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Anxiety sensitivity as a transdiagnostic vulnerability factor for cigarette smoking: Clinical and treatment implications

Sensibilidad a la ansiedad como factor de vulnerabilidad transdiagnóstico para el consumo de tabaco: implicaciones clínicas y para el tratamiento

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Tobacco smoking is the leading preventable cause of morbidity and premature death worldwide (López, Pérez-Ríos, Schiaffino & Fernández, 2016; Soriano et al., 2018; World Health Organization [WHO], 2019). Overall, there are 1.3 billion adult smokers around the world and the mean prevalence of past-year quit attempts are estimated at 42.5% (Ahluwalia et al., 2018; Asma et al., 2015). In Spain, the percentage of daily smokers showed an uptrend in 2018, reaching 34% of the population. However, nearly two thirds of them (65.85%) have reported at least one quit attempt within the last year (National Plan on Drugs, 2019).

Despite the existence of a set of efficacious behavioral and pharmacological smoking cessation therapies (see for a review Notley et al., 2019; Stead, Koilpillai, Fanshawe & Lancaster, 2016), the high rates of relapse that occur soon after quitting (García-Rodríguez et al., 2013; Livingstone-Banks et al., 2019) have prompted the necessity to identify individual characteristics related to sustained abstinence and relapse (Layoun et al., 2017; Rafful et al., 2013).

In this context, smokers with mental health comorbidities are one of the most vulnerable populations deserving attention (Leventhal & Zvolensky, 2015). In particular, symptoms of depression and anxiety have shown to be the most prevalent among smokers (Piper, Cook, Schlam, Jorenby & Baker, 2011; Secades-Villa, González-Roz, García-Pérez & Becoña, 2017). Rates of cigarette consumption and relapse among smokers with these comorbid mental health problems have shown to be higher than those without them (Cook et al., 2014; Secades-Villa et al., 2017). Factors contributing to such poor treatment outcomes include high nicotine dependence (Williams, Steinberg, Griffith & Cooperman, 2013), increased sensitivity to nicotine reinforcement (Tidey & Miller, 2015; Tidey et al., 2018) and tobacco use for coping motives (e.g., smoking to manage negative mood, stress, and cognitive deficits) (Audrain-McGovern, Leventhal & Strong, 2015; Tidey et al., 2018). Additionally, negative emotional symptoms have shown to increase the severity of tobacco withdrawal and the risk of relapse (Zvolensky, Bogiaizian, López Salazar, Farris & Bakhshaie, 2014a), as well as to reinforce maladaptive cognitive beliefs regarding tobacco consumption (e.g., enhanced negative affect/anxiety reduction expectancies).

Consequently, there exists consensus on the convenience to tailor smoking cessation treatments to specific psychological disorders (Almadana-Pacheco et al., 2017; González-Roz et at., 2019; Jiménez-Treviño et al., 2019; Martínez, Fernández del Río, López-Durán, Martínez-Vispo & Becoña, 2018; Sarramea et al., 2019; Ziedonis et al., 2008; Zvolensky, Yartz, Gregor, Gonzalez & Bernstein, 2008). Sev-

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eral studies have focused on developing specialized interventions for smokers with depression (Leventhal, Piper, Japuntich, Baker & Cook, 2014), schizophrenia (Callaghan et al., 2014; Tidey & Miller, 2015), as well as anxiety disorders, such as posttraumatic stress disorder (Kearns et al., 2018), panic disorder (Zvolensky, Lejuez, Kahler & Brown, 2003) or social anxiety disorder (Kimbrel, Morissette, Gulliver, Langdon & Zvolensky, 2014). The most common approach has consisted of combining traditional smoking cessation approaches with interventions aimed at specific mental health disorders, particularly anxiety and depression. However, and despite such valuable efforts, only modest long-term results have been achieved so far (Leventhal & Zvolensky, 2015; Zvolensky, Bonn-Miller, Berstein & Marshall, 2006; Zvolensky et al., 2019a). In recent years, a novel alternative approach is turning towards a transdiagnostic emotional vulnerability model that includes a set of key clinical factors underlying tobacco use and different emotional conditions (Leventhal & Zvolensky, 2015; Zvolensky et al., 2014a). Amongst the several purported transdiagnostic variables accounting for the relationship between tobacco and emotional psychopathology, anxiety sensitivity (AS) is increasingly becoming the focus of attention (Zvolensky, Garey, Kauffman & Manning, 2019b).

Anxiety sensitivity (AS) as a transdiagnostic vulnerability factor for smoking

AS refers to the fear of anxiety-related symptomatology that connects with beliefs and cognitions about the potential harmful consequences of aversive internal states, also known as "fear of fear" (Reiss, Peterson, Gursky & McNally, 1986; Zvolensky et al., 2014a). This construct includes three sub-factors, namely: physical, cognitive and social concerns (Capron, Norr, Zvolensky & Schmidt, 2014; Farris et al., 2015; Taylor et al., 2007). High-AS individuals believe that interoceptive sensations are indicators of imminent harm, leading to: 1) higher anxiety levels and risk of panic, which reinforces negative emotional states, triggers physiological arousal reactions, and ultimately increases panic and anxiety reactions as well (Leventhal & Zvolensky, 2015); and 2) increased aversiveness to physical sensations, which promotes maladaptive avoidance responses when coping with emotionally aversive circumstances (Smits, Otto, Powers & Baird, 2019).

Regarding the emotion-smoking binomial, AS levels have shown to be higher among smokers than among non-smokers (Abrams, Zvolensky, Dorman, González & Mayer, 2011; Zvolensky et al., 2014a; Zvolensky et al., 2019b). Smokers with higher levels of AS perceive more difficulties to quit smoking (Zvolensky et al., 2007) and experience more intense withdrawal symptoms (Johnson, Stewart, Rosenfield, Steeves & Zvolensky, 2012). Moreover, high-AS smokers are emotionally reactive to the distressing withdrawal sensations (e.g., heart rate slowing) that emerge when the abstinence period begins (Leventhal & Zvolensky, 2015). Consequently, those who do not show a reduction in AS during smoking cessation treatments may be at risk of cessation failure or relapse at both short-term and long-term follow-ups (Leventhal & Zvolensky, 2015; Zvolensky et al., 2006; Zvolensky, Stewart, Vujanovic, Gavric & Steeves, 2009).

AS and related constructs (e.g., trait anxiety; Takemura, Akanuma, Kikuchi & Inaba, 1999) have been associated to increased motivation to quit (Zvolensky et al., 2007), perhaps due to concerns about the health effects of smoking (Zvolensky et al., 2007). In this vein, Buckner and Vinci (2013) highlight that if practitioners were able to take advantage of such motivation at an early stage, long-term abstinence rates could be significantly improved (Borland et al., 2010; Leventhal & Zvolensky, 2015).

Counterintuitively, nicotine administration acutely diminishes perceived anxiety symptoms whereas tobacco abstinence increases them (Leventhal & Zvolensky, 2015). Smokers with high AS, especially those endorsing symptoms of panic disorder (e.g., Zvolensky et al., 2003), tend to believe that smoking helps them manage their emotional status by means of reducing negative affect and avoiding anxiety-related symptoms in the short term (Brown, Kahler, Zvolensky, Lejuez & Ramsey, 2001; Gregor, Zvolensky, McLeish, Bernstein & Morissette, 2008; Zvolensky et al., 2003). Consequently, higher levels of AS are related to greater interoceptive threat expectancies due to abstinence (Farris, Langdon, DiBello & Zvolensky, 2014) and to the tendency to use tobacco to cope with withdrawal symptoms (Zvolensky, Farris, Schmidt y Smits, 2014b), increasing in turn the expectation of positive affect after smoking (Wong et al., 2013).

Smoking and AS integrated treatments: A review of the evidence

Preceding research has demonstrated that integrating AS reduction components into broader smoking cessation treatments leads to reduced AS levels as well as improved treatment retention and cessation rates (e.g., Feldner, Zvolensky, Babson, Leen-Feldner & Schmidt, 2008; Zvolensky et al., 2003; Zvolensky et al., 2008; Zvolensky et al., 2014a; Zvolensky et al., 2018). Since high-AS smokers struggle particularly early in treatment with abstinence-related symptoms, treatment approaches are even more relevant to the earlier phases of the smoking cessation process (Brown et al., 2001; Zvolensky et al., 2006; Zvolensky et al., 2009; Zvolensky et al., 2018).

Current treatment protocols

So far, several treatment protocols targeting smoking cessation and AS have been developed, all of them in United

States (see Table 1). The AS components most commonly implemented include psychoeducation, acceptance-based behavioral counseling, cognitive restructuring and interoceptive exposure to anxiety-related sensations (e.g., Zvolensky et al., 2003; Zvolensky et al., 2014a). Despite results being positive in terms of cessation outcomes, sustained abstinence rates at medium and long-term follow-ups still remain low. It is worth mentioning that more intensive protocols (in terms of number and length of therapy sessions) seem to produce larger abstinence effects.

Evidence on the AS transdiagnostic vulnerability model in Spain

It is remarkable that all AS transdiagnostic programs have been developed and evaluated in United States and Argentina. Moreover, most published works are case series, do not include a comparison arm and often rely on small samples. So far, only four randomized controlled trials (RCTs) have implemented smoking cessation treatments in combination with a specific AS protocol.

