0.6	.971	.888	.472**
21	In the past six months, how often were you paid money to have sex with someone?	0-3	0	11.7	.406	.645	.112
22	In the past six months, how often did you give money to someone so you could have sex with them?	0-3	1	2.4	.914	.886	.504**
24	In the past six months, how often did you use condoms when you had sex?	0-3	1	1.8	.818	.898	.432**

Note. [a] Maximum score percentage. [b] Correlation with respect to the total. *p <.05. **p<.001.

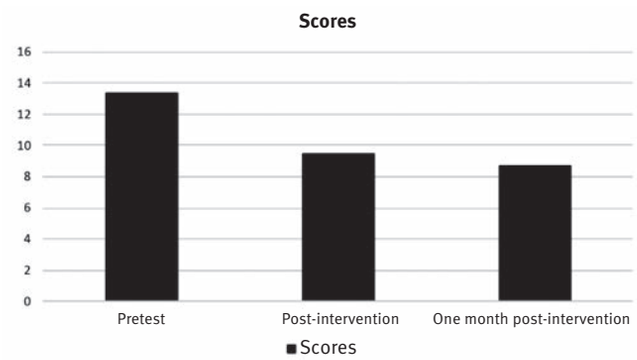

Figure 1. Differences of RAB score means across the three intervention points.

Table 3. *Linear regression model adjusted for intra-group differences. Risk Assessment Battery scale result as dependent variable.*

Parameter	Estimation	Error Est.	gl	t	Sig.	CI 95%	
						Min.	Max.
Intercep.	8.70	0.52	284.86	16.78	‹0.001	7.68	9.73
Assessment (T)[1]	4.57	0.65	208	7.05	‹0.001	3.29	5.85
Assessment (T)[2]	0.76	0.65	208	1.17	0.241	-0.52	2.04
Assessment (T)[3]	0*	0					

Note. * This parameter is zero because it is redundant.

communications per group and week and an average of 48.9 (SD = 31.9) daily communications per group. The average number of communications per person during the eight-week program duration was 208.5 (SD = 214.6).

Of the total communications, 54.7% (n = 11,986) were expressions of doubt or questions related to harm reduction. Of these questions, 38.4% (n = 4,597) were about the main risks of overdosing, 16.5% (n = 1,981) about the procedure to get a quick HIV or HCV test, 10.2 % (n = 1,224) on finding injection material, 9.9% (n = 1,181) on drug interaction, 9.5% (n = 1,136) on levels of drug purity, 8.1 % (n = 976) on access to social services (benefits, overnight services or food) and 7.4% (891) on access to treatment or types of addiction treatment.

According to the data on questions or doubts, groups formulated an average of 1,712.3 questions (SD = 471.4), with an average of 214.1 (SD = 264,1) questions per week and group, and 53.5 (SD = 31.9) questions or doubts per day and group.

Of the 9,907 participant communications that were not expressing doubts or questions, 24.4% (n = 2,421) corresponded to answers to the questions asked by other participants, 12.1% (n = 1196) were messages in support of other participants, 9.9% (977) were statements of information provided by the group managers. Finally, 53.6% (n = 5,313) of the communications corresponded to messages without content in themselves and which were part of the interaction of the conversation (messages of affirmation, emphasis in the form of emoticons on many occasions or use of punctuation marks or acronyms typical of virtual textual language). See Figure 2.

The group managers intervened on a total of 2,431 occasions: 4.3% (n = 104) to propose the contents of the topics to work on in the discussions, 56.3% (n = 1,369) to

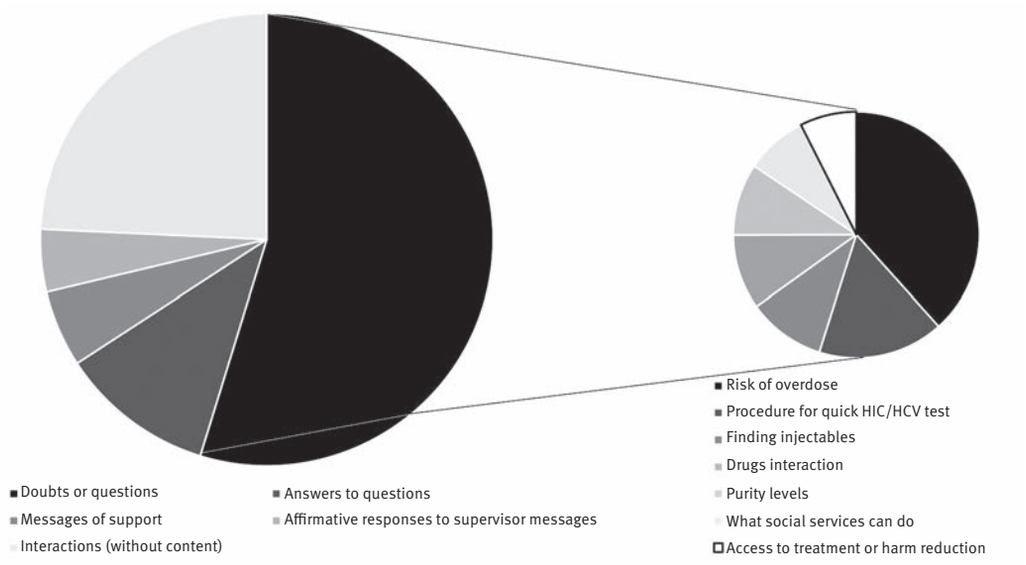

Figure 2. Content of the communications sent in the different WhatsApp® groups.

clear up doubts or answer questions about the proposed content which the users did not answer themselves as part of the discussion process, 24.1% (n = 587) to energize the groups and 15.3% (n = 371) to redirect inappropriate communications (personal questions among participants that had nothing to do with the discussion, jokes, inappropriate audiovisual content such as gags, etc.).

Finally, open responses regarding the experience in the WhatsApp groups were coded and classified to allow analysis. Regarding the content covered in the groups, 102 participants reported that it was suitable and that it answered the questions or extended the information they had previously on the topics discussed, 81 participants highlighted the possibilities offered by immediate access to information and responses from both peers and the group's managers, and 51 stressed that the virtual space could be a complement to the usual benefits of the treatment and harm reduction services which they were receiving: 32 said so because it could overcome access barriers such as fixed schedules since the virtual group could access whenever they wanted, and 19 because the professional of the WhatsApp group responded quickly to the demands of the group. All participants who finished the process would be willing to participate in virtual groups periodically or continuously as part of their therapeutic process.

Discussion

The objective of this study was to test the viability of using an instant messaging service in a clinical context of reducing the risk of HIV infection associated with injected drug use. For this purpose, a longitudinal multicentre study was designed with three assessment points: pretest, post-intervention and one month after the intervention. In the absence of specific damage reduction scales in Spanish, the RAB, a self-administered scale measuring participation in activities which increase the probability of contracting HIV, was chosen. Among the different scales available in English, the RAB was suitable in that it assesses a type of patient who is difficult to retain in treatment, meets the normal clinical history requirements of the public drug addiction services where the study was carried out, and maintains confidentiality regarding practices of exchanging injection material and sexual activity associated with contagion risks among people who inject drugs (National Institute on Drug Abuse, 2018).

Two main lessons can be drawn from this research. The first is the feasibility of using OSNs for this type of intervention. The decrease in RAB scale scores between T^1 and T^3 suggests a reduced potential risk of HIV infection (National Institute on Drug Abuse, 2018). The second has to do with the capacity to retain participants. Outpatient care in drug addiction is affected by a high dropout rate (Martínez-González, Albein-Urios, Lozano-Rojas & Verdejo-García, 2014); in fact, beyond the retention produced by being on opioid substitutes, no behavioural and educational, counselling or supportive treatments have been found to facilitate retention (Timko, Schultz, Cucciare, Vittorio & Garrison-Diehn, 2016). The intervention groups in this study presented a high adherence capacity, superior to other addiction treatment interventions (Calvo et al., 2018), thereby reducing the inherent limitations of face-to-face services, such as schedules, waiting lists, travel expenses, personal organization, etc., something the participants themselves suggested in their evaluation of the intervention (Soto-Pérez & Franco-Martín, 2014)

EHealth has proven useful in harm reduction programs associated with alcohol and tobacco use in controlled clini-

cal trials (Chiauzzi, Green, Lord, Thum & Goldstein, 2005; Kypri et al., 2004; Kypri & McAnally, 2005; Neighbors, Larimer & Lewis, 2004; Neighbors, Larimer, Lostutter & Woods, 2006; Walters, Vader & Harris, 2007). Common benefits have to do with the anonymity of the user and with the possibility of accessing the services at the precise moment they are needed (Marlatt & Witkiewitz, 2010). EHealth improves contact with services and increases the adherence of those in situations of extreme social exclusion (Burda, Haack, Duarte & Alemi, 2012) and has proven its effectiveness in improving overdose assessment and prevention (Baldacchino et al., 2016). Likewise, WhatsApp® presents good results as a means of rapid communication and at very low cost, potentially improving clinical communications and patient learning about their process while preserving their privacy (Kamel-Boulos, Giustini & Wheeler, 2016; Nardo et al., 2016; Schreiner & Hess, 2015).

In the specific use with addictions, group discussion through WhatsApp® groups is effective in reducing relapses thanks to direct and rapid communication and social support (Cheung et al., 2015), and social and health professionals perceive it as potentially beneficial in clinical practice (Ganasegeran, Renganathan, Rashid & Al-Dubai, 2017). Added to this are the general benefits of using mobile phones in health, such as the possibility of transmitting information efficiently and economically, access to social support networks, all featuring the aspect of immediacy (Gravenhorst et al., 2015). Immediacy is a common beneficial factor of mHealth in addiction, regardless of program specificities (Marlatt & Witkiewitz, 2010). As we can see, this benefit is enhanced in instant messaging services because participants can access the support of the group at any time and can obtain a response faster than in specialised treatment centres, thereby positioning itself as a resource with great potential for retaining patients in significantly unstructured socio-economic situations and in social exclusion (La Sala & Mignone, 2014; McInnes, Li & Hogan, 2013). The high number of IDUs among the homeless population in the context of the intervention (Calvo-García, Giralt-Vázquez, Calvet-Roura & Carbonell-Sánchez, 2016), the relationship between chronic injected drug use and risk of homelessness as a situation of extreme social exclusion (Des Jarlais, Kerr, Carrieri, Feelemyer & Arasteh, 2016), and homelessness as a new risk factor for HIV infection among IDUs (Folch et al., 2016) are situations in which mHealth can be efficacious/play a positive role.

In itself, the use of mobile phones has proven effective in increasing retention and treatment adherence in addictions (Ganasegeran et al., 2017; Wolfe, Carrieri & Shepard, 2010). OSN and instant messaging services can be incorporated in virtual interventions in harm reduction because they respect HR principles (retention, support and respect for the time the IDUs need in their addiction process) thanks to their universal character and by being a "virtual presence". In addition, the patient has the possibility of using these virtual features when needed and in a cost-effective way hardly comparable to other types of interventions.

The results obtained in this study have some limitations that should be taken into account. First, the small sample size resulting from the need to design and manage group sessions in an appropriate manner, given the recommendations for the maximum number of participants in this type of group. It would be important, therefore, to replicate the study in other contexts and centres to increase the sample analysed. Second, the RAB has not yet been validated in the Spanish population. It is recommended that the study be extended to validate our adaptation as it constitutes an instrument which allows the assessment of the HIV-infection risk behaviours associated with injection and sexual risk behaviours. In addition, the number of observations taken from the RAB has been limited and the internal consistency analyses, while acceptable, have been lower than those of the scale in its original version. Even so, to reduce the risk of systematic error, participants were randomized and the results have demonstrated the equivalence between the groups at baseline. Nevertheless, even with acceptable internal validity, it is necessary to expand the sample to limit the possibility of random error. Thirdly, it would have been interesting to see, in an observation six months after the intervention, whether the results obtained remained stable, diminished or were nullified, but the complications of accessing the sample after this period made it difficult. Fourth, in the absence of similar research on the use of WhatsApp® as a communication channel for the development of group harm reduction treatments, the results could not be compared to other studies. Finally, access to a mobile phone and services such as OSNs are still an important limitation for a part of the population with higher social exclusion criteria. In our study, not having a smartphone has been a reason for exclusion, and the results are therefore limited to those who did have a mobile phone and routinely used OSNs. In future studies, this fact should be reversed to avoid participation biases due to this circumstance, both in terms of telephone ownership and the ability to use and manage it.

In conclusion, the use of OSNs in the field of harm reduction interventions is at an early stage and we believe that this study supports the use of instant messaging services in virtual treatment. OSNs have great potential to contribute to reducing exposure to HIV infection risks, improving retention and increasing the participation of injected drug users.

Conflict of interests

The authors declare the absence of any type of conflict of interest.

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Appendix 1. Risk Assessment Battery scale - RAB

☐ Check If Asked By Interviewer

ID#: _____

DATE ____ /____ /____

Administered by: _____

Checked by: _____

Risk Assessment Battery

R A B

Please read each of the following questions very carefully. As you will see, many of these questions are personal. We understand this and will make every effort to protect the privacy of your answers.

It is very important that you answer every question honestly. In fact, it's better not to answer a question at all than to tell us something that is not accurate or true. Some questions may not seem to have an answer that is true for you. When this happens, you should simply choose the answer that is most right. Don't spend too much time on any one question. Remember, always ask for help if you're unsure about what to do.

Thank you for your time and cooperation.

PAST MONTH DRUG AND ALCOHOL USE

A. In the past month, how often have you injected cocaine and heroin together (Speedball)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

B. In the past month, how often have you injected heroin (not mixed)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

C. In the past month, how often have you snorted heroin (not mixed)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

D. In the past month, how often have you smoked heroin?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

E. In the past month, how often have you injected cocaine (not mixed)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

F. In the past month, how often have you snorted cocaine (not mixed)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

G. In the past month, how often have you smoked crack, rock, or freebase cocaine?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

H. In the past month, how often have you injected amphetamines, meth, speed, crank or crystal?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

I. In the past month, how often have you snorted amphetamines, meth, speed, crank or crystal?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

J. In the past month, how often have you smoked amphetamines, meth, speed, crank or crystal?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

K. In the past month, how often have you used benzodiazepines (benzos, benzies) such as Xanax, Valium, Klonipin or Ativan?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

L. In the past month, how often have you taken painkillers - pills such as Percodan, Percocet, Vicodin, Demerol, Dilaudid, Darvon, Darvocet or syrup (Codeine)?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday
a. Which types of painkillers did you use? _____
_____

M. In the past month, how often did you inject Dilaudid?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

N. In the past month, how often have you used acid, LSD, or other hallucinogens?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

O. In the past month, how often have you used marijuana?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

P. In the past month, how often have you used beer, wine or liquor?
0. ☐ Not at all
1. ☐ A few times
2. ☐ A few times each week
3. ☐ Everyday

PART I: NEEDLE USE

1. In the past six months, have you injected drugs?
   0. ☐ No
   1. ☐ Yes

2. In the past six months, have you shared needles or works?
   0. ☐ No or I have not shot up in the past six months
   3. ☐ Yes

3. With how many different people did you share needles in the past six months?
   0. ☐ 0 or I have not shot up in the past six months
   1. ☐ 1 other person
   2. ☐ 2 or 3 different people
   3. ☐ 4 or more different people

4. In the past six months, how often have you used a needle after someone (with or without cleaning) ?
   0. ☐ Never or I have not shot up or shared in the past six months
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

5. In the past six months, how often have others used after you (with or without cleaning) ?
   0. ☐ Never or I have not shot up or shared in the past six months
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

6. In the past six months, how often have you shared needles with someone you knew (or later found out) had AIDS or was positive for HIV, the AIDS virus?
   0. ☐ Never or I have not shot up or shared in the past six months
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

7. Where did you get your needles during the past six months? (Check all that apply)
   0. ☐ I have not shot up in the past six months
   1. ☐ From a diabetic
   2. ☐ On the street
   3. ☐ Drugstore
   4. ☐ Shooting gallery or other place where users go to shoot up
   5. ☐ Needle Exchange Program
   6. ☐ Other:_____

8. In the past six months, how often have you been to a shooting gallery/house or other place where users go to shoot-up?
   0. ☐ Never
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

9. In the past six months, how often have you been to a Crack House or other place where people go to smoke crack?
   0. ☐ Never
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

10. Which statement best describes the way you cleaned your needles during the past six months? (Please choose one)
   0. ☐ I have not shot up in the past six months
   1. ☐ I always use new needles
   2. ☐ I always clean my needle just before I shoot up
   3. ☐ After I shoot up, I always clean my needle
   4. ☐ Sometimes I clean my needle, sometimes I don't
   5. ☐ I never clean my needle

11. If you cleaned your needles and works in the past six months, how did you clean them? (Check all that apply)
   0. ☐ I have not shot up in the past six months
   1. ☐ Soap and water or water only
   2. ☐ Alcohol
   3. ☐ Bleach
   4. ☐ Boiling water
   5. ☐ Other:_____
   6. ☐ I did not clean my needles in the past six months
   7. ☐ I ALWAYS used new needles in the past six months

12. In the past six months, how often have you shared rinse-water?
   0. ☐ Never or I have not shot up in the past 6 months
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

13. In the past six months, how often have you shared a cooker?
   0. ☐ Never or I have not shot up in the past 6 months
   1. ☐ A few times or less
   2. ☐ A few times each month
   3. ☐ Once or more each week

14. In the past six months, how often have you shared a cotton?
    0. ☐ Never or I have not shot up in the past 6 months
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

15. In the past six months, how often have you divided or shared drugs with others by using one syringe (yours or someone else's) to squirt or load the drugs into the other syringe(s) (backloading, for example) ?
    0. ☐ Never or I have not shot up in the past 6 months
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

PART II: SEXUAL PRACTICES

16. How would you describe yourself?
    1. ☐ Straight
    2. ☐ Gay or Homosexual
    3. ☐ Bisexual

Please note: For the following questions, sex means any vaginal intercourse, anal intercourse (in the butt) or oral sex (blowjobs, for example)

17. With how many men have you had sex in the past six months?
    0. ☐ 0 men
    1. ☐ 1 man
    2. ☐ 2 or 3 men
    3. ☐ 4 or more men

18. With how many women have you had sex in the past six months?
    0. ☐ 0 women
    1. ☐ 1 woman
    2. ☐ 2 or 3 women
    3. ☐ 4 or more women

19. In the past six months, how often have you had sex so you could get drugs?
    0. ☐ Never
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

20. In the past six months, how often have you given drugs to someone so you could have sex with them?
    0. ☐ Never
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

21. In the past six months, how often were you paid money to have sex with someone?
    0. ☐ Never
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

22. In the past six months, how often did you give money to someone so you could have sex with them?
    0. ☐ Never
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

23. In the past six months, how often have you had sex with someone you knew (or later found out) had AIDS or was positive for HIV, the AIDS virus?
    0. ☐ Never
    1. ☐ A few times or less
    2. ☐ A few times each month
    3. ☐ Once or more each week

24. In the past six months, how often did you use condoms when you had sex?
    0. ☐ I have not had sex in the past 6 months
    1. ☐ All the time
    2. ☐ Most of the time
    3. ☐ Some of the time
    4. ☐ None of the time

PART III: CONCERNS ABOUT HIV AND TESTING

If you know that you are HIV positive, skip to question # 28.

25. How worried are you about getting HIV or AIDS?
    0. ☐ Not at all
    1. ☐ Slightly
    2. ☐ Moderately
    3. ☐ Considerably
    4. ☐ Extremely

26. How worried are you that you may have already been exposed to the HIV or AIDS virus?
    0. ☐ Not at all
    1. ☐ Slightly
    2. ☐ Moderately
    3. ☐ Considerably
    4. ☐ Extremely

27. How many times have you had a blood test for the AIDS virus (HIV)? (circle):

    0 1 2 3 4 5 6 7 8 9 10 or more times

28. When were you last tested for HIV? On the lines below, please write the month and year of your most recent test.

    _____/_____
    MONTH YEAR

29. Were you ever told that you had the HIV, the AIDS virus?
    0. ☐ No
    1. ☐ Yes
    2. ☐ I never got the results

Thank You.
Please let the staff person know that you have finished.

When people who inject drugs speak: Qualitative thematic analysis of the perception of a mobile app for needle exchange programs

Cuando las personas que consumen drogas inyectadas tienen la palabra: Análisis cualitativo de contenido temático sobre la percepción de uso de una aplicación móvil para los programas de intercambio de jeringas

Fran Calvo*,**, Xavier Carbonell***, Mercè Rived****, Cristina Giralt*.

* Grupo de Investigación en Salud Mental y Adicciones, [IdIBGi], Institut d'Assistència Sanitària, Girona.
** Departament de Pedagogia, Universitat de Girona.
*** FPCEE Blanquerna, Universitat Ramon Llull, Barcelona.
**** Escola Universitària d'Infermeria i Teràpia Ocupacional, EUIT, Universitat Autònoma de Barcelona.

Abstract

Spain is the Western European country with the highest prevalence of Human Immunodeficiency Virus among people who inject drugs. The Hepatitis-C Virus affects over fifty per cent of this population. At the same time, the World Health Organization considers that the average coverage of injection material for drug user per year is low. Harm reduction programs and services have been deployed for over thirty years, and these could now incorporate the advantages of eHealth and mHealth to improve harm reduction. The aim of this qualitative and descriptive study is to analyze how people who inject drugs perceive an application for mobile devices. Fifty-one such drug users participated actively in five focus groups. The main results of the thematic content analysis indicated that the application was welcomed as easy and useful. Participants reported that the application contributed to improving access to injection material, reducing the stigma of drug-dependence and optimizing the organization of the ritual of injection. Excessive preventive information and problems downloading the web app were identified as aspects for improvement. In conclusion, the application was seen as a useful eHealth tool that complements the normal intervention of needle exchange programs.

Keywords: Harm reduction; needle exchange programs; drug consumption; eHealth; mHealth; illicit drugs; cocaine; heroin; focus group.

Resumen

España es el país de Europa Occidental con más prevalencia del Virus de la Inmunodeficiencia Humana entre personas que se inyectan drogas. La presencia de Virus de la Hepatitis-C supera el cincuenta por ciento en esta población. Al mismo tiempo, la Organización Mundial de la Salud considera que la cobertura media de material de inyección por usuario y año es baja. Con más de treinta años de experiencia en el despliegue de los servicios y programas de reducción de daños, las ventajas que posibilita la eSalud y la mSalud como la accesibilidad y asequibilidad, pueden incorporarse también a la reducción de daños. El objetivo de este estudio fue analizar la percepción que las personas que consumen drogas inyectadas tienen sobre una aplicación móvil para mejorar el acceso a material de inyección. Partiendo de un enfoque cualitativo se recogió información a través de cinco grupos focales en los que participaron 51 personas consumidoras de drogas inyectadas en activo. Se llevó a cabo un análisis de contenido temático cuyos principales resultados indicaron que la aplicación tuvo una buena aceptación y se consideró sencilla y útil. Los participantes refirieron que la aplicación contribuía a mejorar el acceso a material de inyección, a reducir el estigma de los drogodependientes, y a optimizar la planificación del usuario para adquirir la jeringa en el proceso ritual del consumo. Como puntos a mejorar, destacaron reducir el exceso de información preventiva y simplificar la ruta de descarga de la webapp. En conclusión, la aplicación se posiciona como una herramienta útil para complementar la intervención ordinaria de los programas de intercambio de jeringas.

Palabras clave: Reducción de daños; programa de intercambio de jeringas; consumo de drogas; eSalud; mSalud; drogas ilícitas; cocaína; heroína; grupo focal.

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Send correspondence to:
Fran Calvo. CAS Gironès, Institut d'Assistència Sanitària. c/ Baldiri Reixac 50, bajos. 17003 Girona. Phone +34 617238344
E-mail: fran.calvo@ias.cat; fran.calvo@udg.edu

Introduction

The main harm associated with injected drug use is lethal overdose and infection with diseases such as the Human Immunodeficiency Virus (HIV) and the Hepatitis-C Virus (HCV) (Folch et al., 2016). One of the harm reduction (HR) interventions which has demonstrated the greatest efficacy and effectiveness in reducing HIV and HCV infections is the needle exchange program (NEP) (Platt et al., 2018). Although the name makes reference to the needle itself, NEPs provide people who inject drugs (PWID) with all the material needed to inject safely (filters, containers, sterile water, alcohol swabs). This material, called injection paraphernalia, has proven particularly effective in reducing such infections (Page, Morris, Hahn, Maher & Prins, 2013).

In the European Union, the rate of HIV infection is 6.3 cases per 100,000 inhabitants while in Spain it is 9.4 cases per 100,000 inhabitants, and 2.8% of the total cases of infection are due to intravenous drug use (Elattabi, Ruiz-Algueró, Hernando & Díaz, 2017). Regarding HCV, With a percentage of 1.7% of all adults, Spain is among the European countries with the highest estimated prevalence of people with antibodies (Buti et al., 2017). Twenty-three percent of new cases of HCV infection are related to injected drug use (World Health Organization, 2017).

The prevalence of HIV among all Spanish PWID is the highest in Western Europe (31.5%) followed by Italy (28.8%). The United Kingdom, Malta, Finland, and Norway present percentages below 2% (Stone, 2018). Regarding HCV, Spain is the country with the fourth-highest prevalence of infection in Western Europe (53.3%) after Portugal (65.8%), Sweden (61.3%) and Luxembourg (61%) (Grebely et al., 2019).

At the beginning of the 1990s, Spain reached the highest prevalence of HIV infection and mortality associated with Acquired Immune Deficiency Syndrome among PWID, mainly due to the use of injected heroin (Fuente et al., 2006). Motivated in part by this situation, the drug addiction network was founded and HR services and programs were set up, such as NEPs, which have managed to reduce new infections year on year (Bosque-Prous & Brugal, 2016).

The effectiveness of an NEP depends on good distribution of injection paraphernalia among PWID. The World Health Organization considers that plentiful provision of injection kits per PWID/year is a key strategy in infection prevention (World Health Organization, 2016). According to this report, the provision of sterile needles is currently low, with health services covering 5% of injection drug users' annual needs. Its strategy against infection with viral diseases includes multiplying this by 10, reaching 50% coverage in the year 2020 and increasing it a further 40 points to achieve 90% coverage in the year 2030. The information available to PWID regarding the resources available in their community and, in this case, of the services participating in the NEP is essential for improving the coverage of injection paraphernalia.

Recent years have seen advances in information and communication technologies (ICTs) and their applicability in the form of eHealth or mHealth applications for fixed or mobile devices for the treatment of addictions (Riper et al., 2018). EHealth is understood as the incorporation of ICTs into health care, both in terms of patient care as well as health promotion and disease prevention (Eysenbach, 2001), while MHealth (mHealth –Mobile Health) covers the same aims but on mobile devices and their corresponding applications (apps) (Kay, Santos & Takane, 2011).

In the absence of specific applications for NEPs, an app for smartphones was created in 2017 with the purpose of making injection parapheralia more accessible to PWID. The main objective of this study is to analyze and describe the subjective experience of a group of people who use injected drugs with regard to the use of this application. To this end, a qualitative methodology design with a descriptive approach was used. The specific purposes of this research are i) to analyze the experience of using the application in the autonomous community of Catalonia in Spain; ii) to understand which design elements and aspects of usability of the app prove to be facilitators or barriers to taking up use of the app; iii) to explore the perception of PWID as to how the app affected or could affect their behavior in terms of access to injection material; and iv) to identify future implications for the app in NEPs.

Method

General research design

A qualitative descriptive study was carried out by implementing and analyzing focus groups. The focus group is a research technique consisting of a form of group interview in which interaction between researchers and participants is created to generate a safe space to express points of view and opinions, in order to obtain information about how individuals understand, feel about, experience and perceive a topic (Flick, 2004). Since the aim of the study was to discover and describe the perceptions of PWID regarding the use of mobile technology applied to the reduction of harm associated with drug use, focus groups were considered a more appropriate strategy than individualized approaches (Quintana & Montgomey, 2006). This type of design has been used successfully in analyzing mobile applications with people in situations of extreme social exclusion (Sheoran et al., 2016) and is recommended in the study of communication media, including ICTs (Morgan & Krueger, 1989).

Participants

Fifty-one PWID participated in five focus groups which took place between February and March 2019. Of the 51

participants, 84.6% were men with an average age of 36.7 years (SD = 7.5), with an age range from 28 to 51. People born in Spain made up 75% of the sample, with the rest being immigrants, of which 9 (17.3% of the total) were from the Maghreb. All participants knew how to read and write, but 65% said they had no higher or primary education. Those experiencing homelessness (living in designated shelters for the homeless, in squats or on the street, intermittently staying overnight in institutions) made up 41.4%. The main drugs injected were cocaine (44.2%), heroin (34.7%) and speedball (21.1%). The sociodemographic data of each focus group can be consulted in Table 1.

Participants were recruited between January and February 2019 in five places frequented by PWID to use drugs and which were known to the open environment intervention teams: a habitual drug use area on the outskirts of the city of Girona with an NEP in a primary health care center, two treatment centers, a mobile harm reduction service and a care center for the homeless. One focus group emerged from each context. The research team and a group of university students, all involved in the project of creating and developing the app, went to these places to ask participants whether they would be willing to participate in the focus groups.

Cumulative, sequential (to achieve discourse saturation) and discretionary sampling was performed among people whom we considered to be best able to explain the experience of using the application (Rodríguez, Gil & Garda, 1996), in other words, it was non-probabilistic convenience sampling. Participants were selected on the basis of the following inclusion criteria: i) having used the application during the pilot test; ii) being users of legal age, iii) being active drug users; iv) being in possession of a smartphone; and v) agreeing voluntarily to participate in the focus groups.

