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publishes articles about addictions and their relationship with dual diagnosis (schizophrenia, depression, personality disorders...) and organic pathology

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Stress and drug addiction: an up-to-date perspective from 2020

Estrés y drogadicción: una perspectiva actualizada para 2020

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The problem of drug addiction treatment remains an important problem of society and is subject to advanced research. Discovery of mechanisms driving process of drug addiction seems to be an obvious step on the way to problem solution. Majority of researchers' attention seems to be paid for brain disease model of drug addiction. We suggest, that parallel to studies centered on brain disease model, more attention should be paid to research addressed to the key role of psychosocial factors and stress in emergence and further progressing of drug addiction (Ruisoto & Contador, 2019).

However, a broad and comprehensive perspective is needed in order to bring closer the labor of researchers and therapists. In this sense, the "integration of neuroscience with multiple disciplines (cognition, behavior and contextual in-fluences) holds potential to create new avenues for the application of process-oriented interventions and guidelines for clinical psychological practice" (De Raedt, 2020, p. 35).

In this editorial, using a neuroscientific approach, we highlight main matters of concern of currently ongoing research in relation to addiction and stress and point to possible future research directions which could bring valuable contribution in our knowledge about addictions.

Based on three comprehensive up-to-date review articles (Andersen, 2019; Koob & Schulkin, 2019; Ruisoto & Contador, 2019) addressing a contribution of stress in vulnerability to drug addiction and its development, we claim that the role of stress is multi-levelled. Stress seems to be an important factor both for vulnerability to onset, development, risk of relapse and treatment of addiction and, should be considered as impacting all stages of addiction (binge/intoxication, withdrawal/negative affect, preoccupation/anticipation).

Thus, it has been suggested recently (Koob & Schulkin, 2019) that question of stress in drug addiction fits with an allostatic model and should be considered with regard to this model. Allostasis is a term proposed over 30 years, however its meaning is still subject to discussion (Schulkin & Sterling, 2019). Allostasis is usually presented as a way of achieving stability through change (McEwen & Wingfield, 2003). In contrast to homeostasis, specified by negative feedback, allostasis functioning is based on feed-forward mechanisms (Koob & Schulkin, 2019). In terms of stress, allostasis could be described as an "adaptation in the face of potentially stressful challenges" (McEwen, 1998, p. 33) which "(…) involves activation of neural, neuroendocrine and neuroendocrine-immune mechanisms (McEwen, 1998, p. 33). Following allostatic model, Koob and Schulkin (2019) suggest, that stress is supposed to create an emotional allostatic load and allostatic state, what eventually leads to pathological dysregulation of motivational neurocircuits and addiction. Authors claim, that allostatic changes strongly influence the hedonic reward systems to drive compulsive drug seeking via the construct of nega-

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tive reinforcement (Koob & Schulkin, 2019). One of the primary (but not sole) mediators of allostasis is hypothalamic-pituitary-adrenal (HPA) axis (McEwen & Wingfield, 2003), which is the main stress response system (Dunlavey, 2018). There is a great number of molecules binding issues of addiction and stress, however corticotropin-releasing factor (CRF), being closely related to functioning of HPA axis, seems to be an especially important candidate for further investigation. A key point of future research should be a full evaluation of changes which CRF undergoes in the brain exposed to drug and stress, especially in areas of HPA axis, extended amygdala and prefrontal cortex. Staying in line with suggestion of Koob and Schulkin (2019), allostatic conception appears to be the right direction of further research, enabling to track all stages of transition leading to addiction.

Referring to recent review of Ruisoto and Contador (2019), a noteworthy aspect of addiction research is the question of careful translation of animal studies in drug addiction to humans. Authors underscore, that majority of studies conducted with use of animals evidently limit importance of psychosocial stressors. Thus, future investigation regarding human drug addiction ought to strongly consider psychosocial factors, guaranteeing proper validity (Ruisoto & Contador, 2019). Also, evaluation of individual differences between susceptibility and resilience to stress should be taken under advisement. Another key point of future studies could be a focus on similarities between impact of stress in drug-addiction and other - non-drug/behavioral - addictions, resembling some of the neurobiological mechanisms described in drug addiction (Ruisoto & Contador, 2019). Stress can induce long-term brain changes, similar to these occurring in brain after exposure to drug. Such information suggest that reduction of stress level may significantly improve effectiveness of drug addicts' treatment. Different approaches are proposed to help in treatment, including social support, physical exercise, contingency management, mindfulness treatments or encouraging to non-drug alternative reinforcers for pleasure-seeking or stress-relief (Ruisoto & Contador, 2019). Such a line, incorporated in social policies, could become not just a method of treatment but possibly an effective method of prevention.

An extremely interesting issue of the role of stress in drug addiction was raised in a review of Andersen (2019), underscoring the impact of stress experience occurring in early postnatal life on risk of drug dependence development. In the same line, Bousoño et al. (2019) recall that experiencing stress in form of parental problems, abuse or abandonment during childhood is correlated with later problems in adolescence (both at school and with peers) that, in turn, increase risk of early age drug abuse. It is known that early life stress experience correlates with an accelerated age of drug use onset and also higher vulnerability to drug dependence. Earlier onset of drug abuse correlates with long-lasting addiction (Andersen, 2019). Therefore, as recently it has been stated from a preventive point of view, there is a need to reinforce family prevention in general and the role of parents in particular (Rial et al., 2019). As mentioned by Ruisoto and Contador (2019), developing brains are more vulnerable to the toxic effects of exposure to stress hormones associated with practically every form of stress experiences – beginning from both psychological and physical abuse, through neglect and poverty to major sources of the allostatic load. Such experiences lead to long-term changes in brain.

Understanding of influence of stress occurring in early life (not only during adulthood or adolescence) on vulnerability to addiction onset, prior to emergence of symptoms, seems to be crucial in context of effective prevention.

Elucidation of how experience of stress influences future vulnerability to drug abuse and addiction, with regard to time of emergence of stress, its intensity and duration, remains a challenge and should be subject to further long-lasting research. Future investigations focused on correlation between stress and drug addiction, should have regard to factors such a time of occurrence, duration and type of stressor, as well as sensitive period, age and gender.

Going step further than early postnatal stress, another intriguing issue seems to be a question of inheritance of epigenetic changes provoked by stress. By recalling number of animal and human studies, some authors (e.g. Matthews & Phillips, 2012) claim that prenatal stress can lead to transgenerational effects on stress physiology and behaviors. These findings let to speculate about correlation between inheritance of stress-caused epigenetic changes and vulnerability to addiction. Continuation of the research concerning epigenetic aspects of stress could deliver an interesting information, helpful for (very) early prevention actions.

Following cases of elevated neuroimmune function in individuals with an addiction, Andersen (2019) proposed an idea of potentially pre-exiting condition of inflammation, being result of early life stress exposure, and its impact on drug addiction vulnerability (Andersen, 2019; Frank, Watkins & Maier, 2017). Mentioned article covers also subject of sensitive periods and their relationship to addiction, suggesting need of extensive studies exploring changes undergoing in brain neurochemistry (especially PV, BDNF and its receptor TrkB, and glutamate) while exposure to stress during sensitive periods should be taken into consideration (Andersen, 2019). Full understanding of mentioned changes would be helpful for development of specific treatment.

Different approaches of prevention are proposed (Andersen, 2019), including both existing as well novel pharmacotherapies, applied prior to emergence of symptoms. Suggestions of treatment applied before occurrence of

symptoms are reduction of, recalled above, inflammation, and actions aimed to reduce glutamate activity or increase GABA/PV and/or BDNF level (Andersen, 2019). The key aspect of future studies seems to be proper timing of intervention. Noticing that early postnatal stress experience has occurred and application of immediate prevention treatment without waiting for development of potential addiction may be the case for effective counteracting. In this sense, another key point for addiction prevention in frames of early stress life experience seems to be social buffering expressed by parental care (especially in childhood) and peer support (particularly in adolescence) (Andersen, 2019).

In conclusion, addiction research should take into account aspect of stress experiences in different ways, having regard to:

- allostatic model of drug addiction,
- role of CRF in regard to stress and vulnerability to addiction,
- deliberative translation of animal studies to human beings, especially, considering role of psychosocial factors and individual differences,
- impact of stress on drug-addiction and other (behavioral) addictions,
- studies on the long-term brain changes affected by stress aimed to improve effectiveness of drug addict's treatment,
- early stress experience in prenatal and postnatal life and its effect on vulnerability to addiction onset,
- and proper timing of intervention depending on the moment of stress exposure.

Therefore, the impact of stress on drug addiction is certainly a complicated issue, implicating both physical (brain disease) and psychosocial factors leading to occurrence of addiction, its development and relapse. An interdisciplinary research, making use of the advances of neuroscience, concerning different aspects of the problem, seems to be a promising approach. A proper understanding of the mechanisms driving to addiction is crucial for wellbeing of society, enabling correction of existing social policies.

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Role of Alcohol and Drug Detection by Regular Urine Sample Testing in pre-transplant evaluation for Alcohol Liver Disease

Papel de la detección regular de sustancias en orina en pacientes en valoración pre-transplante hepático por hepatopatía alcohólica

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Abstract

Alcohol Liver Disease (ALD) is one of the most prevalent conditions leading to liver transplantation for end-stage liver disease. There is lacking evidence of regular urine screening testing (RUST) impact on survival or liver transplantation of ALD patients. The aims of this study were to compare the sensitivity of RUST, to assess its impact on survival and liver transplantation, and to evaluate factors associated with adherence to RUST. We performed a single-centered retrospective study (N = 84) with ALD candidates for liver transplantation. Demographic, biochemical and clinical variables were recorded at baseline. Adherence to RUST was evaluated during follow-up. The sensitivity of both RUST and self-reports were calculated for all drugs. Multivariable logistic and survival regression analyses were performed to explore associated factors and the impact of adherence to RUST, and positive results on survival. RUST had high sensitivity for identifying active drinkers (76.9%), smokers (78.9%) and cannabis users (83.3%). High adherence to RUST was inversely associated with mortality during follow-up. Presence of personality disorders negatively impacted (OR 0.29, CI 95% 0.08-0.97) adherence to RUST. Both RUST and self-reports should be carried out in this setting. Professionals involved in liver transplantation programs must promote adherence to RUST, primarily in patients with personality disorders.

Keywords: Alcohol; Liver transplantation; Alcohol liver disease; Adherence; Alcohol dependence; Drug dependence.

Resumen

La enfermedad hepática alcohólica (EHA) es una de las causas más frecuentes de trasplante hepático en enfermedad hepática terminal. No hay evidencia de impacto de la detección regular de sustancias en orina (DRSO) sobre la supervivencia de los pacientes con EHA. Los objetivos de este estudio fueron comparar la sensibilidad de la DRSO, evaluar su impacto en la supervivencia y en el trasplante de hígado, y evaluar el impacto de la adherencia a la DRSO. Realizamos un estudio retrospectivo (N = 84) con candidatos para trasplante de hígado por EHA. Registramos las variables demográficas, bioquímicas y clínicas al inicio del estudio. Evaluamos la adherencia a la DRSO durante el seguimiento. Calculamos la sensibilidad tanto de la DRSO como de las declaraciones de los pacientes para todas las sustancias. Realizamos análisis multivariables (regresión logística) y de supervivencia para explorar los factores asociados y el impacto de la adherencia a la DRSO, y de los resultados positivos en la DRSO sobre la supervivencia. La DRSO tuvo una alta sensibilidad para identificar bebedores activos (76,9%), fumadores (78,9%) y consumidores de cannabis (83,3%). Alta adherencia a la DRSO tuvo una asociación inversa con mortalidad durante el seguimiento. La presencia de trastornos de la personalidad tuvo un impacto negativo (RM ,29, IC 95% ,08-,97) sobre la adherencia a la DRSO. Tanto la DRSO como las declaraciones deben llevarse a cabo en este perfil de pacientes. Los profesionales que participan en programas de trasplante hepático deben promover el cumplimiento de la DRSO, principalmente en pacientes con trastornos de la personalidad.

Palabras clave: Alcohol; Trasplante hepático; Enfermedad hepática terminal; Adherencia; Dependencia del alcohol; Dependencia a sustancias.

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Alcohol liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide (Rehm, Gmel, Sierra & Gual, 2018) and a major cause of end-stage liver disease (ESLD) and death among adults with prolonged alcohol abuse (Mathurin & Bataller, 2015). Liver transplantation (LT) is a well-established treatment for ESLD caused by ALD (Dawwas, Gimson, Lewsey, Copley & van der Meulen, 2007). Survival after a liver transplantation in patients with ALD is similar to that in patients with other ESLD etiologies (Burra et al., 2010).

Prevalence of drug or alcohol metabolites in patients with ALD candidates for Liver Transplantation is high (Carbonneau et al., 2010; Erim et al., 2007; Webzell et al., 2011). Most liver transplantation programs require 6-month alcohol abstinence and 12-month drug abstinence for listing patients (Beresford & Everson, 2000; Lligoña, Freixa, Bataller, Monràs & Rimola, 2009). However, some exceptions are considered (e.g. cannabis or tobacco) (Lligoña et al., 2009). However, there is no international consensus.

In our program, assessment of patients with ALD for liver transplantation includes psychiatric and psychological interviews, in order to identify the presence of psychiatric illnesses, which may preclude transplantation. The use of alcohol and other drugs is also evaluated in these interviews as part of the standard protocols. Detection of alcohol and other drugs on regular urine sample tests (RUST) at least once per week, is recommended in the follow-up of these patients (Lligoña et al., 2009). However, there is mixed evidence about RUST for monitoring alcohol dependant patients (e.g. short half-life) (Barrio et al., 2016; Niemelä, 2016) and limited evidence in candidates for ALD liver transplantation (Allen, Wurst, Thon & Litten, 2013; Carbonneau et al., 2010; Piano et al., 2014; Staufer & Yegles, 2016; Webzell et al., 2011). Further, the majority of these studies were conducted under research protocols, in which adherence might have been overestimated by Hawthorne effect and consequently the validity of RUST. In addition, self-reports are considered a valid strategy to assess alcohol and drug use in many conditions, even in clinical trials (CDER, 2015; EMA, 2010). Further, self-reports of alcohol and drug use is a cost-effective strategy. However, candidates for liver transplantation are considered a special population since they can underestimate alcohol use if they believe their current intake may delay or contraindicate transplantation (Allen et al., 2013).

On the other hand, treatment adherence predicts a good outcome in several conditions, including alcohol use disorders (Oslin, Pettinati & Volpicelli, 2002) and ALD (Rustad, Stern, Prabhakar & Musselman, 2015; Telles-Correia, Barbosa, Mega & Monteiro, 2009). However, there is a lack of studies about the impact of adherence to RUST or its positive results on prognosis for ALD patients.

The aims of this study, focused on patients assessed for liver transplantation, were: 1) to compare the sensitivity of self-reports and RUST for detecting alcohol /drugs use; 2) to assess the impact of adherence to RUST and its positive results on liver transplantation and survival; and 3) to explore baselines factors associated with high adherence to RUST.

Material and Methods

Study design

Observational single-centered retrospective (post-hoc) study.

Participants

All patients with ALD over 17 years old, consecutively evaluated in the pre-transplant (accepted or not for waiting list to liver transplantation) Liver Outpatient Service between January 2008 and January 2014 were recruited.

Exclusion criteria: those patients who did not provide RUST within our addiction unit and did it elsewhere because geographical restrictions

Setting

The current evaluation protocol for liver transplantation in patients with ALD at Hospital Clinic Barcelona requires an exhaustive assessment by a psychiatrist and a psychologist, and RUST for most common drugs of abuse (alcohol, benzodiazepines, nicotine, cocaine, opiates and cannabis) at least once per week (Lligoña et al., 2009). Frequency of RUST was decided according to clinical criteria of the treating psychiatrist, who considered the primary and secondary drugs used and the individual capacity to attend RUST (physical, geographical, work or family restrictions). The psychiatrist usually prescribed RUST twice per week according to common clinical practice, difficulties to attend consultation and resources' availability in our outpatient clinics. Twice per week is enough to identify drug relapse because of the long half-life of most drugs and regular alcohol use, but it is likely insufficient for the detection of occasional alcohol intake. However, this was the real practice in our environment between 2008 and 2014 and before the generalization of ethyl-glucuronide in urine samples for detection of alcohol intake, which took place in our hospital in October 2016.

Recruitment started in January 2008, once the ethics committee of the HCB approved the current protocol for liver transplantation of patients with ALD. Our data refers to the first six year of protocol implementation. Follow-up start-point was first appointment with psychiatrist and end-point was: death or until October 2015.

Data collection was done prospectively during assessment for the liver transplantation with the exception of MELD (Model for End-stage Liver Disease), adherence

to RUST and follow-up, survival and performance of liver transplantation, which were collected during last trimester of 2015.

Variables

During the psychiatric interview, the following data were systematically and prospectively recorded:

1) Socio-demographic data: age (at the first urine sample test day) and gender
2) Psychiatric and clinical data:
   - Current and History of psychiatric illness, according to DSM-IVTR criteria based on clinical diagnosis of the psychiatrist in charge: including Affective Disorders (Depression, Dysthymia, Bipolar Disorder), Psychotic Disorders (Schizophrenia, Schizoaffective disorder and other related disorders) and Anxiety Disorders (Obsessive Compulsive Disorder, Panic Disorder, Generalized Anxiety Disorder, Posttraumatic Stress Disorder, Phobia). Personality Disorders was clustered according to three categories based on DSM IV-TR classification: A (Paranoid, Schizoid, and Schizotypal Personality Disorders), B Borderline, Narcissistic, Histrionic and Antisocial Personality Disorder) and C (Avoidant, Dependent and Obsessive-Compulsive Personality Disorder)
   - Life-time and current alcohol use pattern: using a frequency and quantity questionnaire called Systematic Interview of Alcohol Consumption (SIAC) (Gual, Contel, Segura, Ribas & Colom, 2001) The SIAC sensitivities are 70-81% for men and 46-100% for women. The SIAC specificities are 82-99% and 97-100%, respectively.
   - Life-time and current drug use.
   - The High-Risk Alcohol Relapse (HRAR) score: HRAR is a 3-item scale that evaluates total alcohol consumption per day, years of heavy alcohol use and the previous treatments for alcohol misuse. This system scores 0-2 each evaluated item (maximum total score 6), stratifying patients into 2 alcoholism relapse risk categories (high risk (<4) or low risk (≥4). HRAR score higher than 3 is a risk factor for relapsing in alcohol use after liver transplantation (OR, 10.7; 95% CI, 3.8-30.0) (De Gottardi et al., 2007; DiMartini et al., 2000).

At the end of the study, the following information was retrospectively collected from clinical records:

1) Number of programmed urine samples.
2) Number of accomplished urine samples.
3) Follow-up in the Addictions and/or Hepatology Unit.
4) Performance of liver transplantation.
5) Survival status (Dead/Alive): For the purpose of the study, the combined endpoint of alive at last follow-up or liver transplantation was the main variable used for survival analysis.
6) Adherence to RUST: Adherence was calculated as follows: (number of urine samples performed/number of programmed urine samples) x 100. We stratified adherence in 3 categories: low adherence (<25%), intermediate adherence (25-75%) and high adherence (≥75%). For inferential analysis two categories were considered: high adherence (≥75%) versus non-high adherence (<75%)
7) Model for End-stage Liver Disease (MELD) at the moment of first urine sample testing (Malinchoc et al., 2000).

The following metabolites were analyzed using the Hospital Clinic laboratory-established cut-offs and window of detection:

1) Alcohol: ethanol (cut-off: 100 ng/mL; window of detection ≤12h)
2) Tobacco: cotinine (cut-off: 100 ng/mL; window of detection: 3 days)
3) Opiates: morphine (cut-off: 300 ng/mL; window of detection: 3 days)
4) Cocaine: benzoilecgonine (cut-off: 300 ng/mL; window of detection: 3 days)
5) Benzodiazepines: diazepam (cut-off: 200 ng/mL; window of detection: 10 days-5 weeks)
6) Cannabis: 11-nor-d9-THC (cut-off: 50 ng/mL; window of detection: 5 days-5 weeks)

Statistical Analysis

Descriptive analysis of the sample was carried out. Continuous variables were described as mean (standard deviation). Categorical variables were described by counts and percentages. Comparisons between groups were performed using Student's *t* test, analysis of variance (ANOVA) or Mann-Whitney's *U* test, depending on variable distribution. Differences between categorical variables were assessed by the Chi-squared test or Fisher's exact test, when appropriate. A p-value <.05 was considered significant.

The sensitivity and area under the curve were individually calculated for self-reports and RUST taking both methods (self-reports and RUST) together as the gold standard (objective 1). We chose this gold standard because the combined outcome was the way to identify the largest number of active users considering the previous experiences in research protocols, in which both outcomes separately showed low sensitivity. To investigate variables with prognostic information for the combined end-point (alive/liver transplantation) during patient follow-up (objective 2), Cox regression univariate and multivariable analyses were fitted, entering variables at initial evaluation and during follow-up. The results of the multivariable Cox regression analysis (hazard ratio –HR-) were considered to be the main outcome. In order to evaluate the influence of adherence to RUST in patient survival during follow-up (objective 2), a comparative risk analysis using the Kaplan-Meier

method compared by the log-rank test was performed. To investigate variables associated with a high adherence to RUST (objective 3), those variables with a p<.10, and those that were considered clinically relevant in the univariate analysis were entered into a *backward stepwise* elimination variable selection procedure (multivariable logistic regression). The p-values for the univariate tests were not corrected for multiple testing, because those tests were taken as exploratory. The SPSS statistical package (SPSS Inc., version 15.0, Chicago, IL.) was used for all analyses.

Ethical Issues

This study was approved by the ethical committee of Hospital Clínic de Barcelona, (HCB/2015/0845) according to the Helsinki declaration and Spanish national laws. Informed consent was not required due to the retrospective design (using only routine clinical information) and after guaranteed absolutely anonymity of the participants.

Results

Patient Characteristics

The final sample included 84 patients with 88.1% male and a mean age of 53.7 (SD 6.2) years. 67.9% (n=57) were alive and 34.5% (n=29) were transplanted at the end of the study. The mean MELD at first urine sample test was 14.2 (SD 5.6). Overall mean follow-up was 15.9 (SD 11.4) months. Clinical characteristics are widely described in Table 1.

Mental illness was present in 29.8% patients, being cluster B personality disorder the most frequent diagnosis (n=9; 10.7%). Other diagnoses were depression disorder (n=6; 7.1%), anxiety disorder (n=4; 4.8%), cluster A personality disorder (n=3; 3.6%) and cluster C personality disorder (n=3; 3.6%).

Table 1. *Socio-demographic and clinical characteristics of evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

		n (%)
Gender (male)		74 (88.1)
Age (mean, SD)		53.7 (6.2)
Baseline MELD (mean, SD)		14.2 (5.6).
Mental illness (history or current)		25 (29.8)
SDU[a]/day	<= 9	40 (47.6)
	9-17	36 (42.9)
	>17	8 (9.5)
Years with heavy use	<= 11	26 (31)
	11-25	40 (47.6)
	>25	18 (21.4)
Previous treatment for alcohol use disorder	0	65 (77.4)
	1	13 (15.5)
	>1	6 (7.1)
HRAR[b]	Low risk (<4)	74 (88.1)
	High risk (=>4)	10 (11.9)
Death		27 (32.1)
Follow-up in Addictions service		13 (15.5)
Follow-up in Hepatology service		56 (66.7)
Lifetime Alcohol use		84 (100)
Lifetime Benzodizepine use		10 (11.9)
Lifetime Cannabis use		28 (33.3)
Lifetime Cocaine use		12 (14.3)
Lifetime Tobacco use		39 (46.4)
Lifetime Opiod use		11 (13.1)

Note. [a]SDU: standard drink units (10 gram of pure alcohol); [b]HRAR: High Risk Alcohol Relapse.

Objective 1. Compare sensitivity of Self-reports and RUST for Alcohol and Drugs Use Detection (Combined Gold Standard)

The sensitivity and area under the curve using urine samples + self-reports as a gold standard is shown in Table 3. In the case of alcohol, cannabis and tobacco, sensitivity is better for RUST than self-reports, being worse for benzodiazepines and cocaine.

Objective 2. Impact of RUST (adherence and results) concerning both Liver Transplantation and Mortality

Adherence/At least one positive in RUST and Liver Transplantation. We studied those variables potentially associated with liver transplantation (n=29) in the included patients. Adherence (high adherence n=19, 37.3% versus non-high adherence n=10, 30.3%; p=.531) was not associated with liver transplantation. Neither at least one positive result for alcohol (30% versus 35.1%; p=.749), at least one positive result for nicotine (23.3% versus 40.7%; p=.108) or at least one positive result for other drugs (38.1% versus 33.3%; p=.89) were associated to liver transplantation outcome. Table 4 shows exclusion reasons for liver transplantation.

Adherence/At least one positive in RUST and Mortality. Finally, we studied those variables associated with mortality during follow-up of the included patients. Mean adherence was similar among those who received liver transplantation or were alive at the end of the study and those who died (74.5% versus 64.6%; p=.08) but it was less likely to be classified as high adherent if the outcome was the death (71.9% versus 37%, p=.02). Excluding those who received liver transplantation (target population=55), at the end of the study 26.1% (n=6) of low adherent were alive and 73.3% (n=22) of high adherent were (p=.003). The univari-

Table 2. *Adherence and positive results in urine sample test in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

		All sample (n=84) n (%)	**Psychiatric** (n=25) n (%)	**Non-psychiatric sample** (n=59) n (%)
Adherence to urine sample test	Low (‹= 25%)	5 (6)	3 (12)	2 (3.4)
	Intermediate (26-75%)	27 (32.1)	10 (40)	17 (28.8)
	High (›= 75%)	52(61.9)	12 (48)	40 (67.8)
Mean adherence of RUST (mean, SD)		35 (30.1)	37.5 (35.8)	33.9 (27.6)
				n (%)
Number of patients with at least one urine sample positive for alcohol				10 (11.9)
Number of patients with at least one urine sample positive for benzodiazepine				8 (9.5)
Number of patients with at least one urine sample positive for cannabis				15 (17.9)
Number of patients with at least one urine sample positive for cotinine				30 (35.7)
Number of patients who self-report current alcohol use				6 (7.1)
Number of patients who self-report current benzodiazepine use				12 (14.3)
Number of patients who self-report current cannabis use				12 (14.3)
Number of patients who self-report current cocaine use				2 (2.4)
Number of patients who self-report current cotinine use				23 (27.4)

Note. [a] There were no cases of positive for opioid or cocaine in RUTS, or for opioid in self-reporting.