In Spain, research work on the development of smoking cessation treatments for patients with comorbid symptoms of anxiety is scarce. More precisely, and as of today, there are no published behavioral treatment protocols addressing anxiety and smoking concurrently or using a transdiagnostic approach for this population in our country. Only a few studies (e.g., Becoña, Vázquez & Míguez; 2002; Marqueta, Jiménez-Muro, Beamonte, Gargallo & Nerín, 2010) have analyzed whether a relationship exists between state-trait anxiety and quitting success, concluding that state anxiety is significantly higher for unsuccessful quitters at post-treatment, 1- and 12-month follow-ups. Also, Martínez-Vispo, Fernández del Río, López-Durán & Becoña (2016) evaluated abstinence-related changes in AS at the end of a behavioral treatment for smoking cessation. Among the 92 Spanish smokers included in the study, participants who were abstinent at the end-of-treatment endorsed lower AS scores and nicotine dependence levels than those who remained smoking. Of note is that not only higher overall pre-treatment levels in the Anxiety Sensitivity Index-3 (ASI-3; Sandín, Valiente, Chorot & Santed, 2007; Taylor et al., 2007) but also higher levels at its physical subscale, were associated with a lower likelihood of quitting.

So far, the only cultural adaptation of an AS Reduction Program for Smoking Cessation in Spanish-speaking smokers has been developed in Argentina (Zvolensky et al., 2014a). This protocol consisted of a psychoeducational component on the relationship between AS and smoking, followed by training in strategies to effectively cope with fear of physical anxiety symptoms, and to increase tolerance for such states. The authors concluded that this intervention yielded positive results in terms of attendance and smoking cessation outcomes; nonetheless, further cultural adaptations are warranted to disseminate the treatment in other Spanish-speaking populations (for example, in Spain).

Table 1. *Main characteristics of transdiagnostic AS and smoking cessation treatments.*

Study (country)	**Aim**	**Sample**	**Method** (inclusion criteria, study design, measuring instruments, description of the intervention, duration, follow-ups)	**Findings**
Capron, Norr, Zvolensky & Schmidt (2014) United States	To assess whether an AS augmented smoking cessation program would predict lower suicidality among smokers.	169 adult smokers endorsing elevated AS cognitive concerns *Active group:* 60.2% females *Control group*: 56.8% females *Mean age* 42.22, *SD* = 12.81	**Inclusion criteria:** 18 years or older; daily smoker for at least 1 year; smoke a minimum of 8 cigarettes per day; motivation to quit smoking within the next month. **Study design:** - *Standard cognitive-behavioral smoking cessation program* (N= 81). - *Cognitive behavioral smoking cessation program with an added AS component* (N= 88). **Measuring instruments:** - ASI-3; IDAS; CO levels. **Description of the intervention:** AS treatment (see Funk, Zvolensky & Schmidt, 2011) consisted of an integrated anxiety prevention/management smoking cessation group (Panic/Smoking Program, PSP). This protocol combined elements of CBT for AS and panic (i.e., interoceptive exposure exercises). **Duration:** 4 weeks; 90-minute sessions with a trained therapist. Target quit day: Final session. **Follow-ups:** - *Short-term:* Prospective data (e.g. current suicidality) was collected at the 4th (final) treatment session via self-reported computerized questionnaires.	No mediation effect of AS levels between treatment group and suicidality; however, participants in the active treatment with high baseline AS showed reduced suicidality risk. No effect of treatment group on current depression. Data regarding smoking reduction or abstinence not available.
Gonzalez et al. (2017) United States	To analyze whether smokers with elevated WTC-related PTSD symptoms, who received CSC-T, show greater smoking cessation rates and reductions in PTSD and LRS than similarly affected smokers who received the CSC treatment alone.	90 adult smokers exposed to the 9/11 WTC disaster with elevated PTSD symptoms *CSC treatment:* 71.7% males; *mean age* 48.74, *SD* = 10.66 *CSC-T treatment:* 72.7% males; *mean age* 51.32, *SD* = 7.87	**Inclusion criteria:** 18 years or older; smoking ≥ 5 cigarettes per day; reporting interest in quitting smoking; direct exposure to the WTC disaster (e.g., responding to the event or witnessing the event in person); scoring at least in the intermediate range (≥ 30) on the PCL. **Study design:** - *CSC-T treatment* (N= 44) - *CSC treatment alone* (N= 46) **Measuring instruments:** - SCID-NP; PCL; SHQ; FTND; TLFB for daily cigarette use; LRS; CO and cotinine levels. **Description of the intervention:** *CSC:* Included CBT skills and NRT (24-hour transdermal nicotine patches). Standard cessation elements: (1) Psychoeducation on reasons for smoking and barriers to quitting; (2) Enlisting social support, monitoring and tapering cigarette use; (3) Counseling regarding high-risk smoking situations and unhelpful ways of thinking about smoking; (4) Abstinence and relapse prevention strategies. *CSC-T:* Also included trauma management techniques and transdiagnostic CBT-based anxiety reduction skills. Main components: (1) Interoceptive exposures to feared bodily sensations; (2) corrective information about anxiety and cognitive interventions to teach patients alternatives to catastrophic misinterpretations of somatic sensations; (3) use of graduated in-vivo exposure to feared and avoided situational experiences related to anxiety, WTC-related PTSD triggers, and smoking. **Duration:** 8 sessions (1.5h/session). Target quit day: week 6. **Follow-ups:** - *Short-term:* Primary outcome measures (7-day point abstinence, average number of cigarettes smoked per day in the past 7 days, PCL score, and LRS score) were assessed at each treatment session and at the EOT. - *Medium- and long-term:* 1-, 2-, 4-, 12-, and 26-weeks post-treatment.	The two treatments did not differ regarding: (1) PTSD symptom improvement; (2) 7-day (~15%) and 6-month (~20%) abstinence rates; (3) the number of cigarettes smoked; (4) PTSD and LRS outcomes. Both treatments led to slightly high quit rates compared to previous treatments for smokers with PTSD.

Study (country)	**Aim**	**Sample**	**Method** (inclusion criteria, study design, measuring instruments, description of the intervention, duration, follow-ups)	**Findings**
Smits et al. (2016) United States	To analyze the efficacy of exercise as an aid to quit among adult smokers with high AS.	136 adult smokers endorsing elevated AS levels *ST+EX:* 50.0% females; *mean age* 43.12, *SD* = 11.26 *ST+CTRL:* 54.7% females; *mean age* 45.39, *SD* = 11.30	**Inclusion criteria:** 18 years or older; daily smoker for at least 1 year; smoke a minimum of 10 cigarettes per day; elevated AS (prescreen score of ≥ 20 on the ASI-16); sedentary (moderate-intensity exercise less than twice a week for 30 minutes or less); motivation to quit smoking (reporting a motivation of at least 5 on a 10-point scale). **Study design:** - *Exercise intervention* (ST+EX; N = 72). - *Wellness education control condition* (ST+CTRL) (N = 64). **Measuring instruments:** - TLFB procedure; ASI-16; IDAS; CO and cotinine levels. **Description of the intervention:** *AS treatment (exercise condition):* Vigorous-intensity aerobic exercise for smoking cessation and reestablish a sense of safety around intense bodily sensations. *Wellness education (control condition):* Discussions of healthy lifestyle topics (e.g., healthy diet, time management) alongside setting small weekly wellness goals, prior to quitting smoking. **Duration:** 15 weeks; 7 weekly 60-minute sessions of CBT for smoking cessation. Target quit day: week 6. At week 6, participants were also provided with optional NRT patches for up to 8 weeks. Thrice weekly, 35- minute sessions for 15 weeks for both Exercise vs. Wellness education intervention. **Follow-ups:** - *Short-term:* Primary outcome measures (PPA and PA) were measured at EOT. - *Long-term:* 4-month and 6-month follow-ups.	PPA and PA rates were significantly higher for ST+EX than for ST+CTRL among smokers with high AS, but not among those with low AS. Vigorous-intensity exercise regimen may be useful to facilitate smoking cessation among high-AS smokers.
Zvolensky et al. (2018) United States	To examine abstinence effects of a novel AS reduction-smoking cessation intervention relative to a standard condition.	529 treatment-seeking adult daily smokers *STAMP condition:* 55.28% females; *mean age* 37.48, *SD*= 14.38 *SCP condition:* 50.78% females; *mean age* 40.23, *SD* = 12.98	**Inclusion criteria:** 18 years or older; smoking ≥ 8 cigarettes per day for at least 1 year; motivation to quit smoking (reporting a motivation of at least 5 on a 10-point scale). **Study design:** - *STAMP condition* (N = 296). - *SCP condition* (N = 233). *Because authors were interested in smoking cessation outcomes, participants were included if they attended at least one session when PPA was assessed. Final sample: STAMP condition (N= 161) vs. SCP condition (N= 129). **Measuring instruments:** - Demographics questionnaire; SCID-NP; SHQ; FTND; PANAS; ASI-3; TLFB; CO and cotinine levels. **Description of the intervention:** *SCP condition* (see Schmidt, Raines, Allan & Zvolensky, 2016): Included a standard care intervention for smoking cessation plus provision of general health-related information. Main components: Discussion of prior quit attempts, high-risk situations for smoking, social support, health risks of smoking, and perceived benefits of smoking. *STAMP condition:* (1) Interoceptive exposure, cognitive restructuring, and psychoeducation exercises developed for panic prevention; (2) standard smoking cessation (relapse prevention counseling). *Both treatment groups received NRT (transdermal nicotine patch) from session 4 (quit day). **Duration:** 4 weekly sessions (1h/session). **Follow-ups:** - *Short-term:* Primary outcomes were: (1) In-treatment AS reduction; (2) early PPA (quit week to 2-weeks post EOT); (3) late PPA (1-month post-EOT to 1-year post-EOT); (3) changes in AS (as a mediator of the effects of treatment on PPA outcomes). ASI-3 was completed at all treatment sessions. - *Medium and long-term:* 1-month, 3-month, 6-month, and 12-month post-EOT.	There was a significantly greater decline in AS in the STAMP condition, in comparison to the control group. Smoking reduction was significantly greater in the STAMP condition. There was an indirect effect of STAMP on early PPA, but not late PPA, through AS reduction during treatment. AS was reduced in both conditions, suggesting that individuals engaged in smoking cessation programs could reduce AS levels (regardless of whether AS is a key treatment target).