Two researchers with training in psychology and psychopedagogy, one specialist in qualitative research and implementing focus groups and another in addictions and harm reduction conducted the five focus groups and recorded the information. Two experts in qualitative methodology and one specialist in harm reduction and eHealth carried out the data analysis.

The three specialists in qualitative research were not connected to the specialized harm reduction intervention. Their main task was to ensure a solid structure and provide a guarantee of quality for the process of research design and the recording and analysis of data. The two specialists in harm and addiction reduction had a previous relationship with the participants as professionals in the reduction of harm associated with drug use, which made recruitment and retention of participants possible. The researchers co-supervised and inter-supervised the process in the dynamics of group development and the interpretation of results in a continuous way to generate a transparent and objective process in the coding, expression of topics and interpretation of results.

Procedure

Sequential description of the PixApp project development phases

The technical and community development of the application called *PixApp* is part of a project to improve harm reduction care at the *l'Institut d'Assistència Sanitària*, a public unit providing mental health and addiction services in the province of Girona. *PixApp* consists of a free and non-profit application in the form of a web app, available in three languages (Spanish, Catalan and English), which includes the NEP points in the area (community pharmacies, basic health centers, local clinics, hospitals, specific drug addiction centers and harm reduction centers). The user can choose the radius in kilometers within which the available NEPs will be shown as well as information relevant to each one, such as opening hours, addresses, telephone num-

Table 1. *Characteristics of the focus groups.*

Group code	Participants n (%)	Sex, n (%)		Origin, n (%)		Educational level n (%)			Own or family home	Residential exclusion	Age M (SD), Range	Main Injected Consumptionn (%)		
		Male	Female	Spanish	Immigrant	Primary or without schooling	Secondary or vocational training	Tertiary				Heroin	Cocaine	Speedball
FG1	8 (15.4)	7 (13.5)	1 (1.9)	7 (14.3)	1 (1.9)	6 (11.4)	1 (1.9)	1 (1.9)	6 (11.5)	2 (3.8)	39.9 (6.3), 30-47	3 (5.8)	4 (7.7)	1 (1.9)
FG2	12 (24.1)	10 (19.2)	2 (3.8)	8 (15.5)	4 (7.5)	8 (15.5)	4 (7.7)	0 (0)	9 (18.3)	3 (5.9)	33.2 (4.8), 28-40	6 (11.6)	4 (7.7)	2 (3.8)
FG3	11 (21.6)	8 (15.4)	3 (5.9)	9 (17.3)	2 (3.8)	7 (14.3)	4 (7.7)	0 (0)	6 (11.5)	5 (9.6)	37.1 (7.7), 25.51	3 (5.8)	6 (11.5)	2 (3.8)
FG4	9 (17.3)	9 (17.3)	0 (0)	6 (12.4)	3 (5.9)	5 (9.5)	3 (5.9)	1 (1.9)	0 (0)	9 (18.3)	40.6 (2.8), 36-45	2 (3.8)	4 (7.7)	3 (5.8)
FG5	11 (21.6)	10 (19.2)	2 (3.8)	8 (15.5)	3 (5.9)	7 (14.3)	3 (5.9)	1 (1.9)	9 (17.3)	2 (3.8)	37.4 (7.4), 26-45	4 (7.7)	5 (9.6)	3 (5.8)
Total	52 (100)	44 (84.6)	8 (15.4)	39 (75)	13 (25)	33 (65)	15 (29.1)	3 (5.9)	31 (58.6)	21 (41.4)	36.7 (7.5), 28-51	18 (34.7)	23 (44.2)	11 (21.1)

bers and a map linked to Google Maps®. After the initial download, the application does not require Internet access (works off-line). In addition, users can leave comments on their experience of using the application and the NEP. Figure 1 shows the application interface.

The first phase of the project was to review the scientific literature on the use of ICTs (Calvo, Carbonell & Johnsen, 2019) and online social networks (Calvo & Carbonell, 2019) by people at risk of or experiencing social exclusion, including PWID. These reviews indicate the great potential and low risk involved in the implementation of eHealth and mHealth instruments in socially vulnerable groups with mental health problems and/or addictions. In a second phase and as a feasibility study during 2016, we surveyed the use of ICTs, Internet and smartphones by PWID on the ground and found that the prevalence, frequency and motivations of use of people in situations or at risk of extreme social exclusion and PWID was similar to those of the general population (Calvo, Carbonell, Turró & Giralt, 2018). During the months of March to October 2017, the application was designed in the web app format, downloadable to the smartphone's desktop from any browser. The web app format was chosen precisely because of its technical versatility and ease of updating. Its first version was subjected to four usability tests, carried out by 45 professionals specialized in addictions, mental health and other community health services and 16 users between January and March 2018. During the usability tests, the participants

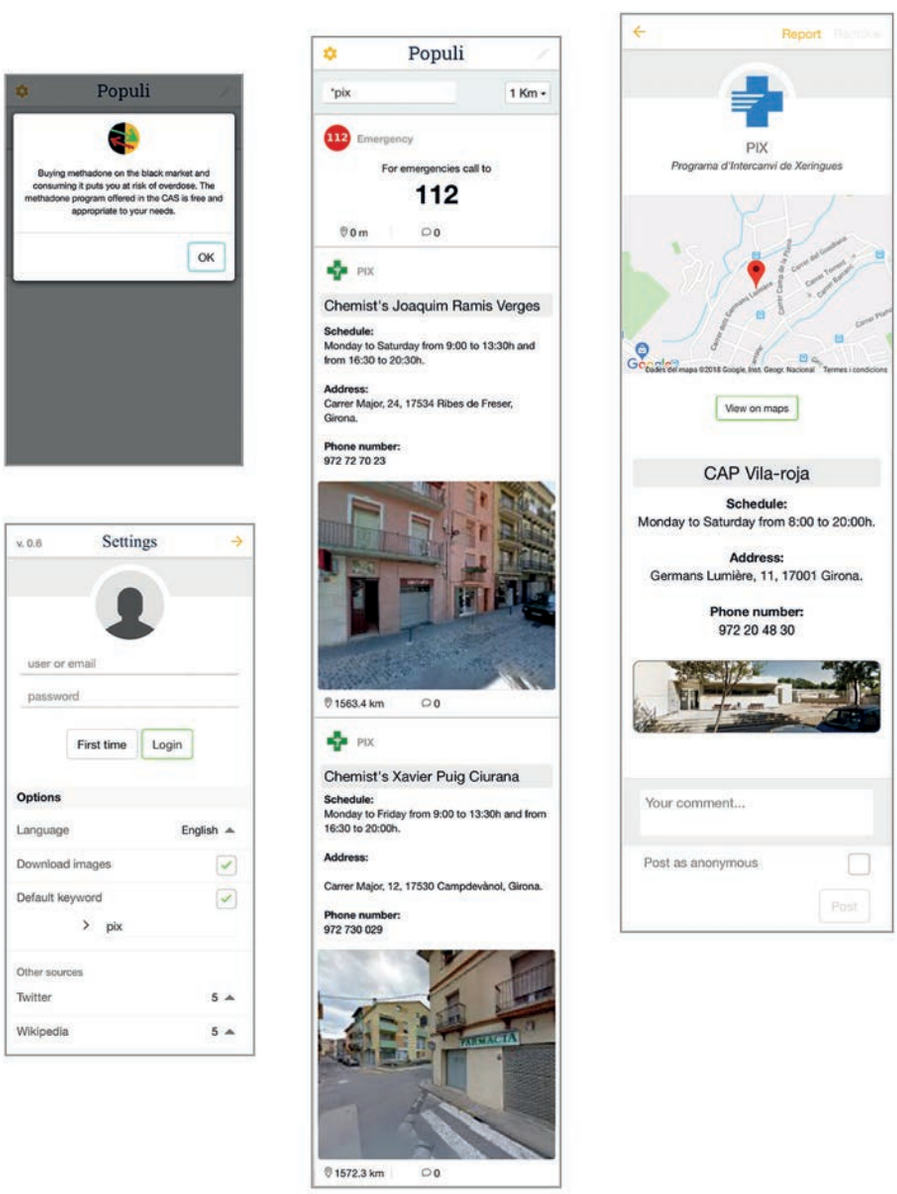

Figure 1. Final interface of the application in its English version. From left to right: First column: Example of health tips and settings screen. Second column: Main interface. Third column: Information regarding a needle exchange point.

tried the app and made suggestions for improvement. Changes were made as a result of these proposals: i) the two columns of the main interface were removed because users considered it to be too dense; ii) the app's random health tips appeared on the main interface in the first version and in a pop-up window in the second version; and iii) the visual map information was prioritized to geolocate position with respect to the NEP point and the relevant written information (schedules, telephone, address). The usability testing process can be consulted in its entirety in the earlier study by Calvo, Carbonell and Mundet (2020).

The application was piloted from September 2018 to February 2019. During these six months, the PWID were able to test it on the ground and then finally participate in the focus groups, where their experiences were assessed. To carry out this test, a team of voluntary social education undergraduates who took part in a training course for this purpose were present in person at the local NEPs. The selection of NEP points was based on the level of demand for injection materials. The eight NEP points selected included the Vila-Roja Primary Care Center in the city of Girona, the point which distributed the most injection materials in Catalonia in 2017 (Calvo et al., 2020), and a specific center for care of the homeless. The volunteers informed the PWID about the existence of the app, advised on how to download and use it, and invited them to use it. During the pilot test, the application was downloaded to 97 mobile devices, producing 297 hits. The estimated total number of PWID in this territory is 300 people.

The researchers asked potential candidates about participating in the focus groups for analysis of the app's trial period. The PWID who used these services and tried the app were offered participation in the groups. Once a number was reached which was considered sufficient to run the group, taking into account the drop-out risk, groups of 15 people from five different centers were offered the opportunity to participate. Of the 75 PWID thus approached, 51 (68%) finally took part.

The 23 PWID who did not want to participate in the focus groups argued that they were not in a position to do so at the time set for the group, or did not agree or had other commitments. It was agreed that there was no profile which could provide information on the type of PWID who did not participate in the groups or their reasons for not doing so, their relationship with the proposal or the project, nor with respect to the type of center. Figure 2 shows the sequence of creation, development and assessment study of the *PixApp* application.

Data Collection

The focus groups were created using a convenience criterion. Participants were asked at the beginning to provide in writing and anonymously their age, sex and the main drug they injected. The rest of the sociodemographic data (level of education, housing situation, origin) was drawn from the databases of the centers.

During the process, there were no circumstances leading us to believe that the data collection strategies needed to be modified, given that we considered the information available was of sufficient quality to answer the research questions.

Participants were informed at the start of each focus group of the approximate duration and that their collaboration would be very useful for the application, the area and the program and, in general terms, for the medical and scientific community. All participants expressed their willingness to collaborate with the team of researchers.

The focus group sessions lasted between 45 and 70 minutes, at an average of 58 minutes. The intention was to let conversation and information flow naturally among the participants. The following opening statement was used: *All of you have voluntarily participated in the pilot test of the needle exchange program application. In this group, we would like to find out what you think about this app in everyday use; what you liked most about what the app provides; what you liked least and doesn't contribute anything in your opinion, or what should be improved. You can speak freely and say whatever you think. It's important that you speak honestly so that our team can evaluate the work they have done and improve it if necessary. I would like to thank you once again for your efforts here and remind you that your opinion is very valuable for the improvement of the app and the NEP program in general.*

After this introduction, the researchers remained silent in an attempt to prompt participants to start talking. If this did not happen, two open-ended questions were asked: i) What positive things would you highlight about the application and its everyday use? and ii) What negative things would you highlight about the application which could be improved to meet your everyday needs? In order to refocus conversations which were not going anywhere, a brief synthesis was made of what had been said so far, and participants were then invited to talk about a subject that had been left open or asked if they wanted to expand on any question that had been dealt with superficially. The sessions closed with a prompt/closing to thank the participants for their attendance and collaboration.

Since the start of usability testing with PWID, researchers have reflected on all phases of the project (De la Cuesta-Benjumea, 2011), especially regarding data collection, the formulation of introductions and closings, and the questions that were being asked during its execution. For example, the information extracted from the first focus group was examined by the members of the research team, who concluded that the protocol was suitable, did not need to be modified, and ensured that the study could be implemented without the need for contributions beyond those already described to motivate the participants to talk.

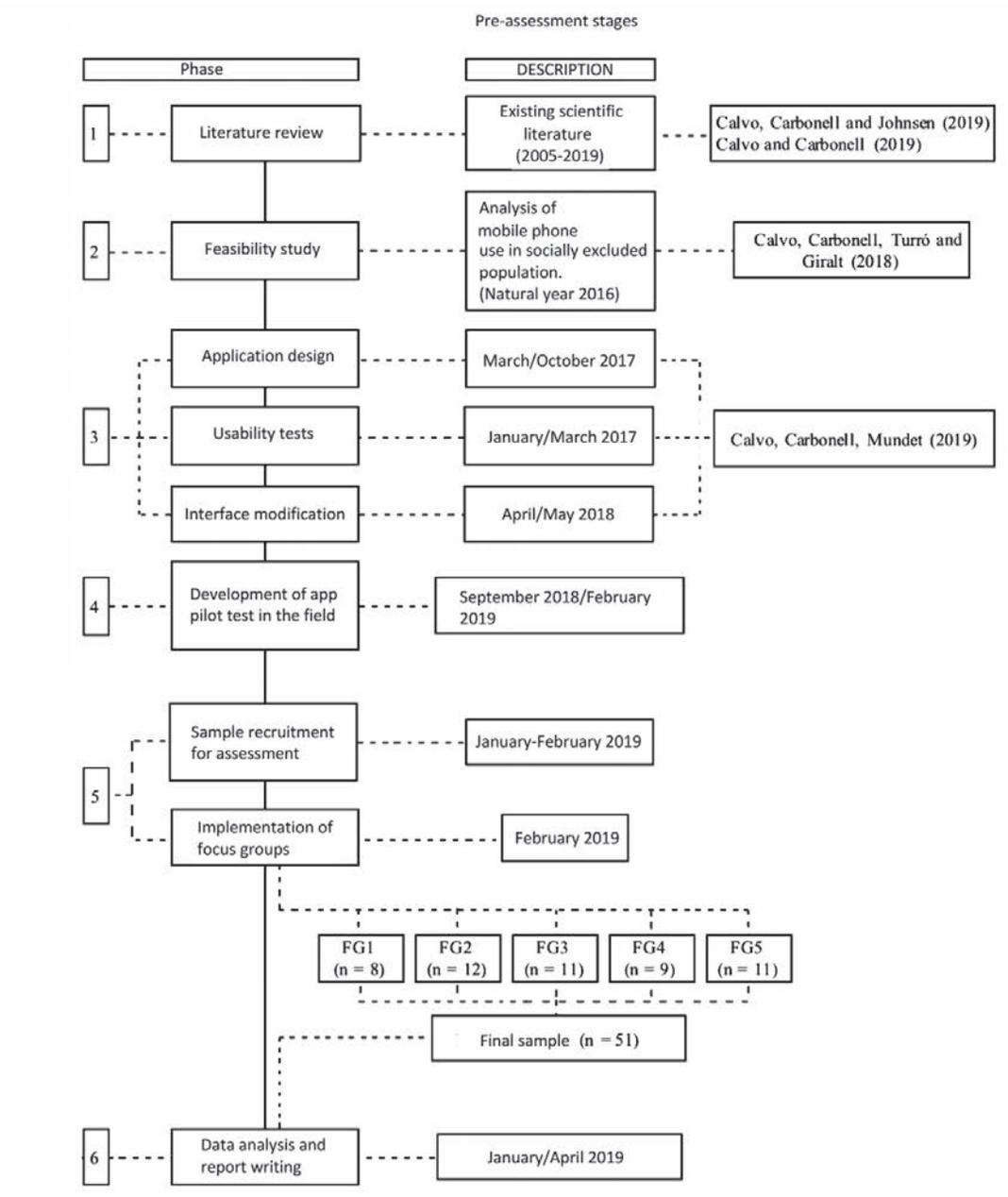

Figure 2. Flowchart of the study phases.

The focus group sessions were recorded in audio format. Once completed, they were transcribed in full. Subsequently, the transcripts were imported into the Atlas Ti program (version 7) for analysis, after ensuring that the computer program was suitable for the chosen design (Hwang, 2007).

Analysis

Analysis Strategies

The qualitative study with a descriptive focus was carried out based on thematic content analysis. The thematic analysis made it possible to identify, organize and analyze patterns (themes) in a detailed manner thanks to the reading and rereading of the information by the research team (Braun & Clarke, 2006). This method led to some cross references being identified between subjects, making it possible to compare them with the rest of the units of analysis; thus, the list of codes and subjects was established gradually until researchers reached a final agreement (Alhojailan, 2012). Open, axial and selective coding techniques were used on the data (Strauss & Corbin, 1990), which was categorized by identifying text fragments and assigning a code (abbreviation of a thematic idea) to each one (Gibbs, 2007).

Two of the five themes were previously chosen by the researchers and were introduced with questions regarding the app's benefits and aspects for improvement. Once the

data was analyzed and after the data reduction process, three further codes (fifteen subcodes in total) were agreed regarding usability, user experience, benefits and aspects for improvement and perception of the NEP; each of these codes corresponded to a theme and thus the results of the study were organized. See Table 2.

Four researchers worked autonomously to establish codes and subcodes, sharing their decisions at different stages and reaching a final consensus. Subsequently, the codes were also analyzed independently and then in teams in order to optimize the reliability of the process (Saldaña, 2013). In this way, any researcher-bias effect was limited. In addition, seven meetings, both face-to-face and virtual, were held to homogenize the analysis and contribute to the quality and thoroughness of the entire process. A fifth person supervised the investigation externally, carrying out a cross-sectional audit of the process to guarantee transparency, objectivity and to encourage consensus on the units of analysis.

The transcribed fragments included in the results section use square brackets and italics for clarification given the widespread use of slang by the participants. No significant contradictions or discrepancies were found that could not be resolved in the analysis process.

This research was approved by the Research Ethics Committee CEI-Girona, code XSO_2017, on June 7, 2017. Participants were informed verbally and in writing about the objectives of the study and its voluntary nature, and they received an information sheet and signed informed consent. At the end of their participation, they were remunerated with 15 Euros. This manuscript took into account American Psychological Association criteria for the preparation of qualitative research (Levitt et al., 2018). The article was written following the research report model of Fernández, Dema and Fontani (2019).

Results

Part one: How did the participants use the application?

Most participants came into contact with the application in the usability tests before or during the pilot test, aided by project volunteers who provided information and helped them download it to their devices. The sequence below with a group of men and women aged between 30 and 47 shows how they found out about the application and started using it.

> Researcher: How did you start using the application?
>
> User 1, 33 years of age: When those girls [*volunteers*] showed it to me. I went to look for [*injection*] material at outpatients and met them at the door. They gave me the information.
>
> User 2, 38: They showed me how to download and use it. I was a bit surprised at first. I showed it to my girlfriend as soon as I got home.
>
> User 1, 33: I also showed it to my partner. She has a problem with this [*mimics injecting herself in the arm*], too.
>
> User 1, 35: I didn't pay much attention at first, but one day I was bored and started to play with it. I was pretty amazed because I'd never seen an app like that before and immediately showed it to my buddies.
>
> (FG1, Men and women aged 30 to 47).

As described in the Procedure section, a group of volunteers at street level in the most active NEP points of the area showed how to download the application. User 2 and

Table 2. *Code Classification.*

Codes	Subcodes
Type of app use[1]	Priority use Reasons for use Frequency
Benefits of the app regarding the NEP [2]	Stigma reduction Improves knowledge of NEP points Facilitates anonymity Improves planning
Aspects of the app that could be improved	Downloading Excessive pop-ups
Usability and user experience	Clear interface Easy and intuitive Health tips Participation
General perceptions of the needle exchange program	Normalization Belief in professionals' change of perception

Note. [1]Application. [2]Needle Exchange Program.

user 3 became interested by what these volunteers were doing, and this curiosity motivated them to start using it. As we have seen, these participants informed family and friends about their first contacts with the app, generating peer-to-peer information transfer, which is greatly used in harm reduction. Beyond the initial surprise generated by an application informing users about NEP points, the following fragment illustrates how the use of the app changes from satisfying mere curiosity to responding to a need.

User 1, 37: The app was just there ... on the screen ... The truth is that I didn't use it after looking at it the first day. I always go to the same place for needles.

User 2, 41: Same with me. I always go to the same place.

User 3, 39: Yes, but one day I got there and it was closed. It had just closed and I remembered the app. I got online and there was a pharmacy right nearby. Really opened my eyes a bit. I thought: "- so easy -".

User 4, 40: The same happened to me. I looked at the app to see if there were any [*NEP points*] in my town and there were. This way I don't have to be going here and there [*to another municipality*] to get needles.

Researcher: Do I understand correctly that the main use has been when you couldn't find needles at the main point?

User 3, 39: Yes.

User 4, 40: Yes. That's been very important. It broadens your horizons.

User 3, 39: Yes, another time I would've used a needle that I had at home. But there was a pharmacy very close by, and I didn't know about it, and in the end I went down. I think it was new in this ... in this exchange business.

(FG4, men aged 36 to 45)

This fragment shows how the researcher focused the users to clarify if they were referring to an informative use of the application when the NEP point they normally used did not meet their needs. User 3's final comment is especially relevant since it indicates that on finding his usual NEP point closed, he used the app and discovered NEP points he had not known about.

Below is a fragment about the informative use of the application and its frequency of use.

User 1, 40: Having the opening hours [*of the NEP points*] right there is great.

User 2, 32: I go up [*to use*] once a week and I'm not sure when they [*the usual NEP point*] close. I checked on the app and it's very easy. It takes me longer on Google.

User 1, 40: Thing is, I never bother to ask at outpatients when they close.

User 3, 35: I forget.

User 4, 28: I don't like it. All the waiting.

User 5, 39: Sometimes there are loads of people queuing up and there's no way you're going to wait there just to ask for opening hours cold turkey [*with withdrawal syndrome*] or high [*intoxicated*].

User 1, 40: Also, the schedules change all the time.

User 2, 32: I was home one night, already quiet, I opened the app and saw that they closed at three [*15h*] and I thought that gives me time.

(FG2, men and women from 28 to 40 years old).

From this fragment we can extract different elements. First, it shows to the need for users to have the schedules of the NEP centers at hand and regularly updated. They also commented on the difficulties of finding this information with an ordinary search engine, and how the application had facilitated this task. Moreover, they expressed their problems with asking for opening times at the primary care center NEP because they had to wait a long time to ask (from the comment we can surmise that this is due to the sheer numbers attending the center) and because of suffering withdrawal symptoms or intoxication.

Part two: Benefits of the application under the Needle Exchange Program

The narratives of the PWID described their perception of the benefits provided by the application. First, the participants emphasized that they saw the application as part of the normalization of health services towards them in terms of using ICTs. The following fragments describe how they perceived the benefits related to the normalization associated with the use of the mobile phone:

Researcher: What benefits does the application have? (...) What is positive?

User 1, 51: The fact that someone actually invented it. That they had the idea [*All laugh*].

User 1, 33: It's true, nobody had thought of us before.

User 2, 38: Because they must think we don't use mobiles because we do drugs.

User 1, 33: That's ... how do you say? ... prejudice. We are normal people with a very big problem.

User 3, 26: They see you lying there, surviving and probably think: They don't use mobiles.

User 2, 25: They probably think we don't even know what the Internet is [*All laugh*].

User 4, 36: Right, of course, the fact that I shoot drugs and have this problem doesn't mean I can't have a mobile like everyone else.

(FG3, men and women aged 25 to 51)

As can be seen in the response of user 1, the first benefit mentioned by the participants was that the design of the application saw PWID as normal users of technology. This element modifies a fairly generalized discourse by health professionals regarding the supposed under-use of technology by people in situations or at risk of social exclusion and PWID, a form of discrimination PWID said they felt. Below, we see an example of a homeless person:

User 1, 42: I live in the street and more than once somebody has looked at me disapprovingly for using a mobile. It seems that by their look they're saying you have no right to have a phone just because you're on the street (...) But the thing is, it [*the phone*] solves many problems: you can contact the family, for free, with WhatsApp over WiFi in some place; you can read the news ... books ... you pass the time ... and the day goes by better (...) It's easier if anybody needs to find me (...) It's always the last thing I sell when I have more problems and it's the first thing I buy back as soon I've got money. This application suits my reality and is useful.

(FG1, men and women aged 30 to 47)

Another improvement perceived by the participants was that the app extended their knowledge of the NEP points in the area. Most participants reported that they got the injection material from one or two usual points, close to where they buy substances or their home. They described how they often traveled specific routes depending on where they could obtain a needle and in relation to the opening times of each NEP point. Having more information also changed the planning of the using process:

User 1, 32: The other day we were (...) and I together [*refers to the person sitting beside him/her*] and I said, why don't you look at the app to see if there's anywhere to grab some needles round here?

User 2, 26: It's true, really. We'd already had some ... but we needed more [*refers to the injection paraphernalia*].

User 1, 32: So we think hey, we do not need to go up [*to the usual NEP point*], they've also got some here. And we went to ask at the pharmacy, and they gave us some and that was it.

(…)

User 1, 33: I freaked out at the number of places that hand out needles.

User 3, 42: I also freaked out that there were so many sites that did exchanges. I didn't know that many.

(FG5, men and women aged 26 to 45).

User 1, 27: The best thing is it helps me to know where else I can get needles. Nobody had told me about this.

User 2, 42: Yes, me neither.

User 3, 39: There's usually no information about that at the PTC [*Public Treatment Center*].

User 1, 25: Actually, there *is* information. There was a paper with the needle exchange points ... I was given it by (...) [*refers to a reference professional*], but I lost it right away.

User 1, 27: I had a paper with the exchange points, but I remember once I went to a pharmacy and they told me that they no longer had any. They didn't do needle exchange there.

User 2, 33: Sure, with the application this doesn't happen: you open it up and there they are [*the NEP points*].

User 2, 42: And it also tells you if it's open at that time or not.

User 4, 33: And it tells you the ones closest to you, so you don't have to worry yourself stupid or walk miles.

User 5, 51: That's also important ... you save yourself a long walk.

(FG3, men and women aged 25 to 51).

As we can see in the comment by user 5, he or she thought the treatment centers did not provide information about NEP points. Participants 1 and 2 indicated that this perception was not correct because they were provided with the leaflets that the organization updates and prints periodically. The final comment by user 1 indicates that on one occasion, he was able to consult this information on paper, and that when he went to the place in question, it was no longer an NEP point. Therefore, the participants perceived it to be positive to have a tool with updated information on the NEP points. The comment of user 6 and the final comment of user 3 reinforce the importance of the geolocation of these services since, if the PWID does not find injection material in a particular place, the experience will make them unlikely to return.

Third part: Aspects of the application which could be improved

Participants were urged to mention the elements of the application which needed improving. In practically all groups, and in general, there was a feeling that application was not easy to download. As described above, this application is not native but rather a web app. After accessing it the first time through a browser, it must be anchored to the smartphone desktop using a shortcut. Once this is

done, the application works like a native application, but the download process is very different from that of native applications for IOS or Android devices. In addition, for optimal functioning of the application, the phone's GPS must be permitted to geolocate the points of the NEP, otherwise the application does not work.

Researcher: What aspects of the app do you think are improvable?

User 1, 40: What things don't we like?

Researcher: Yes. And what things can make it difficult to use, do you think they can be changed to make it better, and so on.

User 1, 40: Downloading it.

User 2, 42: Downloading it.

User 1, 40: That's it.

User 3, 45: It's difficult to follow all the instructions.

User 4, 41: It messes you around a lot. It's one thing after another.

User 2, 42: Wouldn't it be easier if you could download it like any other app?

User 5, 26: Now that I know how to download it, you want to go and change the system [*All laugh*].

User 4, 41: It could be easier, really.

User 1, 40: I tried to teach someone ... to download it ... and the truth is I wasn't able to follow the steps.

User 2, 42: I ended up looking for it in the app store ... but it wasn't there ...

User 1, 40: That's right. That's something that must be changed because if it is difficult to download and in the end the gang [*people*] can't be bothered and in the end they don't use it.

(FG5, men and women aged 26 to 45).

The first response of user 1 comes across with noticeable force, which, added to the final comment of user 2 explaining how he or she had tried to find the application in a virtual application platform for mobiles, indicates the confusion around the download process of the web app format. Participants agreed that the application had to be simplified.

A second aspect for improvement was the excess information appearing in pop-up windows with health tips. The application offers a health tip every time the user opens the app. This advice is random from among more than 25 tips, such as "*Always use clean needles when you use*". Each time the app users do a search, the pop-up window appears with another tip. The participants considered this information to be excessive, as reflected in the following fragment of FG2:

User 1, 35: What bothers me a lot is the automatic screen.

Professional: The health tip?

User 1, 35: Well, it's not that it always bothers me. It's annoying how often it pops up.

User 1, 40: The one that advises you ... stuff.

User 2, 32: The idea is good, but once you've opened it twice you're already fed up with it.

User 2, 37: It should be dialed down a bit.

User 3, 39: One tip each time would be enough.

User 1, 40: Thing is, if not, in the end it's ... how do you say? ... it doesn't have the effect ... the effect it should.

(FG2, men and women aged from 28 to 40).

User 1's final comment emphasizes that too much information can have a dissuasive effect, and that too many health tips in the form of pop-up windows are counterproductive. There were no notable opinions against this, and the participants considered that a single tip when opening the application would be sufficient.