Table 3. *Psychometric characteristics of self-reporting or RUST (gold standard RUST+self-reports) in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

	Self-reporting	**Regular Urine Sample Test**	**Differences (Regular Urine Sample Test -self-reporting)**
Alcohol users (n=13, 15.5%)[c]			
Sensitivity (%)	46.2	76.9	30.7
[a]AUC	0.73 (CI95% 0.549-0.913)	0.89(CI95% 0.00-1.00)	0.16
Benzodiazepines users (n=17, 20.2%)[c]			
Sensitivity (%)	70.6	47.1	- 23.5
[a]AUC	0.85 (CI95% 0.72-0.99)	0.74 (CI95% 0.58-0.90)	-0.11
Cannabis users (n=18, 21.7%)[c]			
Sensitivity (%)	66.7	83.3	16.6
AUC	0.83 (CI95% 0.70-1.00)	0.92 (CI95% 0.00-1.00)	0.09
Cocaine users (n=2, 2.4%)[c]			
Sensitivity (%)	100	0	-100
[a]AUC	1.00 (CI95% 1.00-1.00)	0.5 (CI95% 0.09-0.91)	-0.5
Tobacco users (n=38, 45.2%)[c]			
Sensitivity (%)	60.5	78.9	18.9
[a]AUC	0.80 (CI95% 0.70-0.91)	0.90 (CI95% 0.82-0.97)	0.10

Note. [a]AUC: Area Under Curve; [b]CI: Confidence Interval. [c]According to combined gold standard (RUST+self-reports)

ate Cox regression identified high adherence to RUST and the HRAR score positively associated with mortality during follow-up. To further analyze the independent value of variables predicting mortality, statistically significant and clinically relevant variables were entered in a final multivariable model. We found that low adherence to RUST (HR 0.44; *p=.04*), HRAR score >3 points (HR 2.95; *p=.02*) and MELD score (HR 1.08; *p=.03*) were independently associated with mortality during follow-up. From 51 patients with high adherence to RUST 22 (43%) were alive (without liver transplantation) at last follow-up (mean follow-up 15 [SD 10] months) and 19 (37.3%) patients were transplanted (mean time to LT: 11 [SD 5] months). Patients with low adherence to RUST showed a higher mortality when compared with patients those with high adherence (17/33 [51.5%] vs. 10/51 [19.6%]; *p=.01*). Finally, high adherence to RUST positively influenced overall survival at last follow-up (Figure 1). The presence of at least one positive result for alcohol, nicotine or other drugs during the follow-up was not associated with mortality (*data not shown*).

Objective 3: Baseline factors that predict adherence to RUST

Overall, mean adherence was 71.3% (SD 24.4). During follow-up, 60.7% (51 out of 84 patients) showed high adherence to RUST, as did 66% of transplanted patients. No differences in length of follow-up were found between patients with high vs. low adherence to RUST (16.9 versus 15.3 months, respectively; *p=.52).* In the univariate analysis the presence of mental illness, personality disorder and HRAR scores were negatively associated with high adherence to RUST (Table 5). Patients affected by personality disorders (PD) were less adherent to RUST than patients without this condition (31% *vs.* 10 %; *p=.02).* When including these variables in the multivariable analysis, only the presence of personality disorder (OR 0.29; *p=.04*) showed a negative and independent association with high adherence to RUST. Of note, the HRAR score did not reach statistical significance when adjusted for other co-factors. Finally, no differences in the length of total follow-up between patients with and without any mental illness or with

Table 4. *Exclusion reasons for liver trasplantation.*

Reason	n (%)
Active drinkers	15 (27.3%)
Non-adherence to RUST*	11 (20%)
Improvement of Liver Disease	9 (16.4%)
Death during assessment	1 (1.8%)

Note. * Regular Urine Sample Testing.

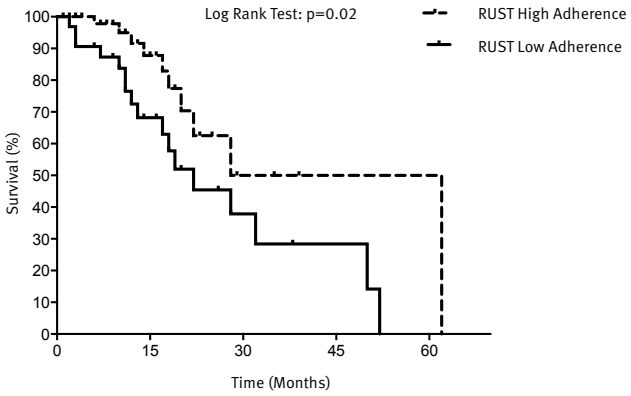

Figure 1. Survival according to RUST adherence during follow-up of patients with ALD.

Table 5. *Univariate and Multivariate Analysis of Factors Associated with High Adherence to RUST in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation During Follow-up since enrollment (first appointment with psychiatrist).*

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	**p**	**OR**	**IC 95%**	**p**
Age (years)	1.03	0.96 - 1.11	.5			
Gender (female)	0.38	0.10 - 1.47	.2			
Psychiatric comorbidity, (y/n)	0.37	0.14 - 0.98	*.04*			
Personality disorder (y/n)	0.25	0.08 - 0.82	*.02*	0.29	0.08 -0.97	*.04*
Other drugs of abuse* (y/n)	0.68	0.28 - 1.65	.4			
HRAR score at admission (points)	0.76	0.56 - 1.03	.08	0.81	0.59 -1.11	.2
HRAR score at admission (>3 points)	0.38	0.09-1.47	.16			

and without personality disorder were found (15.7 vs. 16.1. months; p=.8 and 15.8 vs. 16.2 months; p=.9, respectively).

Discussion

Assessment of patients with ALD undergoing liver transplantation is a challenging task for both, hepatologist and psychiatrists. Initial evaluations includes psychiatric and psychological interviews in order to identify psychiatric conditions, which may be a potentially cause of exclusion to the waiting list (Bunzel & Laederach-Hofmann, 2000; Martin, DiMartini, Feng, Brown & Fallon, 2014; Surman, Cosimi & DiMartini, 2009). Although the length of sobriety is a matter of debate for patients with ALD (Di Martino, Sheppard & Vanlemmens, 2012) who are potentially candidates for liver transplantation, a period of abstinence >6 months before liver transplantation is one of the mostly used criteria in the majority of liver transplantation centers and guidelines ("EASL Clinical Practice Guidelines: Liver transplantation.," 2015; Lligoña et al., 2009; Martin et al., 2014). This "6-month rule" has been proposed as necessary to limit relapse into high-risk alcohol consumption that could jeopardize graft integrity (Allen et al., 2013). There is no doubt that a proportion of patients undergoing liver transplantation return to drinking behavior which eventually results in graft loss or death due to lack of compliance of immunosuppressive treatments or direct liver injury caused by alcohol consumption (Cuadrado, Fábrega, Casafont & Pons-Romero, 2005). Therefore, monitoring of abstinence and patient's compliance to protocols in the pre-transplant setting is of paramount importance and a critical step in the evaluation process of patients with ALD undergoing liver transplantation. Use of self-reports is a valid and cost-effective strategy for assessing alcohol consumption and other drug use in many clinical scenarios (EMA, 2010). However, in the liver transplantation setting, self-reports has shown low accuracy to identify active drinkers given the high rate of under-reporting (Allen et al., 2013).

Sensitivity of self-reports and RUST. In our sample, RUST showed better sensitivity to identify active drinkers and active drug users with the exception for benzodiazepines and/or cocaine, but did not identify all active users. Alcohol and benzodiazepines in urine samples were detected in a similar proportion than other samples of ALD liver transplantation candidate (Webzell et al., 2011). In contrast, we were not able to identify any case of opiate consumption when use of these drugs have been reported as high as 20% among ALD patients candidates for liver transplantation in other countries (e.g. United Kingdom). These differences can be explained since patterns of consumption may vary in each country and also technical differences for drug measurement between cohorts (EMCDDA, 2015; Stewart, Koch, Burgess, Willner & Reuben, 2013; Wurst et al., 2003).

The performance of RUST for alcohol allows identifying almost 31% more cases than self-reports but did not achieve to identify all active users (23.1% false-negative in RUST in our study). Self-reports identified less than one out of two current alcohol users. Our results are consistent with other recent studies focused on treatment of alcohol use disorder in liver transplantation candidates (Erim et al., 2016). Using RUST we were able to detect almost eight out of ten alcohol users but we did not identify all alcohol users. Thus, combining both self-reports and RUST is the best strategy, confirming guidelines recommendation ("EASL clinical practical guidelines: management of alcoholic liver disease.," 2012). In addition, underreporting is higher in our population than other sensible populations such as psychiatric inpatients (56%) or pregnant women (0%) (de Beaurepaire et al., 2007; Horrigan, Piazza & Weinstein, 1996). Underreporting of alcohol use means that alcohol use is perceived as contraindication to transplant in the context of high resistance to declare its use. Also, our laboratory analyses are less sensitive than ethyl-glucuronide in urine sample (uEtG) which is potentially more powerful in order to detect any recent alcohol consumption, has excellent validated properties in liver disease patients and is strongly correlated with amount of alcohol intake (Nanau & Neuman, 2015; Wurst et al., 2015). A recent study of our group showed that abstinent patients were 95% in agreement to ethanol in urine sample but they decreased to 60% if we considered uEtG (Barrio et al., 2016). According with a recent study on LT candidates, the most accurate diagnosis of alcohol consumption was found combining short version of Alcohol Use Disorder Identification Test (AUDIT-C) and uEtG (ROC curve 0.98) (Piano et al., 2014).

Underreporting of tobacco use is explained by a general patient's defensive attitude in front of drug assessment during liver transplantation evaluation (Allen et al., 2013). Underreporting of cannabis is equivalent to a recent meta-analysis (19 studies) which reported sensitivity of 0.60 for cannabis self-reports using biological measures as a gold standard in different populations (Hjorthøj, Hjorthøj & Nordentoft, 2012). Two relevant points must be considered in order to explain no positives for cocaine in our sample: small sample with only two positives for self-reports and technical considerations (short-time of metabolites -48 to 96h- presence in urine sample) (Moeller, Lee & Kissack, 2008). Higher sensitivity of self-reporting compared with RUST for benzodiazepine use means that benzodiazepine use is not perceived as contraindication to transplant. In addition, there is technical limitations on detecting different active compounds in urine samples because poor cross-reactivity with conjugated metabolites and non-diazepam benzodiazepine (Melanson, Ptolemy & Wasan, 2013).
Impact of RUST (adherence/positive results) on survival. Previous data has showed that low adherence to pre- liver

transplantation treatments and evaluations is a robust predictor of high-risk alcohol relapse after LT (Egawa et al., 2014; Sansone, Bohinc & Wiederman, 2015). In our study, we found that high-adherence to RUST during the evaluation for liver transplantation, correlates patient survival after adjusting for well-established outcome predictors in patients with ALD undergoing evaluation for liver transplantation (e.g. MELD). This relationship was also independent to liver transplantation among those with high adherence or persistent negatives in RUST. In addition, the presence of at least one positive result for alcohol, nicotine or other drugs during the follow-up did not increase mortality. 66% of transplanted patients showed high-adherence to RUST accounting as good outcome according to our composite end-point alive/ liver transplantation. Therefore, the assessment of this dynamic parameter during the evaluation period of patients with ALD undergoing liver transplantation may provide additional prognostic information that could be taken into account as part of compliance assessment. Future research on this area is needed to confirm our data. Surprisingly, 30.3% of non-adherent patients and 35.1% of alcohol positive patients in RUST received liver transplantation. Non-adherent patients could be considered valid transplant candidates because the team took into account other characteristics as a priority. One positive for alcohol does not imply that the patient drunk during all the pre-transplant assessment and relapses could be managed by healthcare professionals during evaluation.

Factors associated with adherence to RUST. When evaluating the potential factors associated with adherence to RUST during the patient's follow-up, we found that patients affected by personality disorders were less adherent to RUST than patients without this condition (31% *vs.* 10 %; *p=.02*). When adjusted for other co-factors, the presence of personality disorders negatively influenced the development of high adherence to RUST in our cohort (OR 0.29; p=.04). This is not surprising given that patients with personality disorders in general have lower compliance to general health care (Sansone et al., 2015), drug treatment (Peles, Schreiber, Domany & Adelson, 2014) or psychotherapy (Jensen, Mortensen & Lotz, 2014). In addition, personality disorder is a frequent comorbidity of alcohol use disorders (Sánchez Autet et al., 2018). Up to our knowledge, this is the first study, which found that patients with personality disorders have lower compliance to the different approaches followed in the liver pre-transplant evaluations. It does not mean that personality disorder contraindicates transplantation but it is a vulnerable population, which should have a specific approach. Other studies have failed to demonstrate any relationship among personality disorders and poor prognosis after liver transplantation in ALD (Askgaard et al., 2016; Dom et al., 2015). Psychological and pharmacological (Addolorato et al., 2007; Erim et al., 2016) support are the focus of research in the management of ALD liver transplantation candidates. However, there are no studies based on improving the compliance. Motivational Interviewing and patient-centered care increased compliance in other health problems as medication compliance for hypertension (Conn, Ruppar, Chase, Enriquez & Cooper, 2015) or VIH (Hill & Kavookjian, 2012), alcohol use disorders (Bradley & Kivlahan, 2014), or follow-up of diabetic patients (Page et al., 2015), these approaches probably deserve to be tested in patients with personality disorders candidates for liver transplantation.

Limitations and Strengths. It is relevant to acknowledge that our study has several limitations. Given its retrospective nature, a record bias can exist. However, in our institution, the assessment for liver transplantation candidates has a well-established protocol following the international parameters and multidisciplinary evaluations with strict rules that might minimize the risk for this record bias. Detection of alcohol in urine samples instead of ethyl-glucuronide is also a limitation, but it was the real practice before generalization of ethyl-glucuronide in our setting. False-negatives probably exist despite the combined gold standard (self-reports/RUST) and they might explain a potential underestimation of impact of positive RUST results on survival and liver transplantation. Finally, our small sample size precludes us to give more robust and powered information. As we previously mentioned, this is a single-centered study in which due to geographical restrictions of the local health system only those patients providing regular urine sample testing within our addiction unit were included. However, our study has many strengths. To our knowledge this is the first study exploring the additive accuracy for alcohol consumption detection using both, self-reports and RUST approaches in candidates for liver transplantation. We analyzed and provide information about the detection the most frequently used drugs in Western Europe among patients with ALD undergoing evaluation for liver transplantation. Mean adherence to RUST was low (62%), which make more difficult to interpret validity of RUST. While other studies are based on research protocol, in which adherence is stimulated by Hawthorne effect, our study has a naturalistic approach, which allows examining RUST validity in real world practice. In these sense, our sample had high prevalence of psychiatric disorders (30%) being likely more representative of real practice than prospective studies with strict exclusion criteria or did not report psychiatric diagnosis. Finally, even when the impact of personality disorder and adherence to RUST and survival respectively are preliminary results, this is the first time that a study shows this relationship.

Conclusion

Both self-reports and RUST are required in patients assessed for liver transplantation. It seems that, except for cocaine and benzodiazepines, self-reports are less sensitive. Patients with good adherence to RUST have better outcomes compared with those with low adherence. Patients affected by personality disorders require further efforts in order to improve their adherence.

Contributors

The first (HLP), second (JA), third (EL) and sixth (AL) author have contributed in the conception, design, gathering and interpretation of data. All authors have contributed in the analysis, interpretation of data. All authors have contributed in the writing and intellectual content of the article. All authors have read and approved the manuscript for submission to the journal.

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Annex. Abbreviations

ALD, Alcohol Liver Disease
CI, Confidence Interval
DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders
HR, Hazard Ratio
HRAR, High Risk Alcoholism Relapse
MELD, Model for End-stage Liver Disease
OR, Odd Ratio
RUST, Regular Urine Sample Test
SDU, Standard Drink Unit
UETG, ethyl-glucuronide in urine sample

Evaluation of AUDIT Consumption Items New Adaptation to Improve the Screening of College Students Binge Drinking

Evaluación de la adaptación de los ítems de consumo del AUDIT para mejor el cribado de Binge Drinking en universitarios

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Abstract

The strong presence of Binge Drinking (BD) amongst university students, as well as the consequences associated with the same and the changes taking place over recent years regarding its conceptualization make it necessary to examine the usefulness of screening instruments used to detect this drinking pattern. This study examines the usefulness of a briefer adaptation of the AUDIT proposed by Cortés, Giménez, Motos, and Sancerni (2017a).

College students self-administered the AUDIT, the revised items 2 and 3 (A2r and A3r), and completed a weekly self-report of their alcohol intake. BD was classified according to the amount consumed and the frequency of that consumption over the past six months. The AUDIT, AUDIT-C and items A2r+A3r (AR2I) were examined.

The results obtained from a sample of 605 college students (18–21 years old/55.2% female) indicate that 449 meet the BD criteria. Items A2r and A3r, adapted to the most consensual definition of BD, were found to identify 98% of BD college students when using a cut-off point of ≥ 3 in females and ≥ 4 in males with optimum levels of sensitivity and specificity.

The new adaptation, which includes fewer items, identifies BD college students more accurately. This confirms the need to adjust both consumption items from the model according to the pattern of consumption in college students to detect BD more precisely and as soon as possible.

Keywords: Binge Drinking; Undergraduate; AUDIT; Alcohol Screening; ROC.

Resumen

La importante presencia del Binge Drinking (BD) entre estudiantes universitarios, junto con las consecuencias asociadas al mismo y los cambios experimentados en los últimos años en su conceptualización, hacen necesario revisar la utilidad de los instrumentos de cribado para detectar este patrón de consumo. Este estudio examina la utilidad de una adaptación del AUDIT propuesta por Cortés, Giménez, Motos y Sancerni (2017a).

Una muestra de estudiantes universitarios cumplimentó el AUDIT, los ítems 2 y 3 revisados (A2r y A3r), y un autoinforme semanal de su consumo de alcohol. A partir de la cantidad máxima de alcohol consumido en una ocasión y de la frecuencia de dicho consumo en los últimos seis meses se clasificaron los jóvenes como BD o no-BD. Se examinaron las puntuaciones del AUDIT, AUDIT-C y de los ítems A2r+A3r (AR2I).

Los resultados obtenidos con 605 universitarios (18-21 años/55,2% mujeres) indican que 449 cumplen criterios de BD. Los ítems A2r y A3r, adaptados a una definición más consensuada de BD, identifican el 98% de los estudiantes BD cuando se usa un punto de corte ≥ 3 en mujeres y ≥ 4 en varones, con valores óptimos de sensibilidad y especificidad.

Esta adaptación realizada, que incluye menor número de ítems, identifica a los universitarios BD de manera más precisa. Se confirma la necesidad de ajustar ambos ítems de consumo de acuerdo al patrón de ingesta BD que realizan los estudiantes universitarios mejorando notablemente su detección y facilitando un abordaje temprano.

Palabras clave: Binge drinking; Universitarios; AUDIT; Cribado de alcohol; ROC.

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The most generalized alcohol consumption pattern amongst European youth is that referred to as *Binge Drinking* (BD), a term which has been adapted to the Spanish language as *Episodio de Consumo Intensivo de Alcohol* (Ministerio de Sanidad y Consumo [MSC], 2008). In Europe, two out of every ten youth between the ages of 14 and 24 admit to having engaged in this behavior (European Union, 2010). As for Spanish youth (Observatorio Español de las Drogas y las Adicciones [OEDA], 2017) the highest incidence is found between the age interval of 20 to 29, being cited in approximately 35% of men and 23% of women in this age bracket. However, upon reviewing the prevalence of BD in minors over the past year (OEDA, 2018) this drinking behavior is found to occur in 14% of 14 year olds and in 56% of 18 year olds. Unfortunately, both in Spain and in Europe in general, changes in this drinking pattern in minors have been less pronounced and have only been observed in boys (42% to 37%), with overall rates declining by one percentage point (36% to 35%) over the past 20 years (European School Survey Project on Alcohol and Other Drugs [ESPAD], 2016). Furthermore, for some time now it has been suggested (Kuntsche et al., 2011; Simons-Morton et al., 2009), and now confirmed, that there is a closing in the gender gap for the excessive consumption of alcohol amongst adolescents. Rates of BD generally increased among younger girls, resulting in a narrowing of the gender differences over time (ESPAD, 2016; OEDA, 2018).

It is not possible to decouple this drinking pattern from the consequences that it causes in the youth. Generally speaking, there are noteworthy alterations and problems of distinct degrees and in different areas, from academic or professional to those related to interpersonal relations, exposure to risky sexual behavior, driving under the influence of alcohol, engaging in fights, suffering from injuries, having legal issues, having a propensity to engage in addictive processes or even causing injury to third parties (Barnet et al., 2014; Brewer & Swahn, 2005; Cortés, Motos & Giménez, 2015; Hingson, Heeren, Zakocs, Winter & Wechsler, 2003; Mallett, Varvil-Weld, Turrisi & Read, 2011; McKetin, Chalmers, Sunderland & Bright, 2014; Shield, Gmel, Patra & Rehm, 2012).

The large presence of this drinking pattern in youth, as well as the changes occurring in the same in terms of gender equalization and the consequences resulting, justify the need for screening instruments that facilitate its detection in distinct areas (Primary Care, traumatology departments, university health services, etc.) and the subsequent referral of the youth to the most appropriate care resources (Clark & Moss, 2010).

The AUDIT is a screening instrument used to identify *Binge Drinking* (BD) in the university student population (Hagman, 2016; Seguel, Santander & Alexandre, 2013). Application of its reduced versions is recommended, given their increased effectiveness (Barry, Chaney, Stellefson & Dodd, 2015; Clark, Gordon, Ettaro, Owens & Moss, 2010; de Meneses-Gaya, Zuardi, Loureiro & Crippa, 2009). Of these abridged versions, the AUDIT-C is of special note, given that it has better psychometric properties than those of the complete scale in the university student population (Barry et al., 2015; Cortés, Giménez, Motos & Sancerni, 2016; DeMartini & Carey, 2012; Kelly, Donovan, Chung, Bukstein & Cornelius, 2009).

However, the AUDIT and its abridged versions use an operationalization procedure that is not very precise for BD, making it difficult to identify it with great precision. Of the three items related to the consumption of alcohol, only the third item attempts to reflect binge drinking *(How often do you consume 6 or more drinks a day?*) but is very distinct from that which is currently considered to be Intensive Alcohol Consumption (Cortés & Motos, 2015; Mota et al., 2010).

An additional problem is that many of the studies that have applied the AUDIT or its reduced versions have measured BD in very distinct manners, with the majority considering the number of drinks consumed without taking into account the strength of the drink or without detailing the number of hours of duration of the drinking or only assessing the consumption from the past week or using DSM criteria for substance use disorders (Chung, Colby, Barnett & Monti, 2002; Díaz Martínez et al., 2009; Thomas & McCambridge, 2008). Furthermore, very few have considered that this is a very heterogeneous consumer group.

This diversity justifies the need to be very cautious when comparing results from the distinct studies, while at the same time, demanding the need for increased accuracy when operationalizing BD and the instruments attempting to determine the same.

This need to improve the measurement instruments has resulted in the proposed adaptations of the AUDIT. Initially, new combinations of items from the traditional abridged versions were used, attempting to identify those that were more precise in detecting binge drinkers (Babor, Higgins-Biddle & Robaina, 2017). In the case of McCambridge and Thomas (2009), they report that the best combination would be that consisting of items 3, 5 and 8, whereas Bowring, Gouillou, Hellard, and Dietze (2013) concluded that the best grouping was that of the items 3, 4, 8 and 9.

However, attempts to readjust the drafting of the items or their response scales to a more precise definition of BD have been more effective. We find various studies that have all eliminated the first item from the AUDIT-C due to its low correlation with the overall scale (Gmel, Hebb & Rehm, 2001; McCambridge & Thomas, 2009).

Blank, Connor, Gray, and Tustin (2015) proposed the use of only items 2 and 3 (the most explanatory of the BD in university students) while increasing the number

of response options. Other studies recommend modifying the wording of these two consumption items. For item 2, García, Novalbos, Martínez, and O'Ferrall (2016) suggested limiting the time of consumption to "one unique consumption occasion" (instead of "a given day"). As for item 3, in some cases, it was suggested that the number of drinks be reduced (five or more drinks in one sole consumption occasion -Kokotailo et al., 2004-; four or more drinks for women and five or more drinks for men -Olthuis, Zamboanga, Martens & Ham, 2011-) and in others, it is suggested that the number of drinks be transformed to Standard Drinking Units (SDU), according to the home country (García et al., 2016). The introduction of this type of modifications produces increases in the levels of sensitivity (between 0.82 and 0.87) and specificity (between 0.87 and 0.92) as compared to the traditional scale (Blank et al., 2015; McCambridge & Thomas, 2009).

However, none of these suggestions have been fully accepted given that they do not include an adjusted definition of BD.

Recently, Cortés, Giménez, Motos, and Sancerni (2017a) adapted the wording of items 2 and 3 to the most agreed upon definition of BD which uses more precise operationalization criteria for this behavior, according to research (Cortés & Motos, 2015; Courtney & Polich, 2009; Parada et al., 2011), including aspects of gender, consumption time interval and equivalences to the Spanish SDU. Definitively, BD is defined as the consumption of 7 or more SDUs for males and 6 or more for females during a period of 2 hours, at least once over the last six months (Cortés et al., 2016, Cortés, Giménez, Motos, Sancerni & Cadaveira, 2017b).

Considering these criteria, item 3 was written as: *During the past 6 months, what is the average number of days per month with BD consumptions (seven or more Spanish SDUs for males and six or more Spanish SDUs for females over a 2 h period)?* The response scale was also adapted based on the results obtained in prior studies conducted with minors and university students (Cortés et al., 2017a; Hagman, 2016; Patrick et al., 2013) (Table 1).

The wording of item 2 was also improved, changing the number of consumptions for the number of Spanish SDUs consumed in one day: *How many SDUs do you tend to have on a day when you drink alcohol?* (Table 1).

Upon testing this adaptation (AR2I) with underage alcohol consumers (14-17 years old), an area of .898 was found under the ROC (Receiver Operating Characteristic) curve, identifying 94% of the BDs with a cut-off point of 5.

The objective of this study was to examine the psychometric properties (sensitivity and specificity) of the AUDIT, AUDIT-C and the AR2I adaptation, attempting to identify the one which best classifies BD in the university student population (18-21 years of age), considering the gender variable.

Based on the results obtained in the prior study carried out by Cortés et al. (2017a) on the effectiveness of the AR2I adaptation in the identification of BD adolescents, the hypothesis is proposed that this would be the instrument that best identifies a greater number of BD university students.