Note. AS = Anxiety Sensitivity; SD= Standard Deviation; ASI-3= Anxiety Sensitivity Inventory-3; IDAS= Inventory of Depression and Anxiety Symptoms; CO = Carbon monoxide ; CBT = Cognitive-behavioral treatment; WTC = World Trade Center; PTSD = Post-traumatic Stress Disorder; LRS = Lower respiratory symptoms; CSC = Comprehensive Smoking Cessation; CSC-T = Comprehensive Smoking Cessation and Trauma Management; PCL = PTSD Checklist-Specific Version; SCID-NP = Non-patient version of the Structured Clinical Interview for DSM-IV; SHQ = Smoking History Questionnaire; FTND = Fagerström Test for Nicotine Dependence; TLFB = Timeline follow-back; NRT = Nicotine Replacement Therapy; EOT = End of treatment; ST+EX = Standard smoking cessation treatment, that is, CBT plus nicotine replacement therapy + Exercise intervention; ST+CTRL = Standard smoking cessation treatment, that is, CBT plus nicotine replacement therapy + Wellness education control condition; ASI-16= 16-item Anxiety Sensitivity Index; PPA = Point-prevalence abstinence; PA = Prolonged abstinence; STAMP = Smoking Treatment and Anxiety Management Program; SCP = Standard Cessation Program; PANAS = Positive and Negative Affect Schedule.

Conclusions

Clinical recommendations and novel proposals for tobacco clinical research

Several guidelines can be drawn from the present analysis of the state of the art with regards to the relationship between AS and smoking cessation treatments. Firstly, both clinicians and researchers should focus on designing novel smoking cessation treatments from a transdiagnostic approach. Incorporating transdiagnostic components to address both emotional problems and smoking into existing smoking cessation treatments could enhance cessation rates and improve clinical services (Leventhal & Zvolensky, 2015). Secondly, adapting the AS Reduction Program for smoking cessation to the Spanish context, as previously done in Argentina (Zvolensky et al., 2014a), would allow researchers and clinicians to test the acceptability and clinical implications of the program in our country. However, further attempts to include protocols for AS into broader smoking cessation treatments must overcome prior research limitations. For example, most of the existing evidence has relied on case studies (Zvolensky et al., 2003; Zvolensky et al., 2008) or small samples (Martínez-Vispo et al., 2016; Zvolensky et al., 2014a). Also, since most of these previous studies are secondary in nature (i.e., works informing on ancillary outcome measures from randomized trials) there is no comparison group (i.e., control group). Consequently, further studies with experimental designs that allow us to ascertain the unique effect of AS on smoking outcomes are much needed.

On another note, follow-ups in previous studies are commonly conducted at short- (1-month follow-up; Zvolensky et al., 2008) or medium-term (3- or 6-months; Gonzalez et al., 2017; Smits et al., 2016; Zvolensky et al., 2014a). Abstinence at one year is a robust predictor for sustained abstinence (Nohlert, Öhrvik, Tegelberg, Tillgren & Helgason, 2013) and future studies should consider conducting long-term follow-ups. It is also important to mention that some interventions are still limited in their overall scopes as they comprise a narrow range of clinically-relevant variables from a transdiagnostic perspective (Martínez-Vispo et al., 2016; Richards, Cohen, Morrell, Watson & Low, 2013; Zvolensky et al., 2014a), hindering the generalizability of their results. In this sense, it is necessary to assess and treat other underlying transdiagnostic vulnerabilities (such as anhedonia or distress tolerance) in the same subsample of smokers, allowing us to better understand the relationship between emotional psychopathology, cigarette consumption, and smoking cessation (Leventhal & Zvolensky, 2015).

It should be noted that in our review, only four RCTs were found that included an AS protocol in combination with smoking cessation treatments, which may itself be a limitation in this field. Such RCTs are not exempt from shortcomings such as the inclusion of treatment-seeking smokers with only moderate levels of dependence (Smits et al., 2016; Zvolensky et al., 2018) and moderate retention rates, which underpowers the detection of significant differences (Gonzalez et al., 2017). Perhaps these reasons explain why some studies have traditionally suggested modest improvements or even mixed results (Brown et al., 2007; Hitsman, Borrelli, McChargue, Spring & Niaura, 2003; Zvolensky et al., 2014a). With the aim of overcoming such limitations, RCTs designs should be developed comparing the efficacy of traditional cognitive-behavioral treatments (CBTs) for smoking cessation (e.g., see Becoña & Vázquez, 1997; Secades-Villa, Alonso-Pérez, García-Rodríguez & Fernández-Hermida, 2009) with CBT plus AS Reduction Programs for quitting. Relatedly, it would be essential to do so in different cultures and settings to guarantee generalization of results to other community settings (beyond controlled laboratory studies).

Finally, it seems essential to explore the AS construct among Spanish treatment-seeking smokers from a gender perspective. Women have increased their levels of tobacco consumption in recent years (Amos, Greaves, Nichter & Bloch, 2012; National Plan on Drugs, 2019), and being a female represents a risk factor for maintaining smoking behavior, since they show significantly fewer quit attempts and perceive more barriers to quit smoking (Allen, Oncken & Hatsukami 2014; Allen, Scheuermann, Nollen, Hatsukami & Ahluwalia 2016). In particular, previous studies have shown that female sex is positively related to high levels of anxiety (Nakajima & al'Absi, 2012) and AS (Norr, Albanese, Allan & Schmidt, 2015; Stewart, Taylor & Baker, 1997; Zvolensky, McNeil, Porter & Stewart, 2001). When analyzing lower-order AS dimensions (that is, physical, cognitive and social concerns), some authors have also found that women present higher physical sensations (Zvolensky et al., 2001) when compared to men. Nonetheless, these findings are limited to undergraduate and nonclinical samples (Norr et al., 2015). Future research should address these gaps in the literature by differentially exploring the AS construct among male and female emotionally vulnerable smokers, including as well other clinically relevant variables related to both smoking behavior and smoking cessation, such as negative affect, anhedonia or distress tolerance.

Conflict of interests

The authors declare no conflicts of interest regarding this study.

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Cannabis-induced psychosis: clinical characteristics and its differentiation from schizophrenia with and without cannabis use

Psicosis inducida por cannabis: características clínicas y su diferenciación con la esquizofrenia con y sin consumo de cannabis asociado

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Abstract

Cannabis use is considered an established risk factor for psychosis development. Differentiating between cannabis-induced disorders and schizophrenia is useful for prognostic and therapeutic purposes. Three inpatients groups were differentiated: cannabis-induced psychosis (CIP) (n = 69; mean age = 27.4, *SD* = 6.5; 82.6% males), schizophrenia with cannabis abuse or dependence (SZ + CB) (n = 57; mean age = 31.9, *SD* = 10.1; 94.7% males) and schizophrenia without cannabis abuse or dependence (SZ) (n = 181; mean age = 41.8, *SD* = 13.3; 54.1% males). The *Psychiatric Research Interview for Substance and Mental Disorders* (PRISM-IV) scale was used to differentiate induced psychosis. The CIP group presented lower mean scores on the negative PANSS subscale (*M* = 12.9, *SD* = 5.9; *F* = 32.24, $p < 0.001$), fewer auditory hallucinations (60.3%; $\chi^2 = 6.60$, $p = 0.037$) and greater presence of mania (26.1% vs. 12.3%; $\chi^2 = 32.58$, $p < 0.001$) than the SZ + CB group. There were few clinical differences between patients with schizophrenia, regardless of previous cannabis use. The age of first admission due to psychosis was lower in both psychotic inpatients groups with cannabis use (*M* = 26.1, *SD* = 6.4 in CIP and *M* = 25.3, *SD* = 6.2 in SZ + CB; $\chi^2 = 20.02$, $p < 0{,}001$). A clinical pattern characteristic of cannabis-induced psychosis was not observed, but the precipitating role of cannabis in the appearance of psychotic symptoms was demonstrated, given the lower age of first admission due to psychosis in cannabis user groups.

Keywords: Psychosis; Schizophrenia; Cannabis; Induced psychosis.

Resumen

El consumo de cannabis se considera un factor de riesgo establecido para el desarrollo de psicosis. Diferenciar los trastornos inducidos por cannabis de la esquizofrenia resulta útil desde el punto de vista pronóstico y terapéutico. Se diferenciaron tres grupos de pacientes hospitalizados: psicosis inducida por cannabis (PIC) (n = 69; Media de edad = 27,4, *DE* = 6,5; 82,6 % varones), esquizofrenia con abuso o dependencia de cannabis (EZ + CB) (n = 57; Media de edad = 31,9, *DE* = 10,1; 94,7% varones) y esquizofrenia sin abuso o dependencia de cannabis (EZ) (n = 181; Media de edad = 41,8, *DE* = 13,3; 54,1% varones). Se utilizó la escala *Psychiatric Research Interview for Substance and Mental Disorders* (PRISM-IV) para la diferenciación de cuadros inducidos. El grupo PIC presentó puntaciones inferiores en la subescala PANSS negativa (*M* = 12,9, *DE* = 5,9; *F* = 32,24; $p < 0{,}001$), menos alucinaciones auditivas (60,3%; $\chi^2 = 6{,}60$; $p = 0{,}037$) y mayor presencia de manía (26,1% vs. 12,3%; $\chi^2 = 32{,}58$; $p < 0{,}001$) en comparación con el grupo EZ + CB. Hubo pocas diferencias clínicas entre los pacientes con esquizofrenia, independientemente del consumo de cannabis. La edad del primer ingreso por psicosis fue menor en ambos grupos de psicóticos consumidores (*M* = 26,1, *DE* = 6,4 en PIC y *M* = 25,3, *DE* = 6,2 en EZ + CB; $\chi^2 = 20{,}02$; $p < 0{,}001$). No se observó un patrón clínico característico de las psicosis inducidas por cannabis, aunque sí se demostró el papel precipitante del cannabis en la aparición de psicosis, dada la menor edad de ingreso en los consumidores.