Fourth part: Concrete aspects of usability and user experience

The participants considered that the usability of the application in its real development context was simple and adequate. With the exception of the aspects previously mentioned, they did not consider that there was any difficulty in using the interface, and it was considered to be very intuitive to use. In some cases, participants mentioned how they had to familiarize themselves with the application to make the search for NEP points easier when they needed injection material, but felt this to be no different to the effort required to familiarize themselves with other mobile applications aimed at the general population.

User 1, 39: It's easy.

User 2, 42: Super easy.

User 3: Man, it took me a while to figure out how it worked, really.

User 1, 39: But that's normal, dude! You can't enter and directly be a pro ... you have to study it a little! [*Laughs*]

User 3, 47: It's just, I thought you were pretty handy with all this.

User 2, 42: No, no ... thing is that it is easy once you spend a minute to see what's going on and how it's used. Then it's done in a flash [*quick*].

(FG1, Men and women aged from 30 to 47).

Furthermore, the participants felt that the application could be a tool to communicate with the health services. The application allows the user to leave text comments about their experiences in obtaining injection paraphernalia. Participants considered that this feature of the applica-

tion offered the potential to promote asynchronous communication with the health services, especially in terms of their needs as active drug users.

User 1, 42: Sometimes, you just don't want to talk to anyone.

User 1, 38: That's true.

User 1, 42: [*In the centers*] They stop you to talk, really, (...) many times they stop you but you just don't want to talk. You say – oh no, not now! - but the possibility of having a way to contact them other than the usual appointment would go down well. Sometimes you just feel wrecked [*depressed*] as you're coming down [*fragile*] and the mobile is the only thing you have. Sometimes the person next to you is worse than you ... I don't know ... it's two o'clock in the morning ... you're all high [*intoxicated*] ... who are you going to talk to ... this thing about having another way [*to contact*] is interesting. Sometimes you try it with the family ... but they're fed up with you.

(…)

User 2, 32: Come on. Let's be honest. We are not exactly innocent lambs [*All laugh*] (...). Sometimes we also go too far. This way maybe they [*the professionals*] can also use the app to tell us a thing or two.

(FG5, men and women aged from 26 to 45).

As we saw in the previous excerpt, user 1 (female) identifies and describes the need to be able to access an alternative communication channel. This could increase the range of availability of health services beyond the formal arrangement of face-to-face appointments. This is particularly relevant at the times when the user feels a greater need to communicate, in this case because he or she is suffering the negative effects of active substance use at a time when the normal treatment service is closed.

Moreover, user 3 proposes that the application could be used as a contact tool by the services themselves, something very important given the difficulty in contacting PWID who are less motivated to communicate with the services.

Part Five: General perceptions of the participants regarding the needle exchange program

Finally, we asked participants how they felt about the use of the application within the framework of the NEP and how the use of technology could influence the development of a program which had been running for several decades. Participants stressed that the use of the application could contribute to reducing social stigma as people on the margins of society or to other aspects not related to drug use or its environment. Users described situations in which they felt they were being judged because they had mobile phone devices and how this is seen as a problem for the development of specific eHealth interventions, as the following extract illustrates:

User 1, 45: Well, I want to thank you for your initiative.

User 2, 36: It's great that you called us in to give our opinion ... I don't want to look like a toady [*flatterer*] [*Laughs*].

User 1, 45: (...) But seriously, nobody remembers us ... that we also have a phone and a computer.

User 2, 36: People think that because I'm a junkie, I don't use the Internet, but I bet I have more followers than them on Insta [*Instagram*].

User 3, 41: I remember (...) [*refers to a professional*] who was very surprised that I had an IPhone. It was old but he looked at me ... like judging me ... I felt judged ... hey, I didn't steal it! ... I wanted to tell him. In the end I left the place feeling really down.

User 4, 40: Of course, if many people think like that, that we are all criminals, how are they going to create apps for us ...

User 5, 41: For me, it makes me feel more normal. This [*mimics injecting*] is a disease, right? We also have the right to use this [*pick up the mobile phone*].

(FG4, men aged from 36 to 45)

In his second comment, user 2 highlights the use of the Internet and social networks by PWID. This comment asserts their active use of social networks and argues that despite the stigma weighing on them as injection drug users, they may be much more active on social networks than people who do not have this problem; it also shows how important the use of these social networks is for them and, in a way, the need to accept this normalized use of ICTs despite their addiction. In his last comment, user 3 recounts a situation in which he felt judged for using the mobile and the implied accusation of criminal activity merely by possessing this device. In both cases, the participants considered that the application helped to normalize their situation through the use of technology, to reduce the associated stigma and to see them as actively participating in technological development as eHealth users.

At another level, other users considered that the way the professionals felt about how PWID were using the technology helped to reduce barriers and contributed to generating empathy. That is, the fact that the professionals might be interested in the use of specific health applications such as this was an indicator of how their perceptions were changing regarding people who injected, and the interest in technology of the professionals was a new common in-

terest with the potential to generate empathy. Take the following example:

> User 1, 40: Well, I was in a pharmacy once and [*the clerk*] was very interested in the application ... he already knew it and we talked ... he behaved fine ... I don't know ... he was interested. It seemed more like talking to someone on equal terms (...). He stood there with me ... you know ... side by side ... really ... he stood next to me and it seemed that he was more interested than me ... he was a bit of a *freak* [*Laughs*] ... no ... I mean ... but *geeky* like with the technology, you know ... he liked the idea, you know.
>
> (…)
>
> User 2, 41: Well, I think this will make looking for a needle more normal. It's like when you're looking for a restaurant. You don't have to give so many explanations.
>
> User 1: We should let our opinions be heard more. This would make our voice ... well, we're sick ... to be more widely heard ... not as junkies ... first as people.
>
> User 3, 45: Giving our opinion is fucking great [*all laugh*]. Well it's true ... let's be honest, that's how it is.
>
> User 4, 37: That's it, if anyone looks at me disapprovingly, this is what I do [*the participant makes the thumbs-down sign, the typical "don't like" sign on social networks*], and fuck you very much [*all laugh*].
>
> User 3, 45: That would help to get them to notice us more, right? We are also customers of a service. It's like going to a restaurant and the waiter treats you well so that you don't put bad feedback on the Internet. At least he treats you well for that reason.
>
> (FG4, men aged from 36 to 45)

It can be seen that in the conversation the participants saw themselves as customers of health services and credited the application with the potential to be used as a communication channel through which they could give their opinion as users of these services, as active participants in their own health with the power to give feedback on the service received. Their discourse also highlighted that technology and the application can contribute to this normalization.

Discussion

This is the first study of which we are aware to pilot a mobile application for a needle exchange program. A qualitative descriptive thematic content analysis was employed, involving five focus groups with 51 people who inject drugs, had a mobile phone and had access to the application during the six months of field testing. The main findings indicated widespread acceptance of the *PixApp* application, which was considered simple and useful, especially when the normal injection material exchange points were closed or needles were not available. Participants considered that the application contributed to reducing the stigma of people who inject, increased knowledge of the area's NEPs, ensured anonymity, improved planning to obtain injection paraphernalia and could contribute to the normalization of people who inject drugs as users of eHealth technology. Among the aspects to be improved, the participants highlighted the excessive appearance of health tips in pop-up windows and difficulties in downloading. Participants reported that the application had potential as an alternative channel for communication with health services, especially at those times when users felt the greatest need to communicate and when the services could not meet their needs for structural reasons.

In Spain, the scientific evidence regarding the use of ICTs by people who inject drugs and the possibilities of implementing eHealth or mHealth interventions in this population and context is scarce but promising (Calvo & Carbonell, 2018, 2019). At the international level, educational eHealth interventions have proven effective in preventing HIV infection and Hepatitis-C by increasing knowledge about transmission channels, modifying erroneous beliefs about infection mechanisms and reducing risky sexual behaviors (Noar & Willoughby, 2012). Specific applications for harm reduction have demonstrated the potential for reducing the harmful effects of alcohol consumption (Milward, Deluca, Drummond & Kimergård, 2018) and to prevent the risk of overdosing (Baldacchino et al., 2016).

Involving the users for whom an eHealth or mHealth tool is designed to meet their needs is strongly recommended because it provides insights into the functionality of the tool in a real context, with direct user experience (Law & van Schaik, 2010) and offers the possibility of modifying and adapting it in a bidirectional process of analysis and continuous improvement. In fact, the acceptance by the vulnerable population at risk or in a situation of social exclusion (Byrnes, 2016) depends largely on this since the penetration of ICTs in these populations requires a follow-up which goes beyond providing the technology and Internet access and must try to adjust to the socio-economic needs of those people to whom it is addressed, working with them prospectively and regularly to try to keep them connected (Kaba, 2018).

As they continued to use the web app, participants reported that the application contributed to improvements in their planning and played a part in the process/ritual of obtaining needles. Changing the patterns/rituals of

harmful consumption is, to a large extent, the focus of socio-educational interventions in harm reduction, the success of which depends on their acceptance by and usefulness for the recipients (Calvo, Ribugent & Pontsa, 2015). The anxiety associated with the craving to use a substance and withdrawal symptoms generates situations which those affected describe as desperate and which increase serious high-risk practices such as the shared use of injection material (Castaño-Pérez & Calderón-Vallejo, 2010). It seems clear that the more difficulties PWID have to access the injection material, the greater this risk becomes, since planning drug use (and the material needed to realize it) is potentially influenced by ritual, which in many cases can detract from protective behavior (Roth et al., 2015). An example of this, a frequent occurrence in daily clinical harm reduction practice, is when a person who injects drugs obtains the substance before the needle, arguing that the opposite "brings bad luck" or "awakens" the withdrawal syndrome (Calvo-García, Turró-Garriga & Giralt-Vázquez, 2014). If after obtaining the dose, the injection drug user cannot access a nearby NEP point, the risk of reusing a needle increases. PWID described how they would go to the usual NEP points, but if they were closed or had run out of material, access to updated information through the mobile phone was a potentially effective tool in modifying the process of acquiring material at the usual point and generated the feeling that it was possible to plan their access to needles better.

Thus, complete and up-to-date information regarding the area's NEPs and a suitable channel to make this information accessible to PWID are the basis for improving the coverage of injection material, something that the World Health Organization considers insufficient (OMS, 2016). The use of information leaflets is common but its effectiveness can be increased. Users said they were unaware of the existence of such information and mentioned the risk of losing forgetting it. NEP participating centers can drop out of and rejoin the program for various reasons, which means directories and databases have to be constantly updated. A delay in the transmission of updated information to the user is a risk factor whose impact could be reduced by virtual tools, through a channel with which the user is familiar, i.e., smartphone and internet. Participants considered that the application contributed to reducing the information gap between the health provider and the end user, in addition to including supplementary information considered appropriate by PWID, such as photographs, opening times, address and telephone, which facilitated contact with the service.

In addition, one of the application's functionalities is the possibility of giving health advice in the form of text messages such as pop-up windows every time the user navigates the interface. Health tips delivered on fixed or mobile devices have been proven to have great preventive potential (Mason, Ola, Zaharakis & Zhang, 2015). However, while it is true that the great accessibility of health services to recipients through ICTs is an advantage associated with the ubiquity of technology, an accompanying excess of indiscriminate preventive information which is not adapted to the cognitive capacity of the user can be counterproductive (Nation et al., 2003). Moreover, the web app cannot be installed as a native application, and this posed a considerable problem which was resolved thanks to the help of the volunteers. Providing guidance for users on the ground is important when the target population is in a situation or at risk of social exclusion (Byrnes, 2016). In fact, despite the many opportunities to reduce barriers to accessing health care through ICTs, continuous adaptation to the users' limits is required (McInnes, Li & Hogan, 2013). Given the lack of examples assessing applications for mobile devices aimed at PWID, the study by Sheoran et al. (2016), based on focus-groups, which assessed the development of a geolocation app for young homeless people, concluded that the application contributed to reducing barriers between users and health care providers by reducing the stigma associated with social exclusion and improving the perception of users regarding socio-health services.

Finally, the participants perceived the application as a technological tool which contributed to reducing their stigma. The main reason for this was that they felt the services could better understand their problem, thus normalizing them by appearing to the service providers as users of ICTs. Secondly, it allowed them to describe their experiences in the process of obtaining injection material. For PWID, seeking needles implies a relationship with various health agents who sometimes tend to be judgmental about the injector's behavior, contributing to their stigmatization and reducing the preventive capacity of needle exchange programs, with adverse results (Paquette, Syvertsen & Pollini, 2018). Participants said that the possibility of explaining this discrimination to those responsible for public health was protective and reduced the possibility of such stigmatization. This relationship which technologies enable for service users is no different in other areas where health care users are increasingly active in managing their own health and has the capacity to play a role in the processes of which they are active participants and, therefore, to contribute to optimizing resources and adapting to needs

(Armayones et al., 2015). Increasing PWID participation is important as well as necessary given the fact that it can contribute to social and community integration, which in turn presents proactive potential for reducing health care costs, detecting new needs more quickly, and improving care and research.

This study is not free of limitations. In the first place, limited sociodemographic and clinical information was obtained in a sample where participants and context were specific. For this reason and although it is not the aim of qualitative research to generalize results since it describes a particular context, situation and participants, this limitation must be taken into account and its results must not be generalized. Future lines of investigation are therefore recommended to continue researching the use of eHealth and mHealth by the population of drug injecting users, especially those in a situation or at risk of social exclusion. We also considered that this information was sufficient to describe the participating population, and prioritized the limited focus group time available to try to fulfill the objectives of the study in terms of describing the experience of the participants with the application. Secondly, the likelihood that participants would have responded with a certain degree of social desirability should be taken into account, although this effect was reduced by requesting their sincere opinions and generating a relaxed climate in the focus groups. Thirdly, the participants received financial compensation for their participation, which may have mediated their motivation to do so, although this type of reward is common in health studies with populations in situations of extreme social exclusion and injected drug use in order to facilitate sample recruitment and retention. Fourth, the impact of the application on the distribution of injection material has not been assessed. This fact points towards a future research path to analyze whether the use of the application has the capacity to produce quantitative changes in the number of injection kits distributed or in the geographical areas where NEP activity is concentrated. Moreover, it would have been useful to access other information sources, such as individual interviews, as a complement to the focus groups, but this was not possible due to problems of participant retention. In any case, we consider that the information obtained from the groups provided enough data to answer the research questions. A further limitation was the very limited number of women participating in the study; increasing this number is recommended so that gender can be included as a mediating variable. The gender perspective would have enabled the use of focus group dynamics to determine the possible relationships between different groups in the same way as with other differentiating characteristics, such as the comparison between people who did and did not use the application (e.g., there is no information available on people who did not use the application because, for example, they did not find it useful or did not like it), but the difficulties in accessing and retaining the sample made it impossible to access other subsamples. Finally, this study lacks the necessary information to assess the impact of the app on the coverage of NEPs in quantitative and qualitative terms, but it does guide us towards future research paths related to this question.

In conclusion, the application was considered to be a suitable mHealth tool for its purpose, which is to contribute to improving the access of people who inject drugs to injection material. Users perceived the application as an easy and accessible tool, with the capacity to contribute to more protective planning of drug use due to updated information regarding the exchange points. Excessive tips on prevention and the download process were considered aspects for improvement. Finally, the participants suggested that the application offers potential for reducing the stigma of users because it normalizes their use of technology like that of any other citizen and facilitates the possibility to interact with health care providers by giving feedback on their experiences in the process of obtaining injection paraphernalia.

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Conflict of interests

Fran Calvo is the creator and co-developer of the application referred to in the article, alongside the computer engineer José Núñez, with whom he is co-owner. The application arises from the needs detected in professional practice in a public service, the *Institut d'Assistència Sanitària* in Girona and is a non-profit program whose objective is to improve the access to injection material of people who

inject drugs. Xavier Carbonell, Mercè Rived and Cristina Giralt declare the absence of any conflict of interest.

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Opiate drug use in the city of Madrid: Associated health and sociodemographic factors

Consumo de fármacos opiáceos en la ciudad de Madrid: Factores sanitarios y sociodemográficos asociados

Eduardo J. Pedrero-Pérez*, Sara Morales-Alonso*, Blanca Álvarez-Crespo*, María Teresa Benítez-Robredo*.

* Unidad de Formación e Investigación. Departamento de Evaluación y Calidad. Madrid Salud. Ayuntamiento de Madrid.

Abstract

The use of opiate analgesics has led to a health and social emergency in the United States. In Spain, according to official data, the prescription of these drugs has risen dramatically in the last decade. This study explores the prevalence of the use of these drugs and the health and socio-demographic characteristics of their consumers in the city of Madrid. A telephone survey was carried on a stratified, randomised sample, asking about the use of these drugs and whether or not they were medically prescribed. The sample consisted of n=8,845 subjects aged between 15 and 98 years. Sixteen percent stated that they had used these drugs in the last year and 9.1% had taken them in the last two weeks. Consumption was more frequent among women, lower social class and lower level of education. Among the youngest group (15-29 years old) 12.5% had already used it. Those who use opioids report worse perceived health, lower quality of life, more mental health problems, more loneliness, more use of other psychoactive drugs, more frequent daily use of tobacco and less problematic consumption of alcohol. Ten percent of those who use them do so without a doctor's prescription. Combining these data with the prescription data offered by the Ministry of Health, it is necessary to pay attention to a problem that may become apparent in the coming years, and the adoption of urgent measures to tackle it before it brings the Spanish situation closer to that already well known in countries of our socio-political environment is advised.

Keywords: Opioids; addiction; health survey; mental health; psychopharmaceuticals.

Resumen

El consumo de analgésicos opiáceos ha provocado una situación de emergencia sanitaria y social en Estados Unidos. En España, según datos oficiales, la prescripción de estos fármacos ha experimentado un espectacular ascenso en la última década. Este estudio explora la prevalencia del uso de estos fármacos y las características sanitarias y sociodemográficas de sus consumidores en la ciudad de Madrid. Se realizó una encuesta telefónica aplicando un muestreo estratificado y aleatorizado, en la que se preguntó por el uso de estos fármacos y si fueron médicamente prescritos o no. La muestra estuvo compuesta por n= 8.845 sujetos de edades entre 15 y 98 años. Un 16,0% declara haber usado estos fármacos en el último año y un 9,1 los toma en las dos últimas semanas. El consumo es más frecuente en mujeres, clase social baja y menor nivel de estudios. El grupo más joven (15-29 años) ya lo usa en el 12,5%. Quienes usan opioides refieren peor salud percibida, menor calidad de vida, más problemas de salud mental, más soledad no deseada, más uso de otros psicofármacos, más frecuente uso diario de tabaco y menos consumo problemático de alcohol. Un 10% de quienes los usan lo hacen sin prescripción médica. Combinando estos datos con los de prescripción ofrecidos por el Ministerio de Sanidad, resulta necesario prestar atención a un problema que puede hacerse patente en los próximos años, aconsejando la adopción de medidas urgentes para atajarlo antes de que aproxime la situación española a la ya bien conocida en otros países.

Palabras clave: Opiáceos; adicción; encuesta de salud; salud mental; psicofármacos.

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Send correspondence to: Eduardo J. Pedrero Pérez.
Unidad de Formación e Investigación. Dpto. de Evaluación y Calidad. Madrid Salud. Ay. de Madrid. Av. del Mediterráneo 62. 28007 Madrid. España
E-mail: pedreropej@madrid.es / ejpedrero@yahoo.es

Introduction

Opiates, both prescribed and illegally obtained, have become a major health issue in recent years. The terms opiates and opioids are often used indistinctly, but while the former are natural derivatives, opioids are synthetic. Both are usually used for pain-related problems, although some, such as methadone, are also used to treat people with addiction.

Pain is defined as an unpleasant sensory or emotional experience resulting from actual or potential tissue damage. It is a major health problem and one of the main causes of medical consultation. Chronic pain is defined as pain that lasts longer than three months or longer than expected after the injury or underlying illness has healed or been cured (Merskey, 1986). The treatment of chronic pain includes both pharmacological and non-pharmacological approaches. Among the former are non-opioid analgesics, opioids and adjuvants (used to prevent or treat the side effects of opioids or enhance analgesia). Opioid drugs constitute a group of drugs characterized by having selective affinity for central and peripheral opioid receptors, inhibiting the transmission of nociceptive input and the perception of pain (Rosenquist, 2019). They are widely used for treatment of severe acute pain and moderate to severe chronic pain that does not respond to other treatments (Dowell, Haegerich & Chou, 2016).

The use of this type of drug entails a series of risks. A recent study (Gaspari et al., 2014) has revealed that the use of opioid substances impairs the activity of a specific protein necessary for the normal functioning of the reward centre of the brain. Since the reward centre of the brain has such a strong impact on analgesic responses, the authors argue that non-opioid medications would be more appropriate for the treatment of severe chronic pain. In addition, opioids lead to neuroadaptations which decrease the drug's analgesic action in the medium and long term, producing opposite effects, i.e., an increase in existing pain (opioid-induced hyperalgesia) and the facilitation of chronic pain development (Lavand'homme & Steyaert, 2017). Other studies list complications arising from opioid use for chronic non-cancer pain which should be taken into account (Els et al., 2017). For these reasons and because of the limited usefulness of opioids in the treatment of chronic pain, much less moderate or mild pain, their use beyond a hospital context is currently not recommended. (Ashburn & Fleisher, 2018).

The indiscriminate use of these drugs has generated a significant health problem in developed countries, for example the so-called opiate epidemic in the United States (USA) with more than 250,000 fatalities (Guardia Serecigni, 2018; Marshall, Bland, Hulla & Gatchel, 2019; Skolnick, 2018). This epidemic and all its consequences cannot be explained merely by the pharmacological properties of the substances involved, but are the result of very different psychosocial, cultural and economic circumstances which have not always been considered (Kolodny et al., 2015). For example, recent studies have found a positive correlation between pharmaceutical industry spending on the promotion of these opioid analgesics and the number of deaths in different areas of the country (Hadland, Cerdá, Li, Krieger & Marshall, 2018; Hadland, Rivera-Aguirre, Marshall & Cerdá, 2019).

Before 1997, morphine was practically the only third step opioid prescribed in Spain (94% of the total), but since the appearance of fentanyl in the Spanish pharmacopoeia, this drug has a spectacular rise in use. From 1997 to 2001, the prescription of opiates doubled in Madrid (Alonso Babarro, Varela Cerdeira & Aparicio Jabalquinto, 2003), and then tripled between 2004 and 2011 (Ruiz-López & Alonso-Babarro, 2019). In the last few years, the most prescribed opioid active ingredients in Spain for out-patient treatment of pain have been tramadol (62.2% of opioids), fentanyl (17.5%) and buprenorphine (6.9%), according to data obtained from prescription records of dispensed drugs kept by the Spanish Agency for Medicines and Health Products (Agencia Española del Medicamento & Productos Sanitarios, AEMPS, 2017). The recent AEMPS report (2019) verifies the constant growth of the use of this type of drug, with prescribed daily human doses (DHD) up 179% in 2017 from 2010 (Figure 1). As for fentanyl in particular, the increase since 2008 has been of 185%. The increase in the prescription and use of this drug has been exponential, so that, according to data from the Pain & Policy Studies Group of the University of Wisconsin, Spain rose from 15th in the fentanyl use rankings by volume in 2000 to 5th place in 2014 (Calabozo Freile, 2017).

Tramadol is a special case because it is currently prescribed as a drug of first choice for mild pain and can even be obtained without a prescription, since it is considered a "weak opioid"; however, this drug is linked to premature death, either due to its addictive capacity or its interactions with other drugs (Randall & Crane, 2014). Figure 2 shows how, according to AEMPS data (2019), the prescription of tramadol, in any of its presentations, tripled between 2010 and 2017.

For the first time, the most recent EDADES study by the Spanish National Plan on Drugs (DGPNSD, 2018) includes questions which explore this issue across the whole of the Spanish population. Although the situation in Spain is not nearly as serious as that reflected in the US figures, the increase in prescriptions as well as in the number of cases of addiction in recent years has led several scientific organizations to develop guidelines for the proper use of opioid analgesics (Socidrogalcohol, 2017), similar to those already written in other countries (Busse et al., 2017; Dowell et al., 2016).

All the available data on this topic have been obtained on the basis of the medicines prescribed, without the pos-

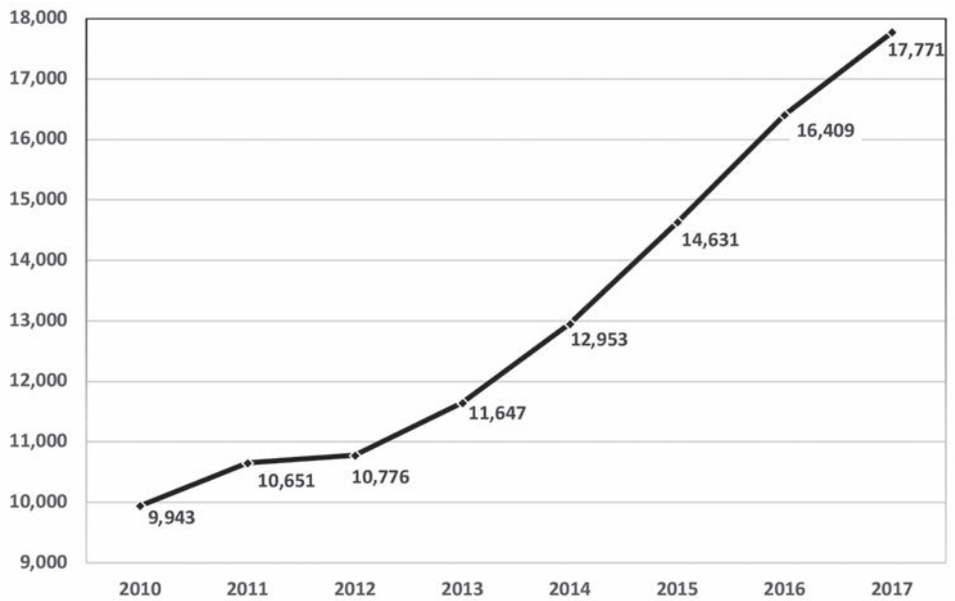

Figure 1. Daily human doses (DHD) of medically prescribed opioid medicines in Spain. SOURCE: AEMPS, 2019.

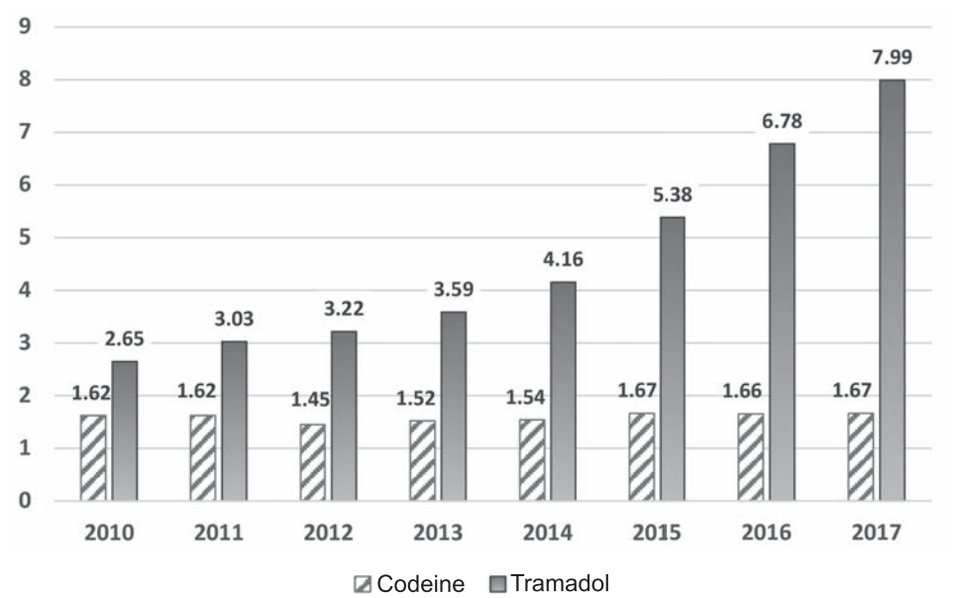

Figure 2. Daily human doses (DHD) of codeine (with ibuprofen or paracetamol) and tramadol (with paracetamol and, en the last year, dexketoprofen) prescribed in Spain. SOURCE: Modified AEMPS, 2019.

sibility of including non-prescribed use sourced from the grey or directly from the black market (nor the possible acquisition of drugs over the Internet). None of the reports explores the individual use of these drugs, the reasons for their use or the characteristics of those who use them. The present study seeks to reveal current levels of use of this type of medication in the population of the city of Madrid and its association with sociodemographic variables and health indicators, as well as to discover how they are obtained and used, by medical prescription or self-administration.

Material and Method

Sample and procedure

The survey population comprised people living in the city of Madrid aged 15 and above. A representative sample of the whole city and its districts was estimated using

the municipal census of 2017, with a sampling error of less than 1% for a 95% confidence level in estimates corresponding to equiprobable categories (p=q=0.5) and in the case of simple random sampling. We designed a stratified random sample, using the 21 city districts as the stratification criteria, with n = 400 at least for each district, and, as a second step, post-stratification by sex and age group with minimum sizes set in advance. In this way, sampling error of less than 5% in districts was ensured under the same conditions as those defined. Of the 9,676 telephone interviews carried out, 8,845 could be completed and considered valid (see descriptions in Table 1). Interviewees for each stratum were selected at random in households by calling landlines and mobile phones. The sample was obtained in two stages: In the first, homes were accessed by telephone call to randomly chosen numbers on a database of landlines classified by city district, and in the second, the interviewee was selected from members of the household until age and sex quotas were completed (poststratification), with a single interview per household. Fifty per cent of the calls were made to mobile phones following the same procedure, although in this case the location of the home of the person answering the call was not known previously. In the final recruitment approximately 70% of participants were called by landline. The telephone interview was conducted by trained interviewers aided by computer and the CATI technique (*Computer Assisted Telephone Interviewing*[7]) using a structured questionnaire. This field work was carried out between October and December 2017.