Methods

Participants

Stratified sampling was carried out on students from the University of Valencia. The degree was selected for each area of knowledge (Basic Sciences, Social Sciences, Health Sciences, Education and Humanities Sciences) having the highest number of registered students, with the group having the highest number in each course responding to the questionnaire. A total of 605 students participated, all of Spanish nationality (334 women / 55.2%). Their ages ranged from 18 to 21, with mean age 19.33 years (SD=1.15). In no case did they have any diagnostic criteria to receive treatment for addictive behavior. Of those surveyed, 74.21% (449) complied with the BD criteria, with similar proportions being found for men (44.5%, 200) and women (55.5%, 249) (X^2=*.044; p=.834*).

The questionnaires were completed during the 2014 academic year in the classrooms and during class hours (morning or afternoon), and in all cases, members of the research team confirmed that all of the items had been answered. Participation was anonymous and voluntary. The study was conducted in compliance with Spanish legislation (approved by the Department of Education) and the Code of Ethics for Research involving human subjects, as outlined by the University of Valencia Human Research Ethics Committee. Students signed an informed consent form.

Variables and Instruments

The parameters relating to alcohol consumption (age of onset of consumption, number and type of drinks and the time when the drinking took place) were assessed with a self-reporting diary. The amounts of consumption were converted to SDUs following the Spanish SDU definition -1 hard liquor=2 SDU; 1 fermented drink=1 SDU- (Rodrí-

Table 1. *Redrafting of items 2 and 3.*

A2r	How many SDUs do you tend to have on a day when you drink alcohol? (0) 1 or 2; (1) 3 or 4; (2) 5 or 6; (3) 7 to 9; and (4) 10.
A3r	During the past 6 months, what is the average number of days per month with BD consumptions (seven or more Spanish SDUs for males and six or more Spanish SDUs for females over a 2 h period)? (0) Never; (1) Sporadically -less than once a month-; (2) between 1 and 4 times; (3) between 5 and 8 times; (4) between 9 and 12 times; (5) 13 or more times.

guez-Martos, Gual & Llopis, 1999). The recoding of all consumption occasions allowed for the identification of the greatest consumption engaged in by each student (*greatest number of SDUs of alcohol consumed in a BD session*). According to this variable, students were classified as BD (individuals who had consumed ≥7 Spanish SDUs for males or ≥6 Spanish SDUs for females), or non-BD.

The frequency of BD was operationalized by asking the *number of total BD days within 6 months* that they had consumed alcohol at this level.

Items A2r+A3r were operationalized according to the description appearing in Table 1.

The AUDIT was also completed (Spanish version validated by Contel Guillamón, Gual Solé & Colom Farran, 1999), thereby obtaining a total score of the AUDIT (the sum of the 10 original items), a score for the AUDIT-C (the sum of the first three original items). AR2I was also completed, obtaining a score of A2r+A3r.

In this study, the internal consistency of AR2I was higher (0.90) than the AUDIT-C (0.80) and AUDIT (0.71).

Data analysis

Following the methodology proposed by Cortés et al. (2016, 2017a, 2017b) two cluster analyses (one for each sex) were carried out with the BD undergraduates, based on the values of *number of SDUs consumed in a BD session* and *frequency of consumption in the last 6 months*. In both cases, the extraction procedure consisted of two phases, which led to a natural classification of the subjects into different groups.

A multivariate analysis (MANOVA) was performed, with its corresponding *a posteriori* tests, using the four groups obtained in the clusters and the no-BD groups as independent variable (IV) to determine whether there were differences in the number of SDUs consumed, and the frequency of consumption in the last 6 months as dependent variables (DVs).

The area under the ROC curve was calculated using the method proposed by Hanley and McNeil (1983), which provides a graphic representation of a classifier's performance.

To determine the optimal cut-off score for the AUDIT, our purpose was to minimize false negatives and thus improve, as much as possible, the detection of young people who engage in this activity, so cut-off scores were used that maximized sensitivity.

All of the analyses were carried out using the IBM SPSS-22 statistics package.

Results

The cluster analysis among BD females produced two groups: the BD1F (n=169), which consumed 8.44 SDUs in one session and engaged in BD 22.85 days over the past 6 months and the BD2F (n=80), which consumed 13.41 SDUs per session with a mean of 45.73 BD episodes over the past 6 months. While in the case of the BD males, two groups were produced: the BD1M (n=160), which consumed 12.04 SDUs per session and engaged in BD 34.24 days over the past six months and the BD2M (n=40) group,

Table 2. *A posteriori Games-Howell test.*

(I) Clusters_only_BD	(J) Clusters_only_BD	Difference in means (I-J)	Std. error	Sig.	95% Confidence Interval (Lower Bound – Upper Bound)	
SDUs						
BD1F	BD2F	-4.968(*)	.469	.001	-6.27	-3.67
	BD1M	-3.606(*)	.298	.001	-4.42	-2.79
	BD2M	-16.687(*)	.738	.001	-18.79	-14.59
	NOBDF	4.867 (*)	.211	.001	4.26	5.47
	NOBDM	4.079(*)	.237	.001	3.40	4.76
BD2F	BD1M	1.363	.509	.063	-.04	2.77
	BD2M	-11.719(*)	.846	.001	-14.09	-9.35
	NOBDF	9.836(*)	.463	.001	8.49	11.18
	NOBDM	9.047(*)	.476	.001	7.67	10.43
BD1M	BD2M	-13.081(*)	.764	.001	-15.24	-10.92
	NOBDF	8.473(*)	.288	.001	7.64	9.30
	NOBDM	7.685(*)	.308	.001	6.80	8.57
BD2M	NOBDF	21.554(*)	.734	.001	19.36	23.75
	NOBDM	20.766(*)	.742	.001	18.55	22.98
NOBDF	NOBDM	-.789(*)	.224	.008	-1.44	-.14

Total consumed days within 6 months						
BD1F	BD2F	-22.873(*)	1.661	.001	-27.47	-18.28
	BD1M	-11.385(*)	1.464	.001	-15.41	-7.36
	BD2M	-24.684(*)	2.264	.001	-31.06	-18.24
	NOBDF	6.334(*)	1.534	.001	1.90	10.77
	NOBDM	5.979(*)	1.776	.013	.82	11.14
BD2F	BD1M	11.488(*)	1.923	.001	6.19	16.78
	BD2M	-1.775	2.584	.959	-9.00	5.45
	NOBDF	29.207(*)	1.977	.001	23.51	34.91
	NOBDM	28.852(*)	2.170	.001	22.59	35.12
BD1M	BD2M	-13.263(*)	2.463	.001	-20.16	-6.36
	NOBDF	17.720(*)	1.815	.001	12.50	22.94
	NOBDM	17.364(*)	2.023	.001	11.53	23.20
BD2M	NOBDF	30.982(*)	2.505	.001	23.64	38.32
	NOBDM	30.627(*)	2.660	.001	22.86	38.39
NOBDF	NOBDM	-.356	2.075	1.000	-6.35	5.64
Years consumption						
BD1F	BD2F	-.69667(*)	.21749	.020	-1.3249	-.0684
	BD1M	.21583	.19221	.872	-.3355	.7671
	BD2M	-.28417	.32799	.953	-1.2556	.6872
	NOBDF	.28200	.23387	.833	-.3938	.9578
	NOBDM	.93379(*)	.25042	.004	.2074	1.6602
BD2F	BD1M	.91250(*)	.23983	.003	.2217	1.6033
	BD2M	.41250	.35798	.857	-.6374	1.4624
	NOBDF	.97868(*)	.27435	.006	.1874	1.7699
	NOBDM	1.63046(*)	.28859	.001	.7966	2.4643
BD1M	BD2M	-.50000	.34321	.692	-1.5103	.5103
	NOBDF	.06618	.25478	1.000	-.6679	.8003
	NOBDM	.71796	.27005	.090	-.0625	1.4984
BD2M	NOBDF	.56618	.36817	.641	-.5109	1.6433
	NOBDM	1.21796(*)	.37889	.023	.1111	2.3248
NOBDF	NOBDM	.65178	.30113	.261	-.261	1.5212

Note. * The difference in means is significant at the .05 level.
BD=Binge Drinking; Std. error= Standard error; BD1F=Group one of binge drinkers, females; BD2F=Group two of binge drinkers, females; BD1M=Group one of binge drinkers, males; BD2M=Group two of binge drinkers males; NOBDF=Group no binge drinkers female; NOBDM=Group no binge drinkers males.

which consumed 25.13 SDUs per session with a mean of 47.50 days.

The remaining subjects that did not comply with the criteria for being considered BD were classified according to gender. The group of females -NOBDF- (n=85) who consumed 3.57 SDUs per session, with a frequency of 16.52 days over the last six months and the group of males -NOBDM- (n=71) who consumed 4.36 SDUs per session, over 16.87 days during this same period.

The MANOVA performed among the 4 BD groups and the 2 NOBD groups (Table 2) indicated that there were significant differences in the number of SDUs consumed and in the frequency of consumption in the last 6 months.

According to Table 2, the 4 BD groups consumed significantly higher amounts and with a higher frequency than the NOBD groups. No significant differences were observed between the NOBD groups in either of the two variables.

Comparing the four BD groups, it can be seen that the subgroups that consumed the largest number of SDUs (BD2F and BD2M) also consumed more frequently than the other two subgroups (BD1F and BD1M). When considering the sex of the two subgroups, it was found that

Table 3. *Performance of the versions of the AUDIT in detecting Binge Drinking for the entire sample and female and male groups.*

	Entire sample				Female				Male			
	Cut-off	Sensitivity	Specificity	ROC (95% Confidence Interval)	Cut-off	Sensitivity	Specificity	ROC (95% Confidence Interval)	Cut-off	Sensitivity	Specificity	ROC (95% Confidence Interval)
AUDIT	≥2	1.000	.397	.948 (.926-.969)	≥2	1.000	.388	.955 (.929-.981)	≥2	1.000	.408	.948 (.917-.979)
	≥3	.993	.571		≥3	.992	.612		≥3	.995	.521	
	≥4	.976	.724		≥4	.964	.753		≥4	.990	.690	
	≥5	.955	.833		≥5	.936	.871		≥5	.980	.789	
	≥6	.878	.897		≥6	.847	.929		≥6	.915	.859	
	≥7	.811	.904		≥7	.743	.929		≥7	.895	.873	
	≥8	.724	.942		≥8	.639	.976		≥8	.830	.901	
AUDIT-C	≥2	1.000	.545	.980 (.968-.993)	≥2	1.000	.576	.986 (.978-.995)	≥2	1.000	.507	.977 (.955-.999)
	≥3	.980	.833		≥3	.980	.824		≥3	.980	.845	
	≥4	.962	.923		≥4	.952	.929		≥4	.970	.915	
	≥5	.875	.974		≥5	.835	1.000		≥5	.925	.944	
	≥6	.724	.987		≥6	.631	1.000		≥6	.840	.972	
	≥7	.584	.994		≥7	.470	1.000		≥7	.725	.986	
AUDIT-CR	≥3	1.000	.718	.992 (.984-1)	≥3	1.000	.776	.995 (.991-.999)	≥3	1.000	.648	.992 (.976-1.000)
	≥4	.989	.910		≥4	.980	.918		≥4	1.000	.901	
	≥5	.958	.974		≥5	.940	1.000		≥5	.980	.944	
	≥6	.898	.994		≥6	.835	1.000		≥6	.975	.986	
	≥7	.733	.994		≥7	.618	1.000		≥7	.875	.986	
AR2i	≥1	1.000	.679	.997 (.995-1)	≥1	1.000	.765	1.000 (1.000-1.000)	≥1	1.000	.143	.998 (.996-1.000)
	≥2	1.000	.968		≥2	1.000	1.000		≥2	1.000	.577	
	≥3	.989	.968		≥3	.980	1.000		≥3	1.000	.930	
	≥4	.906	.994		≥4	.847	1.000		≥4	.980	.986	

Note. ROC= Receiver Operating Characteristic.

men consumed larger amounts compared to their respective subgroups of women. Differences were not found for the frequency of consumption variable, except for the two subgroups of less intensive BD, in which males were involved in BD more frequently than females over the past six months.

As shown in Table 3, the scores from the AUDIT and AUDIT-C have optimal values in the area under the ROC curve; however, these are lower than the values obtained in the modified versions.

The redefining of items 2 and 3 (AR2i) permit a greater area under the ROC curve with both the complete BD sample as well as when differentiating by gender. With a cut-off point of ≥3, 98.9% of all BDs are detected (sensitivity) and 96.8% of the no BDs are detected (specificity). When using cut-off points of ≥3 for women and ≥4 for men, only 2% of the BDs from each group would not be detected.

Discussion

Recent studies (Cortés et al., 2016, 2017a, 2017b; Patrick et al., 2013; Read, Beattie, Chamberlain & Merrill, 2008) allude to the heterogeneity that exists amongst young BD, given that the very definition of BD only indicates a minimum from which it is possible to identify a BD, without considering the distinct levels of seriousness. Along these lines, this work identifies groups of BD that, given both the quantity consumed (duplicating the minimum of the BD definition) as well as the frequency of the appearance of these episodes (twice a week) increasing the risk of experiencing negative consequences as a result of this drinking. This is notably aggravated when this consumption begins at very early age, as in the case of the sample from this study which began to consume alcohol between the ages of 13 and 15. According to the data of the last state survey, the average age of onset is around 14 years (OEDA, 2018), an age period that is associated with a greater seriousness of the consequences in subsequent periods (Hingson, Zha & Weitzman, 2009; Jenkins et al., 2011; Pilatti, Caneto, Garimaldi, Del Valle & Pautassi, 2013), and therefore, with a greater need for proposing interventions that are adjusted to ease or prevent these consequences (Vargas-Martínez, Trapero-Bertran, Gil-García & Lima-Serrano, 2018).

Among the most intense BD groups, a behavior that is much more accentuated in men than in women is found, given that they come to triple the quantity of alcohol whereas women double it. A similarity between both genders is found in the frequency with which this consumption occurs, partially confirming the equalization in the consumption pattern obtained in recent studies and epidemiological surveys (Fernández, Dema & Fontanil, 2019; Kuntsche et al., 2011; OEDA, 2018; Simons-Morton et al., 2009).

It is important to note that the higher frequency of this behavior (more than 7 times a month) implies a notorious increase in the probability of the appearance of bio-psycho-social consequences, as established in some studies as of two or more times a month (Anderson, 1996; Livingston, 2013).

The assessment of the drinking behavior supports the need to analyze the BDs not as a homogenous group but rather, as distinct groups with clearly differentiated risk levels. This suggests a necessary future research line. When specifying the maximum operationalization of the BD, as done over recent years, it is necessary to define subgroups within the general category, without forgetting gender.

A major advance in order to lessen the bio-psycho-social consequences would be to offer screening instruments that permit the detection of the greatest number of young BD not only in educational contexts, but also in healthcare areas, such as Primary Care and health cabinets of university campuses. In these settings, it would be very useful to have early BD detection tools for the youth that visit these services, as well as the possibility of referring them to specialized resources based on the detected problem.

Although the AUDIT-C has been found to suitably classify university students as BD/NOBD (Cortés et al., 2017b; DeMartini & Carey, 2012; García et al., 2016), using the AR2I reduces the number of false positives to a maximum, resulting in an optimal combination of sensitivity and specificity. This result coincides with that obtained with undergraduates in the study conducted by Cortés et al. (2017a).

In this study, as of the cut-off point of 3 in the AR2I, approximately 99% of the BD university students were detected. When using a cut-off point of 4 in males and 3 in females, the capacity to classify BDs (sensitivity) decreased by only one point, but the capacity to correctly identify the NOBDs (specificity), increased notably, reaching 100% in the case of the females. All of this while surpassing the reliability of the original scale. This result is understandable given that the two most explanatory items of the consumption pattern are being used (Blank et al., 2015), reformulated to provide an account of the characteristics of BD (Cortés et al., 2017a).

To sum up, the results provided by this study confirm the utility of this new combination of items for detecting the youth BD population with greater speed and effectiveness, which may be of considerable relevance in care resources such as Primary Care, in which time is a key factor to take into account. Furthermore, upon revealing the effectiveness in both an adolescent and university population, it may be concluded that this instrument is useful for the detection of BD regardless of age and gender. This makes it a suitable BD screening tool for youth, useful for clinical objectives as well as preventive ones, while at the same time, relevant in the research field (Arnaud et al., 2016; Walton et al., 2015), given that a classification that is more closely adjusted to the subjects may have more precise results.

One of the limitations to be considered is the use of self-reports to determine the consumption pattern. However, in the youth population, the self-reports have been considered valid and reliable as they ensure the anonymity and reliability of the data, unlike what tends to occur with other types of registers, such as surveys sent to homes (Degenhardt et al., 2013; Knight, Sherritt, Harris, Gates & Chang, 2003).

Another limitation lies in the generalization of the results obtained from this study, considering that this consumption is quite present in the elderly population. It is necessary to expand the evaluation of AUDIT, adding young people between the ages of 20 and 29 years, the period with the highest prevalence of BD in Spain (OEDA, 2017).

This work is part of a larger research study that attempts to achieve useful screening instruments to identify youth BD of distinct consumption intensities. Specifically, in this work, the usefulness of the AR2I is proved in different types of BD and in a distinct age group.

Future studies may wish to replicate this adaptation with samples from other countries, previously adjusting the measurement of BD to the SDU of the corresponding country. This would allow us to have a collective screening instrument based on a more rigorous definition of BD, thereby facilitating the comparability of the results.

Conflict of interest

No conflict declared.

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Family members affected by multiple substance misuse relatives

Familiares afectados por el abuso de sustancias de otros parientes: características de una muestra brasileña

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Abstract

Purpose: The heterogenic characteristics of affected family members (AFMs) of substance misusing relative (SMR) remain understudied. This study examined the occurrence and correlates of AFMs having more than one relative with substance use problems. *Material and Methods:* A secondary analysis of a cross-sectional study on the characteristics of affected family members in Brazil was performed (N= 3157). Levels of AFM stress, strain, coping and hopefulness were assessed. Factors associated with AFMs having other substance misusing relatives (other-SMRs) were explored using univariate logistic regressions. *Results:* The occurrence of having other-SMR was reported by 61.6% of the sample (1945/3157). Of this, 47% (904/1945) reported that the other-SMR was a member of the SMR's immediate family (spouse/partner/children/siblings). The likelihood of having other-SMRs was related to the AFM being female, from a low socioeconomic background, between the age of 35-44 years older, being SMR's mother or wife/girlfriend/fiancée, scoring higher on family member impact, psychological and physical symptoms, withdrawal coping and to have an older SMR. *Conclusion:* Information about the characteristics of AFMs is key to understanding how the experience of harm associated with the relative's problem might manifest. Our findings offer information that could be used when developing interventions aimed at reducing the harm experienced by AFMs.

Keywords: Affected family members; Substance misusing relative; Characteristics; Strains.

Resumen

Objetivo: Las características heterogéneas de familiares afectados (FA) de familiares con abuso de sustancias (FAS) han sido objeto de pocos estudios. Este estudio revisó la ocurrencia y los correlatos de FA con uno o más familiares con problemas de abuso de sustancias. *Materiales y Métodos:* Análisis secundario de un estudio transversal sobre las características de FA en Brasil (N = 3157). Valoramos los niveles de los FA de estrés, presión, afrontamiento y esperanza. Exploramos los factores asociados con los FA que tenían otros familiares con abuso de sustancias (otros-FAS) mediante regresiones logísticas ordinales. *Resultados:* El 61,6% de la muestra (1945/3157) informó de la ocurrencia de otros-FAS. De estos, el 47% (904/1945) informó que los otros-FAS eran familiares directos del FAS (cónyuge/pareja/hijos/hermanos). La probabilidad de ocurrencia de otros-FAS estaba relacionada con que el FAS fuese mujer, de bajo nivel socioeconómico (NSE), con una edad entre los 35-44 años, fuese la madre o esposa/novia/prometida del FAS, obtuviese una puntuación más alta en impacto familiar, síntomas psicológicos y físicos, evitamiento como mecanismo de afrontamiento, y que tuviese un FAS mayor. *Conclusión:* Información sobre las características de los FA es clave para entender cómo puede manifestarse la experiencia de daños asociados con el problema del familiar. Nuestros hallazgos aportan datos que pueden ser útiles para desarrollar intervenciones con el objetivo de reducir los daños sufridos por los FA.

Palabras clave: Familiares afectados; Familiar con abuso de sustancias; Características; Presiones.

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Introduction

Having a substance misusing relative (SMR) is a leading contributor to disease burden in family members (Mattoo, Nebhinani, Kumar, Basu & Kulhara, 2013; Orford et al., 2013; Richert, Johnson & Svensson, 2018). Among the many adverse effects experienced by affected family members (AFMs) of a substance misusing relative are high levels of anxiety, stress, powerlessness, guilt and shame (Orford, Velleman, Natera, Templeton & Copello, 2013; Bortolon et al., 2016; Bortolon et al., 2017). It is also common for AFMs to detach themselves from friends (Jackson, Usher & O'Brien, 2007), feel isolated and experience difficulties in obtaining good quality social support from their social network (Orford, Velleman, Copello, Templeton & Ibanga, 2010). According to the *stress-strain-coping-support* (SSCS) model of the harm experienced by family members (Orford, Copello, Velleman & Templeton, 2010), the types of support AFMs receive and the strategies which they adopt to cope with the problematic use of substances by the relative are the key moderator factors in the strain-stress relationship (Arcidiacono et al., 2010; Lee et al., 2011).

While there seems to exist a common harm of how AFMs experience the substance use problem of the relative, studies have also shown that the way harm manifests itself might vary (Orford, 2017). Despite this, we know very little about the heterogenic characteristics of AFMs as the majority of studies have been conducted using samples of partners and children of substance using people, or have focused mainly on the family as a system (Orford et al., 2013). This paper seeks to expand the current understanding of the characteristics of AFMs by investigating those family members who have more than one relative misusing substances. While not everyone who misuses substances come from families with substance use problems, epidemiological studies show that patterns of substance use in the family is an influential factor for substance misuse (Mendoza & Vargas, 2017; Canavez, Alves & Canavez, 2017). To our knowledge, there are no studies investigating how family members cope with SMRs in the context of also having other substance misusing relatives (other-SMRs) in the family. Therefore, there is no available information on its prevalence and the experiences of these AFMs. Such information is required to enable family-focused services to understand who are the AFMs and to help reduce the impact to individual family members and to the entire family unit. A growing body of evidence recognizes that direct support of AFMs plays an important role in promoting treatment uptake and engagement of the SMRs (O'Farrell & Fals-Stewart, 2006; Roozen, de Waart & der Kroft, 2010) as well as reducing the psychological, physical and financial burden on AFMs (Copello, Templeton & Powell, 2010)

Our study draws on data from the largest observational study conducted on the experiences of AFMs (Orford, Padin, Canfield, Sakiyama, Laranjeira & Mitsuhiro, 2017). Our objectives are twofold: i) to examine the occurrence of Brazilian family members affected by their relatives' substance misuse also having other family member(s) with substance use problems; and ii) to describe sociodemographic, health and substance using characteristics associated with AFMs having other family members with substance use problems.

Methods

A secondary analysis of data drawn from a cross-sectional study on the characteristics of affected family members in Brazil (Orford et al., 2017b) was performed. The sample consisted of 3,157 participants recruited from all five geographic regions in Brazil. Recruitment sites were: therapeutic communities, self-help group Amor Exigente, pastoral groups Sobriedade, narcotics anonymous, alcoholic anonymous, and residential/rehabilitation clinics. Participants recruited from residential and rehabilitation clinics were invited to participate by researchers during their visits of the SMR, while participants recruited from self-help groups were invited during group sessions. No participation restrictions were imposed in terms of sex, age and relationship with the SMR. Participation in the study was voluntary and all participants gave fully informed consent. Questionnaires were administrated by trained interviewers. Ethical approval for the studies was provided by the Comitê de Etica da Faculdade de Medicina da Universidade Federal de São Paulo (CEP 1784/08).

Assessment

Participants' age, relationship status, family relationship with SMR, number of people living in the same household were collected. Socio-economic status was estimated based on the sum of the following characteristics (each scored 0, 1, or 2): education level, number of cars/bathrooms and housemaids, with the total ranging from 0 to 8.

Participants were asked to report characteristics of the SMR including gender, age and substance of preference. Participants were also asked to indicate whether they had other substance misusing relatives (other-SMR) and whether this other relative had psychiatric problems. Other-SMR being as immediate family was defined as spouse, partner, children or siblings of the SMR.

Psychological and physical characteristics of the participants were measured by the Brazilian adapted version (Sola et al., 2019) of a set of standard measures for the assessment of coping (COPE), hopefulness (HOPE), stress (FMI) and strain (SRT) of family members affected by a relative's substance misuse (Orford, Templeton, Velleman & Copello, 2005) (supplementary material for further information).

Analysis

Descriptive statistics were calculated using frequencies and percentages for categorical data and means and standard deviations for continuous data. The association between variables with having other-SMR was examined in univariate logistic regressions. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported. Table 1 presents the distribution of responses according to having other-SMR in the family.

Results

Sample characteristics

The sample characteristics are described in detail in Orford (2017). Briefly, the majority of participants (68.4%) were aged 45 years or above, 79.6% were female, 68.6% were white, 58.0% were currently married or had an intimate partner and 57.8% reported being the main financial provided in the home/family. Parents of SMRs accounted for 57.9% of the sample, followed by spouses/partners (13.6%) and siblings (12%). According to the AFM respondents, the most commonly used drugs by the SMRs were cannabis, cocaine and crack-cocaine. 18.5% reported alcohol as the SMRs' preferential substance of use.

The occurrence of AFMs having other-SMR was high (61.6%, 1945/3157). Of this, 24% of other-SMR were parents of the SMR (467/1945), while 22.5% were siblings (437/1945). There was also a substantial number of extended family including cousins (24.6%), uncles (16.2%) and grandparents (9.2%) misusing substance.