Palabas clave: Psicosis; Esquizofrenia; Cannabis; Psicosis inducidas.

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Cannabis use is frequent among patients with psychotic disorders. Over 25% of patients with schizophrenia have concomitant cannabis dependence (Koskinen, Löhönen, Koponen, Isohanni & Miettunen, 2010), although polydrug use of other substances is also common (Volkow, 2009).

In recent decades, several cohort studies have been conducted to investigate the relationship between cannabis use and schizophrenia. After an initial study by Andréasson, Allebeck, Engström and Rydberg (1987), other cohort studies have been carried out, producing consistent data. In general, most authors consider that cannabis use may be a risk factor for the development of schizophrenia in vulnerable subjects, especially when it occurs at an early age and in large quantities (Konings, Henquet, Maharajh, Hutchinson & Van Os, 2008; Marconi, Di Forti, Lewis, Murray & Vassos, 2016). It has also been observed that this risk is greater than with other drugs and that cannabis is the only drug which has been shown to bring forward the age of onset of psychosis (Large, Sharma, Compton, Slade & Nielssen, 2011). However, other authors have suggested that, although cannabis use precedes the onset of psychotic symptoms, subjects who are vulnerable to the development of psychosis would already have greater susceptibility to cannabis dependence (Power et al., 2014).

Several studies in healthy volunteers have shown that cannabis produces not only positive symptoms but also negative and cognitive symptoms (García-Álvarez, Gomar, García-Portilla & Bobes, 2019), thus mimicking the typical characteristics of schizophrenia (D'Souza et al., 2004). Cannabis-induced psychosis involves a psychotic state which subsides within a month with antipsychotic treatment and abstinence. The new findings suggest that a large number of patients with cannabis-induced psychosis will subsequently develop chronic psychotic conditions in about 50% of cases (Starzer, Nordentoft & Hjorthøj, 2018). The argument that cannabis plays a causal role is supported by the findings that the use of cannabis of greater potency, as measured by the amount of tetrahydrocannabinol (THC), presents a higher risk of producing psychosis (Pierre, Gandal & Son, 2016). There are also recent studies showing that the use of synthetic cannabinoids is involved in the appearance of transient psychotic symptoms (Monte et al., 2017), induced psychosis (Barratt, Cakic & Lenton, 2013), first psychotic episodes (FPE) (Khan, Pace, Truong, Gordon & Moukaddam, 2016) and psychotic relapses in patients with schizophrenia (Celofiga, Koprivsek & Klavz, 2014).

Given that schizophrenia is a neurodevelopmental disease and the existing evidence that the endocannabinoid system modulates this brain process (cell proliferation, neurogenesis, neuronal migration, axonal projections), cannabis use, especially at an early age, could interfere in neurodevelopment, constituting a plausible biological explanation (Lubman, Cheetham & Yücel, 2015). Keshavan (1999) proposed the integration of three neurobiological models on the pathogenesis of schizophrenia: the early development model, the late development model and the neurodegenerative model. Premorbid vulnerability to schizophrenia is likely caused by an interaction of multiple genetic and environmental factors affecting early brain development. The onset of the disorder in adolescence may be determined by the processes of late brain maturation, as well as by the exclusive stress of adolescence and the impact of repeated exposure to neurochemical or environmental stressors, such as drug use (Keshavan, Gilbert & Diwadkar, 2006).

Some authors suggest that the pathogenic mechanisms behind the appearance of psychotic conditions in patients with cannabis use are different to those involved in the appearance of psychosis in non-users. The action of THC on the cannabinoid system, whether intact or already previously damaged, may produce neurobiological changes other than schizophrenia in non-users, which could lead to different clinical manifestations (Murray et al., 2017). On the other hand, CB2 cannabinoid receptors and neuroinflammatory mechanisms may also be relevant and could play a differential role between users and non-users (Minichino et al., 2019; Suárez-Pinilla, López-Gil & Crespo-Facorro, 2014). Other authors posit that, although psychosis develops by different mechanisms, a common final impairment occurs in the NMDA system, which is intimately regulated by CB1 cannabinoid receptors (Sánchez-Blázquez, Rodríguez-Muñoz & Garzón, 2014).

It is disputed whether cannabis use modifies the clinical presentation of psychosis and whether it constitutes a different clinical entity. An attempt has been made to establish a clinical method to differentiate between the psychotic conditions appearing in cannabis users and non-users which could guide the diagnosis. The data are rather contradictory. Cannabis use has been linked to greater severity of positive symptoms and lesser severity of negative symptoms (Pencer & Addington, 2003). In hospitalized patients, the presence of more neurotic symptoms and more depressive symptoms was observed in induced psychoses (Rubio et al., 2012; Thompson et al., 2016). Other authors report more hostility and anxiety symptoms in drug-induced psychosis versus primary psychoses (Fraser, Hides, Philips, Proctor & Lubman, 2012) or a higher frequency of mania and behavioral disorders, although positive symptoms subsided more quickly and negative symptoms were less prominent (Dawe, Geppert, Occhipinti & Kingswell, 2011). Conversely, some authors observed no clinical differences or differences in family history in cases of already existing schizophrenia when analyzing whether or not they had a history of previous cannabis use (O'Connell, Sunwoo, McGorry & O'Donoghue, 2019). Hence it seems that there may be some clinical differences in induced psychoses, but once

schizophrenia is established there are few differences depending on whether cannabis is used or not, so it is important to take such differences into account (Mauri, Di Pace, Reggiori, Paletta & Colasanti, 2017).

In general, the studies carried out to date are quite contradictory, probably due to the heterogeneity of the inclusion and exclusion criteria applied. Specifically, the exclusion of abuse or dependence on substances other than cannabis has not been taken into account in the research reviewed to date, something which could interfere with results. In addition, there are no studies directly comparing patients with cannabis-induced psychosis, patients with schizophrenia with cannabis abuse or dependence, and patients with schizophrenia without assessing abuse of or dependence on this substance.

The objective of this study was to analyze the possible existence of sociodemographic, clinical, developmental and prognostic differences between three groups of hospitalized patients: patients with cannabis-induced psychosis, schizophrenia with a history of cannabis abuse or dependence, and schizophrenia without a history of such abuse or dependence. In each group, we studied: 1) sociodemographic characteristics, family history and medical history; 2) clinical characteristics; 3) comorbid substance use; 4) age of first admission for psychotic symptoms by sex.

Method

Participants

A total of 331 patients were recruited with the following inclusion criteria: a) patients aged over 18; and b) diagnosed with schizophrenia or other unspecified psychotic disorders according to DSM-IV-TR criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text rev.*) (American Psychiatric Association, 2000). Exclusion criteria were: a) presence of psychosis in the context of affective disorders; b) history of moderate-severe head trauma; c) prior diagnosis of mental retardation; and d) a history of abuse or dependence on drugs other than cannabis and tobacco.

Intentional sampling was conducted and patients were classified into those with psychotic disorder and history of cannabis abuse or dependence and those diagnosed with schizophrenia without drug abuse or dependence except tobacco (SZ). Patients with psychosis and cannabis abuse or dependence were subdivided into schizophrenia with cannabis abuse or dependence (SZ + CB) and cannabis-induced psychosis (CIP). During the assessments, some patients dropped out of the study (see Figure 1) before their classification into groups as well as afterwards, declining consent for the study during admission.

As shown in Table 1, the mean age of the sample was 36.7 years (*SD* = 13.1), with a higher percentage of men (68.1%). The majority of patients were single (71%) and lived with their family of origin (59%). In the comparison between the three groups, baseline age was not distributed equally among the three groups ($p < 0.001$). SZ group patients were older than those in the other groups in a statistically significant way ($p < 0.001$). Among cannabis-using patients, the SZ + CB group were older, although this difference did not reach statistical significance. Regarding sex, the proportion of men in the SZ group was statistically significantly smaller ($p < 0.001$). When comparing both groups of consumers, the SZ + CB group presented a higher percentage of men (94.7%) which was statistically significant ($p = 0.036$). In terms of the remaining variables, SZ group patients lived more frequently with their own family, had a higher educational level and a lower family history of SUD. In addition, they had a higher frequency of medical pathology (mainly arterial hypertension and diabetes), higher BMI (Body Mass Index) and a lower frequency of attention deficit hyperactivity disorder history.