Table 1. *Sample descriptives.*

	Men	Women	Total
n	**4,055**	**4,790**	**8,845**
Age (%)			
15 - 29	18.7	16.3	17.4
30 - 44	28.6	25.6	26.9
45 - 64	32.4	31.5	31.9
› 64	20.3	26.7	23.8
Primary education			
Or les	7.9	13.2	10.8
Secondary	48.3	46.6	47.3
University	43.9	40.2	41.9
Social class			
Advantaged	42.2	37.1	39.4
Middle	23.3	25.3	24.4
Disadvantaged	34.5	37.6	36.2

The relative level of development of each district was obtained by calculating the Combined Index of Health, Education and Income (ICSCR; Díaz Olalla & Benítez Robredo, 2015; pp. 200-201), a composite index involving three indicators: (1) Health: Life expectancy at birth (this study used values for 2016); (2) Education: The proportion of the population aged 30-64 with higher than secondary educational level (2017 data), and (3) Income: Gross disposable income per capita (data available: 2014). After obtaining the index, a cluster analysis was carried out which grouped the districts into four categories, labelled high development, medium-high development, medium-low development and low development.

For social class characterization, respondents were classified into their occupational class, following the recommendations of the Spanish Society of Epidemiology for health research (Domingo-Salvany et al., 2013). Respondents were assigned the social class of the household in which they were included, which is not necessarily that of the person answering the questionnaire, but rather of the main provider of the household.

The survey included the question: *"I am going to read a list of types of medications, please tell me if you have used them."* Medicines included *"strong pain medications"*, listing the most used as examples: *"Tramadol, adolonta, dolantina, pazital, codeine, morphine patches, etc."*. Respondents were asked specifically: (a) if they had taken the drug in the last 2 weeks, in the last year except in the last two weeks, or if they had not taken it in the last year; (b) if it had always been by medical prescription or sometimes without prescription. Similar questions were asked for antidepressant and anxiolytic/sleep-inducing drugs.

The COOP/WONCA is an instrument for estimating health-related quality of life (HRQoL). The adapted Spanish version by Lizán and Reig (1999) was used. Items explore aspects related to this variable through charts in which the five response options are visualized by drawings, with the respondent marking the one that best defines how he/she feels. Although versions with 6, 7 and 9 items have been used, for the present study we opted for the broader 9-item version. However, being a telephone interview, the visual prompts in the charts could not be used and were replaced by verbal stimuli, with previous studies guaranteeing that this administration method provided good results (Pedrero-Pérez & Díaz-Olalla, 2016). Scores were generated on a five-point Likert scale, with higher scores corresponding to worse quality of life.

The 12-item version of the General Health Questionnaire (GHQ-12; Goldberg & Williams, 1998, Spanish version by Rocha, Pérez, Rodríguez-Sanz, Borrell & Obiols, 2011) is a self-administered screening instrument aiming to detect indicators of psychological distress and possible cases of psychopathological disorder in contexts such as primary care or in the general population. Item responses are given on a four-option Likert scale, which can be scored in several ways. The present study used the GHQ Likert 0-3 scoring option, where the highest scores correspond to worse health indicators, and the total test score ranges from 0 to 36 points.

A list of diseases and other health problems was provided, with participants asked to specify whether they had

been diagnosed with any of them one-by-one. The following questions were asked: *"In the last twelve months, would you say that your health has been very good, good, regular, bad, very bad?"* And *"How often have you felt lonely during the last year?"*. Respondents were asked whether they smoked daily. The level of daily physical activity was estimated by calculating the metabolic rate (METs) using formulas by Ainsworth et al. (2000). Demographic variables were also obtained (sex, age, level of education and social class).

Analysis of data

For the comparison of categories, the chi-square test was used (χ^2), with the sub-index stating the degrees of freedom for each comparison. To estimate effect size, Cramer's V was used. For the comparison of continuous variables, the analysis of univariate or multivariate covariance and omega squared (ω^2) was used as an estimator of the effect size of the differences. For these analyses, SPSS 17 was used, and ω^2 was manually calculated from the ANOVA table.

Results

Table 2 summarizes the values of the variables under study.

Of those interviewed, 16.0% (CI95% 15.0-17.0) reported having taken opioid analgesics at some point in the previous year, of which 9.1% (CI95% 8.3-9.9) had done so within the previous two weeks. The proportion of women taking opioid medication was significantly higher than that of men (19.0% vs. 12.4%; $\chi^2_1 = 72.5$; $p < 0.001$; $V = 0.09$), which is repeated in the case of use in the previous two weeks (11.9% vs. 5.8%; $\chi^2_1 = 98.6$; $p < 0.001$; $V = 0.11$). Figure 3 shows the frequencies of opioid use over the previous year by sex and age group.

Opioid use among those with primary education or lower was more frequent (24.1%; CI95% 20.5-27.7) than in those with secondary education (17.6%; CI95% 16.1-19.1) or university studies (12.1%; CI95% 10.7-13.5), and differences were significant ($\chi^2_2 = 95.7$; $p < 0.001$; $V = 0,10$). It was also more frequent in individuals from disadvantaged social classes (20.0%; CI95% 18.2-21.8) than from middle (15.0%; CI95% 13.0-17.0) or advantaged classes (13.0%; CI95% 11.4-14.6), again with significant differences ($\chi^2_2 = 61.3$; $p < 0.001$; $V = 0.08$).

When asked about the perception of health status, 43.4% of those who took opioid drugs answered that it was good or very good compared to 77.9% of those who did not, which represents a significant difference and with a considerable effect size ($\chi^2_1 = 848.1$; $p < 0.001$; $V = 0.31$). When asked about loneliness, 15.5% of those taking these drugs said they always or almost always felt lonely, compared to 9.8% of those who do not take them; again, the difference was significant ($\chi^2_1 = 23.0$; $p < 0.001$; $V = 0.05$).

When considering only those taking opioids at the time of the survey, the percentage of women is double that of men in all age groups, as can be seen in Figure 4. Those who took opioid analgesics in the two previous weeks reported more mental health problems on the GHQ-12 ($M = 12.5$; $SD = 6.3$) than those who did not ($M= 9.5$; $SD = 4.5$), representing a significant difference ($F_1 = 302.9$; $p < 0.001$; $\omega^2 = 0.03$). They also reported worse health-related quality of life (WONCA: $M =25.9$; $SD = 5.9$ vs. $M = 19.6$; $SD = 4.7$; $F_1 = 1305.2$; $p < 0.001$; $\omega^2 = 0.12$).

Table 2. *Summary of study variables.*

	Have used opioids		Have not used opioids
	EIn the last year, but not in the last 2 weeks	In the last 2 weeks	
Sex			
Men	7.0%	5.8%	87.2%
Women	8.1%	11.9%	80.0%
Age			
Mean	47.6	53.4	49.1
SD	16.4	17.9	17.9
Level of education			
Primary or lower	11.2%	20.0%	9.7%
Secondary	50.0%	53.7%	46.4%
University	38.8%	26.4%	43.8%
Social class			
Advantaged	40.0%	26.0%	40.9%
Middle	23.6%	22.4%	24.7%
Disadvantaged	36.5%	51.7%	34.5%
Perception of health			
Good or Very good	55.8%	34.1%	77.9%
Normal/Bad/Very bad	44.2%	65.9%	22.1%
Quality of life (WONCA)			
Mean	2.84	3.35	2.42
SD	0.87	0.73	0.80
Mental health (GHQ-12)			
Mean	11.40	12.50	9.37
SD	5.93	6.29	4.34
Risk of poor mental health	33.2%	40.2%	17.9%
Loneliness			
Always or often	15.5%	21.0%	8.7%
Level of activity			
High	43.0%	40.2%	43.5%
Moderate	46.1%	43.4%	44.4%
Low	10.9%	16.5%	12.1%
Body mass index			
Underweight	2.9%	1.8%	2.6%
Normal weight	47.5%	40.5%	52.1%
Overweight	35.3%	35.5%	34.6%
Obese	14.4%	22.2%	10.8%

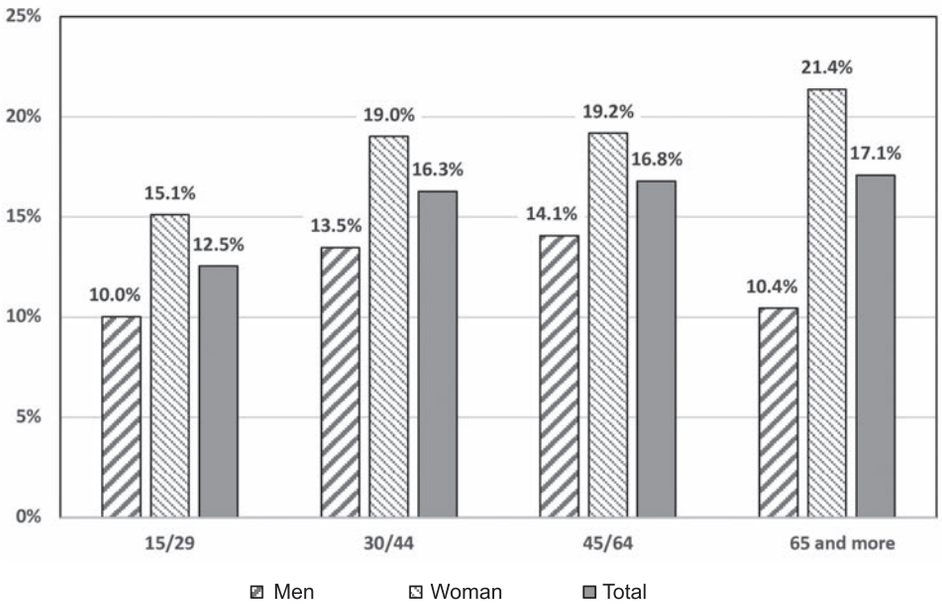

Figure 3. Frequency of use of opioids in the last year by sex and age group.

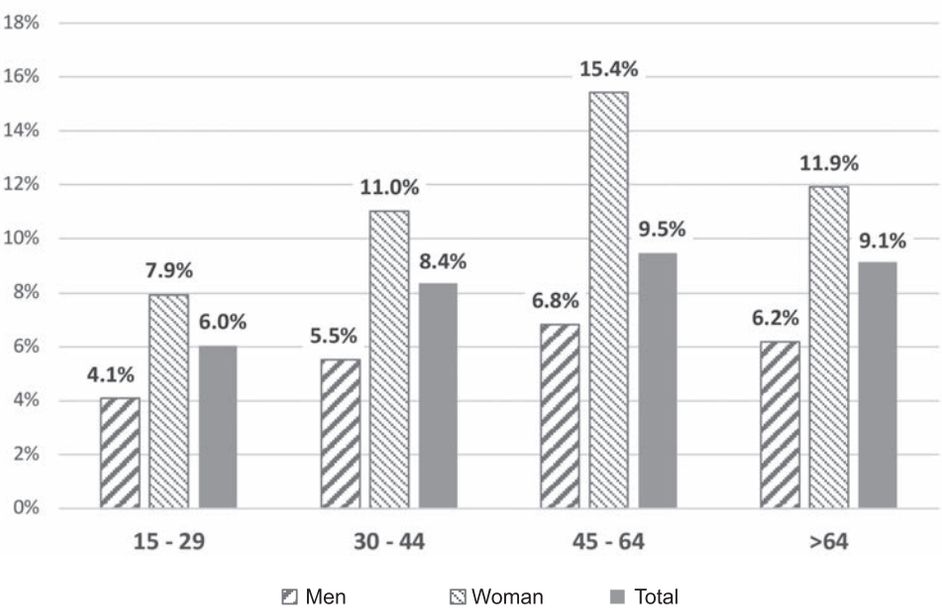

Figure 4. Consumption of opioid analgesics in the last two weeks by sex and age group.

Of those taking opioid analgesics, 14.1% also took antidepressants, compared to 4.9% of those who did not take them ($\chi^2 = 115.3$; $p < 0.001$; V= 0.11) and were also taking more anxiolytics (30.4% vs. 10.1%; $\chi^2 = 284.8$; $p < 0.001$; V= 0.18). Table 3 shows the diagnoses of those taking opioid analgesics in the previous two weeks.

The most frequent diagnoses among the youngest users of opioid drugs (15-29-year olds) were: Headaches or migraine (42.7%), chronic allergy (30.1%), lower back pain (19.8%), asthma (18.5%), neck or back pain (13.9%), hypo/hyperthyroidism (11.8%), depression (8.7%), hypercholesterolemia (8.4%) and anxiety (5.1%).

Those using opioids at the time of the survey presented sedentary habits more frequently than those who did not (16.5% vs. 12.0%; $\chi^2 = 10.9$; $p < 0.001$; V = 0.04), were more often obese (22.2% vs. 11.0%; $\chi^2 = 92.4$; $p < 0.01$; V = 0.10), smoked daily more often (21.6% vs. 18.6%; $\chi^2 = 9.6$; $p < 0.05$; V = 0.03) and presented problematic alcohol use less frequently (9.8% vs. 16.9%; $\chi^2 = 27.1$; $p < 0.001$; V = 0.06).

Of those respondents using opioid analgesics, 9.9% did so without a prescription. The differences by sex between those taking non-prescribed drugs are not significant (men 11.0%, women 9.3%; $\chi^2 = 0.99$; $p = 0.35$). On the other hand, there are significant differences by age group: The

Table 3. *Percentage of subjects diagnosed with health problems, and whether or not they have taken opioid analgesics to treat them in the last two weeks.*

Diagnosis	Have not taken opioids	Have taken opioids	χ^2_1	V
Hypertension	17.7%	29.7%	69.2*	0.08
Heart disease	3.8%	6.8%	17.7	0.04
Arthrosis	14.6%	40.5%	350.0*	0.19
Pain (neck or back)	13.2%	43.4%	495.8*	0.23
Pain (lumbar)	15.2%	51.7%	645.3*	0.27
Chronic allergy	21.6%	27.3%	13.7	0.03
Asthma	7.9%	12.1%	17.6	0.04
Bronchitis, COPD	2.7%	6.7%	37.8*	0.06
Diabetes	5.5%	11.0%	39.2*	0.06
Gastric ulcer	2.0%	6.2%	54.6*	0.07
Hypercholesterolemia	20.1%	30.5%	47.1*	0.07
Depression	6.5%	20.4%	197.4*	0.14
Anxiety	5.3%	15.7%	137.4*	0.12
Migraine	9.8%	30.5%	303.1*	0.18
Hypo/hyperthyroidism	8.3%	17.7%	78.8*	0.09

Note. * p< 0,001.

youngest (aged 15-29) used non-prescription opioids in 17.6% of cases, while 13.9% of the 30-44-year olds did so, as did 8.6% of 45-64 year olds and 3.1% of those aged 65 or older ($\chi^2 = 39.5$; $p < 0.001$; $V = 0.17$).

Discussion

The data of the present study offer striking figures for the use of opioid analgesics in the general population. Between 15% and 17% had used these drugs in the previous year and about 9% were doing so at the time the survey was conducted. These prevalences exceed those found in Spain as a whole in the 2017 EDADES study (DGPNSD, 2018), which showed use standing at 6.7% in the previous year and at 2.9% in the previous month. It is very likely that, as has already happened in other countries, the use of this type of medicine occurs with greater likelihood in urban environments, at least initially, gradually spreading to nearby rural areas (Keyes, Cerdá, Brady, Havens & Galea, 2014). Furthermore, the EDADES findings coincide with those of the present study in the higher prevalence of women users and the increase in the prevalence of use with age.

It is difficult to conceive that almost 10% of the population of a large city like Madrid present pathologies which justify the use of these drugs. Were these pathologies to be present, it would be expected that medication to treat them would be more frequently used among the most advanced age groups. However, there are hardly any differences between the percentages of subjects taking them from the age of 30 until over 65. Even more surprising is the fact that around 12.5% of those aged over 15 but not yet turned 30 had taken them in the last year, and half of these were still taking them at the time of the survey. When reviewing the diagnoses of this age group we discovered that headaches or migraines topped the list, making up more than 40%. In the case of migraine, opioid analgesics are contraindicated (Casucci & Cevoli, 2013; Tepper, 2012), even more so for less severe pain (DeVries, Koch, Wall, Getchius, Chi & Rosenberg, 2014). Back pain at any level is unlikely to require medical treatment in all cases, and it is difficult to conceive why opioids should be prescribed when medication is needed (Fleming, Rabago, Mundt & Fleming, 2007; Sturgeon, 2014). Even more difficult to explain is the relationship between the use of these drugs and problems such as allergy, asthma or hypercholesterolemia, among others.

The link between the use of opioid analgesics and mental health problems is well documented (Richardson et al., 2012). Patients with mental health and substance abuse disorders are more likely to receive long-term opioid treatment for chronic pain and more likely to have adverse outcomes from this therapy, and there is little evidence of any long-term benefits of opioid treatment in people with psychopathological disorders (Edlund et al., 2010; Davis, Lin, Liu & Sites, 2017; Howe & Sullivan, 2014; Seal et al., 2012). Although it is difficult to establish causal direction, there are indications that the chronic use of prescription opioids can cause or at least aggravate various psychopathological disorders (Becker, Sullivan, Tetrault, Desai & Fiellin, 2008). The risk of developing depression grows with increasing length of exposure to opioid analgesics (Scherrer et al., 2014). In our sample, those taking opioid analgesics were diagnosed three times as often with anxiety and depression and simultaneously consumed three times more antidepressant and anxiolytic drugs. It is not possible to determine whether such diagnoses favour the prescription of opioid drugs or whether the acute or chronic use of these analgesics is the factor which increases the anxiety-depressive symptoms, but the link between opiates and mental health problems is beyond doubt.

The use of opioid drugs in the present study is more frequent among women, at a ratio of 2:1, and people with low educational level and from a disadvantaged social class. Differences by sex are commonly found in most studies, and the use of these drugs in women is systematically more frequent (Dale et al., 2015). Women report their pain experience more frequently than men, have higher rates of pain-related diagnoses, are more sensitive to pain and have a variable response to pain and analgesia (Koons, Greenberg, Cannon & Beauchamp, 2018).

Of those who report using these drugs, almost 10% often do so without a prescription, with this being more frequent among younger people. The present study does

not provide information regarding how non-prescribed opioid analgesics are obtained. This may largely be due to the domestic availability of this type of drug in the 'medicine cabinet' and that family members facilitate its use to the rest of the household, assessing the analgesic strength without awareness of risks. It is also possible that a black market for these medicines (which can be purchased without a prescription on the Internet, for example, https://seasano.net/oxycodone) is establishing itself, triggered by youth subcultures, such as that around *reggaeton* and *YouTube*, some of whose figures have popularized songs about "perco" (slang name for Percocet, Oxycodone), which is already known to be used by teenagers in peripheral Madrid neighbourhoods and in specific treatment centre clinics. However, this phenomenon is so recent that we are operating in the field of mere speculation because, although stories abound in the news media, we still lack valid scientific approaches. It must be remembered from previous studies that it is the youngest who can switch more easily from use to abuse, thus multiplying the risk of overdose (Nechuta, Tyndall, Mukhopadhyay & McPheeters, 2018). The National Strategy on Addictions 2017-2024, formulated by the National Plan on Drugs (PNSD, 2018), has barely paid any attention to this potential risk, which may become a serious public health problem in the coming years.

The present study has some limitations. The data have been obtained from three simple questions, with a short list of opioid medications provided. It is likely that an individual identifying some of them will answer affirmatively, but the list does not include all possible commercial presentations containing these preparations. Therefore, it is possible that the frequency of use reported is lower than actual use. Neither does this survey include children under 15, who may be the population group most at risk of starting to use these drugs and becoming accustomed to their use, changing from initially regulated use to the black market, as we know has happened in other cultural contexts. However, the main strength of the study is its focus on a representative sample of an urban population, providing for the first time data to enable an initial quantification of the problem and to suggest more audacious hypotheses in future studies.

In conclusion, the present study finds that opioid drug use is highly prevalent in the population of Madrid, which is not easily justifiable on the basis of pathologies advising their prescription. In addition, a significant quantity is used irrespective of medical prescription. Although we cannot go so far as to draw a parallel with the so-called "opioid epidemic" in the United States, it can be considered that we may be on the threshold of similar problems. Official studies on the prescription of opioid analgesics have long warned of the sustained growth of medical prescription of this type of drug, and the present study finds that there are sectors of the population with special vulnerability (women, young people, the underprivileged and with low cultural level). As we already know from other countries, this problem and those that can arise are of a very complex nature, involving biochemical, psychological, commercial, cultural, political, legal factors, etc. In any case, this study complements the available official data and alerts experts, health authorities and professionals to take into consideration what could be the seeds of an enormously serious problem, which should in no way surprise us given the well-known models of other countries.

Conflict of interests

The authors declare that they do not have any conflict of interests.

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Smoking prevention with narrative messages. An experimental study on the joint effect of audience-character similarity and narrative voice

Prevención del tabaquismo con mensajes narrativos. Estudio experimental sobre el efecto conjunto de la similitud con el protagonista y la voz narrativa

Juan-José Igartua*, Laura Rodríguez-Contreras*, María Marcos-Ramos*, Beatriz González-de-Garay*, Francisco Javier Frutos*.

* Universidad de Salamanca.

Abstract

This study focuses on smoking prevention using narrative messages. In particular, the role of two narrative attributes that can indirectly influence the intention to quit smoking, self-efficacy expectations and the perceived effectiveness of the preventive response were analysed. An experimental study was carried out (N = 680, 50% women and age range 18-55 years) with a 2 (narrative voice: first- vs. third-person message) x 2 (audience-protagonist similarity: low vs. high) between-subjects factorial design. Results showed that the optimal reception condition (first-person narrative with a highly similar protagonist to the audience) induced the highest levels of identification with the protagonist (a former smoker who described the process of quitting smoking and subsequent the improvements he has experienced). Mediational analyses showed that the optimal reception condition exerted significant indirect effects on the dependent variables, due to the increase in identification and reactance reduction. In addition, the optimal reception condition also exerted a significant indirect effect on the perceived effectiveness of the preventive response that was explained by stronger identification and weaker counterarguing. The present study opens an innovative line of research on the construction of narrative messages for smoking prevention. The relevance of the characteristics of these messages is highlighted in order to activate mediating processes that facilitate persuasion.

Keywords: Health communication; smoking prevention; narrative persuasion; character-audience similarity; narrative voice.

Resumen

El presente trabajo se centra en la prevención del tabaquismo utilizando mensajes narrativos. En particular, se analiza el papel de dos características de los mensajes narrativos que pueden influir, de manera indirecta, en la intención de dejar de fumar, las expectativas de auto-eficacia y la percepción de la eficacia de la respuesta preventiva. Para ello, se llevó a cabo una investigación experimental (N = 680, 50% mujeres y rango de edad 18-55 años) con un diseño factorial 2 (voz narrativa: mensaje en primera vs. tercera persona) x 2 (similitud con el protagonista: baja vs. alta). Los resultados mostraron que la condición óptima de recepción (narración en primera persona protagonizada por un personaje similar a la audiencia) indujo niveles más elevados de identificación con el protagonista (un exfumador describía el proceso de abandono del tabaco y las mejoras que ha experimentado desde entonces). Los análisis mediacionales mostraron que la condición óptima de recepción ejercía efectos indirectos significativos sobre las variables dependientes que se debían al aumento de la identificación y la reducción de la reactancia. Además, la condición óptima de recepción también ejerció un efecto indirecto significativo sobre la eficacia percibida de la respuesta preventiva que se explicaba por el incremento de la identificación y la reducción de la contra-argumentación. El presente trabajo abre una línea de estudio sobre la construcción de mensajes narrativos para la prevención del tabaquismo. Se pone de manifiesto la relevancia de las características que dichos mensajes deben tener para que se activen procesos mediadores que faciliten la persuasión.

Palabras clave: Comunicación en salud; prevención del tabaquismo; persuasión narrativa; similitud con el protagonista; voz narrativa.

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Send correspondence to: Juan-José Igartua.
Dpto. de Sociología y Comunicación. Universidad de Salamanca, Campus Miguel de Unamuno. Av. Francisco Tomás y Valiente, s/n. 37007 Salamanca
E-mail: jigartua@usal.es

Smoking has been linked to multiple health problems, such as respiratory and cardiovascular diseases and various forms of cancer (American Cancer Society, 2018; World Health Organization, 2017). At the same time, smoking is also the biggest preventable cause of premature death. Therefore, improving the effectiveness of campaigns for smokers to quit is an important goal in public health management and communication for health. The present work focuses on the prevention of smoking using narrative messages, namely, personal stories featuring former smokers who serve as a model to trigger changes in attitudes and behaviors among active smokers (Dunlop, Wakefield & Kashima 2010; Kim, 2019).

Narrative messages on smoking prevention

To delimit the focus of our study, we must first of all define what a narrative is. Many definitions are available, but they all have one thing in common: that they have a narrative message which includes at least one character who experiences or faces (at least) one specific event in a specific time-space frame (Green, 2006; Kreuter et al., 2007; McDonald, 2014). A character is a human agent whose actions are driven by certain intentions or motives and who seeks to reach a goal. The event faced by the character is a transition between two states which are connected temporarily and causally, although most of the narratives are composed of multiple causally connected events. Although events can be narrated in a non-chronological order, the underlying structure is a cause-effect relationship (or action-reaction) which connects narrative events and characters in a structure that takes the form of a story or tale. These elements (characters, events, space and time) convert the narratives into concrete and specific messages, i.e., "stories of individual cases", in which events occur where one or several people are involved in a certain environment. Focusing on specific cases contrasts, for example, with scientific explanations, which give more abstract and general information based on multiple cases. Non-narrative messages therefore provide more general or abstract facts, which are presented as information ("each cigarette you smoke increases your risk of lung cancer") or statistics (providing figures on the prevalence of a phenomenon, "8 out of 10 people with lung cancer die in the next three years"), compared to the experiential style of the narrative ("chemotherapy to treat lung cancer messes up my whole body, it's as if I were alive but dead inside").

In the context of our project, we will define the narrative messages for smoking prevention as short personal stories featuring a former smoker and offering details of his or her experience with cigarettes. A smoking prevention narrative refers to the personal history of a former smoker, which aims to serve as a model to bring about changes in attitudes, beliefs and behaviors in active smokers (for example, the *Tips from Former Smokers* campaign, developed in the United States by the Centers for Disease Control and Prevention, CDC). Thus, they refer to two different *states*, life as a smoker and life after quitting tobacco, and both are connected to each other in a *causal and temporal sequence*. In addition, the narrative may refer to aspects such as the reasons leading the character to stop smoking (*intentions and goals of the character*), the degree of prior addiction to cigarettes (how many was smoked), the number of times he or she tried to stop smoking, the strategies used to stop smoking, the benefits of quitting smoking and/or the disappearance of negative effects caused by tobacco after quitting. The aim of a smoking prevention narrative is to trigger in the target audience the desire to stop smoking, to reinforce expectations of self-efficacy and convince the listener of the effectiveness of the promoted preventive response (i.e., quit smoking).

Messages constructed as narratives are increasingly used in health communication to achieve public health objectives, such as the prevention and detection of diseases (Frank, Murphy, Chatterjee, Moran & Baezconde-Garbanati, 2015; Green, 2006; Jensen, Yale, Krakow, John & King, 2017; Thompson & Kreuter, 2014). Narrative health messages have been shown to be capable of bringing about changes in coherent beliefs and attitudes, as well as stimulating healthy behaviors (De Graaf, Sanders & Hoeken, 2016). In the case of smoking prevention, studies have proliferated in recent years which demonstrate the effectiveness of narrative formats (De Graaf et al., 2017; Dunlop et al., 2010; Kim, 2019; Kim, Bigman, Leader, Lerman & Cappella, 2012; Kim & Lee, 2017; Kim, Shi & Cappella, 2016; Williams, Green, Kohler, Allison & Houston, 2011).

Meta-analyses show that narrative interventions produce significant effects on the dependent variables considered (in beliefs, $r = .17$; attitudes, $r = .19$; behavioral intention, $r = .17$; and behaviors, $r = .23$; Braddock & Dillard, 2016), but also that there is significant variation in these effects (Shen, Sheer & Li, 2015; Zebregs, Van den Putte, Neijens & De Graaf, 2015). The findings suggest that although narrative messages can serve as a promising health communication tool, not all narratives are effective. Finding out which ingredients of the narratives are most effective from a persuasive point of view therefore becomes an important question and constitutes one of the main objectives of this study.

Explanatory processes of narrative persuasion

A second aim of the present study is to understand and explain the processes or mechanisms responsible for the persuasive impact of tobacco prevention narratives. The main theoretical models of narrative persuasion are the *Transportation-Imagery Model* of Green and Brock (2002), the *Extended Elaboration Likelihood Model* (E-ELM) of Slater and Rouner (2002) and the *Entertainment Overcoming Resis-*

*tance Model (*EORM) of Moyer-Gusé (2008). In this context, the main processes studied are identification with the protagonist, narrative engagement or transportation, counterarguing and reactance.