Table 1. *Characteristics associated with AFMs having any other relative with substance use problems.*

	Having other relative with substance misuse problems		
	No (N = 1211)	**Yes (N = 1945)**	**OR (95% CI)**
AFM			
Female	897 (74.4%)	1616 (83.08%)	**1.73 (1.4.5, 2.07)****
Age			
25 year or below	58 (4.8%)	77 (4.0%)	-
Between 25-34 years	129 (10.7%)	203 (10.4%)	1.18 (.79, 1.78)
Between 35-44 years	169 (14.0%)	343 (17.7%)	**1.53 (1.04, 2.25)***
45 year or above	848 (70.3%)	1314 (67.5%)	1.25 (.88. 1.79)
SES (range 0-8, Mean, SD)	2.96 (2.06)	2.77 (2.05)	**.93 (.89, 97)***
Relation with the SMR			
Mother	529 (43.8%)	936 (48.1%)	**1.20 (1.04, 1.38)***
Father	221 (18.2%)	198 (10.2%)	**.51 (.41, .62)***
Female partner	124 (10.2%)	279 (14.3%)	**1.20 (1.04, 1.38)***
Male partner	6 (.5%)	19 (1.0%)	1.98 (.79, 4.98)
Sibling	142 (11.7%)	258 (13.3%)	1.15 (.93, 1.43)
Child	33 (2.7%)	62 (3.2%)	1.18 (.77, 1.81)
Psychological characteristics (Mean, SD)			
Hopefulness	36.55 (5.34)	36.27 (5.47)	.99 (.98, 1.01)
Family Member Impact	33.00 (11.30)	33.83 (11.55)	**1.02 (1.00, 1.01)***
Psychological symptoms	24.38 (6.28)	25.17 (6.48)	**1.02 (1.01, 1.03)***
Coping engagement	30.15 (11.83)	29.96 (11.78)	1.00 (.99, 1.01)
Coping tolerant	14.49 (5.37)	14.80 (5.24)	1.01 (.99, 1.02)
Coping withdrawal	12.36 (4.13)	12.71 (4.15)	**1.02 (1.00, 1.04)***
Physical health ((Mean, SD)			
Physical symptoms	22.09 (6.31)	22.09 (22.80)	**1.02 (1.01, 1.03)***
SMR			
Female	66 (5.4%)	120 (6.2%)	1.42 (.84, 1.56)
Age ((Mean, SD)	31.02 (10.55)	32.42 (11.56)	**1.01 (1.00, 1.02)***
Substance use regularly			
Cannabis	850 (70.2%)	1309 (67.3%)	.87 (.75, 1.02)
Cocaine	171 (14.1%)	256 (13.2%)	.92 (.75, 1.13)
Crack-cocaine	61 (5.0%)	45 (2.3%)	**.45 (.30, .66)****
Other substances[1]	27 (2.2%)	28 (1.4%)	.64 (.38, 1.09)
Alcohol as substance of preference	155 (13%)	430 (22.7%)	**1.96 (1.60, 2.39)***

Table S1. *Description of the Brazilian adapted version of a set of standard measures for the assessment of coping, hopefulness, stress and strain of AFMs (Sola et al., 2019)*

Questionnaire	Purpose	Number of items	Item example	Scores	Cronbach's alpha
Coping questionnaire (COPE)	To assess three constructs related to how AFM have coped with their relatives' problem substance misusing: engaged coping, tolerant-inactive coping, and withdrawal coping	17	*Sat down with him to help him sort out the financial situation?* (engagement) *Felt too frightened to do anything?* (tolerant-inactive) *Put the interests of other members of the family before his?* (withdrawal)	Participants were asked to report how often in the last 3 months they coped in each way using a Likert Scale ranging from 0 (never) to 3 (often) Scores were calculated for the three subscales separately	.76 for engagement, .75 for tolerant-inactive, and .62 for withdrawal
Hopefulness-hopelessness scale (HOPE)	To assess two constructs related to how AFM currently feels about the future of the substance misuse problem in the relative: AFM own feelings and perceptions of the SMR	9	*I am now starting to anticipate a new future* (feelings) *I worry that s/he will use till the end* (perceptions)	Participants were asked to report the level of agreement with each statement using a Likert Scale ranging from 1 (strongly disagree) to 5 (strongly agree) Total score was calculated	.79 for feelings, and .69 for perceptions
Family member impact (FMI)	To assess the two constructs about how the AFM perceive the impact of the relative's substance misusing on the family: worrying behaviour and active disturbance	10	*Are you worried that your relative has neglected his/her appearance or self-care?* (worrying) *Does your relative have very changeable moods?* (disturbance)	Participants were asked to report how often they experienced each thought in the last 3 months using a Likert scale ranging from 0 (not at all) to 3 (often) Total score was calculated	.78 for worrying, and .86 for active disturbance
Symptom rating test (SRT)	To assess two different constructs: Psychological symptoms and Physical symptoms –	28	*Feeling scared or frightened* (psychological symptoms) *Feeling dizzy or faint* (physical symptoms)	Participants were asked to report how often they experienced each symptom in the last 3 months using a Likert scale ranging from 0 (never) to 2 (often) Scores were calculated for the two subscales separately	.91 for psychological symptoms, and .86 for physical symptoms

The occurrence of other-SMR being a member of SMR's immediate family (spouse/partner/children/siblings) was 46.5% (904/1945). Nearly a quarter of the sample of AFMs with other-SMRs indicated that this other relative also had other psychiatric problems (19.5%, 379/1945).

Characteristics associated with having other relative misusing substances

Univariate analysis (Table 1) revealed that compared to those AFMs that reported not having other-SMRs, those AFMs who had reported were statistically significantly more likely to be female, between the age of 35-44 years older, having a SMR who is older, being SMR's mothers or wife/girlfriend/fiancée, scoring higher on family member impact, psychological and physical symptoms, and engaging in withdrawal coping. AFMs with other-SMRs were also less likely to report higher socioeconomic status and to be SMRs' father.

Discussion

Our results show that a high proportion of AFMs have other-SMRs in the family. Of this, approximately 4 in 10 reported that the other-SMR is a member of SMR's immediate family, specifically a parent or a sibling of the SMR. Female AFMs (in particular mothers and partners) were more likely to have other-SMRs than male AFMs and AFMs were more likely to be in middle age group (35 to 44 years old). While there are no studies looking specifically at AFMs having other-SMR, our findings are comparable to the high prevalence of female caregivers attending substance use treatment/support groups reported in other studies, especially mothers (Bortolon et al., 2016; Sakiyama, Padin, Canfield, Laranjeira & Mitsuhiro, 2015; Tamutiene & Laslett, 2017). Lower social-economic status was associated with the likelihood of AFMs having other-SMRs. This finding has important implications since few other studies highlight the need to recognize the level of hardship of the AFM to be able to understand the effects of addiction in the family (Lee et al., 2011; Orford et al., 2001, 2005).

Reports of mental health problems in the other-SMRs were common. Regarding the characteristics of the SMRs, we found that those participants who reported alcohol as the preferred substance of the relative were more likely to have other-SMRs compared to addictions to other substances. Whilst this could potentially be a reporting bias as alcohol use may be over-reported due to easier disclosure compared to illicit drug use; a growing body of evidence recognizes the role of alcohol intake in the family as a determinant of alcohol use in other members, especially in children (Casswell, You & Huckle, 2011; Hutchinson, Mattick, Braunstein, Maloney & Wilson, 2014; Velleman & Templeton, 2016). Alcohol consumption in Brazil is high (Caetano, Madruga, Pinsky & Laranjeira, 2013). In a study

of adolescents in Brazil, 88% of the respondents reported having a family member who drinks alcohol frequently. Of this, 54% reported parents as the relative and 31% indicated that their alcohol consumption was influenced by the alcohol use in the family (Santos & Almeida, 2013). Our study also found a positive association between the age of the SMR and the likelihood of AFMs having other-SMRs. This may reflect an association between exposure and substance use, where the SMR may play an influential role for other members of the family.

The likelihood of having other-SMRs in the family increased for those AFMs with higher levels of family impact and psychological and physical symptoms. All these health aspects are consistent with the burden domain of the *stress–strain–coping–support* (SSCS) model (Orford et al., 2010). Those family members who reported higher levels of coping by withdrawal also have a stronger tendency to have other-SMR in the family. Potential explanations for these associations might be that in the face of high exposure to substance use problems, family members with other-SMRs might had learn to detach themselves from the SMR and to carry on with their lives while experiencing great levels of strain. Previous studies have demonstrated that certain AFM groups have a greater tendency to adopt certain coping strategies than others (Church, 2018; Lee et al., 2011). For instance, female partners of substance users showed a pattern of high tolerance and engagement coping strategies, while male partners of alcohol users showed a pattern of high withdrawal (Orford, 2017). Our findings provide additional information about strains and coping mechanisms of a particular AFM's group that could be applied when designing interventions to address the burden of family members. In particular, we would recommend that interventions incorporate content related to the extent to which the mental and physical health is affected by AFMs' ability to cope with the problems associated with substance use in the family. Interventions targeting coping strategies have shown promise in reducing AFMs' stress and self-blame, and improving ability to communicate with their relative (Copello et al., 2009; Kelly Fallah-Sohy, Cristello & Bergman, 2017). However, it is necessary to identify AFMs who have experienced the substance use problems in other members of the family, as they may be at increased risk of experiencing higher levels of burden. Our findings showed a need to support those AFMs having other-SMR who are women, from lower socio-economic status and have a SMR with alcohol problems. Interventions to improve the adoption of positive coping strategies and the well-being of AFMs as well as their participation in the SMR's treatment will need to be tailored to these characteristics.

Strengths and limitations

A limitation of this study is that the data is restricted to participants self-reporting substance use problems in other family members. As previously raised, response bias may be present with regards to the self-reported substance use of preference of the SMR. In addition, this secondary analysis is limited by the cross-sectional design of the original study (Orford, 2017), which only allows determining associations between variables rather than causality. Despite these limitations, the study included a large sample size allowing sufficient power to examine a specific group of AFMs.

Conclusion

This study provides evidence that having more than one relative who misuses substances is common among AFMs. Factors associated with having other-SMRs were identified. Understanding the characteristics of AFMs is key to understanding how the experience of harm associated with the relative's problem might manifest across groups. Interventions aimed at AFMs in Brazil are urgently needed (Orford et al., 2017; Sakiyama et al., 2015). The characteristics identified in this study offer information that could be used when developing interventions aimed at reducing the negative impact experienced by AFMs in Brazil.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Stimulant substance use and gambling behaviour in adolescents. Gambling and stimulant use

Uso de sustancias estimulantes y comportamiento de juego en adolescentes. Juego y uso de estimulantes

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Abstract

Gambling is widely recognized as an important public health problem. Despite the rising use of stimulant substances among adolescents, there are still very few studies focusing on whether adolescents' use of stimulants is associated with their gambling behaviour. Therefore, the aim of this study was to investigate the association between gambling habits and consumption of stimulants such as coffee, energy drinks, and new psychoactive substances in a sample of Italian adolescents. A survey was conducted in 2017 with a representative sample of Italians between the ages of 14-17 years, comprising 15,833 students attending 201 secondary schools. Logistic regression analyses were run to assess the association between at-risk/problem gambling (O1) and independent predictors: the model included independent variables (coffee, energy drinks and new psychoactive substance consumption) and covariates (demographic variables, social environment variables and risk-taking behaviour variables). A sensitivity analysis was also conducted to examine a second dependent variable regarding any experience of gambling behaviour (O2). Adolescents who were at-risk gamblers or problem gamblers were significantly more likely to consume energy drinks than non-gamblers or not-at-risk gamblers. A similar pattern was seen for consumption of new psychoactive substances. No significant association emerged with coffee consumption. The sensitivity analysis showed that, compared with non gamblers, the group of gamblers had higher odds for frequent coffee consumption, as well as for consumption of energy drinks and/or new psychoactive substances. Screening for gambling and stimulant use may provide important information, as it may be necessary to take action to reduce stimulant substance use as part of efforts to deal with unhealthy gambling habits.

Key Words: Gambling; Adolescents; Substance abuse; New psychoactive substances.

Resumen

El juego es un importante problema de salud pública ampliamente reconocido. A pesar del creciente uso de sustancias estimulantes entre los adolescentes, todavía son escasos los estudios centrados en verificar la existencia de una asociación entre el uso de estimulantes y los comportamientos relacionados con el juego en adolescentes. Por tanto, este estudio tuvo como objetivo investigar la asociación entre los hábitos relacionados con el juego y el consumo de sustancias estimulantes como el café, las bebidas energizantes y las nuevas sustancias psicoactivas en una muestra de adolescentes italianos. En 2017 se realizó una encuesta en una muestra representativa de jóvenes italianos de 14 a 17 años, constituida por 15 833 estudiantes provenientes de 201 escuelas de educación secundaria. Se realizó un análisis de regresión logística para evaluar la asociación entre juego de riesgo/juego problemático (R1) y factores predictivos independientes: el modelo incluyó variables independientes (café, bebida energética y consumo de nuevas sustancias psicoactivas) y otras covariables demográficas, del entorno social y de conductas de riesgo. También se realizó un análisis de sensibilidad para examinar una segunda variable dependiente con respecto a cualquier experiencia de conductas relacionadas con el juego (R2). Los adolescentes clasificados como jugadores de riesgo o jugadores con problemas tenían una probabilidad significativamente mayor de consumir bebidas energizantes que los no jugadores o los jugadores sin riesgo. Se observó un patrón similar en el consumo de nuevas sustancias psicoactivas. No se evidenció ninguna asociación significativa con el consumo de café. El análisis de sensibilidad mostró que, en comparación con los no jugadores, el grupo de jugadores tenía mayores probabilidades de consumo frecuente de café, bebidas energéticas y/o nuevas sustancias psicoactivas. La evaluación del juego y el uso de sustancias estimulantes puede proporcionar información importante. Por consiguiente, podría ser necesario tomar medidas para reducir el uso de sustancias estimulantes como parte de los esfuerzos dirigidos a lidiar con los hábitos de juego poco saludables.

Palabas clave: Juego; Adolescentes; Abuso de sustancias; Nuevas sustancias psicoactivas.

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It is widely recognized that gambling as an important public health problem associated with substantial personal and social costs, high rates of psychiatric comorbidity, poor physical health and high suicide rates (Nautiyal, Okuda, Hen & Blanco, 2017). Early exposure to gambling in adolescence has been linked to more severe gambling-related problems later in life (Burge, Pietrzark & Petry, 2006). Large-scale prevalence studies have also confirmed high prevalence rates of gambling and problem gambling in youth. A recent review found a wide range (35,7-79,1%) of prevalence of adolescent gamblers in the past year, whereas estimated that 0.2-12.3% of adolescents worldwide exhibit problem gambling (Calado, Alexandre & Griffiths, 2017).

Surveys and reviews on gambling behavior in adolescents have consistently found that adolescent gamblers have stronger impulsive decision-making and sensation-seeking personality traits (Blinn-Pike, Worthy & Jonkman, 2010; Dowling et al., 2017; Nower, Derevensky & Gupta, 2004). There is also evidence to suggest that adolescents likely to become pathological gamblers have higher levels of state and trait anxiety (Floros, 2018). Stimulant substances increase energy levels and concentration, but they may also affect behavioral traits, increasing apprehension, anxiety, irritability, and restlessness (Ste-Marie, Gupta & Derevensky, 2006). Some, but not all studies on adolescents and young adults generally found caffeinated beverages positively associated with risk-taking, impulsivity, and sensation-seeking (Arria et al., 2011; Grant & Chamberlain, 2018; Jones & Lejuez, 2005; Kponee, Siegel & Jernigal, 2014; Temple, Ziegler, Graczyk & Crandall, 2017). In particular, Temple et al found that caffeine dose-dependently influenced decision-making and risk-taking. In other studies, caffeine did not appear to alter behavior inhibition (measured with the stop-signal task (Tieges, Snel, Kok & Richard, 2009)) or decision making (Killgore, Grugle & Balkin, 2009). Energy drinks containing caffeine together with other stimulants, such as guarana, ephedra, yohimbine, gingko, theophylline and L-carnitine (NFSHSASMAC, 2014), are advertised as a means to improve energy levels, athletic performance, and concentration. The market for these products and their popularity has been growing rapidly among adolescents: one study found that 31% of 12- to 17-year-olds reported regularly consuming energy drinks (Al-Shaar, Vercammen, Lu, Richardson, Tamez & Mattei, 2017; Seifert, Schaechter, Hershorin & Lipshultz, 2011). Only a few studies have reported that energy drink consumption was positively associated with gambling, in adolescent males (Gori et al., 2015), and in early adolescence too (Gallimberti et al., 2016).

In recent years, new psychoactive substances (NPS) have rapidly emerged in market of stimulants (UNODC, 2013). Although most NPS are synthetic chemicals, many of them are plant-based substances (Feng, Battulga, Han & Chung, 2017).

Over the last decade, these substances have been introduced in the markets through various modes of distribution, including the Internet, 'smart shops' which sell drug paraphernalia, or street-level drug traffickers as legal alternatives to illicit drugs.

Estimating the prevalence of NPS use is challenging due to methodological and definitional inconsistencies, which also makes comparing national estimates difficult. A recent European study, that collected comparable data on substance use among 15- to 16-year-old students in 48 European countries found that the average of lifetime experience with NPS was 4 %, with a rate in Italy of 6% (ESPAD, 2016). The parallel effects of dopamine on gambling, and of psychostimulants across several domains (reward reinforcement, motivational priming, subjective experiential, cognitive information processing) had already been illustrated in the past (Zack & Poulos, 2009), but no study to date have analyzed the association between the consumption of such drugs and gambling.

The aim of this study was therefore to investigate the link between gambling habits and consumption of stimulant substances such as coffee, energy drinks, and new psychoactive substances in an Italian sample of adolescents.

Methods

The sample population was drawn from the "Gambling in Italy" project, a student population survey conducted in 2017 by the *Istituto Superiore di Sanità*. For the purposes of the present study, the survey is briefly described below.

Sample

The sample refers to the Italian student population between 14 and 17 years of age, taking into account the population's geographical distribution nationwide in order to intercept metropolitan, urban and suburban areas. The sampling method followed a three-stage PPS (Probability Proportional to Size) model, where the first-stage units were represented by the cities, the second-stage units by the schools, and the third-stage units by the classes. The sampling design involved stratifying the first-, second- and third-stage units; in each stratum: the first-stage units (cities) were selected with probabilities proportional to the number of upper secondary school classes within the territory of the cities; the second-stage units (schools) were selected with probabilities proportional to the number of classes in the sample schools; and the third-stage units (classes) were selected in the same numbers for each school in the stratum to which they belonged. All students attending the sample classes were included in the sample. Using this sampling method meant that the probability of

each class and each student in the target population being selected remained constant.

The survey was conducted using a Computer-Assisted Self Interview (CASI) method that enabled the questionnaire to be completed by students online using a non-replicable, unique, and anonymous access ID. Students accessed the questionnaire using a link provided by the technicians in the schools' computer rooms.

A total of 201 schools (187 public, 14 private) took part in the survey, and 859 classes were sampled, accounting for a student population of 18,042. A total of 17,610 online questionnaires were completed by students at school who agreed to participate in the survey. Six questionnaires were rejected because they were answered by students not resident in Italy (step 1); 267 were rejected because they were incomplete (step 2); another 1,504 were rejected because they were answered by students outside the age group considered in the survey (i.e. under 14 or over 17 years old) (step 3); and 231 were rejected because they contained answers judged scarcely plausible, i.e. any unreliable or irrelevant responses were identified by means of a Rasch analysis (step 4). Thus, a final number of 15,602 questionnaires (88.6% of the total) were considered eligible for this study.

Variables

The SOGS-RA scale (Poulin, 2002; Winters, Stinchfield & Fulkerson, 1993) was used to examine respondents' gambling behavior. This validated tool contains 12 items and scores range from 0 to 12. It measures several aspects, such as loss of control over the game, action taken to recover monetary losses, interference with family, school, and relational life, guilt feelings about money spent, and consequences of gambling. To be defined as "gamblers", respondents had to report having been involved in a gambling activity at least once in the previous year. Then the SOGS-RA scale identifies three types of gambler: non-problem (SOGS-RA score = 0–1); at-risk (SOGS-RA = 2–3); and problem (SOGS-RA score higher than 4). Students who reported having no experience of gambling in the previous year were defined as "non-gamblers".

The independent variables considered in the analysis concerned the consumption of energy drinks (ED), new psychoactive substances (NPS), or coffee (C). Each variable was classified according to respondents' self-reported usage in one of six categories: 1. "never"; 2. "only rarely, on special occasions"; 3. "some weekdays (Monday to Friday)"; 4. "only at the week-end"; 5."some weekdays (Monday to Friday) and at the week-end"; 6. "every day of the week".

The demographic variables considered were: age, sex, nationality (Italian, EU countries, other countries). As for the respondents' social environment, they answered questions on: their family's economic level (higher, the same as, or lower than their friends' families); amount of weekly pocket money (€0-20, €21-50, €>50); social network profile (yes, no); academic performance (poor, average, good or very good). The questionnaire also included questions about other risk-related substance use: smoking (never smoked, former smoker, occasional smoker, daily smoker) and alcohol drinking as beer/ wine/ cocktails/ spirits (never, occasionally but less than once a month, frequently from every month to every day).

Statistical analysis

The analysis did not use a complex survey approach. Given the large sample size, Bernoulli's simple random sampling method was adopted. A bivariate analysis was run on each of the above-described variables and gambling status. A set of Pearson's chi squared tests was used to highlight any associations between gambling and the other variables.

Logistic regression analyses were run to assess the association between outcome (gambling status Outcome 1 (O1) = non-gamblers and not at-risk gamblers versus at-risk or problem gamblers, as defined above based on SOGS-RA scores) and predictors. The model included the independent variables (coffee, energy drinks and new psychoactive substances) in the regression as dummy variables for consumption (never, only rarely on special occasions, all other modalities) and the covariates (demographic variables, social environment variables, and risk-taking behavior variables).

A sensitivity analysis was also conducted, assessing a second dependent variable (gambling status Outcome 2 (O2) = non-gamblers versus not-at-risk, at-risk or problem gamblers, as defined above based on SOGS-RA scores), and including the same independent predictors and covariates in the subsequent model.

Ethical issues

The study complied with the Declaration of Helsinki and with Italian Law n. 196/2003 on the protection of personal data. The data were collected anonymously and the analyses were performed on aggregate data, with no chance of individuals being identifiable. Consent to the students' participation was required first from the school director. Afterwards all parents signed to consent to the minors' participation in the survey.

Results

We analyzed 15,602 questionnaires. Table 1 shows the sample's characteristics.

The prevalence of non-gamblers was 70.8% (CI 95% 69.8-71.8), while 22.7% (CI 95% 21.8-23.6) of the students were reportedly not-problem gamblers, 3.5% (CI 95% 3.1-3.9) were at-risk gamblers, and 3.0% (CI 95% 2.7-3.4) were problem gamblers.

Table 2 shows the results of the bivariate analysis on gambling behavior and the different covariates. Among the at-

Table 1. *Characteristics of the sample of adolescents.*

	Total N = 15 602	
	N	%
Sex		
Male	7662	49.1
Female	7940	50.9
Age		
14 years old	3690	23.7
15 years old	3932	25.2
16 years old	4008	25.7
17 years old	3972	25.5
Nationality		
Italian	14 793	94.8
EU countries	217	1.4
Other countries	592	3.8
Family's economic level		
Not known	1359	8.7
Higher than friends' families	1552	9.9
Same as friends' families	11 502	73.7
Lower than friends' families	1189	7.6
Pocket money weekly		
€ 0-20	11 788	75.6
€ 21-50	3003	19.2
› €50	811	5.2
Academic performance		
Poor	403	2.6
Average	11 066	70.9
Good or very good	4133	26.5
Profile on a "social network"		
No	446	2.9
Yes	15 156	97.1
Smoking behavior		
Never smoked	8103	51.9
Former smoker	326	2.1
Occasional smoker	5356	34.3
Daily smoker	1817	11.6
Alcohol drinking behavior		
Never	3999	25.6
Sometimes, but less than once a month	4523	29.0
Often, from every month to every day	7080	45.4
Energy drink consumption		
Never	7926	50.8
Rarely	5155	33.0
Frequently	2521	16.2
New psychoactive substances consumption		
Never	14 952	95.8
Rarely	339	2.2
Frequently	311	2.0
Coffee consumption		
Never	3586	23.0
Rarely	3071	19.7
Frequently	8945	57.3

risk/problem gamblers, 86.9% were male, and 35.8% were frequent energy drink consumers (while this was true of only 14.8% of the non-gamblers and not-at-risk gamblers; p-value <0.001). A statistically significant difference also emerged 1.5% of non-gamblers and not-at-risk gamblers as opposed to 8.5% of at-risk and problem gamblers were frequently users of new psychoactive substances; p-value<0.001. The difference between two gambler groups in frequent use of coffee was lower (56.6% vs 67.6%), but still statistically significant (p-value<0.001).

Table 3 shows the results of the logistic regression for each outcome. Compared with non-gamblers or not-at-risk gamblers (O1), the at-risk or problem gamblers were significantly more likely to be energy drink consumers (rarely: OR 1.28, CI 95 % 1.08-1.52; frequently: OR 1.95, CI 95% 1.62-2.34). Similar patterns emerged between the two groups for new psychoactive substances consumption (rarely: OR 1.37, CI 95 % 0.99-1.89; frequently: OR: 2.96, CI 95 % 2.21-3.95). No significant association emerged for coffee consumption.

The sensitivity analysis showed that, compared with the group of non-gambler, the group of gamblers (O2) was also positively associated with frequent coffee consumption (OR 1.20, CI 95% 1.09-1.33), as well as rarely and frequent energy drink consumption (OR 1.44, CI 95% 1.32-1.58 and OR 1.75, CI 95% 1.57-1.95), and frequent new psychoactive substances consumption (OR 2.02, CI 95% 1.58-2.60).

Discussion

Our study demonstrates that adolescents with experience of at-risk and problem gambling have a higher likelihood of being consumers of energy drinks and new psychoactive substances, after adjusting for socio-demographic factors and consumption of other substances (smoking and alcohol drinking). Frequent coffee consumption is also associated with any experience of gambling in adolescents.

Our data show that almost one third of adolescents are engaged in gambling. Despite legal age restrictions, children and adolescents can easily access various forms of lawful gambling opportunities, and many of them do so (Malgorzata Carran, 2013). These findings warrant attention because studies on adult populations have shown that adult pathological gamblers often began their gambling careers at a relatively young age, and that the earlier people engage in gambling, the more likely they are to become problem gamblers (Burge et al., 2006).