Informed written consent was obtained from each participant once they had received a full description of the study. If patients were unable to make decisions, a family member was informed. The research protocol was ap-

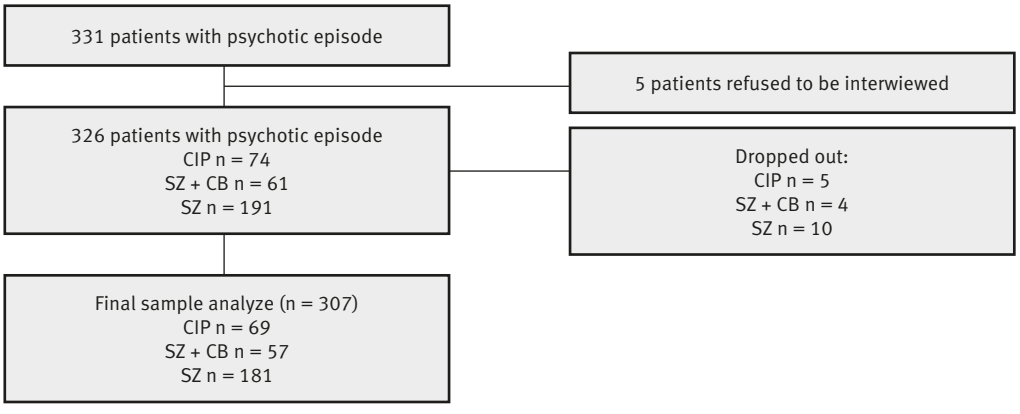

Figure 1. Sample selection process.
CIP: cannabis-induced psychosis; SZ: patients with schizophrenia; CB: patients with cannabis abuse or dependence.

Table 1. *Sociodemographic characteristics, family history and medical history.*

	Total (n = 307)	CIP (n = 69)	SZ+CB (n = 57)	SZ (n = 181)	Test value
Age (years)[a] Mean (SD)	36.7 (13.1)	27.4 (6.5)	31.9 (10.1)	41.8 (13.3)	$\chi^2 = 76.61$ $p < 0.001$***
Sex					
Male	209 (68.1%)	57 (82.6%) R.C = 2.9	54 (94.7%) R.C = 4.8	98 (54.1%) R.C = -6.3	$\chi^2 = 41.51$ $p < 0.001$***
Female	98 (31.9%)	12 (17.4%) R.C = -2.9	3 (5.3%) R.C = -4.8	83 (45.9%) R.C = 6.3	
Marital status					
Single	218 (71%)	57 (82.6%)	45 (78.9%)	116 (64.1%)	$\chi^2 = 11.23$ $p = 0.024$* T appr = 2.84
Married	56 (18.2%)	8 (11.6%)	6 (10.5%)	42 (23.2%)	
Other	33 (10.7%)	4 (5.8%)	6 (10.5%)	23 (12.7%)	
Living arrangements					
Family of origin	181 (59%)	52 (75.4%)	42 (73.7%)	87 (48.1%)	$\chi^2 = 23.7$ $p = 0.003$** T appr = 3.64
Own family	64 (20.8%)	9 (13%)	7 (12.3%)	48 (26.5%)	
Other	62 (20.2%)	8 (11.6%)	8 (14%)	46 (25.5%)	
Educational level					
Primary	192 (62.5%)	36 (52.2%)	40 (70.2%)	121 (66.9%)	$\chi^2 = 17.01$ $p = 0.009$** T appr = -1.33
Secondary	80 (26.1%)	27 (39.1%)	15 (26.3%)	38 (21%)	
University	30 (9.8%)	6 (8.7%)	2 (3.5%)	22 (12.2%)	
Employment					
Unemployed	88 (28.7%)	35 (50.7%)	17 (29.8%)	36 (19.9%)	$\chi^2 = 60.00$ $p < 0.001$*** T appr = 2.43
Working	78 (25.4%)	19 (27.5%)	12 (21.1%)	47 (26%)	
PWD	83 (27%)	1 (1.4%)	12 (21.1%)	70 (38.7%)	
Other	58 (18.9%)	14 (20.2%)	16 (28.1%)	28 (15.5%)	
Infantile hyperactivity	46 (15%)	25 (36.2%)	16 (28.6%)	5 (3.4%)	$\chi^2 = 42.84$ $p < 0.001$***
Family history					
Substance dependence	50 (16.3%)	19 (27.5%)	11 (19.3%)	20 (11%)	$\chi^2 = 10.42$ $p = 0.005$**
Psychotics	67 (21.8%)	12 (17.4%)	15 (26.3%)	40 (22.1%)	$\chi^2 = 1.47$ $p = 0.47$
Medical comorbidity	79 (26.1%)	11 (17.3%)	10 (15.6%)	58 (32.2%)	$\chi^2 = 27.84$ $p = 0.26$
Basal BMI Mean (SD)	26.6 (6.0)	23.4 (3.6)	25.1 (3.8)	28.3 (6.7)	$F = 10.09$ $p < 0.001$***

Note. SD = standard deviation. χ^2 = chi-square. PWD = permanent work disability. BMI = body mass index. *F* = ANOVA value.
T appr = approximate T, using the typical asymptotic error based on the null hypothesis. CR = corrected residuals. (aKruskal- Wallis).
*significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

proved by the Clinical Research Ethics Committee (CEIC) of the Alcorcón Foundation University Hospital.

Instruments

PANSS scale (Positive and Negative Syndrome Scale). The Positive and Negative Syndromes Scale developed by Kay, Fiszbein and Opler (1987) and adapted to Spanish by Peralta and Cuesta (1994) is one of the most frequently used instruments to assess symptoms in patients with schizophrenia. It is a hetero-applied scale which is completed through a semi-structured interview of about 45 minutes. In its original version, the PANSS scale comprises 30 items grouped into three factors: positive syndrome (consisting of 7 items), negative syndrome (also made up of 7 items) and general psychopathology (consisting of 16 items). The scores for each item range from 1 (absent),

2 (normal limit), 3 (mild), 4 (moderate), 5 (moderate/severe), 6 (severe) and 7 (extremely severe). The main psychometric properties of the PANSS scale are currently well documented (Kay, Opler & Lindenmayer, 1989; Kay & Sevy, 1990). Wallwork, Fortgang, Hashimoto, Weinberger and Dickinson (2012) proposed a five-scale model of the scale, commonly labeled as "positive", "negative", "cognitive", "depression" and "excitability". In a Spanish study, the internal consistency for the five-factor model ranged from 0.59 (excitability factor) to 0.90 (negative factor). Although the internal consistency of the excitability factor was below the widely accepted limit of 0.70, it was close to 0.60, an acceptable limit for short scales (Rodriguez-Jimenez et al., 2013).

In addition to the total scores of the PANSS scale, this study used the classical subscales (positive, negative and general psychopathology). The negative subscale requires a special mention as it was used to quantify and compare the negative symptoms of the three groups of patients studied.

PRISM-IV Scale (Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV) (Hasin et al., 1996). This is a semi-structured interview with which many DSM-IV disorders can be reliably diagnosed and which is highly valid in people who abuse substances, including substance dependence, major primary and substance-induced depressive disorder, primary psychotic and substance-induced disorder, and some primary anxiety disorders, dissociative personality disorder and borderline personality disorder. For this study, the Spanish version was used (Torrens, Serrano, Astals, Pérez-Domínguez & Martín-Santos, 2004), which has proven to be a better structured and more accurate interview for the diagnosis of drug-induced psychosis than the version in SCID-1 Spanish (Structured Clinical Interview for DSM-IV) (First, Spitzer, Gibbon & Williams, 2002).

In addition to previous diagnoses, the presence of hetero-aggressive behaviors and the prevalence of dysphoric, depressive or manic humor, as well as the presence of suicidal behavior were collected with this scale.

The reliability of the scale for patients who abuse substances is at least as good as that shown by other interviews with general samples (Hasin et al., 1996).

Substance use questionnaire. For the assessment of substance use, a series of ad hoc questions were formulated regarding alcohol consumption and drug use, specifically cannabis, cocaine, designer drugs and opiates. For alcohol use, information was collected on whether the participant was a non-drinker, drinker or former drinker. Likewise, information was also collected on other substances such as cannabis/marijuana/hashish, cocaine, designer drugs/methamphetamines/ecstasy/LSD and opioids. For each of these, information on the age of onset in years, how long it was used in months, and the days of use in the previous month were requested. These questions were formulated in line with previous research (Dumas et al., 2002) and previously validated scales (Soto-Brandt et al., 2014). Patients with criteria of abuse or dependence other than cannabis or nicotine were excluded from this study.

Addiction Severity Index (ASI) (McLellan et al., 1992). This is a semi-structured interview of between 45 to 60 minutes in length, administered by a trained clinician or interviewer, plus a further 10-20 minutes for scoring. It focuses on seven areas which may be affected by drug use: physical health, employment and financial support, illegal or criminal activity, family and social relationships, psychiatric symptoms and use of drugs and alcohol. For each area, the severity of symptoms and the treatment applied in the previous 30 days and lifetime are assessed.

The psychometric properties of the ASI scale have been demonstrated in different studies (Butler, Redondo, Fernandez & Villapiano, 2009; Carise et al., 2001).

Study Procedure

The recruitment of patients was carried out between January 1, 2005 and December 31, 2011 in a tertiary hospital in the southern area of the Community of Madrid (Alcorcón Foundation University Hospital). This hospital serves an urban area of about 200,000 inhabitants and a rural area of approximately 50,000 inhabitants; it is the only reference hospital for this population.

Patients were recruited consecutively as they attended the short hospitalization unit (SHU) of the hospital with a psychotic episode. The clinical assessments of the study were carried out during admission through standardized data collection by a psychiatric specialist at the SHU, who was the only interviewer in the study.

Some patients who maintained contact with mental health services in the area were monitored until 2013, either through the hospital or in outpatient clinics. This follow-up was performed to assess relapses and readmissions. The sample follow-up was on average 51 months ($SD = 2.1$), median 52 (4-84 months). In the CIP group, 43 patients were followed up (M = 40.2 months, $SD = 30.4$), in the SZ + CB group the follow-up was with 33 patients with a mean of 58.2 months ($SD = 31.9$), and in the SZ group 102 patients were followed with a mean of 59.3 months ($SD = 31.3$) (non-statistically significant differences with respect to the SZ + CB group).