Identification is an imaginative process which involves the gradual loss self-awareness and the assumption of the affective and cognitive point of view of the protagonist of a narration (Cohen, 2001; Igartua, 2010, 2017). Narrative transportation is a psychological process which involves a state of attachment or immersion with the story or tale that is being narrated (Busselle & Bilandzic, 2009; Green & Brock, 2000). Counterarguing is the process of making critical evaluations during exposure to the message (which means thinking negatively about the persuasive or preventive proposal). It has been formally defined as "the generation of thoughts (or cognitive responses) that explicitly refute a message's intended persuasive theme" (Niederdeppe, Kim, Lundell, Fazili & Frazier, 2012, p. 758). Reactance is a second process linked to resistance against the attempted persuasion triggered when the individual considers that their freedom of choice is being threatened.

A two-way classification of mediating processes thus suggests itself: a) those that are directly related to the impact of the message's features, i.e., identification with the characters and narrative transportation; and, b) those that explain how those involved with the narratives and their protagonists are persuaded, thanks to counterarguing and reactance. At the start of the causal chain, identification and narrative transportation are the most relevant processes, the primary mediators, because they initiate the process which will facilitate the persuasive impact, through reducing the generation of counter-arguments and reactance. In this way, counterarguing and reactance are considered *secondary mediating mechanisms* (Banerjee & Greene, 2012; Shen, Seung, Andersen & McNeal, 2017).

The EORM model by Moyer-Gusé (2008) argues that identification and narrative transportation reduce counterarguing and also reactance: people who get engaged by a narrative message *get carried away* by the story that is told (and experience enjoyment and entertainment), thus weakening any positioning or critical attitude towards the message (since these would be processes incompatible with enjoyment or entertainment). However, the empirical evidence in this regard is inconclusive. For example, Moyer-Gusé and Nabi (2010) found that transportation was associated with greater counterarguing while, in contrast, identification actually did reduce the process of resistance to the message.

In any case, given that narrative transportation and identification with the characters are relevant processes in triggering attitudinal changes when narrative messages are received, research is currently focused on understanding how to enhance these processes, that is, which variables related to the characteristics of the characters or the presentation of the narrative have an effect on these processes and, indirectly, on the attitudinal variables (De Graaf et al., 2016). The present study focuses specifically on the analysis of two factors which can increase identification and narrative transportation: the similarity between the protagonist and the target audience and the narrative voice or perspective from which the story is told.

Similarity to the protagonist

The similarity to the protagonist occurs when the person who is exposed to a narrative message shares certain features with the protagonist. This similarity can be based on objective features (in demographic aspects, such as gender or age), but also on psychological or subjective characteristics (such as personality, beliefs, opinions, values or biographical experiences). It is assumed that "if there is a considerable social distance between the audience and the protagonist of the narrative (...), persuasion is less likely to happen" (Walter, Murphy & Gillig, 2018, p. 32). However, empirical evidence on the effect of similarity yields inconsistent results. In the review of Tukachinsky (2014), it is observed that the manipulation of similarity (in objective terms) enhanced narrative transportation and the perception of similarity, but not identification.

It should nevertheless be borne in mind that similarity is a complex construct with several dimensions, and that it has not always been experimentally manipulated in the same way, which could explain the inconsistent results. Thus, Tukachinsky's review (2014) only considered studies where similarity had been manipulated in terms of demographic traits such as sex, age or ethnic origin. In the present study, a new dimension of similarity relevant to the prevention of smoking is introduced: the behavioral similarity depending on the degree of nicotine dependence. The manipulation of behavioral similarity is an innovation with respect to previous studies, in which the similarity in socio-demographic variables has been manipulated (Chen, Bell & Taylor, 2016, 2017; Cohen, Weimann-Saks & Mazor-Tregerman, 2018; Kim, 2019). In order to manipulate similarity, information about the degree of addiction was taken into account both by the protagonist of the narrative and by the participants. The literature on addiction to tobacco has found that among the factors for successful quitting, the severity of dependence (number of cigarettes per day, score in the Fagerstrom test) plays a role (Moreno & García, 2000).

It is also possible, however, that similarity influences identification only under certain reception conditions (Kaufman & Libby, 2012), so it is necessary to continue extending this line of research and further exploring the specific conditions in which the similarity effect can be enhanced. One of these ways, as proposed here, is through the narrative voice.

Narrative voice

The narrative voice or point of view refers to the perspective adopted by the narrator and from which the story is told: first, second or third person (Chen et al., 2017, Nan, Futerfas & Ma, 2017). First-person narratives are those which focus on the feelings and thoughts of the protagonist of the narrative and do so by assuming the first person, thus necessitating the use of first-person pronouns "I", "me" or "my". In such narratives, the narrator is part of the story and sets out his or her view on a topic or experience directly ("I felt bad for continuing to smoke", "I always thought I would never be able to stop smoking"). In third-person narratives, there is a narrator who is not the protagonist of the story and who describes the experience of the character but from an external point of view or by adopting the viewer's perspective. In this way, the character is alluded to by his or her name or by the third-person pronouns "he" or "she" ("Javier felt bad for continuing to smoke", "Javier always thought he would never be able to stop smoking"). Finally, the second-person narrative identifies the target reader as the protagonist ("you felt bad for continuing to smoke", "you always thought you would never be able to stop smoking"). The second-person perspective is useful for developing materials such as guidelines, instruction manuals or self-help books, but it is rarely used in health campaigns in the form of narratives (Christy, 2018).

The first person helps the audience of the message to take the perspective of the narrator, and this taking of perspective constitutes a key element of the identification with the characters. In addition, neuropsychological research has shown that first-person narratives (versus third-person) are processed differently at the neurological level (Van Krieken, Hoeken & Sanders, 2017).

Chen et al. (2016) indicate that research in narrative persuasion has not devoted enough time to analyzing the effect of the narrative voice, despite being a very relevant formal resource for the design of narrative messages to prevent smoking (for example, the *Tips from Former Smokers* campaign). Thus, in the review by De Graaf et al. (2016) of a total of 153 experimental studies on narrative persuasion related to health, only four studies are identified which manipulated this feature, and only one of them focused on smoking prevention. This review showed that first-person narratives have a greater potential for triggering persuasive effects, although the evidence was not consistent and the number of studies considered was low. What has been observed in previous studies is that the messages in the first person (in contrast with those in the third person) are perceived as more personal; they are easier to understand, increase the identification with and taking the perspective of the protagonist, and are more effective in inducing the perception of risk (Chen et al., 2017; De Graaf, Hoeken, Sanders & Beentjes, 2012; Kaufman & Libby, 2012; Nan, Dahlstrom, Richards & Rangarajan, 2015).

However, studies which combined the narrative voice and another independent variable in the same experiment have not produced such clear results. For example, in the study by Nan et al. (2017) the superiority of first-person messages over third-party messages only manifested itself when the story was presented in writing rather than as an audio message. Similarly, Kaufman & Libby (2012), studying identification, observed an interaction effect between narrative voice (story in first or third person) and similarity with the protagonist (belonging to the same university as the participants or not), where the reading of a story told in the first person by a character belonging to the same group as the audience significantly increased identification.

Objectives and hypotheses

Our project aims to deepen the "joint effect" of similarity and narrative voice by establishing, as an original contribution or innovation in the research on narrative persuasion applied to smoking prevention, the concept of *optimal reception condition*, which involves presenting a narrative in first person featuring a character similar to the audience. Given the scarcity of research focusing on these variables in the study of smoking prevention, and the existence of contradictory results on the "main" effects of similarity and narrative voice, we believe it is important to study how both factors can be combined to induce strong identification and narrative transportation, and an indirect effect (through these processes and as well as through counterarguing and reactance) on the persuasive impact of narratives of smoking prevention.

It is expected that if the smoking prevention message is presented in the first person and comes from a person similar to the audience (depending on the degree of nicotine dependence) it will trigger greater identification with the protagonist and greater narrative transportation, and for this reason it is also more likely not to be perceived as a threat (does not generate reactance or counterarguing), which will have an indirect effect on behavioral intention, expectations of self-efficacy and effectiveness of the preventive response. Thus, it is hypothesized (H1) that the combination of a first-person narrative featuring a character similar to the audience will generate the highest levels of identification with the protagonist of the message (H1a) and narrative transportation (H1b). Secondly (H2), it is hypothesized that the optimal reception condition will have an indirect effect on the intention to stop smoking, the expectations of self-efficacy, and the perception of the effectiveness of the preventive response, which will be (serially) mediated by the identification with the characters (H2a) and narrative transportation (H2b) (primary mediators) and counterarguing and reactance (secondary mediators).

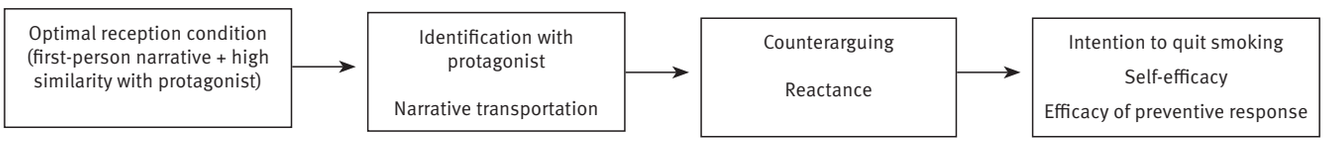


Figure 1. Proposed mediational model.

Methods

To test our predictions, an online experiment was conducted with Qualtrics, accessing a representative sample of 680 adult smokers living in Spain, of both sexes, and aged between 18 and 55. To determine sample size, a preliminary analysis was carried out with the G*Power program (Faul, Erdfelder, Lang & Buchner, 2007). All participants were shown a narrative message featuring an adult former smoker (a 35-year-old man) who recounted his experiences during the process of quitting smoking, emphasizing the positive consequences of quitting. In the narrative message, the narrative voice (first- versus third-person narration) and the protagonist's level of addiction (high versus low) were experimentally manipulated. All materials related to the study have been deposited in the *Open Science Framework* repository (https://osf.io/y3c8f/).

Participants

The study included a sample of 680 adult smokers aged 18 to 55 (M = 35.68, SD = 10.85), selected among the panelists available in Spain through the company Qualtrics (an online *opt-in* survey provider), setting quotas for sex (50% of each sex) and age (20% aged 18-22 years, 30% aged 23-35 and 50% aged 36-55). The field work was carried out between October 2 and 14, 2018. To select the participants in the first part of the online questionnaire, three screener questions were included: "In relation to smoking, how would you define yourself?" (I have never smoked, I have smoked occasionally, I am a habitual smoker), "Throughout your life, have you smoked more than 100 cigarettes?" (no/yes) and "In the last week ..." (I have not smoked, I have smoked less than 5 cigarettes a day, I have smoked 5 or more cigarettes every day). Only those who declared themselves to be habitual smokers, who indicated that they had smoked more than 100 cigarettes during their lifetime and 5 or more cigarettes every day during the last week were taken into account. On the first screen of the online questionnaire, each participant was required to provide informed consent.

Design and procedure

A 2 x 2 between-subjects factorial design was used. Two independent variables were manipulated: the narrative voice (first- versus third person) and the level of nicotine addiction of the narrative's protagonist (low versus high). The was carried out by Qualtrics, which allowed us to work with a totally randomized design in terms of the distribution of participants for the different versions. In this way, 170 participants were randomly assigned to each experimental version.

Given that Qualtrics allows a series of quality controls to be used, the questionnaire was designed in such a way that it was only possible to complete in a single session, from start to finish. In addition, questionnaires were only counted as valid if participants took between 6 and 45 minutes to complete them (M = 11.16 minutes, SD = 4.71), if they took between 60 and 420 seconds to read the narrative (M = 110.67, SD = 50.54), and if they correctly answered a control question included in the final part of the questionnaire. Finally, two memory questions at the end of the questionnaire asked about the name of the protagonist of the narrative (Miguel, correctly remembered by 96.8% of the participants) and his age (35 years, correctly remembered by 93.7% of the participants). Taking both variables into account, 59 people did not correctly remember this information, so that the final sample consisted of 621 participants. The decision was made to eliminate these 59 participants as an additional measure of quality control (a common practice in these type of studies, see Kim, 2019), observing that there were no differences in the percentage of "invalid" cases "(those who did not remember both details of the narration) across the four experimental conditions (χ^2 (3, N = 680) = 3.47, p = .324).

Narrative and experimental manipulations

A narrative whose protagonist was a 35-year-old man who said that he had quit smoking a year before was written using stories from former smokers in forums and web pages[1], advertising from companies that market products to stop smoking (such as *Nicorette*)[2], and narratives used in

[1] http://www.stoptabac.ch/cgi-bin/aff_tem2_sp.pl?aff_all+T2

[2] For example: https://www.youtube.com/watch?v=VpbZYvcEXVI

previous studies (Dunlop et at., 2010; Kim et al., 2012; Kim et al., 2016; Williams et al., 2011). In his story, the former smoker talked about issues such as how old he was when he started smoking, why he decided to stop smoking and how he managed to do so. Similarly, he described the process of giving up and the improvements he has experienced since then, but without including any abstract or statistical information. In the final part of the narrative, the protagonist commented that he had not smoked for more than a year, that he no longer wanted to smoke again, that he noticed how the negative consequences associated with smoking disappeared and that he experienced a series of benefits from giving up smoking.

To manipulate the narrative voice, the elements that mark the grammatical person in written narratives were modified, such as the choice of personal pronouns. In the first-person narrative, the first-person pronouns "I", "me", "my", "myself" (example: "I quit smoking a year ago") were used, while in the third-person narration, the name and the third-person pronouns "he", "she", "him", "her", "it", and the reflexive particle "-self" (example: "Miguel stopped smoking a year ago") were used. In addition, in the first-person narration, the protagonist was presented using his name at the beginning: "my name is Miguel, I am 35 years old and I started smoking at 15". In the third-person narration, the narrator presented the character by giving his name: "Miguel is 35 years old and started smoking at 15". This experimental procedure for manipulating narrative voice has been used successfully in a large number of studies (Banerjee & Greene, 2012; Chen et al., 2017; Chen, McGlone & Bell, 2015; Nan et al., 2015; Nan et al., 2017).

The manipulation of behavioral similarity was carried out taking into account the information on the level of nicotine dependence of both the narrative's protagonist and the participants. In the narrative featuring a former smoker with low nicotine dependence, information was included about the number of cigarettes smoked before quitting ("he was not so hooked, he only smoked 9 or 10 cigarettes a day"), the money he saved by stopping smoking ("I started saving, more than €80 a month, when I stopped buying cigarettes") or the life changes ("I no longer have to make sure I have cigarettes with me, I no longer need to smoke a cigarrette to relax"). In the narrative featuring a former smoker with high nicotine dependence, the greater number of cigarettes smoked before quitting was emphasized ("he was very addicted and smoked more than one pack of cigarettes a day"), greater financial savings on giving up ("I started saving, more than €150 a month, when I stopped buying cigarettes") or a deeper life changes ("I am no longer a slave to tobacco who rummages through household garbage in search of cigarette butts, I no longer wake up at night to smoke").

To create an index of behavioral similarity between the protagonist of the narration and the participants (low, high), in the pre-test measure participants were asked for information regarding their degree of nicotine dependence using the Fagerström test (Heatherton, Kozlowski, Frecker & Fagerstrom, 1991). The Fagerström test is a 6-item scale that assesses people's nicotine dependence (for example, how much time goes by between getting up and smoking your first cigarette? 0 = more than 60 minutes, 1 = between 31 and 60 minutes, 2 = between 6 and 30 minutes, 3 = up to 5 minutes). Combining the scores of the six questions determines the degree of nicotine dependence (with values from 0 to 10). In this way, the characteristics of each participant were matched to those of the narrative's protagonist, and similarity was thus determined using behavioral criteria as a reference. A condition of high similarity was established if the protagonist of the narrative indicated that he was highly addicted to cigarettes and the participant scored 5 or more in the Fagerström test (which was the median value on this scale in the present study), or if the protagonist of the narrative indicated that he had low dependence and the participant scored below 5 in the Fagerström test. Likewise, a condition of low similarity was established if the protagonist of the narrative indicated high dependence and the participant scored less than 5 in the Fagerström test, or if the protagonist indicated low dependence and the participant scored 5 or more in the Fagerström test.

A pilot study was carried out with 120 participants (57.5% women, aged 18-32, M = 20.73 years, SD = 2.69). Participants in the pilot study were randomly distributed across all four versions of the narrative. After reading, they answered a questionnaire with questions about the clarity or degree of comprehension of the message (for example, "The message is clear and understandable"), perception of credibility, interest and perceived realism, through 7-point Likert-type scales (from 1= *strongly disagree* to 7= *strongly agree*). The results showed that the narratives designed were perceived as clear and easy to understand (M = 6.13, SD = 2.69), credible (M = 5.43, SD = 1.33), interesting (M = 5.30, SD = 1.28) and realistic (M = 5.92, SD = 0.97). In all the variables considered, the value obtained was significantly higher than the theoretical midpoint (4), as verified by a Student's t-test for a sample ($p < .001$).

Measurements

The questionnaire consisted of pre-test and post-test measures. The pre-test measure included the screener questions and the Fagerström test (mentioned above), as well as basic socio-demographic information (sex and age). The post-test measure was presented immediately after reading the former smoker's narrative, and contained scales in the following order to measure similarity with the

protagonist of the narrative and memory of the narrative voice (to test the efficacy of experimental manipulation), identification with the protagonist, narrative transportation, counterarguing, reactance (mediating variables), intention to stop smoking, expectations of self-efficacy, and expectations of the effectiveness of the preventive response (dependent variables).

Dependent variables

Intention to stop smoking. A scale composed of three items was created from research by Dunlop et al. (2010), Kim et al. (2012), Kim et al. (2016), Thrasher et al. (2012), Wehbe, Basil & Basil (2017), and Williams et al. (2011): "I think I am going to make an effort to stop smoking", "it is very likely that I will quit smoking in the next 3 months" and "I will definitely quit smoking in the future" (from 1 = *strongly disagree*, to 7 = *strongly agree*). A smoking intention index was constructed from calculating the average of the three items (α = .82).

Expectations of self-efficacy in relation to quitting smoking. Self-efficacy is defined as the confidence that a person has in their ability to perform and maintain a certain behavior in a given situation (in this case, refrain from smoking after quitting the habit) (Spek et al., 2013). To measure the expectations of self-efficacy, a scale composed of six items was used, based on Chen et al. (2015), McQueen et al. (2016), Spek et al., (2013), and Williams et al. (2011): "I think I have the capacity to quit smoking if I put my mind to it", "I'm sure I can quit smoking", "I know what I should do to quit smoking", "if I quit smoking and someone offered me a cigarette I would resist temptation and I would not smoke", "if I quit smoking and went to a party with friends or relatives, I would know what to do so as not to smoke", "once I have already decided not to smoke again I'm sure I would not have a cigarette even if I felt sad or anxious" (from 1 = *strongly disagree*, to 7 = *strongly agree*). An index of self-efficacy expectations was constructed from calculating the average across the six items (α = .88).

Perception of efficacy of the preventive response (quit smoking). This was measured on a scale comprising five items, created using the study by Chen et al. (2015): "I am convinced that if I stop smoking in a short time my health will improve", "I am sure that if I stop smoking my body will soon recover from the harmful effects of tobacco", "I am convinced that quitting smoking will reduce the risk of serious illness in the future", "even if you've smoked for many years, it is possible to recover health if you stop smoking in time", "a life without cigarettes reduces the risk of cancer" (from 1 = *strongly disagree*, to 7 = *strongly agree*). An index of perceived efficacy of the preventive response was constructed from calculating the average in the five items (α = .78).

Mediating variables

Identification with the protagonist. This was assessed with a scale comprising 11 items, the reliability and structural validity of which has been tested in a previous study (Igartua & Barrios, 2012). The instrument was designed to retrospectively measure the identification whit the protagonist of the narrative through items such as "I was worried about what happened to Miguel", "I felt emotionally involved with Miguel's feelings", "I felt like I was Miguel") (from 1= *not at all* to 5= *very much).* An index of identification with the protagonist was constructed from the calculation of the average across the eleven items (α = .93).

Narrative transportation. This was assessed using the *Transportation Scale-Short Form* developed by Appel, Gnambs, Richter & Green (2015), consisting of five items (with a 7-point response format from 1 = *strongly disagree* to 7 = *strongly agree*). The items making up the scale are: "I could imagine myself in the situations described in the narrative", "I felt very involved mentally during the reading of the story", "I wanted to know how the story would end", "The text affected me emotionally", and "while reading the narrative I had a very vivid and clear image of Miguel". A narrative transportation index was constructed from calculating the average across the five items (α = .89).

Counterarguing. A scale consisting of three items created from the counterarguing scale of Moyer-Gusé & Nabi (2010) and Igartua & Vega (2016) was used: "while reading the narrative, I thought that I did not agree with some of the things said by Miguel", "while reading the message, I thought that the information Miguel gave was inaccurate, misleading or exaggerated" and "while reading the story, I tried to find out if there were flaws in the conclusions that Miguel drew on some issues" (from 1 = *strongly disagree* to 7 = *strongly agree*). An index of counterarguing was constructed from calculating the average of the three items (α = .72).

Reactance. This was asessed with the perceived threat to freedom scale by Shen (2015), comprising 4 items: "the message threatened my freedom of choice", "the message tried to make a decision for me", "the message tried to manipulate me", and "the message was trying to pressure me" (from 1 = *strongly disagree* to 7 = *strongly agree*). A reactance index was constructed from calculating the average across the four items (α = .85).

Experimental manipulation check

Perceived similarity with the protagonist. To ensure that the manipulation of behavioral similarity was effective, the participants answered the following questions after reading the narrative: "To what extent do you consider that you have things in common with Miguel?", "To what extent do you think Miguel is like you, considering the amount he smoked before quitting? "(from 1 = *not at all*, to 5 = *very much*). The two items were averaged to create a perceived similarity index (r = .53, p = .001; M = 3.41, SD = 0.84).

Memory of the narrative voice. The participants were asked: do you remember if the story you just read was written in the first person or in the third person? (1 = it was written in first person, "My name is Miguel, I am 35 years old and I started smoking ..."; 2 = it was written in the third person, "Miguel is 35 years old and started smoking ...").

Results

Preliminary analyses

Random assignment of participants to the four experimental conditions was successful. There were no statistically significant differences between the conditions in socio-demographic terms (gender (χ^2 (3, N = 621) = 1.37, p = .712; age (F (3, 617) = 0.04, p = .987) nor in the degree of nicotine dependence (F (3, 617) = 1.05, p = .369).

The manipulation of behavioral similarity was also effective. Moderation analysis (model 1) with PROCESS for SPSS (Hayes, 2018) showed that there was a statistically significant interaction effect between the level of cigarette addiction of the narrative's protagonist and that of the participants (measured with the Fagerström test) on the perceived similarity index (B = 0.19, SE = 0.02, p = .001). The analysis of conditional effects showed that for people with low nicotine dependence (score of 2 or less in the Fagerström test), the narrative in which the protagonist was characterized with low dependence before quitting smoking generated greater perceived similarity than the narration with a protagonist with high dependence (B = -0.58, SE = 0.09, p = .001). Similarly, for people with a high level of cigarette addiction (score equal to or greater than 7 in the Fagerström test) the narrative with the highly dependent protagonist generated greater perceived similarity than the narration with a not very dependent protagonist (B = 0.37, SE = 0.09, p = .001). In contrast, the effect of the protagonist's level dependence on the perceived similarity was not statistically significant among people with moderate levels of addiction (B = -0.01, SE = 0.06, p = .853).

According to O'Keefe (2003), when intrinsic traits are manipulated in a persuasive message (such as the narrative voice in the present study), it is not necessary to test the efficacy of experimental manipulation. Nevertheless, we checked if there were differences in the memory of the narrative voice depending on the version of the message (third or first person). The results showed that the manipulation of the narrative voice was effective since there were

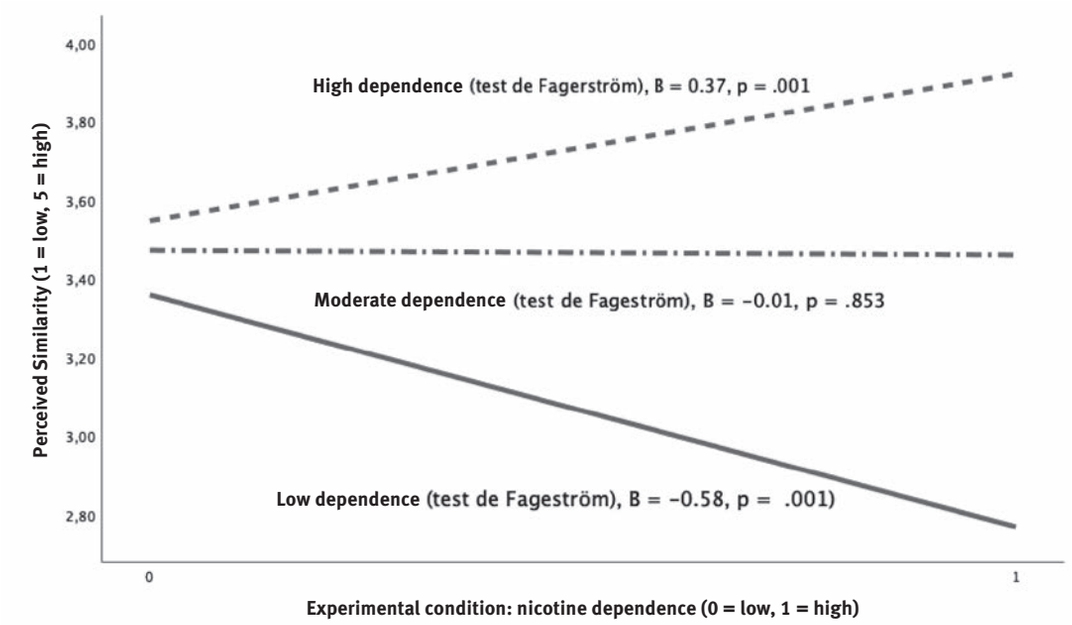


Figure 2. Test of the effectiveness of the manipulation of behavioral similarity. Analysis of conditional effects with PROCESS for SPSS.

statistically significant differences in the recall of the narrative voice based on having read a third- or first-person narrative (χ^2 (1, N = 621) = 536.58, p = .001).

Finally, the correlations between the mediating variables and the dependent variables were analyzed. This analysis allowed us to verify that the mediating processes showed convergent correlations with the proposed hypotheses (for example, between identification and narrative transportation with reactance and counterarguing). In addition, we also tested that the mediating processes showed statistically significant relationships with the dependent variables.

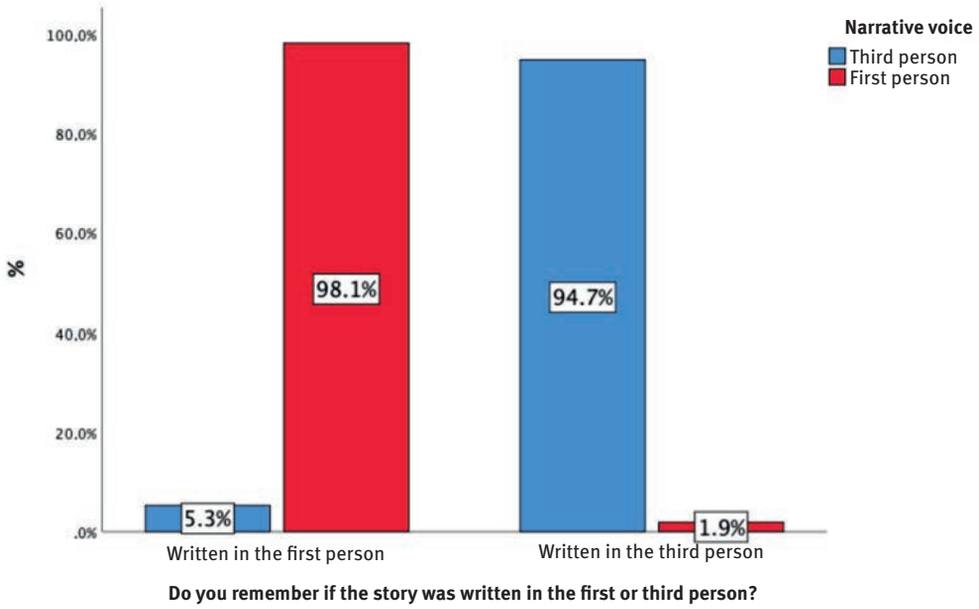


Figure 3. Checking the effectiveness of narrative voice manipulation. Effect on the memory of the narrative voice.

Table 1. *Correlations between mediating and dependent variables.*

	1	2	3	4	5	6	7
1 Identification	-						
2 Narrative transport	.85 ***	-					
3 Counterarguing	-.32 ***	-.31 ***	-				
4 Reactance	-.25 ***	-.28 ***	.47 ***	-			
5 Intention to stop smoking	.51 ***	.49 ***	-.19 ***	-.22 ***	-		
6 Expectations of self-efficacy	.09 **	.13 ***	-.05 +	-.14 ***	.32 ***	-	
7 Efficacy of preventive response	.41 ***	.43 ***	-.27 ***	-.27 ***	.39 ***	.31 ***	-
Mean	3.64	5.27	2.72	2.61	4.69	4.55	5.82
Standard deviation	0.79	1.18	1.22	1.40	1.36	1.30	0.91

Note. $N = 621$. In all variables, higher scores reflect greater intensity of the process in question, from 1= *low* to 7= *high* (except in the scale of identification with a theoretical range from 1= *low* to 5= *high*) + $p < .10$, ** $p < .01$, *** $p < .001$.

These results justify the proposed mediational model, which is presented later.