We found coffee consumption is associated with any gambling experience in adolescents. Similarly, a study on university college students (Temple et al., 2017) pointed to a particularly strong relationship between caffeine intake, earlier age of first gambling experiences and certain types of impulsivity in gamblers. In another study on young adults, there was a significant positive correlation between

Table 2. *Bivariate analysis.*

	Non-gambler / Not-at-risk gambler (N = 14,590)	**At-risk gambler / Problem gambler (N = 1,012)**	***p*-value**
Sex			
Male	46.5% (6783)	86.9% (879)	‹ .001
Female	53.5% (7807)	13.1% (133)	
Age			
14 year	24.4% (3558)	13.0% (132)	‹ .001
15 year	25.3% (3694)	23.5% (238)	
16 year	25.6% (3729)	27.6% (279)	
17 year	24.7% (3609)	35.9% (363)	
Nationality			
Italian	94.8% (13 829)	95.3% (964)	.755
EU countries	1.4% (203)	1.4% (14)	
Other countries	3.8% (558)	3.4% (34)	
Family's economic level			
Not known	8.7% (1267)	9.1% (92)	‹ .001
Higher than friends' families	9.6% (1403)	14.7% (149)	
Same as friends' families	74.1% (10 816)	67.8% (686)	
Lower than friends' families	7.6% (1104)	8.4% (85)	
Pocket money weekly			
€ 0-20	76.9% (11 224)	55.7% (564)	‹ .001
€ 21-50	18.6% (2716)	28.4% (287)	
› €50	4.5% (650)	15.9% (161)	
Academic performance			
Poor	2.4% (348)	5.4% (55)	‹ .001
Average	70.5% (10 284)	77.3% (782)	
Good or very good	27.1% (3958)	17.3% (175)	
Profile on a "social network"			
No	2.9% (423)	2.3% (23)	.247
Yes	97.1% (14 167)	97.7% (989)	
Smoking behavior			
Never smoked	53.5% (7808)	29.2% (295)	‹ .001
Former smoker	2.0% (287)	3.9% (39)	
Occasional smoker	33.9% (4942)	40.9% (414)	
Daily smoker	10.6% (1553)	26.1% (264)	
Alcohol drinking behavior			
Never	26.9% (3924)	7.4% (75)	‹ .001
Sometimes, but less than once a month	29.9% (4359)	16.2% (164)	
Often, from every month to every day	43.2% (6307)	76.4% (773)	
Energy drink consumption			
Never	52.5% (7655)	26.8% (271)	‹ .001
Rarely	32.7% (4776)	37.5% (379)	
Frequently	14.8% (2159)	35.8% (362)	
New psychoactive substances consumption			
Never	96.5% (14 079)	86.3% (873)	‹ .001
Rarely	2.0% (286)	5.2% (53)	
Frequently	1.5% (225)	8.5% (86)	
Coffee consumption			
Never	23.5% (3424)	16.0% (162)	‹ .001
Rarely	19.9% (2905)	16.4% (166)	
Frequently	56.6% (8261)	67.6% (684)	

Table 3. *Logistic regressions results for two outcomes.*

	OR*	95% CI		p-value
		Lower limit	Upper limit	
O1 = at-risk gambler/ problem gambler				
Energy drinks				
Rarely	**1.28**	**1.08**	**1.52**	**.004**
Frequently	**1.95**	**1.62**	**2.34**	**< .001**
New psychoactive substances				
Rarely	1.37	.99	1.89	.057
Frequently	**2.96**	**2.21**	**3.95**	**< .001**
Coffee				
Rarely	1.10	.87	1.38	.446
Frequently	1.03	.85	1.25	.734
O2 = any gambling behavior				
Energy drinks				
Rarely	**1.44**	**1.32**	**1.58**	**< .001**
Frequently	**1.75**	**1.57**	**1.95**	**< .001**
New psychoactive substances				
Rarely	1.14	.90	1.44	.274
Frequently	**2.02**	**1.58**	**2.60**	**< .001**
Coffee				
Rarely	1.09	.97	1.24	.157
Frequently	**1.20**	**1.09**	**1.33**	**< .001**

Note. OR = Odds ratio; CI = Confidence Interval.
*Regression analyses adjusted for the variables: sex, age, nationality, family's economic level, weekly pocket money, academic performance, smoking behavior, alcohol-drinking behavior.

average daily caffeine intake and scores on a risk-taking questionnaire (Ste-Marie, Gupta & Derevensky, 2006).

We also found an association between energy drink consumption and at-risk and problem gambling behavior in adolescence. Energy drinks contain 75-158 mg of caffeine per can, and these beverages have stimulant effects on the central nervous system (CNS). Their consumption is prompted by the expectation that they improve the drinker's physical and mental performance. In fact, through antagonism of the adenosine A1 and A2A receptors, caffeine combats the inhibitory effects of adenosine on dopamine, thus increasing the psychoactivity of the dopaminergic systems D1 and D2, with effects on mood, executive functioning, salience attribution, cognition, and regulation of behavior (Ishak, Ugochukwu, Bagot, Khalili & Zaky, 2012). Risk-taking behavior seems to be manifest in adolescence due to an enhanced sensation seeking related to functional changes in dopaminergic activity between childhood and adolescence (Arenas et al., 2016). In the past, it was demonstrated parallel and dominant role of dopamine in relation to the pathophysiology of gambling, and it could be described as psychostimulant-mimetic (Zack & Poulos, 2009). A recent review on energy drink consumption produced evidence of consumers being high risk-takers, and more likely to exhibit lifestyle behaviors characterized by disinhibition and lack of moderation, including smoking, alcohol drinking, and caffeine consumption, as well as gambling (Verster et al., 2018).

Finally, our study demonstrates that at-risk and problem gambling in adolescence is associated with new psychoactive substances consumption. Little research has been done so far on the use of new psychoactive substances by teenagers. A study on college students showed that those who had used some kind stimulant substance in the previous 3 months had 74% higher odds of problem gambling in the previous 6 months (Geisner et al., 2016). Another study on 12- to 19-year-old high-school students in the USA also found that the use of any stimulant substance was associated with higher odds of more frequent gambling, and problem gambling among both males and females. The psychostimulant-mimetic model predicts that stimulant drugs cross-prime the motivation to gamble (Zack & Poulos, 2009). Consistently, Zack (2004) et al. provided experimental evidence of a neurochemical activation similar to that induced by psychostimulant drugs being an important feature of gambling addiction. A number of reports suggest that gambling can induce effects closely resembling those of a psychostimulant drug, and the profiles of an episode of gambling and psychostimulant use are also similar inasmuch as they both feature a marked behavioral perseveration (Dickerson, Hinchy & Fabre, 1987). Such evidence implies that psychostimulant drugs and engaging in gambling prompt much the same set of effects. If so, a dose of a psychostimulant drug may prime the motivation to gamble in much the same way as a 'dose' of gambling (Zack & Poulos, 2004). Neuroimaging research also indicates that the expectation or receipt of money induces selective patterns of activation in the brain's dopamine pathways (Knutson, Fong, Adams, Varner & Hommer, 2001). These pathways are also crucially involved in the reinforcing effects of psychostimulant drugs (Mackey & van der Kooy, 1985; Spyraki, Fibiger & Phillips, 1982; Yokel & Wise, 1978). Another issue to consider is personality traits: feelings of alienation, anxiety, low self-esteem, and attitudes to deviance, independence and impulsivity could all potentially increase the risk of both problem gambling and stimulant drug use (Brezing, Derevensky & Potenza, 2010; Jessor, 1987; Romer, 2003; Secades-Villa, Garcia-Rodriguez, Jin, Wang & Blanco, 2015).

This study has several limitations, primarily relating to the fact that our data were obtained from a sample of adolescents attending school. This means that anyone who dropped out of school at 16 years old (on completing their compulsory education in Italy) were not considered, so our sample was only representative of Italian school students. A second limitation lies in that the findings are based on self-reports and may be biased by respondents' under- or over-reporting of their risk-taking behavior. To mitigate

this potential bias, we guaranteed respondents' anonymity and confidentiality. Third, the cross-sectional design of this study limited our ability to draw causal inferences, particularly as regards the direction of the association between stimulant substance use and gambling, which might be two-way.

Conclusion

The consumption by teenagers of stimulant substances like new psychoactive substances and energy drinks is associated with gambling at-risk/problem gambling. Adolescence is known to coincide with a natural surge in sensation-seeking and risk-taking behavior, and gambling and/or the use of stimulants may exacerbate this natural tendency with potentially negative psychological, social, and financial implications. Given the significant association identified between the use of stimulant substances and gambling activities in teenagers, it would be important to organize educational schemes that improve people's awareness of the overlaps in multiple types of risk-related behavior.

Mental health counselors, social workers, and psychologists working with secondary-school students and other teenagers need to bear in mind the significant associations between the risk-related behaviors. Screening adolescents for both gambling and stimulant use may provide useful information on what action we can take to reduce the consumption of stimulant substances by the young, also as part of our efforts to prevent and manage gambling problems.

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Conflicts of interest

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Dual diagnosis among medical residents: a systematic review

Diagnóstico dual en médicos residentes: una revisión sistemática

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Abstract

The post-graduate period as a resident doctor (MIR, in Spanish) is usually associated with high emotional distress due to new professional demands and to other psychosocial factors. The objective of this study is to determine the characteristics of dual diagnosis among MIRs. A systematic review was carried out in MEDLINE (PubMed), Web of Science and Google Scholar databases, selecting articles published in English and Spanish between 1984 and 2017. A total of 2,415 articles were obtained: 2,276 were excluded by their title, 105 by the abstract and 17 after a complete review of the article; 17 papers were finally included. The prevalence of depressive symptoms among MIRs ranges from 10.2% to 70%, while the prevalence of anxious symptoms varies from 13.2% to 33.9%, from 6.7% to 25% reported suicidal ideation, 20% hazardous drinking, 2%-13.4% self-prescribed psychotropics, and 2.7%-14% used other drugs. Most studies present important methodological limitations, thus complicating adequate understanding of the phenomenon. High variations in prevalence data are related to differences in the psychometric scales and to disparity in diagnosis criteria, among other limitations. However, most studies report that alcohol and drug use is correlated with severe distress among MIRs. More research is needed to ascertain the nature of dual diagnosis in this professional group in order to effectively prevent and treat its serious consequences.

Keywords: Resident doctor; Substance use disorders; Mental disorders; Dual diagnosis; Self-treatment.

Resumen

El período de preparación como médico residente (en español, MIR) suele asociarse a una elevada sobrecarga emocional tanto por las nuevas exigencias profesionales como por otros factores psicosociales. El objetivo de este estudio es conocer las características del diagnóstico dual en los MIRs. Se llevó a cabo una revisión sistemática de las bases de datos MEDLINE (PubMed), Web of Science y Google Scholar, seleccionando artículos publicados en inglés y español entre 1984 y 2017. Se obtuvieron 2.415 artículos: se excluyeron 2.276 por título, 105 por el contenido del resumen y 17 por el contenido del artículo. En la revisión final se incluyeron 17 artículos. La prevalencia de clínica depresiva varía del 10,2% al 70%, de ansiedad entre 13,2% y 33,9%, de ideación suicida entre 6,7% y 25% mientras que el consumo de riesgo de alcohol se encuentra aproximadamente en torno al 20%, entre 2% y 13,4% se auto-prescriben medicamentos psicótropos y del 2,7% al 14% consumen otras sustancias. La mayoría de los estudios analizados adolecen de limitaciones metodológicas importantes lo que dificulta una adecuada comprensión del fenómeno. Las variaciones en las cifras de prevalencia tienen que ver con la disparidad de escalas y de criterios diagnósticos empleados, entre otros factores. Aún así, los estudios muestran que el consumo de alcohol y/u otras sustancias se correlacionan positivamente con el malestar emocional en los MIRs. Se hace necesario mejorar el conocimiento del diagnóstico dual en este grupo profesional para que se puedan prevenir y tratar sus consecuencias de manera más eficaz.

Palabras clave: Médico residente; Trastorno por uso de sustancias; Trastornos mentales; Diagnóstico dual; Auto-tratamiento.

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The period of postgraduate training as a resident doctor in Spain, known in Spanish as MIR (Médico Interno Residente), has a reputation for being highly stressful for reasons associated specifically with professional practice, with the characteristics of the respective institution and the teams into which resident doctors needs to integrate, as well as with the life changes that this vital transitional period involves (Blancafort, Masachs, Valero & Arteman, 2009; Tyssen, Vaglum, Gronvold & Ekeberg, 2000). Most salient among occupational factors are the new professional requirements at a technical level since most students move from more theoretical training to clinical practice. Demands on professional competence intensify as the years of training (either four or five) go by to ensure that when they finish, residents have the necessary skills to exercise their profession properly. Other occupational factors have to do with the integration into broad and multi-disciplinary professional teams, as well as with the characteristics of the institution in which they develop their specialty.

The sources of emotional overload change throughout the long period of training. A high level of stress usually accompanies the first year of residence (R1), in which residents are confronted by the real world, a new situation where they are expected to begin to develop different practical skills, previously lacking. As time goes by, the causes of distress vary and may be linked to: the characteristics of each specific new stage, the progressive increase of autonomy in decision-making, aspects related to team integration or the possibilities of continued training (Tyssen et al., 2000).

Beyond strictly occupational aspects, medical residents can also face situations such as: change of place of residence (even of country), leaving the family unit behind, or changes in significant affective relationships (Blancafort et al., 2009).

These new professional and contextual demands can lead to situations of emotional distress, especially in cases of abandonment of self-care (Brooks, Gerada & Chalder, 2011; Pereira-Lima, Loureiro & Crippa, 2016; Tyssen & Vaglum, 2002) or when they impact people whose personality traits or previous history hinder healthy coping with distress (neuroticism, perfectionism, self-criticism, obsessive-compulsive traits, personal and/or family history of psychopathology or early bonding problems) (Tyssen et al., 2002; Brooks et al., 2011).

Although the preparation of resident physicians varies from country to country, several studies have shown an increase during this formative period in the incidence of psychological distress and the use of alcohol or other drugs, some of which are self-prescribed (Blancafort et al., 2009). In addition, there has been an increase among medical trainees in the prevalence of suicidal ideation, attempted and completed suicides (Lindeman, Läärä, Hakko & Lönnqvist, 1996; Mousa, Dhamoon, Lander & Dhamoon, 2016; Pereira-Lima et al., 2016).

Prevalence data vary from one study to another because, among other factors, the characteristics of the training vary by country, as do the methods of detecting psychiatric symptoms and the criteria for delimiting harmful from pathological drug use. Moreover, most studies have to date been limited to reporting the prevalence figures for mental pathology and/or substance use independently, but few go as far as to analyze the causes or reasons which can account for the concurrence of both. Regarding the etiology, an attempt has been made to establish a relationship between alcohol use and depression in medical students, but longitudinal studies have yielded conflicting results regarding the causal relationship between the two (Clark, 1988). It is not clear whether alcohol problems precede ("harm" hypothesis) or follow ("self-treatment" hypothesis) depressive symptoms.

With regard to the prevalence of depression or anxiety in resident doctors, estimates are usually based on the presence of mere symptoms or depression-risk indicators. Thus, it is estimated that between 20.9% and 43.2% of the world's resident doctors have depressive symptoms, while this would affect 16% of the general population of the same age and socio-economic level (Mata et al., 2015). A 1986 survey in Spain revealed that 1% of residents had requested sick leave due to emotional problems and that 5% of these MIRs had attempted suicide of which almost half ended as competed suicides (Smith, Denny & Witzke, 1986).

One of the main longitudinal studies of medical trainees in Europe is the "The Young Doctor Cohort of the Longitudinal Study of Norwegian Medical Students and Doctors (NORDOC)". Its main objective was to identify early risk factors in medical students which could lead to the development of depression throughout their professional life. A cohort of students graduating in 1993 and 1994 from 4 medical schools in Norway (n = 631) was followed. Responses were collected at five points in time: T1 (final year of training); T2 (resident physician and first year after graduating); T3 (fourth year after graduating); T4 (tenth year after graduating) and T5 (15 years after graduating). Of all respondents, 219 completed the entire longitudinal assessment. It was observed that the youngest and those with the highest levels of neuroticism presented a risk of depression over time of up to 3 times greater, while suffering from early severe depressive symptoms doubled the risk (Støen Grotmol, Gude, Moum, Vaglum & Tyssen, 2013).

Another longitudinal study, also based on the NORDOC cohort, concluded that a negative parental bond, manifested as low self-esteem and maladaptive coping mechanisms for stress, may be a risk factor for developing severe depressive symptoms over time (Grotmol et al., 2010a).

With respect to substance use and its relationship with a primary psychopathological profile, the NORDOC study indicates that alcohol and psychotropic drug use is acknowledged by up to 21.4% and 13% of respondents re-

spectively as a strategy to alleviate distress. A study some years earlier had already observed that up to 20.3% of the students surveyed met the criteria for alcohol abuse or dependence in the 12 months prior to the interview (Flaherty & Richman, 1993).

One prospective study lasting six years attempted to determine whether doctors' expectations that alcohol reduces emotional stress could predict harmful drinking, and, moreover, whether such an effect would be mediated by the belief that alcohol improved coping with emotional stress (drinking to cope). In this study, 'harmful drinking' was defined as drinking at least 2 or 3 times a month, and to assess beliefs about the effects of alcohol, the "Alcohol Expectancy Questionnaire" was used as a specific instrument. Results showed that the expectation of alcohol's capacity to improve the ability to cope with distress is more important than harmful drinking per se when predicting later problematic use. The behavior differentiated between men and women, with the former clearly associating alcohol with emotional stress relief. Unfortunately, the relationship between specialization and alcohol use was not specifically analyzed, nor was a specific analysis performed on the comorbidity between harmful drinking and/or other mental disorders. Nevertheless, the study did conclude that, if the likelihood of developing pathological alcohol use is to be reduced, it is essential to assess and correct irrational beliefs about the effects of alcohol (Grotmol et al., 2010b).

Some residents begin to prescribe themselves psychotropic medications at the start of their professional life. They may resort to sedatives to relieve emotional distress or stimulants as "performance enhancers" (Arria & DuPont, 2010). Some years previously, an article had already observed that, compared to other medical students, residents consume more benzodiazepines (22.7% versus 19.6%) and barbiturates (8.5% versus 7.3%), while cocaine use was lower (29.2% versus 32.5%) (Hughes et al., 1992). Among trainee anesthetists, the most abused substances are, in order of frequency, fentanyl, alcohol, cannabis, cocaine, midazolam, oral opioids, other anesthetics such as propofol or inhalers (Mayall, 2016).

In a recent longitudinal study carried out in Catalonia with MIRs (Salamero & Baranda, 2018), the risk of suffering from mental disorder, according to the General Health Questionnaire, was 17.8% higher in the first years of residence and 29.7% higher in the final years. At the same time, self-perceived health, hours of sleep, available free time and self-care habits (such as regular physical exercise) gradually declined.

With respect to hazardous drinking, defined as ≥28 SDUs per month for men or ≥17 SDUs for women, or having 5 consecutive drinks at least once a month, this was greater in men (29% initially, 33% during the first year and 17% at the end of the fourth) than in women (12%, 10% and 5%, respectively). The most frequently correlated factor in the greater or lesser use of alcohol was family situation (those living with a partner or having children are at lower risk).

Sixty-five percent of respondents acknowledged having taken medication (especially analgesics and/or anti-inflammatories) in the 15 days prior to the survey, with an increase from 73% the first year to 78% at the end of the fourth. The use of hypnotics, tranquilizers and/or antidepressants rose from 7% at the beginning of residence, to 12.8% during the first year and up to 15.7% in the fourth. Self-medication, with or without psychotropics, is greater in women than in men.

Regarding substance use, 50% of the MIRs in Catalonia acknowledged having tried some at some time in their life but only 10% in the previous 30 days. Men were usually more frequent users (11%) than women (6%), and use increased at the beginning of residence and during the first year, while remaining stable at the end of the fourth year. The most used substance was cannabis, with approximately half of the MIRs having tried it at some point, and 6-7% using it recently, while use among MIRs born outside Spain was higher. Amphetamines were taken by up to 10% of respondents and cocaine by between 3% and 5%.

Like the rest of the medical profession, residents do not find it easy to ask for help when they suffer from a mental disorder, and this is exacerbated in the case of addiction (Braquehais et al., 2016). Added to the culture of invulnerability associated with the practice of medicine instilled in undergraduates, there is also the stigma associated with mental or emotional suffering, one which is even greater among health professionals. While some defense mechanisms may be effective in practicing as a doctor, they can lead to denial, rationalization or minimization of one's distress when it comes to dealing with one's own suffering, which only contributes to worsening it in the medium and long term (Gerada, 2019; Schwenk, Davis & Wimsatt, 2010).

Failure to adequately address emotional distress among medical residents has negative implications for their professional practice given its association with higher medical error rates, greater difficulties in interpersonal and interprofessional relationships, and a decrease in learning capacity (Brooks et al., 2011; Fahrenkopf et al., 2008; Pereira-Lima et al., 2016), while also reducing levels of patient satisfaction (Saipanish, 2003).

The main objective of this study is to investigate the prevalence and risk factors specifically of dual diagnosis in medical residents through a systematic review of articles published to date on this phenomenon.

Methods

A systematic review was carried out in the MEDLINE (PubMed), Web of Science and Google Scholar databases and studies published in Spanish and English between

01/01/1984 to 07/01/2017 were selected. The approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) was used to structure the systematic review.

The type of studies selected included: case reports, original articles, meta-analyses, multicenter studies, observational studies, reviews, scientifically rigorous reviews and systematic reviews.

Keywords were: "internship or residency" or "resident" or "interns" or "medical resident" or "resident internal doctor" or "MIR". Those mentioning "interns" (undergraduate intern) were excluded as this term does not correspond to the definition of "resident doctor" (MIR, in Spanish). Once the articles were selected, the search continued with the terms: "substance related disorders", "cannabis", "marihuana", "cocaine", "alcohol", "opioid", "burnout", "stress", "mental disorders", "addiction", "depressive disorders" or "suicide".

Of the 2,415 articles obtained, 2,276 were excluded by title, 105 by the content of the abstract and 17 by the complete article content; the final review included the 17 articles dealing specifically with dual diagnosis (or pathology) (see Figure 1).

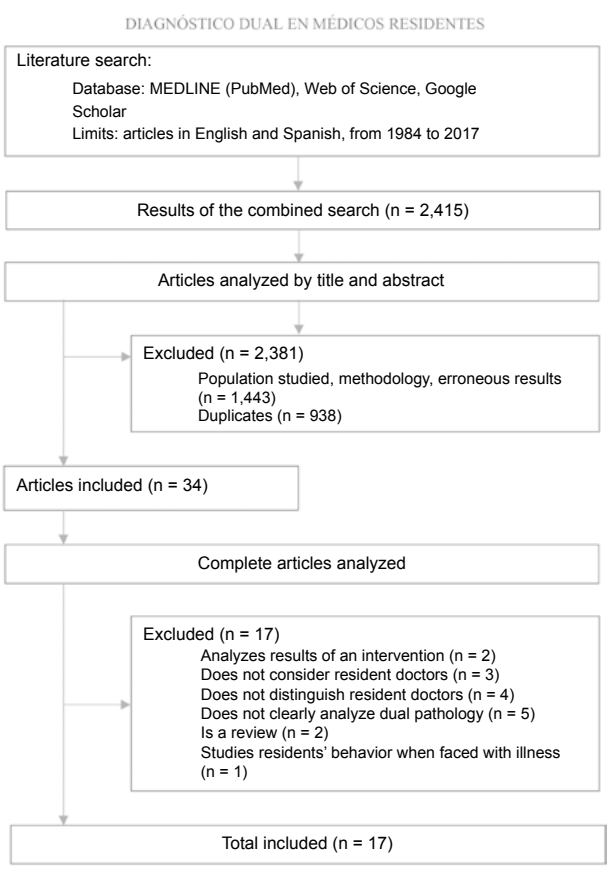

Figure 1. Systematic review methodology

Results

Of the studies included in this review, about 60% (n = 10) were conducted in the United States, United Kingdom and Canada, 17% (n = 3) in South America (Brazil), 6% (n = 1) in Lebanon, 6% (n = 1) in Turkey and 11% (n = 2) in Nigeria (see Table 1). The majority are cross-sectional studies. The most frequent comorbidity reported was the presence of a depressive symptoms and alcohol use (Koran & Litt, 1988; Lebensohn et al., 2013; Martinez et al., 2016; Talih, Warakian, Ajaltouni, Shehab & Tamim, 2016).

It is worth highlighting that according to one article, almost 50% of residents experienced stress during residency. The most important factors contributing to stress in men were financial situation (33.3%), economic status (23.8%) and time pressure (14.3%), while for women, work situation (33.3%), time pressure (20%) and work status (20%) were the most relevant (Ogunsemi, Alebiosu & Shorunmu, 2010). Another article found professional relationships to be source of stress, and 46% of residents reported fear of being labeled "trouble makers" if they complained about their residency programs (Koran et al., 1988).

The different studies show that prevalence of depressive symptoms varies from 10.2% to 70%, and of anxious symptoms from 13.2% to 33.9% (Akvardar, Demiral, Ergor & Ergor, 2004; Earle & Kelly, 2005; Fagnani Neto, Obara, Macedo, Cítero & Nogueira-Martins, 2004; Koran et al., 1988; Lebensohn et al., 2013; Lydall, Malik, Blizard & Bhugra, 2009; Matheson et al., 2016; Melo et al., 2016; Mousa et al., 2016; Ogunsemi et al., 2010; Olagunju, Ogundipe, Lasebikan, Coker & Asoegwu, 2016; Talih et al., 2016; Zisook et al., 2016). When psychiatric diagnostic instruments were used instead of symptoms, the prevalence of major depressive disorder ranged from 13% (Earle et al., 2005) to 22% (Talih et al., 2016), generalized anxiety from 4.9% (Olagunju et al., 2016) to 12% (Earle et al., 2005); obsessive compulsive disorder (OCD) has a prevalence of 3.4% (Olagunju et al., 2016), simple phobias 2.4% (Olagunju et al., 2016), panic disorder 2% (Earle et al., 2005) and social phobia 1.5% (Olagunju et al., 2016). Interestingly, one author established a prevalence of 30.5% for social phobia, according to the *SPIN (Social Phobia Inventory)* questionnaire (Melo et al., 2016).

Among the factors associated with symptoms of anxiety and depression we find lower competence in social skills, personality traits such as neuroticism, social and family instability and work overload (> 8 on-call shifts per month) (Pereira-Lima et al., 2016; Talih et al., 2016). Other factors positively correlated with these symptoms were sleep deprivation, both acute and chronic (Mansukhani, Kolla, Surani, Varon & Ramar, 2012), the use of illicit drugs and alcohol, burnout, suicidal behavior and the presence of life stressors at the family and/or social level (Mansukhani et al., 2012; Mousa et al., 2016; Talih et al., 2016).