Data analysis

All analyses were performed comparing SZ patients to SZ + CB patients and patients with CIP. Comparisons were made between the three groups using chi-square test (χ^2) or Fisher's exact test (F) for categorical data and ANOVA variance analysis or Kruskal-Wallis test for continuous data, depending on whether assumptions of normality and sample size were met. The Bonferroni test was used for post-hoc analysis and multiple comparison between the three clinical groups. The Kolmogorov-Smirnov test was used to

check normality. Inter-group effect size was calculated using Cohen's d *(d)*. All tests were bilateral with a $p < 0.05$. The analyses were performed with SPSS 20.0 (*Statistical Package for the Social Sciences,* 2011).

Results

Clinical differences

As Table 2 shows, the SZ group had a higher age of first admission for psychosis compared to the other groups. In the post-hoc analysis, this difference was found both with the CIP group *(*$t = -3.44$; $p = 0.001$; $d = 0.48$) and with the SZ + CB group ($t = -3.67$; $p < 0.001$; $d = 0.56$).

There were no differences between the groups regarding the total scores on the positive PANSS subscale. However, when comparing the different items of the subscale, there were differences in the excitability ($p < 0.001$) and hostility items ($p = 0.001$). In the post-hoc study, it was found that these differences occurred mainly between CIP and SZ groups. In direct comparison, the CIP group had a higher score in excitability with respect to the SZ group ($t = 4.64$; $p < 0.001$; $d = -0.76$) but not to the SZ + CB group ($p = 0.70$). As regards hostility, the CIP group again scored higher than the SZ group ($t = 3.52$; $p = 0.001$; $d = -0.56$) as did the SZ + CB group with respect to the SZ group ($t = 2.43$; $p = 0.01$; $d = -0.008$). Conversely, the SZ + CB group had a higher score on the negative PANSS subscale, a difference which did not occur with the SZ group ($p = 0.54$) but with the CIP group ($t = -8.14$; $p < 0.001$; $d = 1.22$).

Finally, in the SZ group dysphoric mood was less frequent ($\chi^2 = 12.92$; $p = 0.02$; $d = 0.13$), as was hetero-aggressive behavior ($\chi^2 = 23.75$; $p < 0.001$; $d = 0.25$). The SZ and SZ + CB groups had a higher frequency of auditory hallucinations ($\chi^2 = 6.60$; p = 0.037; $d = 0.08$), a lower frequency of expansive mood ($\chi^2 = 30.46$; $p < 0.001$; $d = 0.1$), and greater disorganization with respect to the CIP group ($\chi^2 = 4.34$; $p = 0.11$; $d = 0.14$).

Differences in follow-up

Table 3 reflects the following results: in the SZ and SZ + CB group there was less interepisodic remission and more relapse during follow-up with respect to the CIP group. In the post-hoc analysis, the difference in relapse occurred between the SZ + CB group and the CIP group ($t = -2.92$; $p = 0.05$; $d = 0.59$). In both subgroups of patients with schizophrenia, there were no differences in development nor in the percentage of relapses. There were no differences in follow-up time either.

Differences in drug use

With respect to drug use (see Table 4), there were more alcohol users in the SZ + CB group, but the age of habitual drinking was higher. They also smoked more. There were no differences regarding cannabis use compared to the CIP group. On the ASI scale, there was greater severity in the area of drug use with induced cases ($M = 6.5$; $SD = 1.3$ vs. $M = 5.2$; $SD = 1.8$; $F = 6.7$, $p < 0.001$; $d = -0.78$) and greater severity in the medical area in the SZ + CB group ($M = 1.1$; $SD = 0.5$ vs. $M = 1.6$; $SD = 1.3$; $F = 27.7$, $p = 0.002$; $d = 0.55$).

In the SZ group there were fewer users of tobacco, alcohol and cocaine compared to the SZ + CB group. On the ASI scale there was greater severity in the SZ + CB group in alcohol ($M = 2.2$; $SD = 1.5$ vs. $M = 1.4$; $SD = 1.1$; $F = 8.6$, $p < 0.001$; $d = -0.7$), drugs ($M = 5.2$; $SD = 1.9$ vs. $M = 1.8$; $SD = 1.4$; $F = 7.8$, $p < 0.001$; $d = -2.22$), and employment ($M = 5.4$; $SD = 1.8$ vs. $M = 4.3$; $SD = 1.9$; $F = 6.6$, $p < 0.001$; $d = -0.58$).

Age of first admission adjusted by sex

Since the age of hospital admission may be influenced by sex, a stratified analysis was performed. Statistical significance was maintained in men ($F = 5.08$; $p = 0.007$), with means of 25.9 ($SD = 5.6$) in the CIP group, 25.2 ($SD = 5.9$) in SZ + CB, and 28.7 ($SD = 8.5$) in SZ. The post-hoc study showed a difference between the CIP and SZ groups ($t = -2.23$; $p = 0.04$; $d = 0.37$) and between the SZ + CB and SZ groups ($t = -2.94$; $p = 0.01$; $d = 0.45$), but not between both groups of users. Statistical significance was not found in women, probably due to poor representation in the SZ + CB group (n = 3).

Discussion

Most recent studies examine the demographic and clinical differences between two groups of patients: schizophrenia patients who use cannabis versus those who do not, and do not consider whether induced psychosis or established schizophrenia is involved. As to studies addressing the concept of induced psychosis, most include patients with a diagnosis of substance-induced psychosis and those with a diagnosis of schizophrenia and substance abuse (Caton, Samet & Hasin, 2000; Dawe et al., 2011; Fraser et al., 2012) regardless of whether the psychosis was induced by cannabis or other drugs. Only two studies also consider a third cohort of patients: those with a schizophrenia diagnosis who had no abuse or dependence on other substances (Dragogna et al., 2014; Weibell et al., 2013). Of these, only Dragogna et al. (2014) specifically speak of cannabis as a substance of abuse and of cannabis-induced psychosis. In addition, due to the sample inclusion criteria, research to date has been heterogeneous with respect to the selected sample, including FPE with or without cannabis use, schizophrenia with or without a history of cannabis, or comparing chronic patients with acute episodes in terms of cannabis use or the results of a toxicological analysis.

The concept used by some authors of "cannabis psychosis" implies the presence of a specific psychopathology of a potentially different psychotic subtype. In a review

Table 2. *Clinical characteristics*.

	Total (n = 307)	**CIP (n = 69)**	**SZ+CB (n = 57)**	**SZ (n =181)**	**Test value**
Age of first admission, mean (SD)	28.9 (9.8)	26.1 (6.4)	25.3 (6.2)	31.1 (11.2)	$F = 11.56$ $p < 0.001$***
Number of previous admissions, mean (SD)	2.6 (3.7)	0.6 (1)	2.2 (2.2)	3.5 (4.4)	$F = 16.56$ $p < 0.001$***
Positive PANSS mean (SD)	23.3 (7.1)	24.3 (5.6)	23.3 (7.2)	22.9 (7.6)	$F = 0.81$ $p = 0.445$
Negative PANSS mean (SD)	20.4 (8.9)	12.9 (5.9)	22.1 (8.9)	23 (8.3)	$F = 32.24$ $p < 0.001$***
Disorganization (thought and behavior)	69 (22.5%)	10 (14.5%)	17 (29.8%)	42 (23.2%)	$\chi^2 = 4.34$ $p = 0.114$
Suicide					
Ideation	28 (9.1%)	5 (7.2%)	8 (14%)	15 (8.3%)	
Gestures	23 (7.5%)	5 (7.2%)	2 (3.5%)	16 (8.8%)	$\chi^2 = 4.53$ $p = 0.605$
Attempts	22 (7.2%)	4 (5.8%)	3 (5.3%)	15 (8.3%)	
Delirium					
Paranoid	275 (89.6%)	65 (94.2%)	50 (87.7%)	160 (88.4%)	$\chi^2 = 2.06$ $p = 0.357$
Reference	189 (61,.%)	48 (69.6%)	34 (59.6%)	107 (59.1%)	$\chi^2 = 2.41$ $p = 0.299$
Megalomaniac	66 (21.5%)	16 (23.2%)	15 (26.3%)	35 (19.3%)	$\chi^2 = 1.40$ $p = 0.496$
Mystical	74 (24.1%)	17 (24.6%)	12 (21.1%)	45 (24.9%)	$\chi^2 = 4.68$ $p = 0.321$
Somatic	23 (7.5%)	4 (5.8%)	3 (5.3%)	16 (8.8%)	$\chi^2 = 1.16$ $p = 0.557$
Other	95 (30.9%)	16 (23.2%)	15 (26.3%)	64 (35.4%)	$\chi^2 = 4.16$ $p = 0.125$
Hallucinations					
Auditory	222 (72.3%)	41 (60.3%) R.C = -2.3	43 (75.4%) R.C = 0.2	138 (76.2%) R.C = 1.7	$\chi^2 = 6.60$ $p = 0.037$*
Visual	20 (6.5%)	6 (8.7%)	2 (3.5%)	12 (6.6%)	$\chi^2 = 1.38$ $p = 0.5$
Somatic	46 (15%)	10 (14.5%)	4 (7%)	32 (17.7%)	$\chi^2 = 3.88$ $p = 0.143$
Other	13 (4.2%)	3 (4.3%)	1 (1.8%)	9 (5%)	$\chi^2 = 1.11$ $p = 0.574$
Predominant mood state					
Dysphoria	77 (25.1%)	23 (33.3%) R.C = 2.1	22 (38.6%) R.C =2.3	32 (17.7%) R.C = 3.8	
Depressive	65 (21.2%)	9 (13%) R.C = -1.9	12 (21.1%) R.C = 0.0	44 (24.3%) R.C = 1.6	$\chi^2 = 30.46$ $p < 0.001$***
Mania	41 (13.4%)	18 (26.1%) R.C = 3.1	7 (12.3%) R.C = 0.2	16 (8.8%) R.C = -2.8	
Hetero-aggression					
Mild	37 (12.1%)	8 (11.6%)	7 (12.3%)	22 (12.2%)	
Moderate	89 (29%)	28 (40.6%)	20 (35.1%)	41 (22.7%)	$\chi^2 = 23.18$ $p < 0.001$***
Severe	17 (5.5%)	4 (5.8%)	8 (14%)	5 (2.8%)	