Joint effect of behavioral similarity and narrative voice on narrative identification and transportation (H1)

It was hypothesized that the participants would experience greater identification with the protagonist (H1a) and greater transportation (H1b) in the optimal reception condition compared to the reference condition. To test this hypothesis, two analyses of variance (ANOVA) were carried out with the experimental condition as an independent variable and identification and transportation as dependent variables, carrying out two planned contrast analyses (post hoc tests) (see Walter et al., 2018, for a similar analytical approach in their Study 3, with a 2 x 2 factorial design, as in the present investigation). The first contrast (contrast coefficients: -1, 0, 0, 1) compared condition 4, or optimal condition of reception, (i.e., reading a first-person narrative with a protagonist of high behavioral similarity to the reader of the message, coefficient 1) with reference condition 1 (i.e., reading a third-person narrative and low behavioral similarity, coefficient -1). The second planned contrast (coefficients:

-1, -1, -1, 3) compared the optimal reception condition with the average of the three experimental conditions.

Regarding identification, statistically significant differences were observed depending on the experimental condition (F (3, 617) = 2.79, p = .040, η_p^2 = 0.013). In addition, the two planned contrasts performed were statistically significant (contrast 1: t (617) = 2.59, p = .010, r = .10; contrast 2: t (617) = 2.30, p = .020, r = .09). Results showed that the optimal reception condition induced the highest levels of identification with the protagonist, confirming H1a (see Figure 4).

With respect to narrative transportation, no statistically significant differences were observed according to the experimental condition (F (3, 617) = 1.58, p = .192, observed

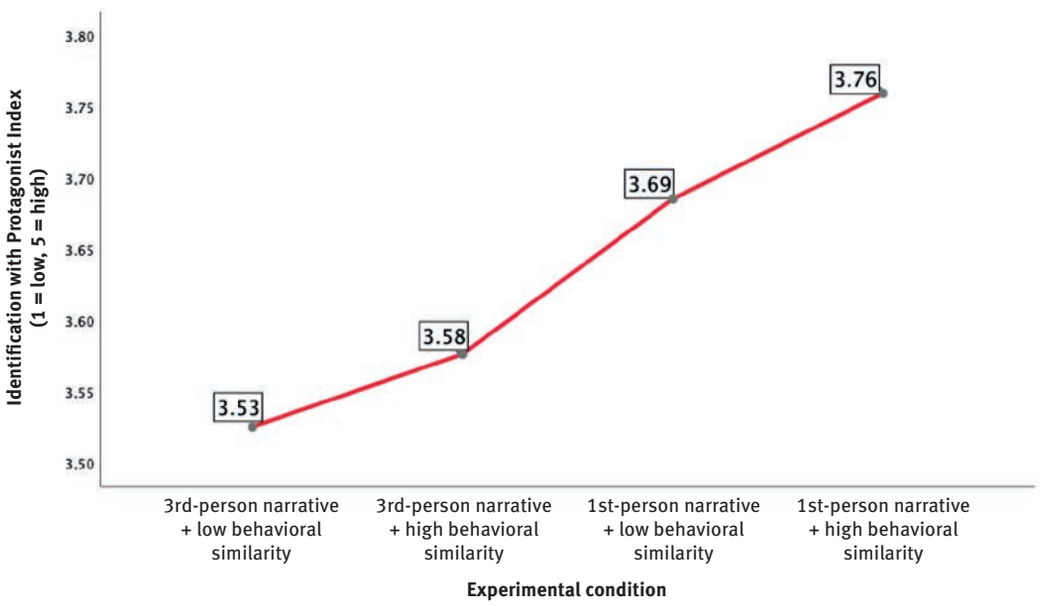


Figure 4. Effect of the experimental condition on identification with the protagonist (H1a).

power = 0.419). Moreover, the two planned contrasts performed were not statistically significant either (contrast 1: t (617) = 1.756, p = .080, r = .07; contrast 2: t (617) = 1.276, p = .202, r = .05); therefore, H1b was not confirmed, although the descriptive results did show that the optimal reception condition induced the highest levels of narrative transport, which is consistent with this hypothesis (see Figure 5).

Mediational analysis (H2)

The second hypothesis predicted an indirect effect of the optimal reception condition on the intention to stop

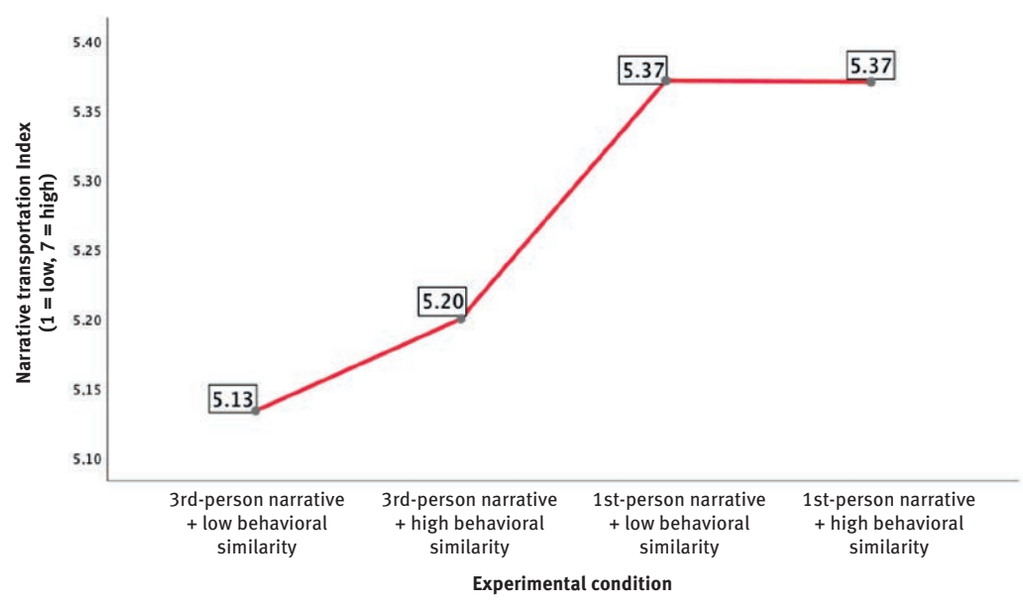
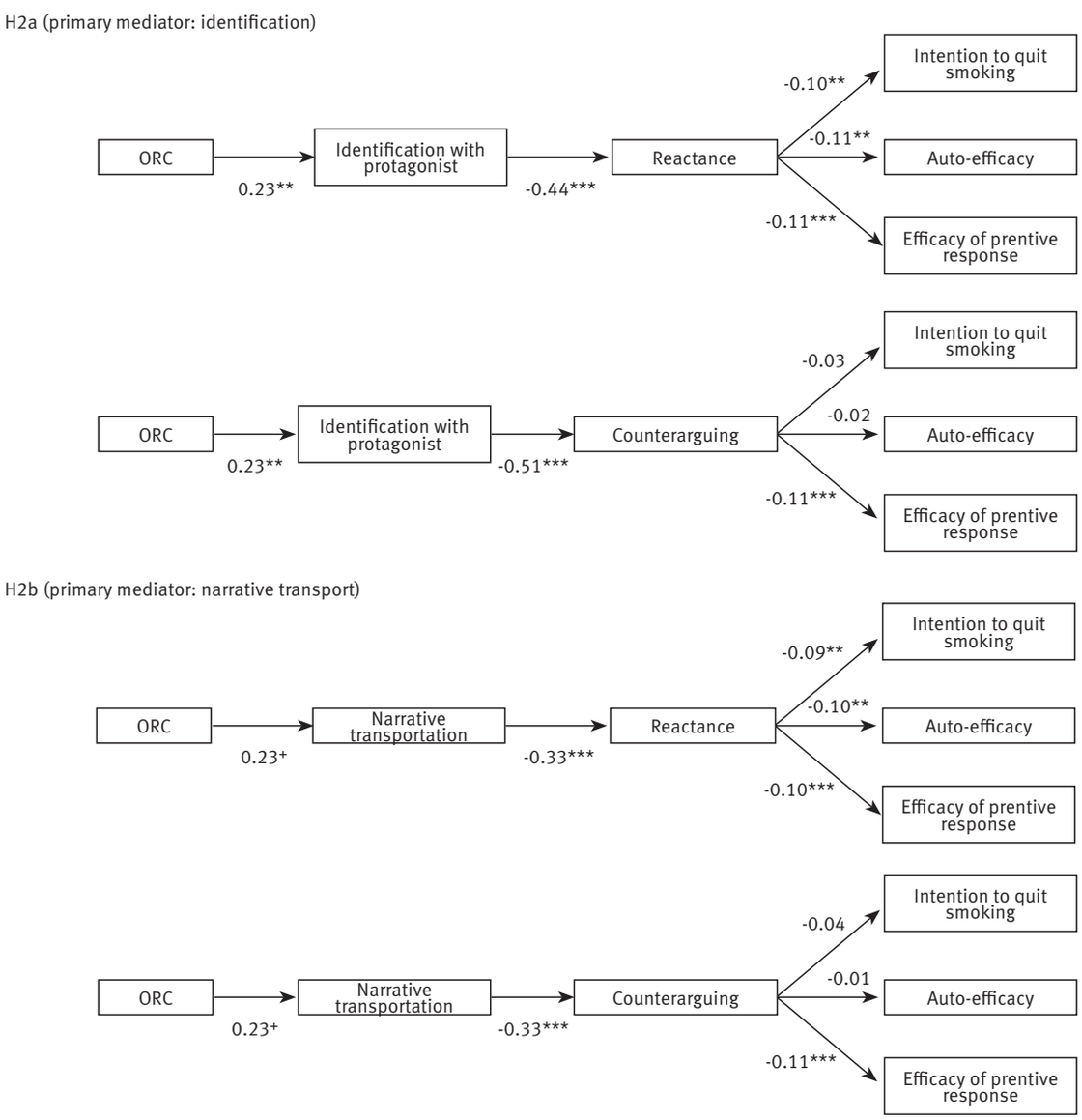


Figure 5. Effect of the experimental condition on narrative transport (H1b).

smoking, expectations of self-efficacy and the perception of efficacy of the preventive response, which would be mediated by identification (H2a) and narrative transport (H2b) (primary mediators) and counterarguing and reactance (secondary mediators). To examine whether the optimal reception condition triggered a significant indirect effect on the dependent variables, we used the PROCESS macro for SPSS (Model 6, serial mediation, 10,000 *bootstrapping* samples to generate 95% confidence intervals by the percentile method; Hayes, 2018). The independent variable (experimental condition) was coded as a multicategorical variable, giving rise to three *dummy* variables (X1, X2, X3) and the establishment of the control condition (third-person narrative with a protagonist of low behavioral similarity) as the reference category (for a similar analytical approach, see: Bolkan, Goodboy & Myers, 2017; Walter et al., 2018). This procedure required the estimation of the indirect effect of the optimal reception condition (X3), while the other two *dummy* variables acted as covariates (Hayes & Preacher, 2014). In this way, the regression coefficients which estimate the indirect effect quantify the difference between exposure to a narrative written in the first person with a protagonist of high behavioral similarity as opposed to exposure to a third-person narration with a protagonist of low similarity. The results of the 12 mediational analyses are shown in Figure 6 and Table 2.

It was observed that the optimal reception condition increased identification with the protagonist of the narrative, which in turn reduced reactance and counterarguing. In addition, the reduction of reactance as a consequence



Note. COR = Optimal Reception Condition (first-person narrative, plus a protagonist with high behavioral similarity to participant by level of nicotine dependence). The figure shows the non-standardized regression coefficients *(B)*. *N* = 621. + *p* < .10, ** *p* < .01, *** *p* < .001.

Figure 6. Mediational analyses (H2).

Table 2. *Indirect effects of the optimal reception condition (ORC) on the intention to stop smoking, expectations of self-efficacy and perception of efficacy of the preventive response (H2).*

Indirect effects	B	Boot *SE*	Boot 95% *CI*
ORC → Identification → Reactance → Intention of stop smoking	**.0108**	**.0065**	**[.0012, .0261]**
ORC → Identification → Reactance → Expectations of self-efficacy	**.0121**	**.0073**	**[.0015, .0297]**
ORC → Identification → Reactance → Efficacy of the preventive response	**.0121**	**.0059**	**[.0027, .0255]**
ORC → Identification → Counterarguing → Intention of stop smoking	.0041	.0057	[-.0051, 0.180]
ORC → Identification → Counterarguing → Expectations of self-efficacy	.0031	.0062	[-.0086, .0167]
ORC → Identification → Counterarguing → Efficacy of the preventive response	**.0138**	**.0069**	**[.0030, .0299]**
ORC → Transportation → Reactance → Intention of stop smoking	.0075	.0059	[-.0009, .0217]
ORC → Transportation → Reactance → Expectations of self-efficacy	.0083	.0067	[-.0010, .0246]
ORC → Transportation → Reactance → Efficacy of the preventive response	**.0083**	**.0056**	**[.0005, .0187]**
ORC → Transportation → Counterarguing → Intention of stop smoking	.0037	.0046	[-.0026, .0154]
ORC → Transportation → Counterarguing → Expectations of self-efficacy	.0009	.0043	[-.0076, .0108]
ORC → Transportation → Counterarguing → Efficacy of the preventive response	.0080	.0060	[-.0009, .0226]

Note. The independent variable was coded with the values 0 = shown a third-person narrative with a protagonist of low similarity (reference category or control group) and 1 = shown a the first-person narrative with a protagonist of high behavioral similarity (ORC). An indirect effect is considered to be statistically significant if the established confidence interval (95% *CI)* does not include the value 0. If the value 0 is included in the confidence interval, the null hypothesis cannot be rejected, as this posits that the indirect effect is equal to 0, i.e., there is no association between the variables involved (Hayes, 2018). The non-standardized regression coefficients *(B)* are shown in the table. The indirect effects which are statistically significant are marked in bold.

of increased identification was associated with a greater intention to stop smoking, more positive expectations of self-efficacy and a greater perception of the effectiveness of the preventive response. However, despite the fact that identification reduced counterarguing, this process was only associated with one of the dependent variables considered: so that the lower counterarguing during the reading of the narrative, the greater the perceived efficacy of the preventive response. Therefore, confirming H2a, we observed three statistically significant indirect effects of the optimal reception condition on the three dependent variables considered which were explained by the increase in identification and the decrease in reactance. Furthermore, we also observed a statistically significant indirect effect of the optimal reception condition on the perceived effectiveness of the preventive response, which was due to higher identification and lower counterarguing.

As for the role of narrative transportation, the results were less consistent, mainly because the optimal reception condition had a marginally non-significant effect (p = .079) on this process. However, it was observed that narrative transportation reduced both counterarguing and reactance. In turn, the reduction of reactance (thanks to the greater narrative transportion) increased the intention to stop smoking, the expectations of self-efficacy and the perceived effectiveness of the preventive response. However, the reduction of counterarguing due to greater transportation was only associated with greater perceived effectiveness of the preventive response. Therefore, a statistically significant indirect effect was only observed through greater narrative transportation and reduced reactance, which implies partial support of H2b.

Discussion

The present study provides evidence on how smoking prevention interventions aimed at adults can be enhanced. It was possible to verify that the variables related to the construction of prevention messages (in particular, the joint effect of narrative voice and behavioral similarity with the audience) have a significant impact on the intention to stop smoking, on the expectations of self-efficacy and on the perception of the effectiveness of the preventive response thanks to the fact that they trigger processes of empathic involvement which, in turn, reduce resistance towards the persuasive message.

Our research includes two innovative aspects with respect to previous studies: the concept of behavioral similarity and the concept of optimal reception condition. To date, similarity has been manipulated only in socio-demographic terms such as sex, age, nationality or ethnic group, and the results have been contradictory (Cohen et al., 2018; Kaufman & Libby, 2012; Tukachinsky, 2014). In our work, we have verified that it is possible to effec-

tively manipulate behavioral similarity by emphasizing in the narrative that the protagonist of the message shares a "common story" with the audience (about nicotine dependence, in this case), which was shown to increase perceived similarity. The second original contribution of our study (within the field of narrative persuasion aimed at smoking prevention) is the concept of *optimal reception condition* (first-person narrative with a protagonist with high behavioral similarity to the audience), given that in previous research, the effect of these variables (similarity and narrative voice) had only been analyzed in isolation (e.g., De Graaf et al., 2016).

Thus, and in accordance with hypothesis 1, it was observed that the optimal reception condition did indeed induce the highest levels of identification with the protagonist (H1a), but did not significantly increase narrative transportation (H1b). As regards the mediational analyses (H2), the optimal reception condition exerted three significant indirect effects on the dependent variables due to increased identification and reduced reactance. In addition, the optimal reception condition also had a statistically significant indirect effect on the perceived efficacy of the preventive response, which was explained by stronger identification and weaker counterarguing.

These results are convergent with previous studies which established that first-person narratives, by being perceived as more personal (because they encourage greater closeness between the reader and the main character) and easier to understand, enhanced identification with the protagonist (Chen et al., 2016, 2017; Christy, 2018; De Graaf et al., 2012; Kaufman & Libby, 2012; Nan et al., 2015). However, the optimal reception condition exerted a marginally non-significant effect on narrative transportation, something not far removed from previous studies such as Banjerjee and Greene (2012), in which the use of the third or first person did not influence narrative transportation. Likewise, in Tukachinsky's meta-analysis review (2014), it was concluded that while the narrative voice did influence identification, this was not the case with narrative transportation. Moreover, in our study it was observed that both narrative transportation and identification reduced reactance, so these results are consistent with the E-ELM (Slater & Rouner, 2002) and the EORM (Moyer-Gusé, 2008), theoretical models, which are widely applied in narrative health communication. In fact, our study showed that both narrative transportation and identification lead to lower levels of counterarguing. Therefore, in accordance with previous research, and as proposed in our second hypothesis, identification and narrative transportation acted as mediating variables (Cohen, Tal-Or & Mazor-Treerman, 2015; De Graaf et al., 2012; Green & Brock, 2000; Hoeken & Fikkers, 2014; Igartua, 2017; Igartua & Barrios, 2012; Walter et al., 2018).

One of the limitations of this study is not having properly controlled for (in the design of the narrative) the effect of demographic similarity, sex and age of the protagonist. Although the meta-analysis of Tukachinsky (2014) concluded that objective similarity (based on demographic criteria such as sex, age, or ethnic group) did not exert a significant effect on identification (but it does do so on narrative transportation and perceived similarity or homophily), this systematic review was based on 48 experimental studies of narrative persuasion in general. Therefore, it is recommended that future studies test whether this result can be extrapolated to the particular field of smoking prevention.

The results obtained allow us to think about various applications in the field of smoking prevention and treatment. First of all, in Spain, the main prevention approach for the risks involved in smoking are the health warnings on cigarette packets, which can be avoided and cause reactance (Rodríguez-Contreras & Igartua, 2018). We therefore propose that tobacco prevention campaigns should be implemented in narrative form, using the first person and designed to stimulate the behavioral similarity between the protagonist and the audience, since the present research has proven that these variables have a significant impact on the intention to quit smoking, on the expectations of self-efficacy and on the perceived effectiveness of the preventive response thanks to the fact that they trigger mechanisms of *affective connection* with the message (in this case, identification with the characters) which weaken reactance.

We believe that a narrative intervention such as the one proposed may target the treatment of smoking, but also constitute a primary prevention tool, since any attempt to reduce tobacco consumption indirectly seeks to prevent the appearance of smoking-linked diseases or health problems. In this sense, as seen in the *Tips from Former Smokers* campaign (developed in the United States), the experience of a former smoker (i.e., someone who has overcome nicotine addiction) would be used to prevent smoking (i.e., not start smoking) as well as helping active smokers to quit, thus avoiding the harm that this may cause them.

Secondly, a strategy that is increasingly present in the field of health, and more specifically, in the field of smoking prevention, is the development of mobile applications to stop smoking (Iacoviello et al., 2017; Ubhi, Michie, Kotz, Wong & West, 2015). It would therefore be interesting to create mobile smoking prevention applications in which the user is allowed to configure their avatar based on behavioral similarity (since, as observed in previous studies, demographic similarity does not yield conclusive results) and to test whether the fact that the user can choose that the protagonist has similar characteristics to him- or herself makes the application more effective. This type of application would be particularly useful in the prevention

of smoking in young people and adolescents, given their intensive use of smartphones. In addition, although smoking has decreased in recent years among 15 to 24-year-olds (Rodríguez Muñoz, Carmona Torres, Hidalgo Lopezosa, Cobo Cuenca & Rodríguez Borrego, 2019), the prevalence of smoking among adolescents aged 15-18 still stands at 8.7% (Leal-López, Sánchez-Queija & Moreno, 2019).

In conclusion, the present study yields relevant insights for health-related narrative persuasion research showing how certain characteristics of narrative messages (such as the use of narrative voice in the first person and the inclusion of elements establishing similarity between the protagonist and the audience) can be useful in improving interventions for the smoking prevention and treatment.

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Conflict of interests

The authors of this study declare that they have no conflict of interests.

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The role of personality on disordered gaming and game genre preferences in adolescence: Gender differences and person-environment transactions

El papel de la personalidad en el juego problemático y en las preferencias de géneros de videojuegos en adolescentes

Francisco J. López-Fernández*, Laura Mezquita*,**, Mark D. Griffiths***, Generós Ortet*,**, Manuel I. Ibáñez*,**.

* Department of Basic and Clinical Psychology and Psychobiology, Universitat Jaume I, Castellón, Spain.
** Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Castellón, Spain.
*** International Gaming Research Unit, Psychology Department, Nottingham Trent University, Nottingham, England, UK.

Abstract

Playing video games is one of the world's most popular leisure activities, especially for teenagers. The main aim of the present study was to examine additive and moderation effects of gender and personality to explain individual differences in problematic gaming and video game genre preferences in adolescence. 776 Spanish high school students (mean age = 14.29 years, *SD* = 1.59, 50.64% girls) completed the questionnaires of the Five-Factor Model of personality, frequency of video gaming, disordered use, and the video games they mostly played.

Gender differences were observed for gaming behaviors: boys played more and presented much more disordered gaming than girls. Boys preferred competitive genres; for example, action-*shooters*, sport, fight and strategy games. Girls preferred nonviolent and ocasional game genres; for example, social simulation, and brain and skill games. Gender moderated the association between personality and disordered gaming: disordered gaming was associated with low agreeableness and low conscientiousness in boys, and with low extraversion and low conscientiousness in girls. Low consciousnness moderated the association between gaming frequency and problematic use of video games: playing more video games led to disordered gaming, mainly in irresponsible and impulsive individuals. Though small, significant associations were found among all of the personality domains and video game genre preferences. These findings highlight the relevance of gender and personality for gaming behaviors in adolescence, and suggest paying more attention to gender-dependent differences and person-environment transactional processes when studying gaming-related behaviors.

Keywords: Video games; addiction; game genres; personality; gender.

Resumen

Jugar a videojuegos es una de las actividades de ocio más populares en adolescentes. El principal objetivo de este estudio fue examinar los efectos aditivos y de moderación del género y la personalidad en el juego problemático y en la preferencia en géneros de videojuegos durante la adolescencia. 776 estudiantes españoles (media de edad = 14,29; *DT* = 1,59; 50,64% chicas) cumplimentaron cuestionarios del Modelo de los cinco grandes de personalidad y de conductas relacionadas con videojuegos. Se observaron diferencias de género en conductas relacionadas con videojuegos: los chicos jugaban más y presentaron mucho más uso problemático que las chicas. Ellos prefirieron géneros competitivos; por ejemplo, juegos de acción-*shooters*, deportes, lucha y estrategia. Las chicas prefirieron géneros no violentos y ocasionales; por ejemplo, simulación social, y juegos de habilidad y lógica. El género moderó las asociaciones entre personalidad y juego problemático: el juego problemático se asoció a baja amabilidad y baja responsabilidad en chicos, y a baja extraversión y baja responsabilidad en chicas. La baja responsabilidad moderó las asociaciones entre frecuencia de juego y uso problemático: jugar más a videojuegos conducía a un uso problemático de éstos, principalmente en individuos irresponsables e impulsivos. Se encontraron asociaciones pequeñas pero significativas entre la personalidad y preferencias en géneros de videojuegos. Estos hallazgos destacan la relevancia del género y la personalidad en las conductas relacionadas con videojuegos durante la adolescencia, y animan a prestar más atención a las diferencias dependientes del género y a las transacciones persona-ambiente al estudiar estas conductas.

Palabras clave: Videojuegos; adicción; géneros de videojuegos; personalidad; género.

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Send correspondence to: Manuel I. Ibáñez.
Depart. of Basic and Clinical Psych. and Psychobiology, Univer. Jaume I, Av. de Vicent Sos Baynat, s/n, 12071 Castellón, Spain. Phone +34 964729690
E-mail: iribes@uji.es

Playing video games has become one of the world's most popular leisure activities in recent decades (Entertainment Software Association —ESA— 2018). Approximately 47% of the Spanish population regularly plays video games (*Asociación Española de Videojuegos* —AEVI— 2018). For a minority of players, gaming can lead to negative effects that resemble the addiction components of other addictive disorders, including salience, mood modification, tolerance, withdrawal or relapse (Griffiths, 2005). Accordingly, DSM-5 (American Psychiatric Association —APA— 2013) has included Internet Gaming Disorder (IGD) as a potential behavioral addiction that deserves further study. Recently Gaming Disorder diagnosis has been incoporated into ICD-11 (Bobes, Flórez, Seijo & Bobes, 2019; World Health Organization —WHO— 2017).

The prevalence of disordered gaming is estimated between 1-9%, depending on cut-off criteria, age, gender or socio-cultural differences (Gentile, 2009; Gentile et al., 2017; Mihara & Higuchi, 2017; Paulus, Ohmann, Von Gontard & Popow, 2018). Disorder gaming may lead to loneliness and poor academic performance (Gentile et al., 2011; Lemmens, Valkenburg & Peter, 2011), and has shown strong associatons with symptoms of affective, emotional and attention deficit hyperactivity disorders (González-Bueso et al., 2018; Mihara & Higuchi, 2017; Müller et al., 2015). Therefore, a better understanding of the factors that facilitate disordered gaming would help prevent such detrimental effects.

One widely studied risk factor for IGD is personality (Gervasi et al., 2017; Mihara & Higuchi, 2017; Paulus et al., 2018; Şalvarlı & Griffiths, 2019). Personality traits have shown to be relevant in a wide variety of life outcomes (Ozer & Benet-Martínez, 2006), including several addictive-related behaviors (Andreassen et al., 2013; Ibáñez et al., 2010; Mezquita et al., 2015). Nowadays, the most accepted personality framework of personality is the Five-Factor Model (FFM) (John, Naumann & Soto, 2008), which proposes five basic dimensions: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience (McCrae & Costa, 2008). According to recent systematic reviews, the most consistently FFM personality domains related to IGD are neuroticism, low conscientiousness and low agreeableness (Gervasi et al., 2017; Şalvarlı & Griffiths, 2019).

Most of these studies have been conducted with adults (e.g., Braun, Stopfer, Müller, Beutel & Egloff, 2016; Charlton & Danforth, 2007). Therefore, their relevance in preadolescence and adolescence is still not well-stablished. This is a major gap in IGD research because this lifespan stage is particularly important for the development of psychological problems associated with problematic video gaming (Mihara & Higuchi, 2017; Paulus et al., 2018). As far as we know, very few studies have explored the association of FFM domains and disordered gaming in preadolescents and adolescents. At these ages, problematic video gaming has been consistently associated with low conscientiousness (García-Oliva & Piqueras, 2016; Vollmer, Randler, Horzum & Ayas, 2014; Wang, Ho, Chan & Tse, 2015). However, and with regard to other FFM dimensions, the results are less conclusive: low extraversion has been shown to be associated in two studies (García-Oliva & Piqueras, 2016; Vollmer et al., 2014), whereas low agreeableness, high neuroticism (Vollmer et al., 2014) and low openness (Wang et al., 2015) only in one study. This scarce and somewhat inconsistent finding reveals the necessity for more research in the additive effects of personality on disordered video gaming during adolescence, which is our first study aim.

Another scarcely explored issue in the video games and personality field is *person-environment transactional processes*; i.e., how personality complexly interplays with the environment to influence behavior (Caspi & Roberts, 2001). Such processes have been described in the video games and aggressivity field, with some studies suggesting that exposure to violent video games may promote aggressive behavior, but mainly in individuals with an aggressive personality (e.g., Anderson & Dill, 2000; Markey & Markey, 2010). This data may be indicative of a *reactive transaction,* i.e. different individuals face the same environment but react to it differently according to personality characteristics (Caspi & Roberts, 2001). However, and as far as we know, the role of person-environment transactions in the development of disordered gaming remains uncharted. One environmental risk factor for IGD is the amount of time spent playing video games (Gentile, 2009; Mihara & Higuchi, 2017), although only a minority of enganged players tends to develop problematic gaming (Charlton & Danforth, 2007). This may be suggestive of a *person-environment transactional process*, i.e. higher gaming frequency would impact more negatively to certain gamers but not others because of their personal characteristics. Exploring if personality moderates the association of exposure to video games on gaming disorder is our second study aim.

Personality may also be relevant for genre gaming preferences but, as far as we know, this topic has not yet been explored in adolescents. Studies suggest that low agreeable adults would prefer violent video games (Chory & Goodboy, 2011; Greitemeyer & Sagioglou, 2017), extraverted gamers would prefer action games, and players high in openness would opt for role-playing games –RPGs– (Braun et al., 2016). It has been suggested that some genres may be more potentially addictive than others (Rehbein, Staudt, Hanslmaier & Kliem, 2016). Particularly, it has shown that preference of Role Playing Games (RPGs), shooter and simulation games contributes to elevated gaming time (Rehbein et al., 2016), and that RPGs, specially Massively Multiplayer Online Role-Playing Games (MMORPGs), and shooter games, tend to present the stronger associations with disordered gaming (Lemmens & Hendrix, 2016; Müller et al., 2015). Therefore, exploring the personality characterstics related to genre preferences in adolescence is also a relevant issue, and is our third study aim.