Table 1. *Articles selected for review*

Source	Country	Type of study	Type of population	Design	Results
Mousa et al., 2016	USA	Transversal	336 MS, 126 HS	Study based on self-administered questionnaire and scales *PHQ-2, GAD-7*	HS: Screening: 15.1% positive for depression, 15.9% positive for moderate to severe anxiety. Coping: 21.4% reported using alcohol and 2% self-prescribed psychopharmaceuticals
Martínez et al., 2016	USA	Transversal	411 MS, 267 HS, 398 practicing doctors	Study based on self-administered questionnaire and scales *Modified stress and depression questionnaire includes items on use of alcohol, drugs, PHQ-9 and suicide.*	Prevalence of depressive disorder not established in HS. HS: 27% reported "drinking more than normal" and 18% "drinking too much".
Pereira-Lima et al., 2016	Brazil	Transversal	270 medical residents	Study based on self-administered questionnaire and scales *PHQ-4, AUDIT-3, NEO-FFI-R, SSI-Del-Prette*	Alcohol addiction: 15.93%. Anxiety and/or depressive symptoms: 41.85%. Association of personality traits such as neuroticism, deteriorating social skills, work overload (number of on-call shifts >8/month) with anxiety and/or depressive symptoms. Male sex, surgical resident, work overload (number of on-call shifts >8/month), extraversion with alcohol addiction.
Melo et al., 2016	Brazil	Transversal	59 Psychiatry residents	Study based on self-administered questionnaire and scales *BDI-II, BAI, SPIN, AUDIT-10, Fägerstrom test.*	Anxiety symptoms: 33.9%. Social phobia disorder: 30.5%. Depressive symptoms 19%. Alcohol use: 81.4%. Harmful alcohol use: 22%.
Olagunju et al., 2016	Nigeria	Transversal	204 medical residents	Study based on questionnaire *(GHQ-12)*, and structured interview *(SCID-1/NP) based on DSM-IV*	Emotional stress: 28.9%. Clinical anxiety: 13.2%, with 4.9% meeting GAD criteria. TOC: 3.4%. Specific phobia: 2.4%. Social phobia: 1.5%. Substance induced anxiety disorder: 1%.
Talih et al., 2016	Lebanon	Transversal	118 medical residents	Study based on self-administered questionnaire and scales. *PHQ-9 (question 9 assesses autolytic ideation), BM, GAD-7, AUDIT-10, DAST-10*	Mild depressive symptoms: 30%. Moderate to severe depressive symptoms: 22% (MDD). Autolytic ideation, associated with severity of depression and emotional burnout syndrome: 13%. Residents with MDD and suicidal ideation: 58%. Alcohol use: 59%, of which harmful use: 10%. Abuse of illicit drugs: 14%.
Zissok et al., 2016	USA	Transversal	369 MS, 237 HS, 396 medical specialists	Study based on *HEAR Stress and Depression questionnaire (includes PHQ-9)*	HS: depressive syndrome: 10.2% (minimal 38.2%, mild: 39.1%, moderate: 15%, moderate-to-severe depression: 7.7%). Suicide risk (ideation and previous attempts): 10.5%. Drinking more than normal: 25.3%. Feel they drink a lot: 17.3%. Use of other substances/self-prescribed drugs: 4.6%.
Matheson et al., 2015	Canada	Transversal	232 medical residents	Study based on *Kessler-10* self-administered *online* questionnaire.	Medical residents: psychological stress: 44.3% (high or very high stress: 9%). Alcohol use: 75.8%. Use of other drugs (unspecified): 2.7%. Suicidal ideation in previous 12 months: 6.7%.
Lebensohn et al., 2013	USA	Transversal	168 FM residents (1st year)	Study based on questionnaires and scale. PSS, CES-D, MBI, SWLS, Wellness behavior survey.	Risk of clinical depression: 23%. Drinking more than 3 SDUs per week: 19%. Use of medication for anxiety, mood or sleep: 10% (not stated whether self-prescribed); reported more by women (94.4%).
Mansukhani et al., 2012	USA	Systematic review	14,836 medical residents	Search of studies assessing the effects of sleep deprivation.	Severe and chronic sleep deprivation results in increased use of alcohol, psychotropic medication (such as zolpidem, 2.4%, and modafinil, 21.8%) and deterioration of mood.
Ogunsemi et al., 2010	Nigeria	Transversal	58 medical residents	Study based on self-prescribed questionnaire	Reporting significant stress during residency: 50%. To cope with stress, many residents reported using alcohol (5.2%), nicotine (1.7%), drugs and medication (8.6%) and eating more (15.5%).
Lydall et al., 2009	UK	Transversal	1,002 medical residents	Study based on self-administered *online* questionnaire (designed by the authors).	Four of more depressive symptoms: 70%. Autolytic ideation: 23%. Alcohol use: 37%.
Earle et al., 2005	Canada	Transversal	254 FM residents	Study based on self-administered questionnaires and scales, designed by the authors (based on DSM-IV diagnostic criteria).	Depressive syndrome: 20% (MDD, 13%, other depressive disorders, 7%). GAD: 12%. Panic disorder: 2%. Regarding alcohol and substances: 61.8% recreational, 1.2% addiction, and 5.9% as a coping mechanism. Medication with psychotropics as coping mechanism: 13.4% (not stated whether self-prescribed).
Fangnani Neto et al., 2004	Brazil	Retrospective study	233 Master's or Doctorate students, medical residents (24%) and nursing residents	Semi-structured questionnaire (designed by the authors). Main diagnoses covered in ICD-10	Medical residents: autolytic ideation: 25%. Alcohol use: 45.1%. First year of residency considered the most stressful.
Akvardar et al., 2004	Turkey	Transversal	52 MS, 73 medical residents, 80 practicing doctors	Study based on self-administered questionnaires and scales. Fägerstrom test of nicotine addiction, CAGE scale, HAD.	Depressive symptoms: 40%. Anxiety symptoms: 19.2%. Risk of alcohol abuse: 8.9%. Use of benzodiazepines (the most frequently used hypnosedatives): 8.2%. Prevalence of illicit drug use: 5.5%. Most frequently used drug: cannabis (prevalence not stated).
Bunch et al., 1992	USA	Transversal	80 surgical residents, 179 other surgical specialities, 1,495 other specialities	Study based on self-administered questionnaires (designed by the Center for the Study of Impaired Professionals)	Low level of alcohol use, similar to other specialities (70% drink 10 times per month). Low level of use of marihuana, cocaine or other drugs, lower than in other non-surgical specialities (prevalence not stated). Low levels of irritability and hostility, high level of tiredness (sign of stress).
Koran et al., 1988	USA	Transversal	281 medical residents	Study based on self-administered questionnaire (designed by the authors).	Depressive or anxiety symptoms: 40%. Substance abuse: 12% (greater use of alcohol, marihuana or cocaine), and increase in use of sedatives, stimulants and opioids since the start of residency. Of those reporting increased use of alcohol, marihuana or cocaine, 79% also reported increased use of sedatives, stimulants or opioids.

Note. **Abbreviations:** *MS* medical students; *HS* house staff, *FM* family medicine, *MDD* major depressive disorder, *GAD* generalized anxiety disorder, *BAI* Beck anxiety inventory, *AUDIT* alcohol use disorders identification test, *SPIN* social phobia inventory, *PHQ* patient health questionnaire, *GHQ* general health questionnaire, *BM* burnout measure, *GAD-7* generalized anxiety disorder 7, *DAST-10* drug abuse screening test 10, *PSS* perceived stress scale, *CES-D* Center for Epidemiologic Studies depression scale, *MBI* Maslach burnout inventory, *SWLS* satisfaction with life scale, *NEO FFI R* neo five-factor inventory revised, *SSI Del-Prette* Del-Prette social skills inventory.

In terms of suicide ideation, this was found to be prevalent in between 6.7% and 25% of residents surveyed in five studies (Fagnani Neto et al., 2004; Lydall et al., 2009; Matheson et al., 2016; Talih et al., 2016; Zisook et al., 2016). Suicidal ideation was associated with the severity of depression and the presence of emotional burnout; indeed, when diagnostic criteria for major depressive disorder were met, suicidal ideation was present in 58% of respondents (Lydall et al., 2009; Talih et al., 2016; Zissok et al., 2016). One study observed that suicidal ideation and previous suicide attempts were moderately correlated with six variables: year of residency, specialty, presence of professional burnout, major depressive disorder, self-prescription of psychotropic drugs, and stressful life events. However, after multivariate analysis, only professional burnout and stressful life events maintained a statistically significant correlation with suicidal ideation (Talih et al., 2016).

While some studies show that the depressive and anxiety symptoms increase throughout residency (Earle et al., 2005; Mousa et al., 2016), others point to greater distress in the first year (Fagnani Neto et al., 2004). One author found a positive correlation between the presence of stressful situations and the appearance of anxiety symptoms, which are experienced by 50% of residents (Olanguju et al., 2016).

With regard to sex, while some studies did not find significant differences between the two (Earle et al., 2005; Koran et al., 1998; Lebensohn et al., 2013), others pointed to a higher prevalence of psychological distress (either as anxiety or depressive symptoms) in women (Fagnani Neto et al., 2004; Matheson et al., 2016).

In terms of speciality, one study with psychiatry residents (Melo et al., 2016) showed high levels of anxious symptomatology (33.9%) and prevalence of social phobia (30.5%). As for resident family/community doctors, 23% are said to be at risk of depression during the first year (Lebensohn et al., 2013) and 20% if the entire training period is taken into account (Earle et al., 2005). In another study (Talih et al., 2016) it was observed that the resident training in internal medicine, pediatrics and anesthesiology were more likely to present depressive symptoms than those in surgical specializations, although the differences ceased to be statistically significant on performing multivariate analysis.

Regarding the prevalence of alcohol use among residents, estimates range from 20% to 81.4% (Akvardar et al., 2004; Bunch, Dvonch, Storr, Baldwin & Hughes, 1992; Earle et al., 2005; Fagnani Neto et al., 2004; Koran et al., 1988; Lydall et al., 2009; Matheson et al., 2016; Melo et al., 2016; Mousa et al., 2016; Ogunsemi et al., 2010; Talih et al., 2016; Martinez, et al., 2016; Zisook et al., 2016). Such variation in the prevalence figures may result from the diverging criteria used to define use which is harmful or at risk of becoming pathological. Two studies (Martinez, et al., 2016; Zisook et al., 2016), for example, use the concepts of drinking "more than usual" and "too much", yielding a prevalence of 25.3 - 27% and 17.3 - 18% respectively among surveyed residents. One author reported that 19% of residents drank in excess of 3 units of alcohol per week (Lebensohn et al., 2013). In another article, an AUDIT-3 score of over 3 units corresponded to alcohol dependence and that 15.93% of the residents met this criterion (Pereira-Lima et al., 2016). Other authors, however, identify pathological use at AUDIT-10 scores of higher than 8 points, representing 10% (Talih et al., 2016) and 22% (Melo et al., 2016) of the respondents. For others, the pathological use criterion is a score of greater than 2 on the CAGE Scale, which is met by 8.9% of residents studied (Akvardar et al., 2004).

Among the factors associated with alcohol use are: being male, residents of surgical specialities, extraversion, sleep deprivation, greater number of on-duty shifts, depressive symptoms, anxiety symptoms, active suicidal ideation, previous suicide attempts, illicit drug use and greater perceived stress (Bunch et al., 1992; Lebensohn et al., 2013; Mansukhani et al., 2012; Martinez, et al., 2016; Olagunju et al., 2016; Pereira-Lima et al., 2016).

Some authors (Earle et al., 2005; Lebensohn et al., 2013; Martinez, et al., 2016; Mousa et al., 2016; Talih et al., 2016) found an association between drinking and depressive symptoms. This comorbidity is related to greater severity of depressive symptoms, intense moods, active suicidal ideation, history of suicide attempts, and the use of other psychoactive substances. Some articles suggest that up to 21.4% of resident use alcohol as a method of coping with symptoms of depression or anxiety (Earle et al., 2005; Lebensohn et al., 2013; Martinez, et al., 2016; Ogunsemi et al., 2010). Some authors, on the other hand, observed that the most frequent motivations for drinking were to relax after a tense day (31.5%) and/or reduce stress (17.8%) (Akvardar et al., 2014). Several authors point out that, since the residency period is usually associated with greater stress, there is an increased risk of developing pathological alcohol use as an unhealthy coping mechanism when facing emotional overload (Bunch et al., 1987; Pereira-Lima et al., 2016; Talih et al., 2016).

Regarding the self-prescription of psychotropics for handling distress, studies reveal prevalence figures that fluctuate between 2% and 13.4% (Akvardar et al., 2004; Earle et al., 2005; Fagnani Neto et al., 2004; Koran et al., 1988; Lebensohn et al., 2013; Mousa et al., 2016; Ogunsemi et al., 2010; Talih, et al., 2016; Zissok et al., 2016). One article specifies that it is the benzodiazepines which are most frequently self-prescribed (8.2%) (Akvardar et al., 2004). In a study cited in a systematic review (Mansukhani et al., 2012), 38% of residents reported having used a sedative-type drug to sleep after an on-call night shift, 2.4% said they used zolpidem, and up to 21.4% used the modafinil psychostimulant. While some authors (Lebensohn et al., 2013) report that women report greater self-adminis-

tration of sedatives than men, others find no differences between the sexes (Earle et al., 2005).

One article reported an association between self-prescription of drugs and use of illicit drugs (Talih et al., 2016), and in terms of substance use, the prevalence figures vary from 2.7% to 14% (Akvardar et al., 2004; Earle et al., 2005; Matheson et al., 2015; Ogunsemi et al., 2010; Talih et al., 2016; Zissok et al., 2016). According to one article, the illicit drug most frequently used among residents was cannabis, although its prevalence was not clearly defined (Akvardar et al., 2004). A study with surgical residents describes them as less likely to use marijuana, cocaine, tobacco, tranquilizers, amphetamines, LSD, barbiturates, opiates or heroin in the previous year than other trainees (Bunch et al., 1992).

Other authors point out that 79% of those who started using alcohol, marijuana or cocaine also ended up using sedatives, stimulants or opioids (Koran et al., 1988). A more recent study mentions that substance use correlates positively with the abuse of psychotropic drugs and alcohol, and the severity of depressive symptoms (Talih et al., 2016).

The negative impact of emotional distress and substance use on the quality of care is reflected in several studies. In some studies, 3% of residents acknowledge that their professional performance may have been diminished by alcohol use (Martinez, et al., 2016). Others mention that anxiety and depression impair performance in at least 33% of the cases studied (Mousa et al., 2016). Among psychiatry residents, high levels of anxiety and depressive symptoms are associated with worse relationships with peers, preceptors and patients (Melo et al., 2016). Additionally, those whose use of alcohol increased during their training period showed greater deterioration in the interprofessional relationships and increased concern regarding the worsening of anxiety/depressive symptoms, with fear of failure in interpersonal relationships. Some authors point out that the onset of impaired professional performance in a resident may be an alarm signal leading to suspicion of depression, an anxiety disorder, and ultimately contributing to the development of alcohol or drug addiction (Minter et al., 2014).

Discussion

Most studies conducted to date on medical residents focus their attention on analyzing the state of participants' mental health, identifying those at risk of developing mental disorders and understanding the characteristics of alcohol and/or other drug use. By limiting the scope of the systematic review to those studies specifically addressing dual diagnosis among residents, the number of articles was significantly restricted. Most of these are cross-sectional, which therefore only allow correlations to be established between variables without determining possible causal relationships. Regarding the identification of psychological distress and substance use, the definitions and the threshold used to define normal pathology vary significantly across the studies. Many simply identify the presence of anxiety or depressive symptoms without a clear diagnosis of mental disorder. As for substance use, the definitions of risk behaviors vary widely and few studies show the presence of a defined addiction disorder. The studies also lack a clear description of the characteristics of this training period in the different countries. Given the above, it can be said that the phenomenon of comorbidity between mental and addictive disorder is, at least, poorly defined in the literature to date despite the existence of enough data to raise awareness of the importance of analyzing the coexistence of both among medical residents in depth.

In the studies analyzed, the prevalence of depression and anxiety among resident doctors varies from 10.2% to 70%, and from 13.2% to 33.9% respectively, with the lowest figures pointing to the presence of a defined mental disorder and the highest reflecting the presence merely of anxiety or depression symptoms or the risk of developing a mental disorder. In any case, these estimates exceed the prevalences within the general population of an equivalent socio-economic and educational level. Between 6.7% and 25% of studies report that the residents studied had suicidal ideation at the time of the evaluation.

For some authors, depressive and anxiety symptoms increase throughout the residency, which is probably related to growing responsibilities and new challenges over the years (Earle et al., 2005; Mousa et al., 2016), but others suggest that it is at the beginning of the residency when the emotional distress is greatest (Fagnani Neto et al., 2004).

Some personality traits of residents (such as neuroticism), certain work circumstances typical of the residence period (work overload, time pressure, sleep deprivation), in addition to the concurrence of other family and/or social stressors (Mansukhani et al., 2012; Ogunsemi et al., 2010; Talih et al., 2016; Zissok et al., 2016), have been associated with the presence of emotional distress in this period.

In relation to alcohol use, prevalence is estimated to range from 20% to 81.4%, although hazardous drinking is closer to 20%. Regarding the self-prescription of psychotropics for coping with distress, studies reveal prevalence figures fluctuating between 2% and 13.4%, with those of a sedative or hypnotic type being more frequently used, although the use of stimulants is not negligible, in some cases exceeding 20%. Substance use, meanwhile, is estimated at between 2.7% and 14%, with cannabis the most frequently used.

Most studies concur that the presence and severity of emotional distress symptoms (anxious and/or depressive) is associated with increased drinking and greater use of illicit drugs and/or psychotropic drugs. Moreover, higher alcohol use is positively correlated with the self-prescription of psychotropic drugs and substance use. Drinking is also

associated with the presence of active suicidal ideation and previous suicide attempts.

Results regarding sex differences are not consistent, probably because of the differences in detection methods and temporal and spatial divergence of the studies. An increased risk of anxiety/depressive symptoms is apparent in women using sedatives, which may be related to factors such as a tendency to internalize psychological conflicts, greater number of demands in training programs, difficulty in achieving a career-life balance, as well as the lack of role models in leadership positions (Matheson et al., 2016). Nevertheless, the use of alcohol and illicit drugs is greater in men.

Regarding medical specialities, there are some which continue to be identified by some studies as being at greater risk (psychiatry, anesthesiology, internal medicine and family medicine), compared to others, such as in the surgical field, where the known prevalence of emotional distress and/or addictive behaviors is lower.

Studies agree that a decline in professional performance not previously present may be a significant alarm signal for depression, anxiety disorder or perhaps something which could develop into an addiction to alcohol and/or other drugs (Minter et al., 2014).

This systematic review raises awareness of the importance of taking dual diagnosis into account in medical residents. From a methodological point of view, we recommend that future studies:

- Expand sample size.
- Use structured diagnostic interviews following the initial screening surveys. Merely carrying out self-administered surveys increases the likelihood of bias both in terms of selection and those related to the self-report of symptoms or problematic behaviors.
- Use only definitions and scales which have been standardized and internationally validated when analyzing substance use.
- Conduct longitudinal or prospective studies which help analyze the etiological relationships between drug and/or alcohol use and other mental disorders.
- Provide a clear description of the characteristics of the residency period covering: weekly work hours, remuneration, number of on-call shifts, number of patients at the healthcare facility, number of residents per year, transversal and longitudinal competencies of the resident.
- Perform a differentiated analysis by specialization or by year of training, and a differentiated analysis by sex.

Despite the methodological limitations mentioned above, the link between severity of resident doctors' emotional distress and the presence of risky behaviors regarding substance use, from alcohol to self-prescribed medication and even illicit drugs is clear. Improving our knowledge of residents' psychological distress in and, in particular, of the simultaneous appearance of mental and addictive disorders, is vital when laying the foundations for promoting the healthy exercise of medicine, while ensuring that professional practice is safe from the start. From the preventive point of view, offering therapeutic or interpersonal support during residency is known to be a fundamental protective factor in preventing the onset of mental disorders (Tyssen et al., 2007). In addition, the percentage of residents requesting emotional support and self-care supervision services during their training is growing (Matheson et al., 2016). Specialized services engaging with doctors as patients, such as the Program for Comprehensive Care of the Sick Physician (PAIME) in Spain (Braquehais, Tresidder & DuPont, 2015) and training activities for trainee doctors and tutors, such as those developed by entities such as Fundació Galatea in Catalonia, can be inspirational in improving the personal well-being of these professionals, while also positively improving the quality of care.

Conflicts of interest

None.

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Measurement instruments of Internet gaming disorder in adolescents and young people according to DSM-5 criteria: a systematic review

Instrumentos de medida del trastorno de juego en internet en adolescentes y jóvenes según criterios DSM-5: una revisión sistemática

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Abstract

The inclusion of Internet Gaming Disorder (IGD) in the DSM-5 has generated controversy over its diagnosis, and it therefore seems necessary to establish a clear cut-off point to identify when excessive gaming becomes problematic. Such identification is especially difficult in adolescents and young people, who frequently dedicate a great deal of time to online games. The goal of this systematic review was to analyze the instruments developed to assess IGD in adolescents and young people since its inclusion in the DSM-5. We identified 13 studies which included validations of seven assessment instruments for IGD in adolescents and young people. Each instrument and its validations in different languages are described. In comparison to previous reviews, a lower diversity of assessment instruments, a reduction in the number of items and a more uniform form of measurement was observed, maintaining high internal consistency and good criterion validity. However, problems related to sample selection, the lack of sensitivity and specificity studies, and the establishment of cut points and profiles of gamers remain. Advances in the analysis of the psychometric qualities of the instruments and their validation in different countries are needed, and cultural differences should be considered in order to allow the prevalence of this problem to be compared.

Key Words: Assessment, Measurement, Internet Gaming Disorder (IGD), youth and adolescents, DSM-5.

Resumen

La inclusión del Trastorno de Juego en Internet (TJI) en el DSM-5 ha generado polémica sobre su diagnóstico, no obstante parece necesario establecer un punto de corte claro para identificar cuando este juego excesivo se convierte en problemático. Esta identificación se hace especialmente difícil en adolescentes y jóvenes, entre los que suele ser frecuente la dedicación a este tipo de juegos. El objetivo de esta revisión sistemática fue analizar los instrumentos desarrollados para la evaluación del TJI en adolescentes y jóvenes desde su inclusión en el DSM-5. Se identificaron 13 estudios que incluían validaciones de 7 instrumentos de evaluación del TJI en adolescentes y jóvenes. Se describió cada instrumento y sus validaciones en distintos idiomas. En relación con revisiones previas, se observó una menor diversidad de instrumentos de evaluación, una reducción en el número de ítems y una forma de medida más uniforme, manteniéndose una alta consistencia interna y una buena validez de criterio. Sin embargo, siguen presentes los problemas referidos a la selección de muestras, la falta de estudios de sensibilidad y especificidad, y el establecimiento de puntos de corte y perfiles de jugadores. Se recomienda avanzar en el análisis de las cualidades psicométricas de los instrumentos, y su validación en distintos países para considerar las diferencias culturales y poder comparar la presencia de este problema.

Palabras clave: Evaluación, Medida, Trastorno de Juego en Internet (TJI), jóvenes y adolescentes, DSM-5.

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When Internet gaming involves young people and adolescents, it is associated with negative personal, family and/or social consequences, such as sleep problems (Lam, 2014), an impact on well-being (Scott & Porter-Armstrong, 2013), and greater frequency of mental problems and less self-control (Dinh, Yasuoka, Poudel, Otsuka & Jimba, 2013). The prevalence of Internet Gaming Disorder (IGD) was estimated by a recent meta-analysis to lie between 0.7% and 15.6% (Feng, Ramo, Chan & Bourgeois, 2017), while a recent study with a Spanish-speaking population highlighted problematic video game use at 10.9% and dependence at 1.9% (Pedrero et al., 2018).

Before the inclusion of IGD in the DSM-5 (APA, 2013), the criteria used to diagnose problems of Internet gaming addiction in empirical studies were based on the criteria for diagnosing pathological gaming, or on the criteria for substance dependence. For example, a systematic review of studies on Internet gaming disorder in children and adolescents between 2000 and 2011 (Kuss & Griffiths, 2012) found that the diagnosis in 18 studies was based on pathological gaming criteria, while three studies used substance dependence criteria, and mixed criteria were used in three others. Including IGD in the DSM-5 was an important step in terms of establishing normative criteria for what should be considered symptomatic of this disorder. The classification includes nine criteria: (1) concern about playing on the internet; (2) withdrawal symptoms; (3) tolerance; (4) failed attempts to control participation in online games; (5) loss of interest in previous hobbies and entertainment behavior as a result of, and with the exception of, online games; (6) excessive and continued use of online games despite knowing the psychosocial problems it causes; (7) deception of relatives, therapists, or other people about the amount of play on the Internet; (8) use of online games as a way of escaping or alleviating negative moods; and, (9) having risked or lost significant interpersonal relationships, work and educational or professional opportunities due to participation in gaming on the Internet. At least five of the nine criteria have to be met during a 12-month period, although levels of severity are not established depending on the number of criteria met.

DSM-5 inclusion sparked controversy both in terms of the acknowledgment of IGD as an addiction and its diagnosis (Kuss, Griffiths & Pontes, 2017a, 2017b; Starcevic, 2017; Van Rooij & Kardefelt-Winther, 2017). Despite the social alarm it has caused, playing video games is in most cases a normal leisure activity, which only becomes a health problem necessitating professional help in a small percentage of players. However, when addressing this issue it is important that the scientific community and professionals agree on criteria and cut-off points which make it possible to distinguish when a person plays in a non-problematic way and when it is damaging to their daily lives. Nevertheless, it becomes difficult to establish a clear and precise distinction between what is safe gaming, excessive gaming and problematic gaming. This distinction is especially difficult among adolescents and young people, who frequently dedicate themselves single-mindedly to online gaming (Carbonell, Torres-Rodríguez & Fuster, 2016); hence the interest in having suitable tools for diagnosis.

King, Haagsma, Delfabbro, Gradisar and Griffiths (2013) conducted a systematic review of psychometric instruments used to evaluate IGD between 2000 and 2012, prior to DSM-5 inclusion. Table 1 shows a summary of the 18 instruments their research covered. The major strengths of the instruments were: (a) their ease of application, (b) relative brevity, (c) ease of scoring and administering; (d) high internal consistency (between .70 and .96, although this was not reported for seven of the 18 instruments), and (e) good convergent validity (unreported for four instrument) with related measures, such as social competence, education, impulsivity, sensation seeking, aggressiveness, depression, anxiety, attention problems, sleep difficulties, life satisfaction, etc. In terms of criterion validity, defined as a positive correlation between the severity and/or number of symptoms and the time spent playing video games, seven of the instruments yielded significant correlations, while 11 did not measure it. The authors note that, of these 18 instruments, only the *Problem Video Game Playing Scale* (PVP) (Salguero & Morán, 2002) would be able to assess IGD by covering the 9 DSM-5 criteria. Additionally, the *Game Addiction Scale* (GAS) (Lemmens, Valkenburg & Peter, 2009), would allow eight of the nine criteria to be assessed.