Note. SD = standard deviation. χ^2 = chi-square. *F* = ANOVA value. CR = corrected residuals.
* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

Table 3. *Follow-up characteristics.*

	Total (n = 205)	CIP (n = 43)	SZ+CB (n = 33)	SZ (n = 102)	Test value
Interepisodic remission	117 (57.1%)	43 (100%)	17 (51.5%)	57 (55.8%)	$\chi^2 = 49.32$ p ‹0.001***
Relapse	112 (54.6%)	13 (29.5%) R.C = -3.2	25 (64.1%) R.C =1.8	74 (54.4%) R.C =1.2	$\chi^2 = 11.41$ p = 0.003**

Note. χ^2 = chi-square. CR = corrected residuals.
* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

Tabla 4. *Substance use.*

	CIP (n = 69)	SZ+CB (n = 57)	SZ (n = 181)	Test value
Cannabis: age of habitual use, mean (SD)	18 (5)	16.4 (3.4)		F = 1.99 p =0.107
Cannabis: maximum joints/day, mean (SD)	7.7 (6.2)	7.2 (5.3)		F = 0.82 p = 0.697
Tobacco: lifetime	65 (94.2%)	53 (93%)	102 (56.4%)	$\chi^2 = 50.9$ p ‹ 0.001***
Tobacco: cigarettes/day, mean (SD)	19.1 (11.8)	24.1 (13.9)	25.7 (16.2)	F = 3.07 p = 0.049*
Alcohol without use/ dependence data	22 (34.9%)	26 (50%)	28 (16.5%)	$\chi^2 = 25.71$ p ‹ 0.001***
Alcohol age of habitual use, mean (SD)	15.6 (1.9)	16.8 (3.5)	18.8 (3.1)	F = 2.85 p = 0.073
Alcohol maximum SDUs, mean (SD)	2.2 (6.4)	3.4 (4.7)	0.6 (1.6)	F = 7.93 p ‹0.001***
Alcohol days/week, mean (SD)	2.1 (2.4)	3.2 (2.7)	1.1 (2.1)	F = 10.7 p ‹ 0.001***
Cocaine without use/ dependence data	7 (10.9%)	11 (20.8%)	0 (0%)	$\chi^2 = 33.52$ p ‹ 0.001***
Substance use remission	38 (55.1%)	35 (61.4%)		$\chi^2 = 86.64$ p ‹ 0.001***

Note. SD = standard deviation. χ^2 = chi-square. *F* = ANOVA value. SDU = standard drink units.
* significant values $p < 0.05$; ** very significant values $p < 0.01$; *** highly significant values $p < 0.001$.

of the literature with eight selected studies, seven of these observed at least one statistically significant clinical difference. The authors thus conclude that it is not that there is no "cannabis psychosis", only that from the psychopathological point of view it is not qualitatively different from other forms of psychosis (Baldacchino et al., 2012). The data in the present article supports this conclusion, finding no relevant clinical differences that would help establish an entity distinct from other psychoses.

The sociodemographic differences observed are as expected. Cannabis users are more often male and young (Kavanagh et al., 2004). Data on sex, marital status, employment status are similar to other studies (Dawe et al., 2011).

No differences were observed between the groups regarding family history of psychosis, which supports the role of family vulnerability to the development of psychosis that can be precipitated by cannabis use, and thus highlights the importance of preventing cannabis use in subjects at high risk of developing psychosis. Similarly, other authors have supported the idea that individuals with cannabis-induced psychosis are genetically similar to those with schizophrenic disorders (Wilson, Szigeti, Kearney & Clarke, 2018), and high rates of family history of psychosis have been described in patients with schizophrenia and cannabis use (Bersani, Orlandi, Kotzalidis & Pancheri, 2002). This supports a possible interaction between cannabis use and genetic vulnerability to psychosis in increasing the risk of psychosis in these patients. However, differences regarding family history of substance use disorders were found.

Fewer negative symptoms were observed in the induced conditions, but there were no differences between the two groups of patients with schizophrenia. One of the findings reported more consistently in the literature is the presence of fewer negative symptoms in cannabis and drug users in general (Baldacchino et al., 2012). In any case, it is not normally considered whether or not they are induced or schizophrenic, nor is the progress of the clinical picture.

The data in the present study suggest that there are indeed fewer negative symptoms in induced disorders, as other authors have pointed out (Caton et al., 2005), but when considering the presence of schizophrenia, this difference disappears. Similarly, in studies which only consider the presence of schizophrenia this difference depending on use was also not observed (Boydell et al., 2007).

During the acute phase of psychosis, there was no difference in the total score on the positive PANSS subscale across the three groups of patients, as reported by other authors (Boydell et al., 2007; Stone et al., 2014). However, a higher score was observed in the items of excitability and hostility in those induced compared to the other groups, as described by other authors (Baeza et al., 2009). Our study further observed that differences also existed in hostility between both groups of patients with schizophrenia.

One of the clinical characteristics seen as related to induced psychosis, the lower frequency of auditory hallucinations (Caton et al., 2005; Drake et al., 2011), was also observed in our study. Patients with disorganization were also less frequent in the induced condition. However, there were no differences in disorganization in schizophrenia with or without cannabis use. The presence of hetero-aggressive behaviors occurred more frequently in both groups of users, which has also been described in other psychotic patients with addictions (Fraser et al., 2012), so it can be seen as related to the presence of drug use. In a sample of patients with schizophrenia and cannabis use, there was greater hostility than in non-users (Caspari, 1999).

Regarding the predominant mood during the acute phase, more dysphoria was observed in the SZ + CB group and more manic symptoms in the induced cases. Another characteristic which has been suggested in induced cases is the presence of an expansive mood. Other studies have found that cannabis users had more overt symptoms (McGuire et al., 1994; Núñez & Gurpegui, 2002; Rottamburg, Ben-Arie, Robins, Teggin & Elk, 1982; Stone et al., 2014;), which was also the case in our study. One explanation is that psychotic symptoms with an expansive mood in non-users would tend to be labelled as affective psychosis or schizoaffective disorder. Other authors noted that patients with induced psychosis experience more severe manic symptoms and disruptive behavior upon arrival at the hospital than those with a primary psychotic disorder (Dawe et al., 2011). A recent study divided cannabis-induced disorders into two subtypes, cannabis-induced psychosis and cannabis-induced affective disorder (Shah, Chand, Bandawar, Benegal & Murthy, 2017), claiming that such differentiation at the time of diagnosis may be valuable in predicting the course of the disease and in deciding on a plan of treatment. However, the majority of patients with cannabis-induced psychosis which developed into psychotic disorders had high percentages of affective symptoms.

Several authors have pointed out that there are few clinical differences between patients with psychosis, regardless of cannabis use (McGuire et al., 1994). The cross-sectional assessment of the clinical picture does not permit differentiation between psychosis in cannabis users and other psychotic conditions. The few clinical differences do not allow an adequate differential diagnosis to be established exclusively through psychopathological assessment. Induced psychoses may be the initial stage of schizophrenia, since over 50% of these develop into the disease (Arendt, Rosenberg, Foldager, Perto & Munk-Jørgensen, 2005; Caton et al., 2007; Mauri et al. , 2017; Sara, Burgess, Malhi, Whiteford & Hall, 2014; Starzer, et al., 2018) and once schizophrenia is established, the picture seems indistinguishable from schizophrenia in non-users (Boydell et al., 2007). Therefore, taking whether or not they are induced psychoses into consideration in clinical studies may partly explain the observed discrepancies.

Another aspect to consider is the presence of other comorbid addictive disorders, since polydrug use is common. Thus, by excluding the effects of drug abuse or dependence on patients with schizophrenia and cannabis dependence, the impact of cannabis use can be much better analyzed (Dubertret, Bidard, Adès & Gorwood, 2006). Therefore, one of the strengths of this study is the exclusion of abuse or dependence criteria involving drugs other than cannabis.

The age of first admission was lower in the two groups of users, in line with multiple studies (Dawe et al., 2011; Van Dijk, Koeter, Hijman, Kahn & Van den Brink, 2012) which suggest that cannabis use is at least one precipitating factor of psychosis. In a meta-analysis, it was pointed out that it was the only drug capable of bringing forward the age of onset of psychosis (Large et al., 2011). Given its effect on this variable, the sample was stratified by sex. In men, the youngest age of first admission was confirmed in the user groups. It has been reported that cannabis is associated with early onset of symptoms compared to other drugs, especially among women (Allegri et al., 2013), and the differences in the age of onset according to sex is lower in cannabis users, although other authors observe an advance independent of sex (Dekker et al., 2012).