Last, another well-established risk factor for gaming-related behaviors is gender. Males play video games and experience disordered gaming much more than females (Mihara & Higuchi, 2017; Paulus et al., 2018). Males also tend to prefer more competitive and aggressive video games genres, e.g. action-shooters or sports games. Females tend to prefer more casual nonviolent games, e.g., puzzles or platform genres (Lemmens & Hendriks, 2016; Rehbein et al., 2016; Scharkow, Festl, Vogelgesang & Quandt, 2015). Yet despite these clear gender differences, the possibility that risk factors for disordered gaming were different for males and females has scarcely been studied. Regarding personality, as far as we know, only one study has explored the association between personality and adolescents disordered gaming separately for boys and girls (Garcia-Oliva & Piqueras, 2016). It found that low conscientiousness and low extraversion were associated with addiction to video games in boys, but no significant effects of personality were noted for girls. Although this preliminary finding requires replication, it indicates that the possible gender-dependent role of personality on video game-related behaviors deserves more research attention, which is our fourth study aim.

In short, we have reviewed some relevant gaps regarding the role of gender and personality in the field of adolescent video game-related behaviors, and our main aim is to systematically explore them. Specifically, the additive role of gender and FFM personality traits will be examined in disordered gaming and game genres preferences. Additionally, we will explore the moderation role (a) of personality on the association between video game frequency and disordered gaming; and (b) of gender on the association between personality and video game-related behaviors. It was hypothesized that boys would present more problematic video gaming than girls, and that boys would prefer competitive and aggressive genres, whereas girls would opt for puzzle and casual games. Regarding the role of personality, low conscientiousness and low extraversion would be associated with disordered gaming, principally among boys. As studies about personality and genre preferences are scarce, no systematic hypotheses were proposed, but it could be expected low agreeableness to be associated with competitive genres, extraversion with action games, and openness with RPGs. Last, according to previous data on other topics such as violent video games and aggressive behavior, it was hypothetized that those personality risk factors for disordered gaming would interact with gaming frequency in predicting disordered gaming.

Method

Participants and procedure

The participants were recruited from two public high schools in the urban area of Castellón de la Plana, located in the east of Spain. Of the 1106 students invited to participate, 835 returned signed parental written consent. Of these, 59 participants did not attend asssessment sessions or did not complete all the questionnaires. The final sample consisted of 776 adolescents (393 girls), whose ages range was 12-17 years, with a mean age of 14.29 years (*SD*=1.59).

This *ex post facto* and transversal study (Montero & León, 2005) formed part of broader research about psychosocial risk factors involved in adolescent mental health. Trained research assistants administered a battery of questionnaires in three one-hour sessions separated by one week. Those students previously authorized by their parents/legal guardians voluntarily completed a socio-demographic survey together with the rest of the battery of self-administered and paper-pencil questionnaires. Research assistants gave detailed instructions to the students, highlighted the confidentiality of the data and the importance of the honesty in their responses, and helped the students when necessary (for more details see Moya-Higueras et al., 2020).

Measures

The JS NEO-A60, (Walker, López & Mezquita, 2018) was used to assess the FFM personality dimensions of neuroticism, extraversion, openness, agreeableness and conscientiousness. This scale is a 60-item abridged form of the Junior Spanish version of the NEO-PI-R (Costa & McCrae, 1992), namely the JS NEO (Ortet et al., 2012), which replicated satisfactorily the adult NEO-PI-R factor structure in samples aged from 12 to 17 years and showed adequate scores in reliability (every personality trait showed a coefficient α higher than .82) and construct validity (a joint factor analysis of the test and a Big Five questionnaire focused on children was provided). The Cronbach's alphas for this study were .83 for neuroticism, .83 for extraversion, .75 for openness, .82 for agreeableness, and .89 conscientiousness.

Gaming frequency was reported on a 6-point Likert scale (from 0 = *"never or almost never"* to 5 = *"between 3 to 5 hours a day")*. Furthermore, players reported up to five of their most frequently played video games, which were categorized according to previous studies (e.g., Lemmens & Hendriks, 2016; Rehbein et al., 2016) as: action-shooter (e.g., *Call of Duty*); sports (e.g., *FIFA,* also including driving sports like *MotoGP*); strategy (mainly MOBA games, e.g. *Clash Royale*); brain+skill (including highly intercorrelated genres —Rehbein et al., 2016—: puzzle brain games, e.g. *Candy Crush Saga*; puzzle skills games, e.g. *Piano Tiles*; fitness games, e.g. *Wii Sports*; and skill platform games, e.g. *Super Mario Bros)*; adventure (including adventure games without shooter components, e.g. *Assassins' Creed*); social simulation (e.g., *The Sims*); construction (e.g., *Minecraft*); RPGs (e.g., *Skyrim,* including MMORPGs, e.g. *World of Warcraft*); and fighting (e.g., *Mortal Kombat*).

A Spanish adaptation of a disordered gaming scale for youths was employed (Gentile, 2009). The original 11 items was back-translated, which included addiction components such as salience, mood modification, tolerance, withdraw-

al or relapse. Those participants considered pathological gamers by the original scale's study displayed higher spent time on gaming, lower academic performance, and attention problems (Gentile, 2009). For the current study, the participants indicated their frequency of video game-related problems on a 4-point Likert scale (from 0 = "*never or almost never*" to 3 "*almost always or always*") during the last 12 months. According to the parallel analysis run using Monte Carlo PCA (Watkins, 2006), a one-factor structure was obtained with the EFA, where all items presented adequate factor loadings ranging from .49 to .81. Cronbach's alpha in this sample was .88. In order to establish the cut-off point for the categorization of disordered gamer, we followed the procedure of the original study (Gentile, 2009). Specifically, we coded categories *"almost always or always*" and "*many times*" as 1, category "*sometimes*" as .5, and *"never or almost never"* as 0, and those adolescents who exhibited at least 6 of the 11 criteria assessed by the scale were considered pathological gamers.

Statistical analysis

Version 21 of the SPSS statistic package was used to calculate the descriptive statistics, correlations, t-test analyses and multiple linear regression analyses. Those missing values that represented less than 5% in a questionnaire were replaced with the mean score of the items remaining in that scale. In order to depict graphically interactions between personality risk factors and gaming frequency in disordered gaming; it was employed the InterActive software, an open-source analysis and data-visualization application (McCabe, Kim & King, 2018).

Ethics

This research was approved by the Ethical Committee of the Universitat Jaume I, and was authorized by the School Board of the participating high schools and by the Regional Valencian Authorities. Participants and their parents/legal guardians were informed about the study and provided parental informed consent. All the study procedures were followed in accordance with the Declaration of Helsinki.

Results

Regarding the descriptive data, 560 of the 776 participants reported playing video games in the last month, 92.69% for 383 boys and 52.16% for 393 girls. In addition, 38.9% of boys and 8.3% of girls played daily. Moreover, 6.4% of all the participants were labeled as "disordered gamers", 11.1% boys (43 individuals) and 0.8% girls (3). The *t*-test analyses showed that girls presented lower gaming frequency (Cohen's $d = 1.26$, $p < .001$), and higher scores for openness (Cohen's $d = .54$, $p < .001$), neuroticism (Cohen's $d = .43$, $p < .001$), agreeableness (Cohen's $d = .30$, $p < .001$) and conscientiousness (Cohen's $d = .23$, $p < .001$) than boys.

Multiple linear regression analyses were run to explore if personality predicted gaming frequency, but only openness presented a significative association that explained 1.3% of variance ($b = .08$, $p = .01$) after controlling for age and gender (age; $b = -.05$, $p = .070$; gender; $b = .54$, $p = .000$). The additive role of age, gender, personality and gaming frequency was explored on disordered gaming. In addition, it was also examined in a last step: a) if gender moderated the prediction of personality and gaming frequency on disordered gaming; and b) the moderation role of personality in the gaming frequency-disordered gaming association. All the possible relevant interactions were included in the regression model in this last step to control for potential confounders, according to the recommendations by Keller (2014). Interactions between personality and gaming frequency were found (conscientiousness x gaming $b = -.09$; $p = .007$) as well as between gender and personality (agreeableness x gender, $b = .09$; $p = .008$; conscientiousness x gender; $b = .15$; $p = .000$). These two last interactions indicated that the association between some personality domains and disordered gaming differed for boys and girls. Consequently, the regression analyses were performed separately for each gender.

Table 1 presents the regression analyses for the whole sample, and also for boys and girls separately. Low conscientiousness was associated with disordered gaming for both genders. Low agreeableness was related to pathological gaming among males, whereas low extraversion and high openness were associated with disordered gaming in females. Gaming frequency was also related to disordered gaming for both genders. A significant gaming frequency-low conscientiousness interaction was found for both boys and girls.

Table 1. *Multiple Linear Regressions of Disordered Gaming as Dependent Variable.*

		Disordered gaming		
		Total sample (776)	**Males (383)**	**Females (393)**
Step 1				
	Gender	-.44***	-	-
	Age	.07*	.09	.05
	ΔR^2	.20***	.01	.01
Step 2				
	Neuroticism (N)	.04	.09	.03
	Extraversion (E)	-.06	-.01	-.20***
	Openness (O)	.06	.04	.11*
	Agreeableness (A)	-.13**	-.17**	-.05
	Conscientiousness (C)	-.18***	-.27***	-.12*
	ΔR^2	.07***	.15***	.08***
Step 3				
	Gaming frequency	.25***	.24***	.30***
	ΔR^2	.04***	.06***	.09***
Step 4				
	NxGaming frequency	.01	.04	.02
	ExGaming frequency	.00	.01	-.03
	OxGaming frequency	.01	.00	.05
	AxGaming frequency	.05	.05	.09
	CxGaming frequency	-.08*	-.11*	-.13*
	ΔR^2	.01	.01	.02
	R^2	.32	.22	.19

Note. Males were assigned 1 and females were assigned 2.
* $p < .05$. ** $p < .01$. *** $p < .001$.

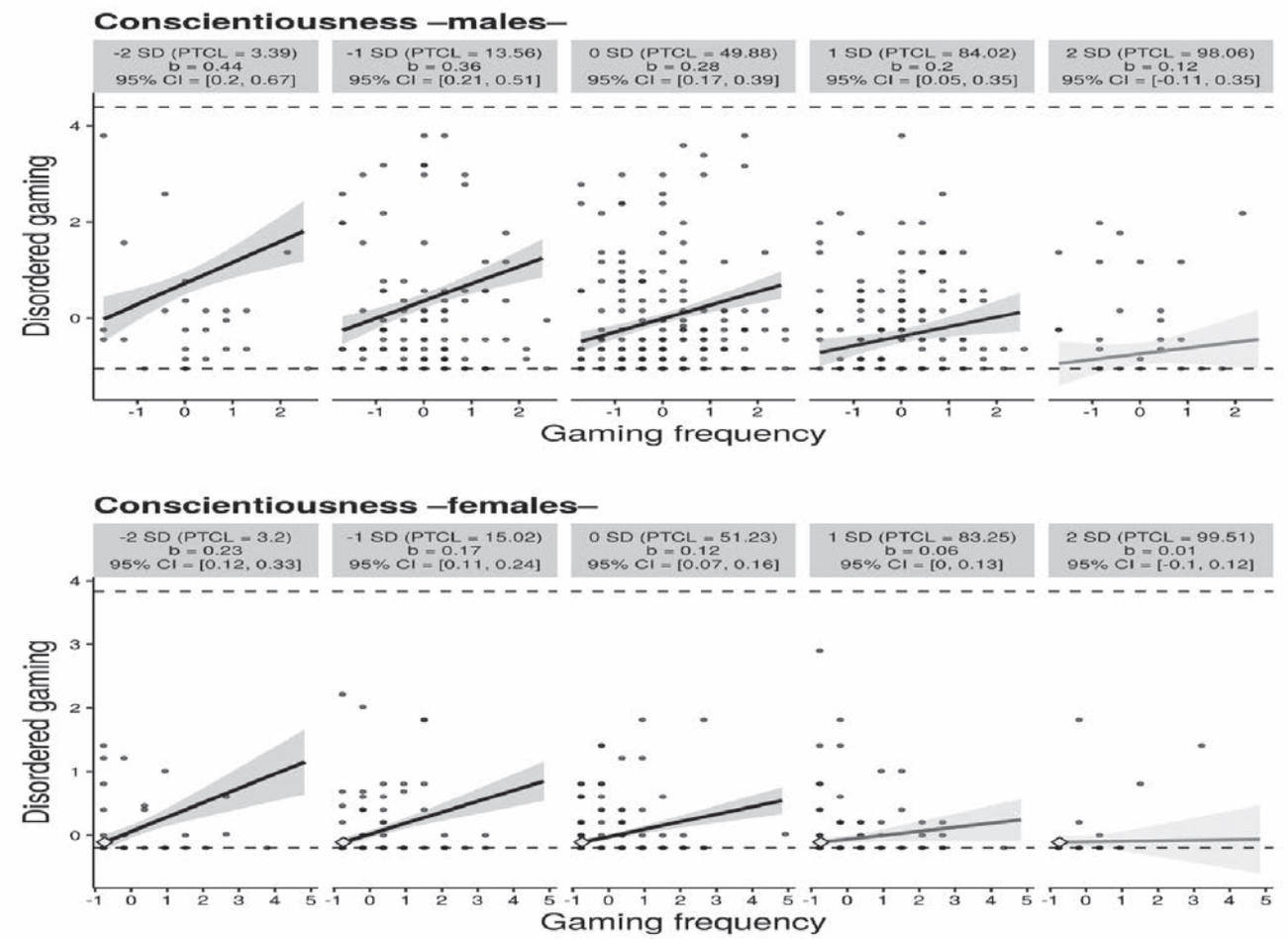

Figure 1. Illustrations of moderating effects between conscientiousness with gaming frequency on disordered gaming. Simple slopes are provided for levels of the moderator 2 SD and 1 SD below the mean, at the mean, and 1 SD and 2 SD above the mean. Each graphic shows the computed 95% confidence region (shaded area), the observed data (gray circles), the maximum and minimum values of the outcome (dashed horizontal lines), and the crossover point (diamond). The x-axes represent the full range of the focal predictor. CI = confidence interval; PTCL = percentile.

Figure 1 graphically presents the interactions found in the regression analyses. It depicts the negative impact of gaming frequency on problematic gaming according to different levels of conscientiousness as a moderator. The results showed that gaming frequency was highly associated with disordered gaming at low conscientiousness levels, whereas no associations appeared at high conscientiousness levels.

Multiple linear regressions were peformed for each game genre with 547 participants (375 males, 172 females) who indicated the name of at least one played video game. The role of age, gender, personality and gender-personality interactions was explored. It was found no moderation effects of gender on most genres, except for action-shooter (extraversion x gender; b = -.09; p = .032) and social simulation (openness x gender; b = .10; p = .03) games. The regression analyses for the whole sample are presented in Table 2.

Regarding gender and genre preferences, the regression coefficients indicated that boys prefered playing more competitive games, (action shooter, sports games, strategy and fighting games), and girls reported using more social simulation and brain+skill games. For personality, all the dimensions presented minor associations with genre preferences. The most played genres (action-shooter, sports) presented a similar pattern of associations, with less openness and more extraverted teenagers prefering these games (in action-shooter, this pattern was found only for boys; for extraversion, b = .15; p = .006; for openness, b = -.10; p = .069). Strategy games were asociated with low aggreableness. Brain+skill category was associated with openness and conscientiousness. Social simulation and adventure games presented a similar pattern of relationships, with open to experience and introverted youngsters preferring these genres (in social simulation games, these effects were more evident in females; for extraversion, b = -.15; p = .073; for openness, b = .14; p = .085). Construction games were predicted by neuroticism. Fighting games were associated with low aggreeableness, low consciousness and openness. Openness, low conscientiousness and introverson predicted preferences for RPGs games.

Table 2. *Multiple Linear Regressions of the Videogame Genres as Dependent Variables.*

	Game Genre (n of players)	Action *-shooter* (292)	Sport (251)	Strategy (175)	Brain +Skill (152)	Adventure (65)	Social simulation (47)	Construction (40)	Fighting (32)	RPG (31)
Step 1	Gender	**-.40*** **	**-.26*** **	**-.20*** **	**.41*** **	-.06	**.35*** **	-.09	**-.16*** **	-.06
	Age	-.05	-.01	-.02	-.07	-.03	**-.12** **	**-.14** **	.01	.02
	ΔR^2	**.15*** **	**.06*** **	**.04*** **	**.17*** **	.01	**.15*** **	**.03** **	**.02** **	.00
Step 2	Neuroticism	.03	-.05	-.04	.03	.02	-.02	**.17*** **	-.08	.05
	Extraversion	**.10***	**.09***	-.05	.05	**-.09***	**-.09***	.01	.00	**-.10***
	Openness	**-.11***	**-.10** **	.04	**.12** **	**.10***	**.09***	.06	**.10***	**.19*** **
	Agreeableness	.04	.03	**-.14** **	.05	-.03	-.03	.04	**-.16** **	-.02
	Conscientiousness	.06	-.03	-.01	**.11***	-.03	.01	.00	**-.11***	**-.11***
	ΔR^2	**.02***	**02***	.02	**.04***	.02	.01	**.03** **	**.04** **	**.05*** **
	R^2	.17	.10	.06	.21	.01	.16	.06	.05	.05

Note. RPG = Role-playing Game; b = standardized beta; ΔR^2 = change in variance; R^2 = total R^2. Males were assigned 1 and females were assigned 2.
* p <.05. ** p < .01, *** p <.001.

Discussion

The present study shows the relevance of personality and gender for disordered gaming and game genre preferences in adolescents. As it was hypothetized, boys showed much more disordered gaming and preferred different game genres than girls. Furthermore, specific profiles of personality seemed to modestly guide the preference for certain genres. Personality also showed rellevance for disordered gaming, with low conscientiousness to be related in both boys and girls, and other FFM dimensions showing gender-dependent associations: low agreeablennes in boys, and introversion and high openness in girls. Last, we also found person-environment transactional process in disordered gaming: a higher frequency of video gaming appeared to impact more negatively in some players than others, partially because of its personality characteristics; thus low consciencious adolescents who played more frequenly tended to present higher disordered gaming levels than other youngsters.

In our sample, 72.16% played video games in the last month, which is a very similar percentage of gamers reported in Spain (Buiza-Aguado, Alonso-Canovas, Conde-Mateos, Buiza-Navarrete & Gentile, 2018). Nevertheless, the percentage of daily gamers was much lower (22.7%), another comparable result found among Spanish adolescents (Gonzálvez, Espada & Tejeiro, 2016). In addition, 6.4% of the total sample was categorized as disordered gamers, which is similar to the original study estimated prevalence of 7.5% (Gentile, 2009), to the estimates of 7.7%-8.3% of the pathological gaming prevalences in Spanish adolescents (Buiza-Aguado et al., 2018; Lopez-Fernandez, Honrubia-Serrano, Baguley & Griffiths, 2014), and to the 5.1% estimate of IGD risk in a representative European adolescent sample (Müller et al., 2015).

Regarding the role of gender, boys were much more likely to play video games and to show disordered gaming than girls, as previously found (Mihara & Higuchi, 2017; Paulus et al., 2018). Genre preferences were also affected by gender, with girls preferring social simulation and mental/skill puzzle games; while boys choose competitive and aggressive video games, e.g. action-shooter, sports, strategy and fighting games, which fall in line with previous research (e.g., Lemmens & Hendriks, 2016; Rehbein et al., 2016; Scharkow et al., 2015). Gender differences on personality may partially explain these findings. Girls tend to show higher scores in openness whereas boys tend to present lower levels of agreeableness (e.g., Ortet et al., 2012; Costa & McCrae, 1992), what may led girls to prefer more intellectual video games whereas led boys to play more competitive and violent ones. These gender-based differences on genre preferences may help to explain why males, who prefer games featuring more time-consuming and engagement characteristics, get more involved in gaming and are more hard-core players than females (Rehbein et al., 2016; Scharkow et al., 2015).

In relation to personality, our results replicated the role of low conscientiousness observed in adults (Gervasi et al., 2017; Şalvarlı & Griffiths, 2019) and in the few studies done with adolescents (García-Oliva & Piqueras, 2016; Vollmer et al., 2014; Wang et al., 2015). The other relevant personality domain for video game addiction in adulthood is neuroticism (Gervasi et al., 2017; Şalvarlı & Griffiths, 2019). Nevertheless, no effect of this dimension was found in adolescent disordered gaming, which agrees with other studies in youngsters (García-Oliva & Piqueras, 2016; Wang et al., 2015). Collectively, these results suggest that negative emotionality is less important for disordered gaming in adolescence than in later life stages.

Other personality factors that have also been associated with adolescent disordered gaming are introversion (Garcia-Oliva & Piqueras, 2016; Vollmer et al., 2014) and low agreeableness (Vollmer et al., 2014). Our data support the relevance of these personality characteristics, but suggest a differential role according to gender: introversion was related to disordered gaming in females while low agreeableness presented a significant relation for males. This latter association may imply that competitive and aggressive motives seem more relevant for boys and lead to greater gaming perseverance despite their negative consequences (Vollmer et al., 2014). The role of introversion in disordered gaming exclusively for girls can be explained by the gender differences associated with game genre preferences. Girls preferred social simulation and brain/skill games with fewer social and exciting components than other genres like action-shooter or sport games, which are mainly preferred by boys. Playing these games constitutes a solitary leisure activity, and girls with few social skills (Gentile et al., 2011; Kowert, Vogelgesang, Festl & Quandt, 2015) and introverted characteristics (Garcia-Oliva & Piqueras, 2016; Vollmer et al., 2014) would be at increased risk of disordered gaming. Although these suggestive findings require replication, they imply that future research should pay more attention to gender-dependent differences in risk and protective variables involved in gaming-related behaviors.

Another risk factor for IGD is gaming frequency (Gentile, 2009; Mihara & Higuchi, 2017; Vollmer et al., 2014). In our study, gaming frequency was related to disordered gaming, but the magnitude of this association was between low and moderate. This effect size may suggest that the detrimental effects of longer video gaming would affect some adolescents but not others. Accordingly, it was found that the amount of time playing video games would more negatively impact those adolescents who are less responsible and more impulsive. The effects of this interaction have been found for both genders, and remained robust when controlling for other interaction confounders (Keller, 2014). Similar moderation effects have been described in video gaming-related behaviors. It has been shown that exposure to violent video games adversely affects mainly those individuals with aggressive-related personality dispositions, which make them susceptible to such violent media (e.g., Anderson & Dill, 2000; Markey & Markey, 2010). Similar effects have been observed in other addictive behaviors, such as alcohol use, where environmental risk factors (i.e. poor parental monitoring and high alcohol availability) seem to exert detrimental effects on drinking behavior mainly in disinhibited youngsters (Pedersen & McCarthy, 2008). Altogether, these findings would reflect person-environment transactional processes (Caspi & Roberts, 2001), which suggest that low conscientiousness and impulsive trais would exacerbate the harmful effects of environmental risk factors on addictive behaviors.

Regarding gaming genre preferences, the present study found a minor, but significant, role of personality. Openness was related to playing RPGs, brain+skills, adventure, fighting, and social simulation games. RPGs, adventure, and fighting games involve fantastic and unrealistic elements, so those youngsters with a fertile imagination can be more attracted by them (Braun et al., 2016). Open-to-experience individuals, especially girls, would also prefer less conventional and mentally challenging game genres, such as brain+skill and social simulation games, whereas low-open adolescents would prefer more conventional and realistic games like sports and action-shooter games. Extraversion also plays a significant role when choosing games. Action-shooters and sports genres were associated with extraversion, probably because these games contain a more social component (e.g., multiplayer online features) and tend to be more exciting and arousing (Braun et al., 2016; Chory & Goodboy, 2011). In contrast, introverted adolescents tend to prefer RPG, adventure, and social simulation games. These data suggest that introverted players would prefer to spend their time playing more solitary games, some of them to cope with their social necessities by simulating social interactions in a virtual world (Kowert et al., 2015). Low agreeable players tend to choose fighting and strategy games (mainly MOBA), probably because of their competitive tendencies and the violent gratification of in-game fighting (Chory & Goodboy, 2011; Greitemeyer & Sagioglou, 2017). Consciousness was also relevant for game preferences, with high scores for choosing "positive" and "responsible" games like training games for cognitive and psychomotor abilities. Conversely, low consciousness predicted fighting and RPGs preferences, genres that usually involve a lot of time on gaming (Rehbein et al., 2016) and have been associated with an increased IGD risk (Lemmens & Hendrix, 2016). Finally, neuroticism was associated with construction games (e.g., *Minecraft*). Neuroticism has been related to obsessive-compulsive symptoms (e.g., Samuels et al., 2000), which could explain why high players in neuroticism prefer playing them where the performed activity is repetitive.

This study presented some limitations. First, the study consisted of a convenience sample since the high schools were not randomly chosen. Second, the data were collected via self-report questionnaires, so data may be affected by biases such as social desirability. Third, the assignation of a given game to a specific genre was artificial to some extent because games usually include mixed features from different genres. Furthermore, there was a significant range restriction for the game genres variable (participants were allowed to mention up to five games, but of the nine genres, only one, presented a range from 0 to 5). This range restriction, together with the relative heterogeneity of the games included in each genre, may explain partially the small effect sizes found in the genres-personality as-

sociation. Fourth, the 'disordered gamers' categorization should be better understood as an index of problematic video game use instead of a clinical IGD diagnosis. In addition, the original scale (Gentile, 2009) was developed before the inclusion of the IGD in the DSM-5. Therefore, the study's prevalence could be underestimated due to the fact that the DSM-5 establishes 5 criteria for IGD diagnosis instead of the 6 that our study scale uses. Furthermore, the cut-off point could vary due to cultural differences and gamer profiles (Bernaldo-de-Quirós, Labrador-Méndez, Sánchez-Iglesias & Labrador, 2020). Last, causal inferences should not be made because of this study's cross-sectional design. Personality traits may predispose to gaming behaviors, but video games have been shown to also influence certain personality characteristics (e.g., Greitemeyer & Sagioglou, 2017). Further research should examine the longitudinal relationships between personality and gaming to establish the direction that underlies the associations of the examined variables. Despite these limitations, this study also presents some remarkable strengths. It deals with the relatively unexplored topic of the role of gender and personality on the use and abuse of video games in adeolescence. To this end, instruments with sound psychometric qualities were administered in a relatively wide sample of preadolescents and adolescents, and followed a novel approach by examining the moderator role of gender and personality in disordered gaming.

The present study highlights the importance of gender and personality in explaining gaming behavior. Boys prefer more competitive aggressive video games, whereas females opt for more nonviolent and occasional games. Distinct personality characteristics appeared to be differentially involved in disordered gaming for boys and girls: low conscientious and introverted girls and low conscientious and disagreeable boys presented higher disordered gaming levels. Personality moderated the negative impact of gaming frequency on problematic gaming: regular video game use was related to disordered gaming mainly in low conscientious adolescents. Last, different personality profiles would partly guide the choice of specific video games. These findings may help us to better understand the adolescent gaming field, and might be useful for developing personalized treatment programs and prevention strategies for problematic video game use based on gender and/or personality characteristics, in line with personality-targeted prevention and intervention programs developed for other addiction-related behaviors (Conrod, 2016).

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Conflict of interests

The authors declare no conflict of interests.

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Parkinson's disease after psychosurgery for the treatment of cocaine addiction

Enfermedad de Parkinson después de la psicocirugía para el tratamiento de la adicción a la cocaína

Alejandro Fuertes-Saiz*,**, Mercè Correa***, John Salamone****, Lidia Salais*****, María Teresa Pérez-Saldaña******, Gonzalo Haro*,**.

* Universidad Cardenal Herrera-CEU, CEU Universities, Castellón. España.
** Departamento de Salud Mental. Consorcio Hospitalario Provincial, Castellón. España.
*** Universitat Jaume I, Castellón. España.
**** Universidad de Connecticut, Storrs. EE. UU.
***** Departamento de Neurología. Consorcio Hospitalario Provincial, Castellón. España.
****** Departamento de Neurología. Hospital de Manises. España.

In 2018 we published a clinical case (Haro et al., 2018) of a 32-year-old patient who began to use cocaine at the age of 14 and was diagnosed with "limbic dysfunction syndrome" at 17. The treatment recommended by his psychiatrist was psychosurgery. It was performed in two separate interventions in which radiofrequency-induced thermal coagulation lesions were performed with the aim of deactivating the anterior cingulate cortex (AC), disconnecting it from the ventral striatum and the amygdala in both hemispheres. Shortly after the surgery, the patient began to have delusions and was diagnosed with paranoid schizophrenia. At the age of 27, he showed negative psychotic symptoms and cognitive deficits, he scored 27/36 on Tower of London test (Krikorian, Bartok & Gay, 1994) which implied a reduced capacity for problem solving and planning.

With this letter, two years after the first publication of the case, the authors present the evolution of the patient after the appearance of a probable late complication of psychosurgery. New neuroimaging data, neurological evaluation and discussion conducted from a translational point of view are included.