Meanwhile, the reviews by Kuss and Griffiths (2012) and King et al. (2013) noted the characteristics of the samples used and the lack of sensitivity of the measures as the major problems with the measurement instruments prior to DSM-5.

Regarding sample characteristics, Kuss and Griffiths (2012) indicated that the samples are specific to a certain age or nationality (which does not allow generalization to other populations), mixed (which cannot be generalized to specific groups), and/or convenience samples (basically involving people who are particularly motivated to participate); the authors therefore recommend cross-cultural studies which allow the comparison of results in different socio-cultural contexts. Similarly, King et al. (2013) noted that samples are usually recruited on the Internet (only a third were recruited through schools), with the biases that this implies. They recommend using random selection methods to recruit participants from the general population and the development of manuals with standardized norms for each instrument.

With regard to the qualities of sensitivity and specificity, meeting both requirements is a complex proposition. On the one hand, it is preferable that screening instruments, aimed at detecting possible cases, be highly sensitive so that

Table 1. *Internet gaming disorder assessment instruments prior to DSM-5 criteria*

Instrument	Country of origin	Language	*N*	Items	Format (options)	Factors
Adaptation DSM-IV-TR pathological game	USA	E	9995	10/11	Yes/No	2
Adaptation DSM-IV-TR dependence substances	USA	E	516	7	Yes/No	2
Addiction Engagement Questionnaire	UK	E	482	24	Likert (7)	2
Compulsive Internet Use Scale (CIUS)	UK	E, G	3744	14	Likert (5)	5
Engagement Addiction Questionnaire	UK	E	404	19	Likert (6)	2
Exercise Addiction Inventory (adaptado)	UK	E	119	6	Likert (5)	-
Game Addiction Scales (GAS)	UK	E, G, N	3413	7/21	Likert (5)	7
Korean Internet Addiction Test (KIAS)	South Korea	K	627	40	Likert (4)	7
Online Game Addiction Scale- Adolescents in Taiwan (OAST)	Taiwan	T	666	29	Likert (4)	4
Online Game Addiction Index (OGAI)	China	C, E	195	12	n.i.	3
Problem Videogame Playing (PVP) Scale	Spain	E, F, C	4988	9	Yes/No	7
Problematic Internet Use Scale (ISS-20)	Austria	G	468	20	Likert (6)	5
Problematic Internet Use Scale (POGU)	South Korea	E, K	1422	20	n.i.	5
Problematic Online Gaming Questionnaire (POGQ)	Hungary	E	3415	18	Likert (5)	6
Video Game Addiction Test (VAT)	Netherlands	E, G	2894	14	n.i.	5
Video Game Dependency Test (KFN-CSA-II)	Germany	G	15168	14	Likert (4)	5
Young Internet Addiction Scale (YIAS)	USA	E, C, F, IT, TU	2025	8	Yes/No	5
Young Internet Addiction Test (YIAT)	USA	G, E, F, C	7874	20	Likert (5)	6

Note. AR = Arabic; C = Chinese; E = English; F = French; G = German; IT = Italian; K = Korean; N = Norwegian; T = Taiwanese; TU = Turkish. n.i. = no information
Adapted from King et al. (2013).

all cases with a disorder may be identified, even at the risk of increasing false positives. On the other, highly specific instruments are preferable in order to confirm a possible diagnosis and reduce the rate of false positives. King et al. (2013) recommend prioritizing sensitivity in epidemiological studies and specificity when identifying clinical cases for treatment. Kuss and Griffiths (2012) pointed out that with the assessment instruments analyzed in their review, it is difficult to judge whether they are sufficiently sensitive to determine the level of gaming addiction of children and adolescents, or whether they are able to identify adolescents who are not addicted to online gaming.

Finally, King et al. (2013) observed that most of the instruments (11 of 18) used Likert-type scales instead of dichotomous response options in order to increase sensitivity, and that there were problems of standardization in their application related to the lack of reference manuals or precision at cut points. Thus, different cut points were used with some instruments in different studies, with five of them not even applying cut points or not providing information in this regard.

Given this state of affairs, the aim of the present systematic review is to analyze the instruments that have been developed for the assessment of IGD in adolescents and young people since this disorder was included in the DSM-5. In particular, the characteristics of the instruments, the samples used in their validation and their psychometric qualities will be analyzed, bearing in mind the changes detected since the publication of the DSM-5 IGD criteria.

Method

A bibliographic search was carried out from January 2012 to May 2018 in *PsycINFO, Academic Search Premier, PubMED* and *Web of Science* databases, using the following Boolean logic terms and operators: (video gam* OR online gam* OR internet gam* OR computer gam* OR internet OR internet use) AND (addict* OR problem* OR pathological OR excessive or compulsive OR disorder* OR depend*) AND (measurement* OR psychometric* OR assessment), in an attempt to reproduce the systematic review by Kuss and Griffiths (2012). Searches were made in the keyword field or meSH terms.

The inclusion criteria were: (a) that the main subject of the article was the measurement instrument, (b) that IGD was assessed, (c) that minors were included as participants, (d) that it was an original article or clinical study and (e) that was published in English or Spanish. The exclusion criteria were: (a) that the main topic of the article was the analysis of explanatory models or associated or IGD risk factors, (b) that the instrument assessed Internet addiction in general without a specific section on IGD, (c) that only participants older than 18 years were included, (d) that it was a systematic review, meta-analysis or case study.

The articles were reviewed by two independent reviewers. The bibliographic search was complemented with the manual consultation of the reference lists of the selected articles.

Results

The search parameters used yielded a total of 361 results, which included the following results from each database: *PsycINFO* (85 results), *Academic Search Premier* (83 results), *PubMED* (71 results) and *Web of Science* (122 results).

Figure 1 shows the flow diagram for article selection. The database search strategy located 361 articles. After eliminating 190 duplicate entries, the remaining 171 were subjected to the inclusion and exclusion criteria by reading titles and abstracts, with 159 being eliminated for not meeting the criteria and 12 being selected for exhaustive analysis through a complete reading. After consulting the bibliographies of these articles, seven further articles were submitted to the selection criteria. Finally, 13 articles meeting the criteria were included in the review.

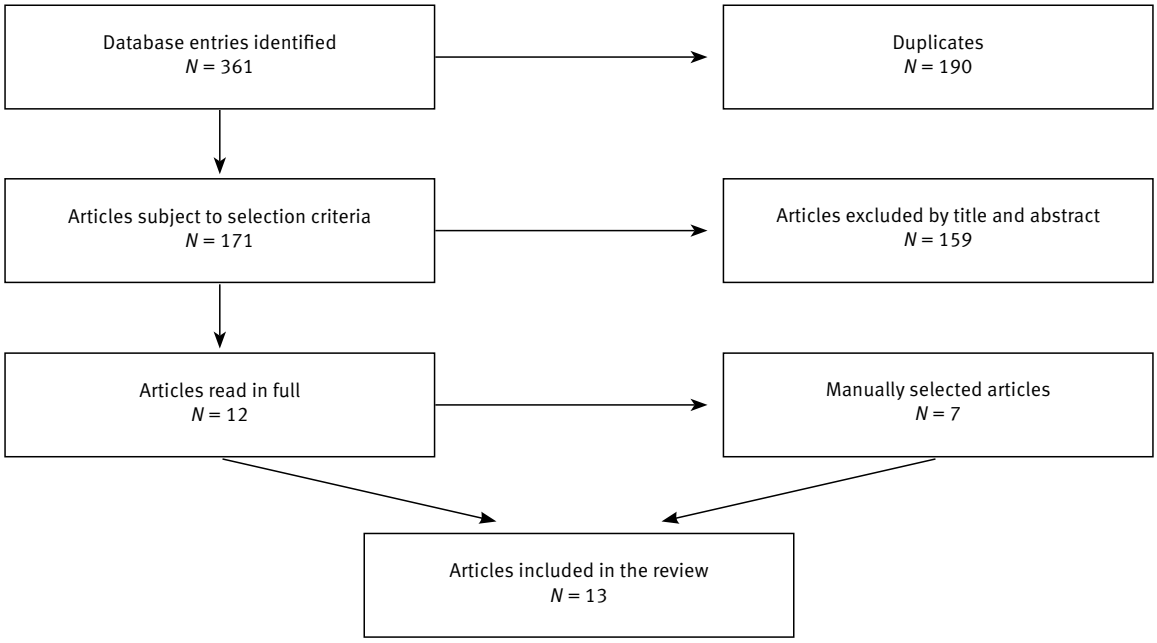

Figure 1. Flow diagram of the process of identification and selection of articles.

Table 2 summarizes the measurement instruments found in the review of articles and shows country of origin, languages in which they can be found, number of items, response options and underlying factors. Table 3 summarizes the studies included in the review, indicating the reference instrument, studies reviewed, number of participants, age range of the sample and psychometric properties of the instrument, including, when analyzed, cut-off points, number of player types, sensitivity, specificity, and correlation with time spent playing. In total, seven instruments were found (see Tables 2 and 3) which had been validated with adolescents and/or young people, and these will be described below.

Internet Gaming Disorder Test (IGD-20)

The *IGD-20* consists of 20 items which are answered on a 5-point Likert scale: (1) totally disagree, (2) disagree, (3) neither agree nor disagree, (4) agree, and (5) totally agree. It was developed by Pontes, Király, Demetrovics and Griffiths (2014) as a valid and accurate instrument to evaluate IGD, incorporating DSM-5 diagnostic criteria and at the same time reflecting the six dimensions of the Griffiths addiction model (2005). These six dimensions are: salience, mood modification, tolerance, withdrawal, conflict, and relapse. The study measures online and offline gaming activity during the previous 12 months.

To validate the original instrument, Pontes et al. (2014) used a sample of 1003 participants over the age of 16, with an average age of 26.5 years (SD = 8.2), recruited through a survey advertised on gaming forums. The presence of six dimensions was confirmed; it was reliable, with good internal consistency; it displayed criterion validity, significantly correlating with time spent playing per week and DSM-5 diagnostic criteria ($r = .82$; $p < .001$). Five types of players

Table 2. *Internet gaming disorder assessment instruments included in the review*

Instrument	Country of origin	Language	Items	Format (options)	Factors
IGD-20	UK	E	20	Likert (5)	6
		SP, AR	20	Likert (5)	1
IGDS9-SF	UK	E, SL, PO, IT, PE, TU, P	9	Likert (5)	1
POGQ	Hungary	E	18	Likert (5)	6
POGQ-SF	Hungary	E	12	Likert (5)	6
VAT	Netherlands	G, PO	14	Likert (5)	1
C-VAT 2.0	Netherlands	G	14	Yes/No	n.a.
IGD Scale	Netherlands	G	27	Yes/No Likert (5)	1
			9	Yes/No Likert (5)	1

Note. AR = Arabic; E = English; G = German; IT = Italian; SL = Slovene; SP = Spanish; P = Polish; PE = Persian; PO = Portuguese; TU = Turkish. n.a. = not assessed.

Table 3. *Characteristics and psychometric properties of the assessment instruments*

Instrument	Reviewed studies	N	Age evaluated	Cut-off points	Types	Sensitivity	Especificity	Internal consistency	Corr. time
IGD-20	Pontes et al. (2014)	1003	16-58	71	5	96%	100%	.88	.77***
	Fuster et al. (2016)	1074	12-58	75	5	71%	99%	.87	.42**
	Hawi y Samaha (2017)	375	14-19	n.a.	n.a.	n.a.	n.a.	.915	.48***
IGDS9-SF	Pontes y Griffiths (2015)	1060	16-60	36	n.a.	n.a.	n.a.	.87	n.a.
	Pontes y Griffiths (2016)	509	10-18	5 of 9 criteria	n.a.	n.a.	n.a.	.87	.36***
	Pontes et al. (2016)	1071	12-16	5 of 9 criteria	n.a.	n.a.	n.a.	.93	.52***
	Monacis et al. (2017)	687	>16	21	n.a.	86.1%	86%	.99	n.a.
	Wu et al. (2017)	2389	12-19	n.a.	n.a.	n.a.	n.a.	.90	n.i.
	Evren et al. (2018)	1250	15-48	5 of 9 criteria	n.a.	n.a.	n.a.	.89	n.a.
	Schivinski et al. (2018)	3377	12-49	5 of 9 criteria	n.a.	n.a.	n.a.	.82	.36***.
POGQ	Smohai et al. (2017)	1964	13	n.a.	n.a.	n.a.	n.a.	.92	n.a.
POGQ-SF	Papai et al. (2013)	2774	15-16	32	3	96%	97%	.807	c^2, ***
VAT	Van Rooij et al. (2012a)	2894	13-16	n.a.	n.a.	n.a.	n.a.	.93	n.a.
C-VAT 2.0	Van Rooij et al. (2017)	32	13-14	5 of 9 criteria	n.a.	91%	n.a.	n.e.	n.a.
IGD	Lemmens et al. (2015)	2444	13-40	5 of 9 criteria	3	66-87%(1)	72-98%(1)	.94 .93 .97 .83	n.a.

Note. Corr. = Correlation; * = p <.05; ** = p <.01; *** p <.001; n.a. = not assessed; n.i. = no information; (1) = minimum and maximum values of item sensitivity/specificity.

were discerned: (1) occasional players, (2) regular gamers, (3) low risk gamers, (4) high risk gamers, and (5) gamers with disorder. Taking the group of gamers with IGD as a gold standard, the cut-off point was established at 71, with a sensitivity of 96% and a specificity of 100%. The original instrument has been validated in Spanish and Arabic.

The Spanish validation of the IGD-20 (Fuster, Carbonell, Pontes & Griffiths, 2016) was carried out with a sample of 1074 participants aged between 12 and 58 from different Spanish-speaking countries in Europe and Latin America, recruited through a link on different gaming forums. The internal consistency of the instrument was .87. As in the original study, six factors were identified, and good criterion validity was in evidence, with significant correlations with hours per week spent playing (r = .42, p <.010) and participant age (r = - .12, p <.01). As in the original validation, five player types or subgroups were identified: (1) occasional gamers, (2) regular gamers, (3) low risk gamers, (4) high risk gamers, and (5) addicted gamers. Using the players with IGD as the gold standard, the cut-off point was established at 75, with a specificity of 99% and a sensitivity of 71%.

The Arab validation (Hawi & Samaha, 2017) included a sample of 317 students aged 14 to 19 from eight random-

ly selected private schools in Lebanon. The instrument yielded an internal consistency of .915 and good criterion validity, showing a significant correlation with time spent playing video games daily and on weekends. Factor analysis confirmed the existence of only one factor.

Internet Gaming Disorder Scale – Short Form (IGDS9-SF)

The *IGDS9-SF* is a brief instrument developed by Pontes and Griffiths (2015) consisting of nine items covering the nine DSM-5 diagnostic criteria. Its objective is to assess the severity of IGD and its harmful effects by evaluating online and offline gaming activities during the previous 12 months. Each item has a 5-point Likert scale: (1) never, (2) rarely, (3) sometimes, (4) often, and (5) very often, producing a score range of 9–45. Although the main objective of the instrument is not to diagnose IGD but to evaluate its severity and harmful effects on the player's life, a cut-off point is established at 36 points to differentiate between players with and without disorder, with the former corresponding to those participants who answer "often" or "very often" on all items. As in the case of the *IGD-20*, the validation of the original instrument (Pontes & Griffiths, 2015) was carried out with 1060 English-speaking players aged between 16 and 60 (average age =27 years, SD = 9.02) The instrument yielded an internal consistency of .87, a single factor, and good criterion validity with significant correlations with the IGD-20, and time spent playing per week. This instrument has been validated in Portuguese, Slovenian, Italian, Persian, Turkish and Polish.

The Portuguese validation (Pontes & Griffiths, 2016) was carried out with a sample of 509 adolescents and young people from 10 to 18 years of age (average age 13 years, SD = 1.64) from a high school in the Algarve, selected by random sampling in the classes from 6th to 9th grade. The cut-off point to consider a player as having a disorder was reached when answering more than five items with "very often". The analyses confirmed the existence of a single factor, with an internal consistency of .87, and good criterion validity, with significant correlations with daily and weekly gaming time, as well as good nomological validity, which is a predictor of depression ($R2 = .17$, $p < .001$), anxiety ($R2 = .15$, $p = .001$), and stress ($R2 = .21$, $p < .001$).

The Slovenian validation (Pontes, Macur & Griffiths, 2016) was carried out with a sample of 1071 of 8th grade adolescents, with an age range of 12 to 16 (average age 13.44 years, SD = .59), through stratified random sampling in the 12 regions of Slovenia. As in the Portuguese validation, a cut-off point was reached when any five of the nine criteria were met, i.e., on answering "very often". The analyses confirmed the existence of a single factor. In addition, the instrument yielded excellent internal consistency and good criterion validity, showing significant correlations with time spent gaming daily and on weekends; as well as good concurrent validity with participants' self-assessment regarding life satisfaction ($r = -.11$, $p < .001$) and mental health ($r = -.12$, $p < .001$).

The Italian validation (Monacis, De Palo, Griffiths & Sinatra, 2017) was carried out with a sample of 687 participants aged over 16 (with an average age of 21.62 years, SD = 3.9) from secondary schools, universities and gaming forums. The schools and universities were chosen on the grounds of convenience and in those available, classes to be assessed were selected at random. Different age groups were distinguished within the sample: adolescents ($n = 254$), aged between 16 and 19; and young adults ($n = 433$), older than 19 years of age. The analyses confirmed a unifactorial structure, as well as excellent internal consistency. Likewise, the *IGDS9* showed good convergent validity with the *Internet Addiction Test (IAT)* ($r = .83$, $p < .001$) and the short version of the *Gaming Addiction Scale (GAS-SF)* adapted to Italian ($r = .81$, $p < .001$), as well as good criterion validity, showing significant correlation with the *Bergen Social Networking Addiction Scale (BSNAS)* ($r = .76$, $p < .001$), which was chosen because it used the same six addiction criteria as the *IGDS9-SF*. The cut-off point was set at 21 according to the *GAS* gold standard of 21+, to distinguish between players with and without disorder, yielding a sensitivity of 86.1% and a specificity of 86%.

The Persian validation (Wu, Lin, Årestedt, Griffiths, Broström & Pakpour, 2017) was carried out with a sample of 2389 students from 12 to 19 years of age (average age 15.6, SD = 1.2) from 15 randomly selected schools in the city of Qazvin (Iran), of which most ($n = 2010$) repeated the assessment after two weeks. The analyses confirmed the instrument's unifactorial structure, which yielded excellent internal consistency and adequate test-retest reliability of .87. Criterion validity was also in evidence as significant correlations with weekly online gaming time ($\beta = .66$, $p < .001$) and with the measures of depression ($\beta = .14$, $p < .001$), anxiety ($\beta = .15$, $p < .001$) and stress ($\beta = .10$, $p < .001$) were shown.

The Turkish validation (Evren, Dalbudak, Topcu, Kutlu, Evren & Pontes, 2018) involved a sample of 1250 participants aged 15 to 48 (aged on average 21.8 years, SD = 3.42) from the university of Ankara, the database of an Istanbul sporting events company, and Turkish players on gaming forums. The unifactorial structure of the instrument was confirmed, yielding good internal consistency, adequate criterion validity with a significant correlation with average online gaming time in the previous year, and convergent validity with significant correlations with *Young's Internet Addiction Test - Short Form (YIAT-SF)* ($r = .46$, $p < .001$), and the *Internet Gaming Disorder Scale (IGDS;* Lemmens et al., 2015) ($r = .77$, $p < .001$).

The Polish validation (Schivinski, Brzozowska-Woś, Buchanan, Griffiths & Pontes, 2018) was carried out with a sample of 3377 participants aged 12 to 49 (with an average age of 20), of which 21% were between 12 and 16 years

of age, and 69.2% between 17 and 25. They came from different gaming forums, and to be included in the study they had to have played at least once in the previous year. The analyses confirmed the instrument had a unifactorial structure, which displayed adequate internal consistency, criterion validity, with significant correlations with average time spent gaming on weekdays (β =.08, p =.001) and weekends (β = .36, p =.001) and with the average duration of video game sessions (β = .09, p = .001).

Problematic Online Gaming Questionnaire (POGQ)

Demetrovics et al. (2012) developed an instrument with 26 items answered on a 5-point Likert scale, from never to always/almost always. Based on a review of the literature and interviews with players, it aims to detect problems related to online gaming. It was tested in a sample exclusively of adults, recruited through the 18 video game websites in Hungary. Of the original 26 items, 18 were retained and organized in six dimensions: preoccupation, overuse, immersion, social isolation, interpersonal conflicts, and withdrawal symptoms. The cut-off point was set at 65, with a sensitivity of 96% and a specificity of 100%. Four types of gamers were identified: below average use, gamers with low risk of problematic use, gamers with medium risk of problematic use, and gamers with high risk of problematic use.

Since this instrument had only been tested with adult online players, Smohai *et al.* (2017) applied it to online and offline players, with a sample of 1964 adolescents, 13-year-old high school students from 47 schools in 33 cities in Hungary who had played at least once in the previous month. Cronbach's alpha consistency coefficients for the different dimensions ranged from .75 (for the preoccupation dimension) to .86 (for withdrawal), with internal consistency for the total scale at .92. However, data on the validity of the instrument are not available.

Problematic Online Gaming Questionnaire – Short Form (POGQ-SF)

Papay et al. (2013) developed an abbreviated form of the *POGQ* by selecting the two items with the highest load of each factor. Thus, the *POGQ-SF* is composed of 12 items covering the six *POGQ* dimensions. Responses to each item are provided on a 5-point Likert scale of 1, never; 2, rarely; 3, occasionally; 4, often; and 5, always.

The instrument was applied to a sample of 2774 grade 9 and 10 general and vocational secondary school students aged 15 to 16 years. The average age of the participants was 16.4 years (SD = .87). Those who had played online video games at least once in the previous month were selected. The six dimensions were confirmed and three types of gamers were identified: below average users, low risk of problematic use, and high risk of problematic use. Taking membership of the high-risk category as the gold standard, the cut-off point was established at 32, with a sensitivity of 96% and a specificity of 97%. The instrument showed good internal consistency, as well as validity since high-risk gamers showed a greater chance of playing more than five hours a day (χ^2 = 133.6, p < .001), had higher scores in depression as measured with the Depression Scale (*CES-D*) (χ^2 = 54.5, p < .001) and lower self-esteem as measured through the Rosenberg Self-Esteem Scale *(RSES)* (χ^2 = 33.9, p <.001).

Video Game Addiction Test (VAT)

The *VAT* is a direct adaptation of the items on the *Compulsive Internet Use Scale* (CIUS), focusing specifically on video game playing. It consists of 14 items with the following components: loss of control, conflict, preoccupation/salience, coping/mood modification and withdrawal symptoms. Responses to each item are given on a 5-point Likert scale of 0, never; 1, rarely; 2, sometimes; 3, often; and 4, very often. The term gaming is used in a general sense in the items to refer to online gaming. Although this study predates the appearance of the DSM-5, it is included because the questionnaire used in subsequent studies or as a starting point for the development of other instruments (*C-VAT 2.0*) originated here.

Van Rooij, Schoenmakers, Van den Eijnden, Vermulst and Van de Mheen (2012a) applied the instrument to a sample of 2894 students from 10 secondary schools in the Netherlands, aged between 13 and 16, with an average age of 14.3 (SD = 1.0). The instrument yielded a one-dimensional factorial structure, excellent internal consistency, and construct validity, with significant relationships to the *GAS* (r = .74, p <.001) and the *CIUS* (r = .61, p <.001), and a weaker but nevertheless significant relationships to depressed mood (r = .29, p <.001), negative self-esteem (r = .22, p <.001), loneliness (r = .29 p <.001), social anxiety (r = .22, p <.001) and weekly online video game playing time (r = .37, p <.001).

This questionnaire has been validated in Brazil and adapted to the Portuguese language (Lemos, Cardoso & Sougey, 2016); however, it was not included in the present review because it only includes university students, i.e., participants of legal age.

Clinical Video Game Addiction Test (C-VAT 2.0)

The *C-VAT 2.0* is an assessment instrument to be administered by a clinician and was developed to identify and diagnose gaming addiction among the clinical population. It is an adaptation of the *C-VAT* (Van Rooij, Van Duin, Frielink, Defuentes-Merillas & Schoenmakers, 2012b) to the DSM-5 criteria and consists of three questions about video game playing habits, 11 questions with a dichotomous response format (Yes/No) about IGD symptoms in the previous year (nine of which cover the nine DSM-5 criteria for IGD, plus two more related to craving and health problems), and a short table of recommendations for identifying comorbid problems.

Van Rooij, Schoenmakers and Van de Mheen (2017) validated the instrument using a sample of 32 patients aged 13 to 23 in treatment for video gaming disorder. The cut-off score used to establish a diagnosis is 5 of 9, as proposed by DSM-5, with a sensitivity of 91%. Of the 32 patients, 27 had video game disorder as their main diagnosis, while for the other 5 cases it was a secondary disorder. They also had other comorbid disorders, which included depression, anxiety problems, hyperactivity and developmental disorder.

Internet Gaming Disorder Scale (IGDS)

Lemmens, Valkenburg and Gentile (2015) developed a 27-item German-language instrument in which each DSM criterion is measured with three items, each of which representing different central aspects of the criterion by using synonyms or making slight changes in the wording. There are two versions, one answered dichotomously (yes/no), and another with a 6-point Likert-type scale: (0) never, (1) 1-4 times in the previous year, (2) 5-11 times in the previous year, (3) 1-3 times in the previous month, (4) 1 or more times a week, (5) every day or almost every day.

The scale was validated with a sample of 1912 German-speaking adolescents and adults (n = 989 for the dichotomous version and n = 923 for the Likert-type version) of the Netherlands aged 13 to 40 with an average age of 24.8 (SD = 8.1) and 24.4 (SD = 7.6) years, respectively. Three age groups were established: adolescents (n = 922) aged 13 to 20, average age 17.6 (SD = 2.2); young adults (n = 568) aged 21 to 30, average age 25.1 (SD = 2.8); and medium-age adults (n = 425) from 31 to 40, average age 35.9 (SD = 2.8).