During the last two years, the patient has remained stable within his chronic psychopathology. Daily drug treatment consisted of 30mg of olanzapine, 12mg of paliperidone, 450mg of quetiapine, 1500mg of valproic acid, and 4mg of biperiden. Although dopamine antagonists used as typical antipsychotics (haloperidol, pimozide, etc.) produce severe motor effects (akinesia and tremor), atypical antipsychotics such as those prescribed here (olanzapine, paliperidone, and quetiapine) act as dopamine receptor antagonists but also of serotonin and / or acetylcholine (biperiden) receptors, and they tend to have fewer motor effects in humans, and even improve tremor in animal models of Parkinson's disease (PD) (Betz, Ishiwari, Wisniecki, Huyn & Salamone, 2005). Thus, after the appearance of tremors in the upper limbs, which also did not remit with reductions in antipsychotic drugs, the patient was referred to the Neurology Department to rule out PD.

On neurological examination, the patient presented moderate hypomimia, mild hypophonia and dysarthria, decreased bilateral arm movement, moderate axial stiffness, moderate and symmetrical upper limb stiffness, bradykinesia in the right hemibody and marked slowness when performing finger tapping and movements alternating with the right hand. He did not show resting tremor or tremor in the lower limbs, maintaining correctly postural stability. In the evaluation of the motor state, using the unified scale for PD (UPDRS III) (Fahn, Elton & Members of the UPDRS Development Committee, 1987), the patient scored 25/68 (mild-moderate motor impairment) and he scored 2,5 (mild bilateral disease with recovery on pull test) on the Hoehn and Yarh scale (Hoehn & Yarh, 1967).

The last MRI performed on the patient revealed abnormal cavities in the right putamen, the left nucleus accumbens (Nacb) and the AC of both hemispheres, together

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Send correspondence to:
Gonzalo Haro. Universidad Cardenal Herrera-CEU. Castellón (Spain).
E-mail: gonzalo.haro@uchceu.es.

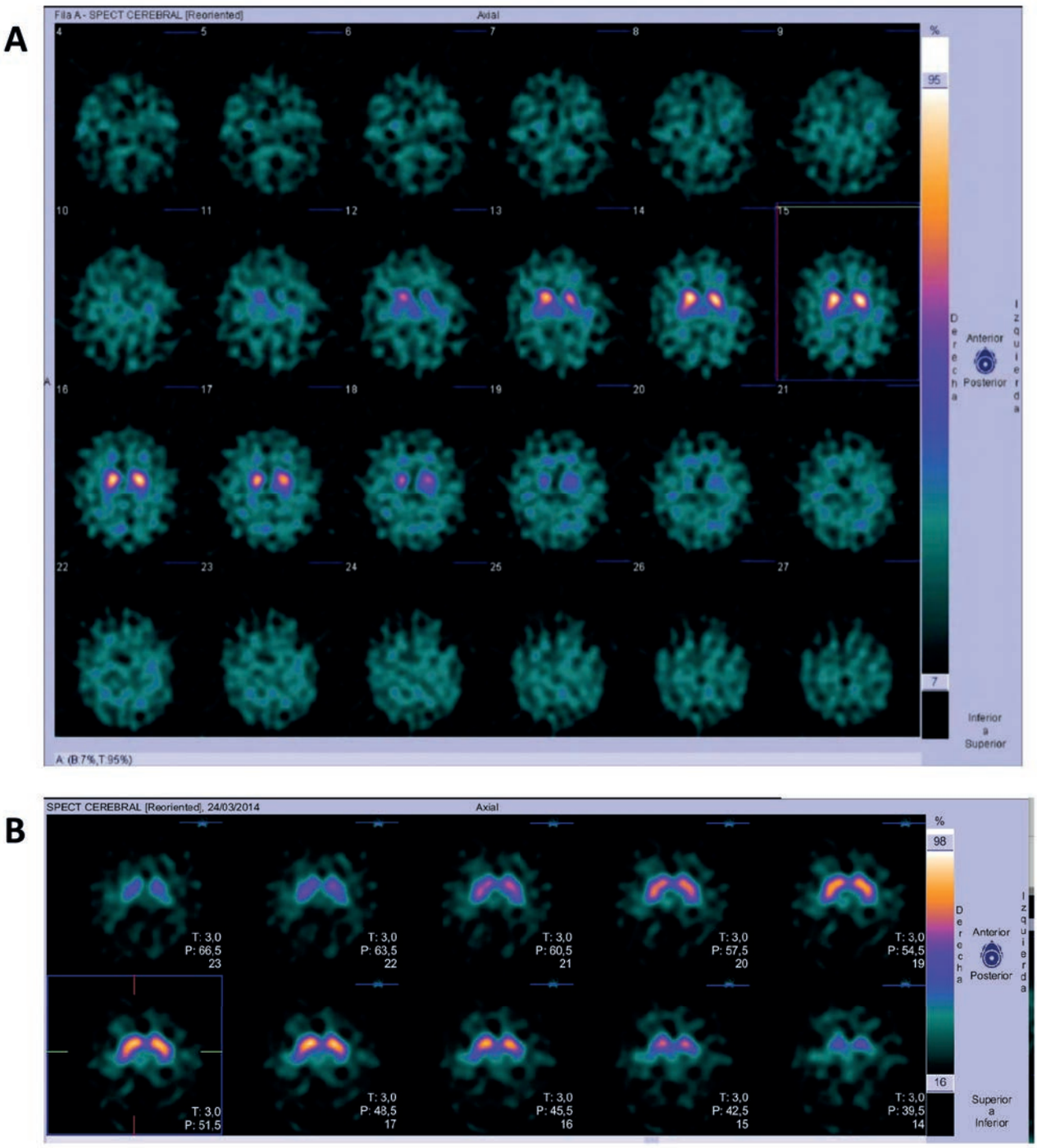

Figure 1. Axial view of SPECT with DaTscan A) performed on the patient in which a moderate decrease in the right putamen and a severe decrease in the left one of dopamine transporters, or B) performed on a patient of similar age without alterations in the basal ganglia.

with a marked reduction in the volume of the parietal and medial prefrontal cortices (mPFC), including orbital and ventromedial cortex. Thus, a monophotonic computed tomography (SPECT) of dopamine transporters (DAT) with Ioflupane-123 (DaTscan) was requested, in which a decrease in DAT was observed bilaterally in the presynaptic neurons of putamen, being moderate in the right and severe on the left (Figure 1), thus confirming the diagnosis of PD (de la Fuente-Fernandez, 2012) as a consequence of the structural changes produced by psychosurgery and the subsequent neuroadaptations. After diagnosis, 60mg of propanolol per day was added to his usual treatment, showing slight improvement in tremors.

Although no association between psychosurgeries and PD has been described (most studies analyze postsurgical periods of 6 months to 2 years), side effects such as bradykinesia or gait alteration have been described in surgeries that have affected the dorsal striatum (putamen) (Yampolsky & Berdensky, 2014). On the other hand, a possible outcome of Nacb disconnection is a hypodopaminergic

state such as the one described here with the decrease in DAT, which has been associated in animal models with abnormal corticostriatal oscillations that can alter the striatal dopaminergic balance resulting in the release of alpha-synuclein whose accumulation plays a fundamental role in the pathogenesis of PD (Sharott, Vinciati, Nakamura & Magill, 2017). In addition, a neurodegeneration of the cerebral cortex such as that detected in the patient would be compatible with the hypothesis proposed by Foffani and Obeso (2018) which indicate that the origin of the prodromal focal motor symptoms, such as those observed in the patient, could be in a retrograde nigrostriatal degeneration initiated in the corticostriatal fibers.

In this letter we suggest that the extensive psychosurgery for cocaine addiction that the patient underwent not only had medium-term repercussions such as schizophrenia, but in the long term (15 years later) may also have triggered or contributed to an early and irreversible neurodegenerative process such as PD. It is unclear the extent to which the extensive cocaine abuse may also have contributed to the vulnerability of the dopamine neurons, or interacted with the other factors present. In the authors' opinion, surgery for behavioral disorders should be limited to exceptional cases due to the significant sequelae that can occur even after years; PD could be included among them.

Conflicts of interests

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Ethical aspects

Informed consent was obtained from the legal guardian and the patient for experimentation (neuroimaging) and publication.

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Considerations about population-level alcohol-attributable mortality estimates

Reflexiones sobre las estimaciones de mortalidad atribuida al consumo de alcohol a nivel poblacional

Sergi Trias-Llimós*,**.

* Centre d'Estudis Demogràfics, Bellaterra. Spain.
** London School of Hygiene & Tropical Medicine, London. UK.

Population level alcohol-attributable mortality estimates are essential metrics for public health policy makers. Underlying causes of death provide important insights on alcohol-attributable mortality in populations, but are highly underestimating the overall impact of alcohol on mortality (Rehm et al., 2017; Trias-Llimós, Martikainen, Mäkelä & Janssen, 2018). Few causes of death are considered wholly-attributable to alcohol (e.g., alcoholic liver disease, alcohol use disorders), which means that alcohol is necessary and that this death would not have occurred in absence of alcohol use. Yet, for a large group of causes alcohol is contributing to the disease incidence and development, but it is not a necessary component (e.g., ischaemic heart disease, several cancers) (Rehm et al., 2017). Therefore, the impact of alcohol on these diseases cannot be directly obtained from underlying cause of death data, and it is usually indirectly estimated.

The most popular methods to estimate population level alcohol-attributable mortality estimates are comprised within the family of attributable-fraction (AF) approaches. The work done by Rehm and colleagues shed light on these estimates in an international perspective (Rehm et al., 2007), and was followed by the developments from the Global Burden of Disease (Stanaway et al., 2018), and by other publications, including the recent update of estimates for Spain (Donat, Sordo, Belza & Barrio, 2020). In general terms, these approaches require two different data sources, namely: age- and sex-specific alcohol prevalence, and relative risks (RR).

The combination of these different data sources may be problematic as previously discussed elsewhere (Rehm, 2010; Rey & Jougla 2014). For example, the alcohol prevalence is well known to be largely underreported in health surveys, and although corrections are applied the extent of the underreported consumption varies across population groups unpredictably, particularly regarding drinking patterns. Furthermore, the relative risks, retrieved from other analyses, can also be problematic. First, they are often derived

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Send correspondence to:
Dr. Sergi Trias-Llimós. Centre d'Estudis Demogràfics, Centres de Recerca de Catalunya (CERCA), Carrer de Ca n'Altayó, Edifici E2, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain. E-mail: strias@ced.uab.cat.

from studies assessing disease incidence and not cause-specific mortality. Second, RR are uncertain for certain causes and drinking categories. For example, several studies still use cardioprotective RR whereas for cardiovascular diseases these effects are disputed and may be inexistent (Holmes et al., 2014). Third, the RR are not often stratified by age groups, which could play a major role, particularly at old ages. Furthermore, the RR for acute conditions (e.g., external causes) are known to have an inconsistent relationship with alcohol-related outcomes. Despite specific approaches developed for acute causes, the estimation of the impact of alcohol on acute causes of death is complex and uncertain. These main limitations have a substantial impact on age- and cause-specific estimates. For example, estimates based on AF approaches tend to potentially overestimate the impact of alcohol on ischaemic heart disease at old ages due to the rising number of deaths at those ages and to the use of adult age RR for the old population.

One alternative approach that can partly overcome some main limitations of AF approaches is the one that directly estimates alcohol-related mortality using detailed data from death certificates, multiple causes of death (MCOD). This approach assumes that those deaths with a wholly-attributable to alcohol cause in the death certificate, either as underlying or as a contributory cause, are related to alcohol. Finnish studies were pioneers adopting this approach to estimate population level alcohol-attributable mortality, and this approach has been punctually adapted in other countries and regions (Martikainen, Mäkelä, Peltonen & Myrskylä, 2014; Trias-Llimós et al., 2018).

The comparison of AF and MCOD approaches can lead to interesting insights to identify strengths and limitations of both approaches. This comparison is an essential need for most populations, but the scarce related research suggested that AF approaches largely overestimate alcohol-attributable mortality at older ages (Trias-Llimós et al., 2018), particularly for cardiovascular causes (Manthey & Rehm, 2019). Furthermore, alcohol-related estimates derived from MCOD approaches seem to account for a substantial share of deaths at relatively young ages in Finland, which seems to indicate that this approach can capture the often challenging to estimate, external causes of alcohol-related deaths (Martikainen et al., 2014).

Using all information in the death certificate to estimate alcohol-attributable mortality (MCOD approaches) requires facing challenges related to mortality coding practices, but also offers new opportunities for making comparisons and further improving estimates. The main strength of this approach is that it does not require any indirect estimation, and thus the uncertainty and potential biases in the AF-related estimates do not apply in that case. MCOD approaches can offer new insights into mortality related with alcohol at the age groups in which AF approaches are more problematic, as well as shed new light in the cause-specific interrelations. Furthermore, an important number of MCOD data exists in several developed countries, and these are gradually becoming available in other countries, including Spain.

In conclusion, AF approaches have important well-known limitations that particularly apply to alcohol-related estimates. Alternative methods using all the information in the death certificate offer new opportunities to partly overcome those limitations when estimating alcohol-related deaths. Further studies should specifically assess the strengths and limitations of MCOD approaches for estimating cause-specific alcohol-attributable mortality.

Conflict of interests

None.

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COVID-19: A need for stricter control over unrecorded alcohol in Russia

COVID-19: La necesidad de un control más estricto sobre el alcohol no registrado en Rusia

Artyom Gil*.

* Institute for Leadership and Health Management, I.M. Sechenov First Moscow State Medical University. Sechenov University, Moscow. Russia.

The COVID-19 pandemic has had a significant impact on various aspects of life and directly or indirectly affected the health of the population in many countries (Lancet COVID-19 Commissioners et al., 2020; WHO, 2020). In Russia, in January-August 2020 the total number of deaths per 100,000 population increased by 0.8 cases compared to the same period in 2019 (13.2/100,000 in 2020 vs. 12.4/100,000 population in 2019). The registered unemployment rate increased by 2.1% and accounted for 6.4%. In the second quarter of 2020, when a regime of "self-isolation" was introduced to curb the spread of SARS-CoV-2 infection, the real disposable income of the population decreased by 8.4% compared to the same period in 2019 (RosStat, 2020). 61% of Russia's population noted a decrease in income, 13.5% reported a complete loss of income, while 9.8% completely lost their employment (Artamonov & Lavrentyev, 2020).

Simultaneously with these changes, during the first months of the SARS-CoV-2 pandemic, several regions of the Russian Federation (Karelia, Yakutia, Tuva, Khakassia, Bashkortostan, Vladimir and Sverdlovsk Oblasts, and other regions) introduced restrictions on the sale of alcoholic beverages due to concerns about the possible induced by the pandemic increase in alcohol consumption and associated with it adverse health and social outcomes.

These various changes and disruptions of life caused by the pandemic crisis suggested a high probability of an increase or, at least, a slowdown in the reduction in unrecorded alcohol consumption in Russia in 2020, particularly among the most disadvantaged sections of the Russian population (e.g. unemployed/on irregular employment, poor, homeless, heavy drinking populations). During the pandemic, unrecorded alcohol consumption might have again become more prevalent, just as it has repeatedly become during a number of previous socio-economic crises that have occurred in Russia over the past 35 years (Nemtsov, 2011; Leon & Shkolnikov, 1998; Lysova & Pridemore, 2010; WHO, 2019).

Unrecorded alcohol in Russia includes various sources of cheap ethanol, such as undeclared untaxed and falsified alcoholic beverages, homemade alcohol, nonbeverage/surrogate alcohols, and other sources. Nonbeverage alcohols include a variety of types of consumed for drinking alcohol-containing liquids: legal and illegal falsified perfumery/cosmetics spirituous liquids, spirituous bath additives, medicinal tinctures, antiseptics, technical/medicinal ethanol, and other types (Gil et al., 2018b). Over the years, these alcohols were available in retail in Russia (Gil et al., 2009; Koshkina et al., 2013; Neufeld, Lachenmeier, Hausler & Rehm, 2016; Gil et al., 2018a) and their consump-

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Send correspondence to: Dr. Artyom Gil. Institute for Leadership and Health Management, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia.
E-mail: gil.artyom@gmail.com.

tion was associated with a seven-fold increase in the risk of death, particularly among the working-age population (Leon et al., 2007). The main hazard of nonbeverage alcohols is associated with contained in them low-cost highly concentrated ethanol (up to 95% by volume). The small size of bottle (usually no more than 100 ml of volume) and associated with it low cost per single bottle also makes them affordable to most alcohol abusers, including the poorest ones.

During the period from January 2018 to September 2020, we conducted a brief assessment of the availability of nonbeverage and illegal beverage alcohols in five Russian cities: Odintsovo, Moscow, Izhevsk, Chelyabinsk, Petushki. In each city, fieldworkers visited up to 5 retail outlets and purchased samples of nonbeverage alcohols. Illicit alcoholic beverages were also purchased if they were identified in the outlets visited.

In total, 27 outlets were visited: pharmacies, markets, supermarkets, small shops, kiosks, pavilions. From these outlets, 126 samples of nonbeverage alcohols were purchased, which typically cost no more than 45 rubles ($ 0.57, € 0.49, £ 0.44) and contained 60% or more ethyl alcohol by volume. Of the 126 samples, 59 were purchased in 2020: 35 medicinal tinctures, 9 antiseptics, 1 bottle of medicinal ethanol, 4 denatured and 7 not denatured eau-de-cologne, 1 not denatured lotion, 2 spirituous sanitizers for hand disinfection. 62.7% of them were of sorts reported to have been consumed for drinking by subjects with alcohol use disorders (Bobrova et al., 2009; Neufeld et al., 2016; Gil et al., 2018a). 57.6% and 32.2% of them contained cheaper unit of ethanol (10 ml of pure ethanol) than that in the standard Russian vodka and in the illegal vodka, respectively. Six visited outlets sold nonbeverage alcohols used for drinking 24 hours a day.

The spirituous hand sanitizers we purchased appeared on the market in the first months of the SARS-CoV-2 pandemic in 2020. They were sold 24-hours a day in small street shops at a low price per single bottle (36 roubles: $0.45, €0.39, £0.35), were not denatured, contained highly concentrated ethanol (95% by volume) with a unit cost (10 ml pure ethanol) below that of standard legal and illegal vodka, came in bottles without a dispenser, were not displayed at show-windows and were consumed for drinking according to observations of a fieldworker (Figure 1).

In 4 visited in 2020 retail outlets selling nonbeverage alcohols fieldworkers identified and purchased 9 samples of illegal alcoholic beverages. They included illegal vodka, falsified cognacs, whiskeys, and rum, which were all sold at prices below minimum prices established by the state for alcoholic beverages for 2020.

Results of our brief assessment of availability of unrecorded alcohol suggest that a variety of types of consumed for drinking nonbeverage alcohols and illegal alcoholic beverages remained available in Russian cities in 2020, while new sorts of suitable for drinking unrecorded alcohol were introduced to the market during the first months of the COVID-19 pandemic (e.g. spirituous hand sanitizers). These alcohols are mainly manufactured from the cheapest ethanol available, which is usually a pharmaceutical/medicinal ethanol diverted from the legal market. Reinforcement of the previously implemented control policies described in detail elsewhere (WHO, 2019), as well as introducing new regulations targeting availability and consumption of unrecorded alcohol are warranted in Russia. Tightening control over this alcohol can be particularly important during the pandemic, which, via a combination of different mechanisms, such as stress, reduced affordability and physical availability of legal alcoholic beverages, may have increased the demand for and consumption of various types of unrecorded alcohol. Stricter control over unrecorded alcohol during the pandemic may be especially beneficial for the prevention of alcohol-attributable premature mortality among the most socially and economically disadvantaged and affected by the pandemic crisis

Figure 1. Anti-SARS-CoV-2 hand sanitizer ("hand tonic Ethyl Alpha") used for drinking as was observed by a fieldworker, and a small street shop selling it round-the-clock, Chelyabinsk, Russia, 2020.

sections of the working-age population, whose mortality rates for several decades have had a strong influence on the mortality fluctuations in Russia as a whole.

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Conflict of interests

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Prioritizing COVID-19 vaccination for people with addictive disorders

Por una priorización de las personas con trastornos adictivos en la vacunación frente a la COVID-19

Joan Trujols*,**, Josep Cadafalch***, Pedro J. Alvarado*, Santiago Duran-Sindreu*,**.

* Unitat de Conductes Addictives, Servei de Psiquiatria, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Barcelona, Spain.
** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
*** Unitat de Malalties Infeccioses, Servei de Medicina Interna, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Despite the risks involved in relying solely on COVID-19 vaccines to eradicate the pandemic, given uneven vaccine rollout and acceptance, the limited duration of immunity and the emergence of new SARS-CoV-2 variants, mass vaccination against COVID-19 is key to returning to what was normal life before the appearance of SARS-CoV-2 (Oliu-Barton et al., 2021).

At the time of writing, the rate of vaccination against COVID-19 continues to increase in Spain, with just over 10% of the population already fully vaccinated. However, within this context, the prioritisation of certain population groups in the different stages or phases of Spain's COVID-19 vaccination strategy, as set out in its technical paper (Grupo de Trabajo Técnico de Vacunación COVID-19, de la Ponencia de Programa y Registro de Vacunaciones, 2020) and successive updates, does not take into account the evidence supporting the need to prioritise COVID-19 vaccination for people with substance use disorder (SUD) (e.g., Allen et al., 2020; Wang, Kaelber, Xu & Volkow, 2021).

The only reference to this group of people in the paper, or in successive updates, regarding prioritisation among the different occupations (e.g., health and social-health workers), age groups (e.g., those aged 65 years or over), vulnerability to socioeconomic circumstances (e.g., living in substandard housing) or high-risk health conditions (e.g., immunosuppression after solid organ transplantation) is found, curiously, under the heading *People in vulnerable populations due to socioeconomic situation* and not in the section *People with high-risk* [health] *conditions,* a section which does include, on the other hand, the specific subgroup of "smokers". In any case, this mention in the original paper has not, to date, led to people with SUD being prioritised in any of the subsequent updates of the multiple and different population groups to be vaccinated.

This is particularly serious when one considers, as highlighted above, the available evidence on the increased SARS-CoV-2 infection risk and the greater severity and mortality of COVID-19 in people with SUD (Allen et al., 2020; Wang et al., 2021). More specifically, the retrospective case-control study by Wang et al. (2021), based on the electronic medical records of more than 73 million unique patients, shows that those with a recent diagnosis of SUD (e.g., diagnosed in the last year) have a significantly higher risk, adjusted for age, gender, race and insurance type, of contracting COVID-19 (adjusted Odds Ratio [aOR] = 8.699 [8.411-8.997]); this is highest in opioid use disorder (aOR

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Send correspondence to: Joan Trujols. Unitat de Conductes Addictives. Servei de Psiquiatria. Hospital de la Santa Creu i Sant Pau. Sant Antoni Maria Claret 167. 08025 Barcelona.
E-mail: jtrujols@santpau.cat

= 10.244 [9.107-11.524]) followed by tobacco use disorder (aOR = 8.222 [7.925-8.530]). Similarly, COVID-19 patients recently diagnosed with SUD have significantly worse outcomes (hospitalisation: 43.8%; death: 9.5%) than other COVID-19 patients (30.1% and 6.6%, respectively). The outcomes for COVID-19 patients with lifetime SUD diagnosis (41.0% and 9.6%, respectively) are also significantly worse compared to COVID-19 patients without SUD. It is possible that these results can be explained by the multiple comorbidities – many of which are known risk factors for higher COVID-19 morbidity and mortality – usually presented by people with SUD, with the study itself showing these patients having a significantly higher prevalence of different comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, cardiovascular diseases, HIV infection). However, this possibility should not prevent such results from being considered in the decision-making processes regarding the definition of the population groups to be prioritised in the vaccination strategy.

In any case, a study recently published online (Allen et al., 2020) suggests that the association between SUD and higher COVID-19 morbidity and mortality would be independent of comorbidity. This study had a retrospective case-control design and was carried out with almost 200,000 patients who had taken the PCR diagnostic test for SARS-CoV-2 in four New York hospitals. It shows that COVID-19 patients with SUD were more at risk, adjusted for age, gender, race and comorbidities, of being both hospitalized (aOR = 4.35 [3.30-5.73]) and admitted to an ICU (aOR = 2.50 [1.92 -3.25]) and even, in the case of patients with SUD and overdose history, of dying from COVID-19 (aOR = 3.03 [1.70-5.43]).

Given these data, and paraphrasing Prado-Abril (2021) regarding the vaccination against COVID-19 of patients with severe mental disorder, it is clear that the only justification for not prioritising access to the vaccination process for people with SUD can be issues linked to the stigmatization of SUD and discrimination with respect to other disorders or pathologies of equivalent impact on health.

Conflict of interests

The authors declare no conflicts of interest related directly or indirectly to the content of this article.

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Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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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).

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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.

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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).

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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. COMPOSICION CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de paliperidona equivalentes a 175 mg de paliperidona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de paliperidona equivalentes a 263 mg de paliperidona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de paliperidona equivalentes a 350 mg de paliperidona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de paliperidona equivalentes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a 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 x 10^9/l) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥ 50 a < 80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina < 50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. 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_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, el suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. 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[c], hiperinsulinemia, aumento del apetito, anorexia, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[c]	agitación, depresión, ansiedad	trastornos del sueño, mania, disminución de la libido, 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[a], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardíacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor		embolia pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión respiratoria, sibilancias, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores		hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, 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 lumbar, dorsal, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical	rabdomiólisis, hinchazón de las articulaciones		alteraciones posturales
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria		
Embarazo, puerperio y enfermedades perinatales						síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastornos de la eyaculación, trastornos menstruales[a], 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[a], aumento de la temperatura corporal, alteraciones de la marcha, dolor torácico, molestias en el pecho, malestar general, induración	hipotermia, escalofríos, polidipsia, síndrome de abstinencia de fármacos/drogas, abscesos en el lugar de inyección, celulitis en el lugar de inyección, quistes en el lugar de inyección, hematomas en el lugar de inyección		descenso de la temperatura corporal, necrosis en el lugar de inyección, úlceras en el lugar de inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas			

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica*. Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección*. En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP)*. En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, emprostótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, 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 tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administrados 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 período, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o el final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

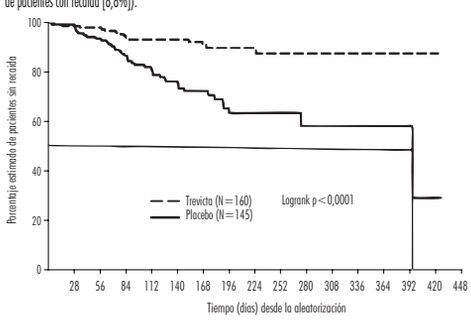


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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

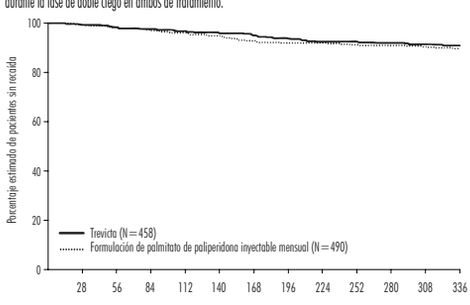


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{min}. 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 período de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC$_\infty$) 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_{min} 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 FARMACEÚTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.**

Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/ RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. Fecha de la última renovación: 14 noviembre 2019. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 11/2019.

La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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 los dosis de mantenimiento puede no resultar evidente durante varios meses. *Cambio desde paliperidona oral de liberación prolongada o risperidona oral a Xeplion.* El tratamiento con Xeplion se debe iniciar según se describe al comienzo de esta sección 4.2 . Durante el tratamiento de mantenimiento mensual con Xeplion, los pacientes previamente estabilizados con diferentes dosis de paliperidona comprimidos de liberación prolongada, pueden alcanzar una exposición similar a paliperidona en estado estacionario por vía inyectable. La dosis de mantenimiento de Xeplion necesaria para alcanzar una exposición similar en el estado estacionario se muestra a continuación:

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

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

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

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Medidas para evitar la omisión de dosis.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y 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 o grave (aclaramiento de creatinina < 50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes < 18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). *Administración en el músculo deltoides.* El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinada por el peso del paciente. En los pacientes ≥ 90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes < 90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. *Administración en el músculo glúteo.* El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos $<1x10^9/l$) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma diabética 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 todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10); *frecuentes* (≥1/100 a <1/10); *poco frecuentes* (≥1/1.000 a <1/100); *raras* (≥1/10.000 a <1/1.000); *muy raras* (<1/10.000); y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas[a]
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, amigdalitis, onicomicosis, celulitis	infección de ojos, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos 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[d], 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[c]	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	catatonía, estado confusional, somnambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[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[e], 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[a], ginecomastia, disfunción sexual, dolor de mamas	malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[a], aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección	disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

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

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia post-comercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basada en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3 con Xeplion. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poco frecuente) y nódulos (raro). *Síntomas extrapiramidales (SEP).* SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano, reflejo de la glabella anormal y temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y mioclonía), distonía (incluye distonía, hipertonía, torticolis, 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).

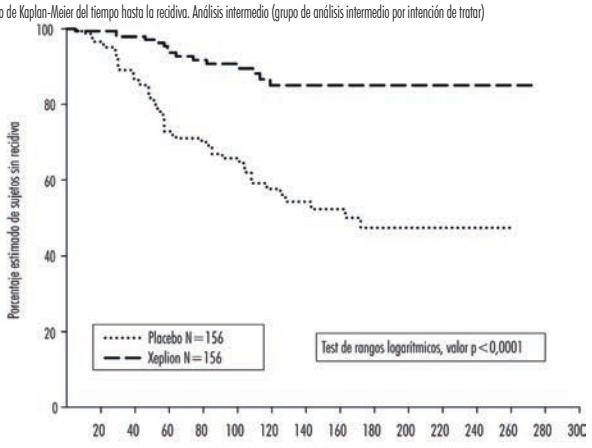
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (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 AUTORIZACION/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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