The instrument yielded high internal consistency in both versions. With the aim of building an abbreviated version, the item with the highest load of each criterion was selected which also showed high internal consistency, of .97 for the Likert-type version, and .83 for the dichotomous version. Both scales (27 and 9 items respectively) displayed adequate criterion validity, showing a small-to-moderate significant correlation with time spent playing video games, loneliness, self-esteem and prosocial behavior; and a highly significant correlation with aggressive behavior. However, the dichotomous version showed greater criterion validity than the Likert version because in contrast to the dichotomous version, the latter did not yield significant correlations with life satisfaction. The dichotomous nine-item version was used to diagnose IGD, adopting the 5-of-9 criteria as a cut-off point, as recommended in the DSM-5. Three gamer types were identified: normal gamers, at-risk gamers, and gamers with disorder. Class analysis results led the authors to suggest that it would be appropriate to raise the criteria to be met to 6 in order to avoid overdiagnosis. Sensitivity and specificity for each of the diagnostic criteria were examined using the 5-or-more criterion the DSM-5 and the 6-or-more criterion after class analysis, taking the players with disorder as reference point. Although both yielded high specificity and adequate sensitivity, the 6-or-more criteria diagnosis displayed greater sensitivity.

Discussion

The main objective of this systematic review was to carry out an analysis of the instruments developed to measure online gaming problems in adolescents and young people since the publication of DSM-5 criteria for IGD. The changes detected in the characteristics of the instruments, samples used for their validation, and psychometric properties are analyzed below.

Instrument characteristics

The diversity of instruments is currently smaller, reduced from 18 instruments in the review by King et al. (2013) to seven. Differences have also been observed in terms of content; whereas previously, instruments in many cases assessed Internet addiction in general, they currently focus on the assessment of IGD.

Prior to the publication of the DSM-5 criteria, the instruments used were of a more general nature, measuring Internet addiction, and tending to originate in the United States. At present, however, the development of new instruments already focused on problematic video game use is concentrated in the United Kingdom, Hungary and the Netherlands. It should be pointed out that only instruments developed in the United Kingdom have been validated in other countries, with the *IGDS9-SF* being the most widely used instrument, and with a greater number of translations and validations in different languages. Also noteworthy is the fact that the instruments developed in the Netherlands were developed in German and some of the articles are not in English.

In general, as was the case previously, with the exception of *C-VAT 2.0*, these are self-report measures. However, their length has changed, from greater heterogeneity in terms of length, ranging from seven to 40 items, to shorter instruments of between nine and 27 items in which the number of items used has been reduced to practically half. In some cases, a short version of the original instrument was created, as in the case of the *POGQ*, reduced from 18 to 12 items in the abbreviated format, and the *IGD Scale*, down to 9 items from 27.

The type of response format is currently also more homogeneous. Whereas previously the two types of formats were used practically equally, now Likert-type scales tend to be favored, with the scale points (previously oscillating between four and seven) also becoming unified: items are now usually answered on 5-point Likert-type scales. Only the IGD Scale, in one of its formats, is answered dichotomously. The *C-VAT 2.0* also has a dichotomous response

format, but in this case it is to be completed by the clinician.

Sample characteristics

Few studies include young people and adolescents, with a good number of the instruments being developed with an adult population, despite the fact that internet gaming is a fairly frequent activity among the younger population. This shortage is even greater when considering studies which exclusively use adolescents and young people (Hawi & Samaha, 2017; Papay et al., 2013; Pontes & Griffiths, 2016; Pontes et al., 2016; Smohai et al., 2017; Van Rooij et al., 2012a; Wu et al., 2017). On occasion, heterogeneous age ranges are used for instrument validation without distinguishing age groups (Evren et al., 2018; Fuster et al., 2016; Van Rooij et al., 2017), although in some cases at least the number of participants corresponding to particular age groups is mentioned or some type of distinction is made (Monacis et al., 2017; Schivinski et al., 2018).

As mentioned by Kuss and Griffiths (2012), and King et al. (2013), problems related to sample selection continue: the use of convenience samples, such as links in gaming forums (Evren et al., 2018; Fuster et al., 2016; Schivinski et al., 2018), or the use of schools which are available and accessible to researchers (Monacis et al., 2017; Pontes & Griffiths, 2016). Random samples are scarce, and in some cases there are samples taken in a single city (Hawi & Samaha, 2017; Wu et al., 2017). Nationwide stratified randomized studies are usually included in larger research projects and focused on a single school grade (Papay et al, 2013; Pontes et al., 2016; Smohai et al., 2017; Van Rooij et al., 2012a). More studies with a clinical population are also still necessary; the only study of this nature is by Van Rooij et al. (2017), with a small convenience sample (n = 32).

Psychometric properties

In terms of its dimensionality, three of the instruments assess a single factor (*IGDS9-SF, VAT, IGD Scale*) while three others measure six factors (*IGD-20, POGQ and POGQ-SF*), usually corresponding to the addiction model.

The internal consistency shown by the instruments is excellent, even better than the previous instruments, ranging from .82 to .99, and in seven of the 13 studies it is equal to or greater than .90. Criterion validity is similarly good, usually taking as a reference hours of gaming per week, with some instruments distinguishing between game time on weekdays and at weekends. Some studies also analyze its convergence with other measures such as: instruments prior to the publication of the DSM-5 criteria which have demonstrated their effectiveness in measuring IGD or Internet addiction (Evren et al., 2018; Pontes et al., 2016; Van Rooij et al., 2012a); depression, anxiety, and stress (Pontes & Griffiths, 2016; Wu et al., 2017); depression and self-esteem (Papay et al., 2013; Van Rooij et al., 2012a); loneliness and social anxiety (Van Rooij et al., 2012); aggressive behavior (Lemmens et al., 2015); and satisfaction with life and mental health (Pontes et al., 2016).

However, only three studies offer information regarding the specificity and diagnostic accuracy of the instrument evaluated, and four regarding sensitivity. The lowest score for sensitivity is for the *IGD-20* in its validation with Spanish-speaking adolescents and young people (71%), although it should be noted that this is due to the cut-off point being raised by the authors to 75, rather than being kept at the 71 of the original instrument (in which case the sensitivity would be 96%, as in the original instrument), in order to favor greater specificity and better diagnostic accuracy (99%). The *POGQ-SF* is the instrument obtaining the highest levels of both sensitivity (96%) in specificity (97%), with excellent diagnostic precision (97%). It may be the case that those instruments which value more factors or dimensions have greater sensitivity and diagnostic precision.

Only three studies offer cut-off points with reference to empirical studies (*IGD-20, IGDS9-SF* and *POGQ-SF)*; in six cases the cut points are those recommended by the DSM-5, and in five they are not specified. As previously mentioned, in the case of the *IGD-20*, the cut points are different in the Spanish and English-speaking samples, with a slightly higher cut point in the Spanish validation highlighting the importance of taking into account cultural variation.

In addition to analyzing cut-off points, it is also important to assess gamer profiles. However, only three studies offer information on the type of gamer, with one establishing five gamer profiles *(IGD-20)* and two studies describing three types of gamers (*POGQ-SF* and *IGD Scale).*

Conclusions

The inclusion of IGD in the DSM-5, in the section of conditions for further study, is a first step towards an attempt to establish unified criteria in the assessment of this problem. Reflecting this, changes have been detected in terms of reduced heterogeneity and shorter measurement instruments, adapted for the most part to the DSM-5 criteria. The 5-point Likert scale is the most frequently used response format, probably due to its greater sensitivity, with scores of 4 and 5 being used to establish the presence of the DSM-5 diagnostic criterion. Conversely, the only instrument found for clinical use employs the dichotomous form and the clinical judgment of the therapist.

The instruments which seem to enjoy the broadest acceptance internationally are those developed in the United Kingdom. The *IGDS9-SF* is the most widely used, with the greatest number of translations to different languages and validations, although a more complete study of its psychometric qualities is lacking. Moreover, different player types are not identified in most of its validations, and it is neces-

sary to empirically establish cut-off points outside the 5 of 9 recommended by the DSM-5 to analyze their specificity, sensitivity and diagnostic accuracy. On the other hand, the advantage of the *IGD-20* is its ability to analyze different gamer profiles, although translations and validations are not available for other countries. Although Spanish-language validation is fairly complete, it suffers from being one of the longest instruments and in some cases there may be problems in understanding certain items, specifically those whose phrasing involves negation (ex. "I never play video games to feel better").

This systematic review is not without weaknesses. Firstly, only those instruments published in English and Spanish were included, so that some publications in German or in Asian countries could have been be overlooked. On the other hand, the scarcity of publications utilizing samples of young people and adolescents has led to the need to include some studies in which responses are not distinguished by the age of the participants.

For the future development of IGD assessment instruments, a complete study of the psychometric qualities of the instruments should be considered, including their sensitivity, specificity, diagnostic accuracy and cut-off points in order to establish different gamer types and their risk levels. For detection of the problem in large populations and the application of prevention programs in schools, it would be advisable to use a brief, highly sensitive self-report instrument and, after detection, a test with high specificity able to reduce false positives and confirm a diagnosis involving clinical judgment. To improve communication and collaboration between researchers and professionals at an international level, making the instruments and their authors accessible through web pages seems an appropriate strategy, as is the case of the instruments developed in the United Kingdom.

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Conflicts of interest

The authors declare that there is no conflict of interest in any aspect of this study.

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A non-participant naturalistic observational study on the use of slot machines in northern Spain

Un estudio observacional no participante sobre el uso de máquinas tragaperras en el norte de España

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Around 1.5% of the adult population suffers from Gambling Disorder (GD) (Gowing et al., 2015), with slot or fruit machines being one of the most addictive gambling activities (Calado & Griffiths, 2016). The Spanish regulation allows restaurants and bars to operate type B slots, with more than 180,000 machines in Spain (Dirección General de Ordenación del Juego, 2016) and almost all hospitality venues having at least one slot. Despite concerns regarding their high accessibility to special populations (minors, problem gamblers), the number of slot machine users and their associated characteristics remains unknown. This study aimed to report for the first time an estimation of slot machine use at the population level and the associated characteristics.

A non-participating observational randomized two-step cluster sampling was performed using the official record of licensed venues of the hospitality sector to operate slot machines in Asturias. Clusters were formed considering: geographical area (coastal vs. inland areas), residence (rural vs. urban), economic sector (primary, secondary or tertiary) and the number of slot machines per local (one vs. two). The selected areas comprised 66.05% of the total slot machines located in public venues: Oviedo, Gijón, Avilés, Ribadesella, Pravia, Pola de Siero and the coal-mining areas (Mieres, Langreo, La Felguera, Sama, Ciaño, Lada and Riaño). Each area was divided into venues with one or two machines. Based on the total number of locals operating EGM in each cluster, 55 public venues were visited in three time periods (Morning: 8:00–12:00; Afternoon: 12:00-16:00; Evening: 16:00–22:00). Following prior research (Dirección de Juego y Espectáculos del Departamento de Interior del Gobierno Vasco, 2009), a 60-minute observational session was performed over each venue (total sessions = 165) by two Master-level trained experimenters. Ethical review was not required as data were generated by observation of public behavior (World Health Organization, 2016).

Participants were classified by sex and age in three ranges: < 18, 18-25, 26-35, 36-50, + 50 years old. The prevalence of any beverage use (No use, non-alcoholic beverage, alcoholic beverage or both) and the level of alcoholic intoxication were estimated. Five gambling behavior indices were assessed: Persistency (persistent/intermittent gambling), time spent per gambling occasion without pauses, company (alone/with others), slot switch in venues with two machines, and urge when accessing to the venue (direct access/after ordering a drink).

Chi-squared tests with Bonferroni adjusted z-tests were performed to analyze differences in demographics and gambling behaviors. To estimate the prevalence of slot machine use, we used census data for each of the seven selected areas (Instituto Nacional de Estadística, 2016), comprising 622,663 (59.72%) of the total 1,042,608 inhabitants in the region. A total of 3,502 slot machines were located in public venues, of which 74 (2.11%) were included in this study (38 slots located in venues with two machines). Considering the binary nature of the observed variable with a binomial distribution and a maximum variance of 0.25, the maximum error was ± 1.08 (α = .05).

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A total of 89 users were recorded during the observation protocol (Table 1). Due to the low prevalence of users under 25 years old, the first two age groups were merged into the same category: 18-35 years old (n = 17, 19.1%). Main significant results showed that while the youngest group was more likely to gamble with others, the oldest one used to gamble alone (χ^2 (2) = 10.34, p = .006, Cramer's V = .34). Lonely gamblers were also more likely to gamble persistently (χ^2 (1) = 7.3, p = .007, Φ = .33).

Table 1. *Sample characteristics of slot users*

Variables	n (%)
Sex (male)	84 (94.4)
Age	
18-25 years	2 (2.2)
26-35 years	15 (16.9)
50 or more years	26 (29.2)
Geographic area	
Oviedo	13 (14.6)
Gijón	20 (22.5)
Avilés	14 (15.7)
Ribadesella	2 (202)
Pravia	8 (9)
Pola de Siero	14 (15.7)
Coal-mining areas	18 (20.2)
Day of gambling (working day)	46 (51.7)
Gambling period	
Morning	33 (37.1)
Afternoon	33 (37.1)
Evening	23 (25.8)
Time spent gambling (minutes) [a]	89 (5)
Gambling persistency (persistent)	73 (82)
Company (alone)	77 (86.5)
Switched slots (no) [b]	46 (85.2)
Use of slot (after drink) [c]	64 (71.9)
Type of drink [d]	
None	8 (9.2)
Non-alcoholic	33 (37.9)
Alcoholic	46 (52.8)
Drunkenness (no)	85 (95.5)

Note. [a] Median. [b] Considering only conglomerates with two slots. [c] 11 participants missed due to observational issues. [d] 2 participants missed due to observational issues

Based on the observed users and the registered inhabitants within each area, the estimated prevalence of slot use in Asturias was about 44,637 gamblers (4.28% of the total population). Although most of the estimated gamblers were located in the two biggest cities (Gijón: n = 7,285; Oviedo: n = 4,940), Pravia (9.88%) and the coal-mining areas (8.56%) showed the highest proportions of slot users per capita. Oviedo showed the lowest proportion (2.62%). Most users were estimated to be male (n = 42,129, 94.38%) and 26-35 years old (n = 4,969, 6.13% of the inhabitants of this age group). Considering both sex and age, there were the most males in the 26-35 age group (n = 4,969, 12.35% of the total male inhabitants within the age group) and the most females in the 36-50 group (n = 994, 1.12% of the female inhabitants within the age group).

Several preventive implications arise from this study. The reduction of the addictive potential of EGMs by modifying certain structural characteristics has been widely highlighted in a myriad of studies (e.g., Griffiths & Auer, 2012). The implementation of electronic identifications to activate slots would reduce EGMs accessibility and prevent extended gambling sessions (Rockloff, Donaldson & Browne, 2015) whilst registering gambling-related information and prompting feedback messages (Monaghan, 2008). The reduction of licensed venues to operate EGMs based on the proximity to schools or healthcare centers, or even the introduction of a state gambling monopoly on EGMs (Rossow & Hansen, 2016) are some other recommended environmental preventive strategies.

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Conflict of interest

The authors declare no conflicts of interest.

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Discriminative capacity for functional impairment of the Personality Inventory for DSM-5 Short Form in patients with substance use disorder

Capacidad discriminativa del deterioro funcional del Inventario de Personalidad DMS-5 Short Form en pacientes con trastorno por uso de sustancias

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The specialized literature shows that personality disorders (PD) are highly comorbid with substance use disorder (SUD). The greater dysfunctionality and worse therapeutic response of comorbid patients (Van Den Bosch & Verheul, 2007) highlight the need to assess personality among patients with SUD.

The Alternative Personality Disorder Model (APDM) proposed in the DSM-5 presents the organization of personality traits on a dimensional basis (Krueger & Markon, 2014). One of the most commonly used instruments to assess this model is the DSM-5 Personality Inventory (PID-5; Krueger, Derringer, Markon, Watson & Skodol, 2012). It has been considered necessary to find formulas which reconcile the dimensional approach with the categorical decisions of clinical practice (Alarcón, 2010). In this regard, normative cut points have been suggested for the PID-5 which are intended to facilitate clinical decisions (Gutiérrez et al., 2017; Samuel, Hopwood, Krueger, Thomas & Ruggero, 2013).

Despite studies showing links between the higher trait values and functional and psychosocial maladjustment (Keeley, Flanagan & McCluskey, 2014), no study to date has analyzed the PID-5's discriminative capacity with regard to functional impairment. This study analyzes the sensitivity and specificity of each of the traits to detect functional impairment in a group of patients with SUD. In addition, we compare the use of a functional and a normative criterion to establish cut points which represent pathological functioning in the APDM traits.

The study involved 178 patients with SUD attending outpatient addiction treatment centers. Men constituted 82.6% of the sample, with a mean age of 41.28 years (*SD* = 11.24).

The Spanish version of the PID-5 Short Form was administered (Díaz-Batanero, Ramírez-López, Domínguez-Salas, Fernández-Calderón & Lozano, 2019). Functional disability was assessed with the World Health Organization Disability Assessment Schedule (WHODAS 2.0; Üstün et al., 2010).

The instruments were administered by a psychologist with experience in the assessment of patients 15 days after the start of treatment. This study was approved by the ethical committee of the University of Huelva.

ROC curves were estimated, with a total score on the WHODAS 2.0 of > 25 as a threshold to classify patients with moderate to extreme disability (Üstün et al., 2010). Cut points were estimated to offer the best balance between sensitivity and specificity in accordance with the functional criterion, with minimum specificity set at .70. These were compared with the normative cut points, calculating T-scores > 65 (Gutiérrez et al., 2017).

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Of the sample, 35.4% had moderate or extreme disability. AUC values ranged from .503 (95% CI = [.41, .59]) (Attention seeking) to .787 (Depression) (95% CI = [.71, .86]), with a mean of .657. AUC values > .7 were observed in: Anhedonia, Anxiety, Depression, Distractibility, Eccentricity, Irresponsibility, Perseveration, and Submissiveness. However, six traits do not show discriminatory ability: Attention seeking, Grandiosity, Intimacy avoidance, Manipulativeness, Restricted affectivity, and Rigid perfectionism. The cut points using the functional criterion were higher in all traits which are discriminatory of functional deterioration with respect to those obtained according to normative criteria (except Submission and Risk Taking).

Table 1. *Results of the ROC analyses and estimated cut points based on normative and functional disability criteria.*

	AUC [95%CI]	*p*	Functional criterion	Sensitivity	Specificity	Normative criterion	Sensitivity	Specificity
Anhedonia	.744 [.66 - .82]	‹.001	1.87	.710	.722	1.25	.823	.583
Anxiety	.770 [.70 - .84]	‹.001	2.37	.613	.765	1.78	.806	.574
Attention seeking	.503 [.41 - .59]	.949	0.87	.403	.722	1.49	.145	.835
Insensitivity	.595 [.50 - .68]	.036	0.62	.436	.748	0.64	.436	.748
Deceitfulness	.648 [.56 - .73]	.001	0.87	.403	.739	1.02	.403	.774
Depression	.787 [.71 - .86]	‹.001	1.12	.677	.765	0.95	.742	.696
Distractibility	.777 [.70 - .84]	‹.001	2.12	.677	.757	1.54	.855	.574
Eccentricity	.760 [.68 - .83]	‹.001	1.62	.678	.730	1.33	.726	.591
Emotional lability	.648 [.56 - .73]	.001	2.12	.516	.722	2.03	.516	.722
Grandiosity	.557 [.46 - .64]	.209	0.87	.290	.782	1.24	.177	.896
Hostility	.688 [.60 - .77]	. ‹.001	1.62	.565	.765	1.56	.565	.765
Impulsivity	.642 [.55 - .72]	.002	2.12	.403	.730	1.60	.758	.609
Intimacy avoidance	.585 [.49 - .67]	.078	1.87	.387	.765	1.15	.468	.643
Irresponsibility	.702 [.62 - .78]	‹.001	1.37	.532	.801	0.92	.774	.487
Manipulativeness	.574 [.48 - .66]	.105	0.87	.355	.735	1.27	.226	.878
Perceptual dysreg.	.635 [.54 - .72]	.003	0.87	.403	.774	0.87	.403	.774
Perseveration	.713 [.63 - .79]	.001	1.87	.565	.747	1.54	.662	.661
Restricted affectivity	.543 [.45 - .63]	.346	1.62	.355	.725	1.41	.516	.614
Rigid perfectionism	.574 [.48 - .66]	.106	1.62	.339	.713	1.82	.290	.791
Risk taking	.631 [.54 - .72]	.004	1.12	.532	.703	1.65	.323	.896
Separation insec.	.677 [.59 - .75]	‹.001	2.12	.435	.774	1.61	.677	.643
Submissiveness	.703 [.62 - .78]	‹.001	1.12	.548	.765	1.47	.468	.861
Suspiciousness	.669 [.58 - .75]	‹.001	1.62	.468	.713	1.30	.629	.609
Unusual beliefs and experiences	.639 [.55 - .72]	.002	1.62	.3556	.783	1.03	.581	.574
Withdrawal	.684 [.60 - .76]	‹.001	1.62	.532	.735	1.23	.597	.835

The results show that the PID-5 has good discriminative capacity for dysfunctionality assessed by the WHODAS 2.0 in most traits. Previous studies have shown this relationship, particularly in the dimensions Comprehension and Communication, Relationships and Participation in society (Díaz-Batanero et al., 2019; Keeley et al., 2014). Greater discriminative capacity has been observed in traits linked to Negative affectivity, a dimension associated with higher levels of pathology and dysfunctionality (Watson, Stasik, Ro & Clark, 2013). Conversely, the traits of Attention seeking, Insensitivity, Grandiosity, Hostility, Impulsivity, Intimacy avoidance, Manipulativeness, Restricted affectivity and Rigid perfectionism have not shown discriminative capacity. Congruently, previous studies found that Attention seeking, Grandiosity, Restricted affectivity, Intimacy avoidance and Rigid perfectionism yielded minor differences between clinical and community samples (Gutiérrez et al., 2017).

Of the 25 traits, 17 presented higher cut points using the functional criterion than those obtained with normative and rational criteria (Samuel et al., 2013). Overall, it could be suggested that the use of normative criteria would be more suitable for population epidemiological studies. However, functional criteria could be more useful in cli-

nical samples, allowing therapists to plan more specific treatments for disorders which cause patients greater functional disability.

Assessing functional maladjustment exclusively with self-reports can be a limitation. Optimal use of multiple data sources could improve behavior prediction in psychopathological and functional assessment. Future studies should complement data obtained with information provided by other close informants.

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Conflicts of interest

None declared.

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

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

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

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

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

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

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

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

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

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

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

PRESENTACIÓN DE LOS TRABAJOS

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

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

Copyright y permisos. Los derechos de copyright de todos los artículos publicados en la revista Adicciones pasan a ser propiedad de la revista. La cesión de derechos será firmada por el autor o autores cuando envían su manuscrito para su consideración de publicación. Los autores se comprometen a acompañar el manuscrito de todos los permisos correspondientes para reproducir material previamente publicado que se va a incluir en el manuscrito, como texto, tablas, figuras, etc.

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 media 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 a 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 dado 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 creatinofosfoquinasa 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 los 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 excretada inalterada en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre 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, oniconicosis, celulitis	infección oftálmica, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, aumento del recuento de eosinófilos	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, pérdida de peso, apetito disminuido	diabetes mellitus[d], hiperinsulinemia, aumento del apetito, anorexia, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[e]	agitación, depresión, ansiedad	trastornos del sueño, manía, disminución de la líbido, nerviosismo, pesadillas	catatonía, estado de confusión, sonambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[c], acatisia[c], sedación[c]/somnolencia, distonía[c], mareo, discinesias[c], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotriz, mareo postural, trastornos de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, falta de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones[e], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

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

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

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

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

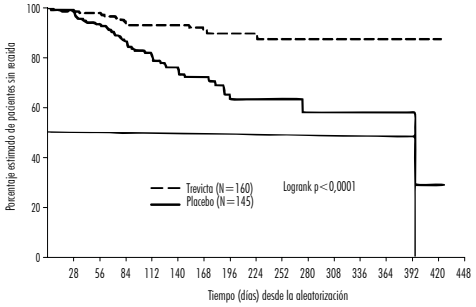


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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

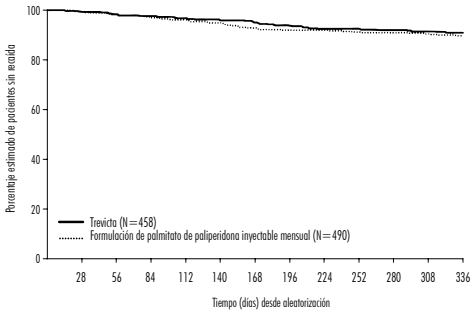


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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

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

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

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

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

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

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

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

Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queilitis	obstrucción del intestino, íleo
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción debida al medicamento, hiperqueratosis, caspa	angioedema, decoloración de la piel, dermatitis seborreica
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda, artralgia	aumento de la creatina fosfoquinasa en sangre, espasmos musculares, rigidez en las articulaciones, debilidad muscular, dolor de cuello	rabdomiólisis, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales					síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastorno de la eyaculación, trastornos menstruales[2], ginecomastia, disfunción sexual, dolor de mamas	malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[4], aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección	disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[1]La frecuencia de estas reacciones adversas se clasifica como "no 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. [2]Referido a "Hiperprolactinemia" a continuación. [3]Referido a "Síntomas extrapiramidales" a continuación. [4]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xeplion comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,65% en todos los pacientes tratados con palmitato de paliperidona. [5]**Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

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

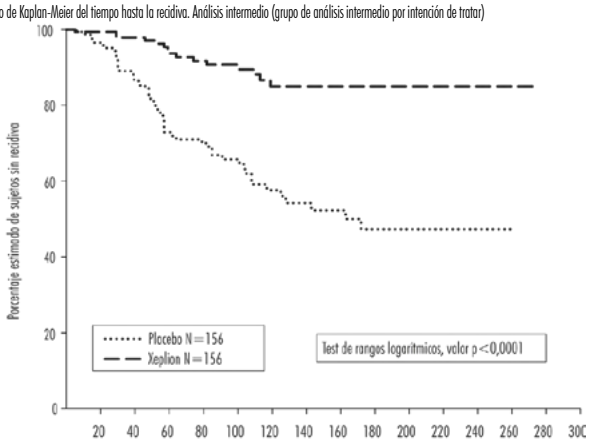
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la 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 AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

MIRANDO *al* FUTURO

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