No differences were observed in follow-up between the SZ + CB and SZ groups. Users usually have more relapses and poor treatment adherence (Zammit et al., 2008). In several studies, cannabis use was not associated with psychopathological differences, but relapses were significantly higher among users (Caspari, 1999; Van Dijk et al., 2012). Given the small number of patients followed up in the SZ + CB group, these differences may not have been detectable in this study.

This study has several strengths: it compares the sociodemographic, clinical, follow-up and prognostic characteristics across three groups of patients (CIP, SZ + CB, SZ),

thus making it possible to differentiate between subjects with induced psychosis and patients with chronic psychotic disorders. Although there are few psychopathological differences between cannabis-induced psychosis and schizophrenia with cannabis use, it is fundamental to differentiate between them in the different studies and in clinical practice given that in the case of the former the prognosis is more favorable and antipsychotic treatment can be seen as a short-term treatment, with an emphasis on the treatment of drug abuse or dependence. Thus, cessation of cannabis use can in some cases lead to complete remission of the condition, without a chronic psychotic disorder setting in, which, moreover, seems indistinguishable from schizophrenia once established. In addition, the study used standardized assessments based on drug use, sociodemographic aspects and psychopathology, as well as operational diagnostic criteria for clinical diagnoses. Finally, the sample size allowed us to analyze exclusively the presence of cannabis abuse or dependence criteria, thereby eliminating the confounding effect of abuse or dependence on other drugs, although not their sporadic use.

However, the findings must be interpreted taking into account certain methodological limitations. This study only included patients who had contact with psychiatry services, excluding all patients who did not, such as those attending addiction services. In addition, substance use data were based mainly on what the patients themselves reported. Induced psychoses were not compared with primary FPEs to try to differentiate which differential characteristics of induced psychoses may be due to cannabis use and which to the fact of being initial episodes, such as the presence of negative symptoms. Furthermore, there are no data on continuing use during follow-up, and patients dropped out during this period.

In conclusion, the clinical differences of the CIP group were few compared to the other groups: there was a greater presence of affective disorders of the overt type, a lower percentage of auditory hallucinations and negative symptomatology and, finally, more aggressive behaviors. However, these clinical differences disappear once schizophrenia establishes itself. In addition, patients with cannabis dependence have an earlier age of onset of psychosis, suggesting at least a precipitating role of this substance in the onset of psychotic disorders. Future studies should consider differentiating between induced psychosis and schizophrenia with cannabis abuse or dependence.

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FA set the objectives, designed the literature search, wrote the first draft of the article, and consecutive drafts were reviewed by DR, SS, RR and GR. FA contributed to the complete design of the study and the interpretation of the data. FA and DR contributed in defining the data analysis procedures and carrying out the statistical analysis. FA and SS participated in data collection. All authors reviewed the draft and approved the final version.

Conflict of interests

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Study to determine relevant health outcome measures in opioid use disorder: Multicriteria decision analysis

Estudio para la determinación de medidas de resultados en salud relevantes en el trastorno por consumo de opiáceos. Análisis de decisión multicriterio

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Abstract

The aim of the current study was to establish the most relevant health outcomes to assess opioid substitution treatment programmes (OSP) in patients with opioid use disorder (OUD) in Spain. A multicriteria decision analysis was applied in 3 phases: 1) concepts and criteria definitions; 2) criteria screening and weighting by means of a discrete choice experiment; 3) deliberative process. Criteria established in phase 1 were: substance use (opioids, alcohol, tobacco, stimulants and cannabis), other mental disorders (affective/anxiety disorder, psychosis, attention deficit hyperactivity disorder, borderline personality disorder, antisocial personality disorder, gambling disorder and other impulse control disorders), level of disability, adherence, medical illnesses (medical comorbidities, risk behaviours, infectious and sexually transmitted diseases), psychosocial aspects (hostile and/or violent behaviour and work problems), functional disability (quality of life, treatment and service satisfaction, social functionality). In phase 2, the most relevant factors in OSP were determined, and subsequently assessed in the deliberative process: remission of substance use (opioids, alcohol and stimulants), improvement of other mental disorders (psychosis and borderline personality disorder), improvement in comorbidity management, and improvement in social functionality, with a weighting of 56.5%, 21.9%, 11.0%, and 10.7%,

Resumen

El objetivo fue establecer los resultados en salud con mayor relevancia en la evaluación de programas de tratamiento de sustitución de opiáceos (PTSO) en pacientes con trastorno por consumo de opiáceos (TCO) en España. Se realizó un análisis de decisión multicriterio con 3 fases: 1) definición de conceptos y criterios a evaluar; 2) cribado y ponderación de criterios mediante un experimento de elecciones discretas; 3) proceso deliberativo. Los criterios de la fase 1 fueron: consumo de sustancias (opiáceos, alcohol, tabaco, estimulantes y cannabis), trastornos mentales (trastorno afectivo ansioso, psicosis, trastorno por déficit de atención e hiperactividad, trastorno límite de personalidad, trastornos de personalidad antisocial, trastorno por juego y otras alteraciones del control de los impulsos), nivel de discapacidad, adherencia, enfermedades médicas (comorbilidades, conductas de riesgo, enfermedades infecciosas y de transmisión sexual), aspectos psicosociales (conducta hostil y/o violenta, presencia de problemas laborales), discapacidad funcional (calidad de vida, satisfacción con el tratamiento y servicio, funcionamiento social). En la fase 2 se determinaron los factores fundamentales en la elección de un PTSO, revisados en el proceso deliberativo: remisión del consumo de sustancias (opiáceos, alcohol y estimulantes), mejoría en el manejo de otros trastornos mentales (psicosis y trastorno límite de la personalidad),

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respectively. The current analysis defines the main health outcomes in OSP in patients with OUD in Spain, supporting decision making and socio-health management of existing resources.

Keywords: Opioid use disorder; Opioid substitution programmes; Multicriteria decision analysis; Health outcomes; Discrete choice experiment.

mejoría en manejo de comorbilidades médicas y mejoría en el funcionamiento social, con un peso del 56,5%, 21,9%, 11,0% 10,7% respectivamente. Este análisis define los resultados sanitarios más relevantes en PTSO en pacientes con TCO en España, favoreciendo la toma de decisiones y la gestión socio-sanitaria de los recursos existentes.

Palabras clave: Trastorno por consumo de opiáceos; Programas de tratamiento de sustitución de opiáceos; Análisis de decisión multicriterio; Medidas de resultados en salud; Experimento de elecciones discretas.

The management of opioid use disorders (OUD) represents a major challenge both from healthcare and social perspectives. A series of pharmacological and psychological approaches defined by professional experts in mental health and addictions have been consolidated to manage OUDs in different healthcare contexts (Pilling, Strang & Gerada, 2007; Socidrogalcohol, 2016). Nevertheless, it has been estimated that opioid users in Europe have a probability of mortality at least 5-10 times greater compared to the rest of the population of same age and gender, with overdose being the main cause of death. It is estimated that in 2015 at least 7,585 overdose deaths associated with the use of at least one illegal drug occurred in European Union member states, with opioids detected in 81% of these overdose deaths (European Monitoring Centre for Drugs and Drug Addiction, 2017). Similarly, an increase in the problems derived from opioid use and from deaths associated with overdoses of heroin and synthetic and legal and illegal opioids has been detected in the United States in recent years (Hedegaard, Warner & Miniño, 2017).

Addiction management is particularly complex given its multidimensional impact, which significantly compromises the lifestyles of people who suffer it and of the communities in which they live (Barrio et al., 2016; Fernández Miranda, 2001; Gedeon et al., 2019; Jiménez-Treviño et al., 2011; Martínez-Luna et al., 2018; Pedrero-Pérez & Grupo MethaQoL, 2017; Torrens, Mestre-Pintó, Montanari, Vicente & Domingo-Salvany, 2017). Therefore, when assessing the health outcomes of interventions used in the initiation and maintenance of opioid substitution treatment programs in patients with OUD, psychiatric, psychological, biological, and socioeconomic indicators should be considered. While the key measure of the effectiveness of these interventions has traditionally been abstinence, undoubtedly a very important factor, it is not enough to ensure patient recovery (Cloud & Granfield, 2008).

Other indicators have also been used, such as treatment program retention, reduction in the use of non-prescribed opioids or other secondary drugs, or decrease in crime and morbimortality (Iraurgi, 2000). In addition, a number of factors have been incorporated into the assessment of opioid substitution treatment programs, such as satisfaction with and perception of treatment in studies of healthcare quality and effectiveness (Bobes, Casas & Gutiérrez, 2011; Pérez de los Cobos et al., 2004; Sociedad Española de Toxicomanias, 2006; Stahler & Cohen, 2000; Treolar, Fraser &Valentine, 2007; Trujols & Pérez de los Cobos, 2005). Patients who are more satisfied with the intervention have been shown to have greater acceptance of treatment programs, in turn resulting in better adherence and retention to these programs (Bilbao Acedos, Lozano Rojas, Ballesta Gómez & González-Saiz, 2009; Fan, Burman, Mcdonnell & Fihn, 2005; World Health Organization, United Nations International Drug Control Program and European Monitoring Centre on Drugs and Drug Addiction, 2000). The great challenge for decision-making based on health outcomes arises when integrating and weighting all the indicators to help decision-makers (healthcare professionals and managers, political and social administrators) to establish the safest, most effective and efficient strategy, without oversimplifying the problem. Multicriteria decision analysis (MCDA) offers a suitable approach for decision making in complex environments since it allows the systematization of the decision in different stages, establishing and estimating the preferences of the decision makers explicitly (Marsh et al., 2016; Thokala et al., 2016; Thokala & Duenas, 2012).

The number of MCDAs at international level is low and have been focused, among other things, on specific pathologies, such as rare diseases or HIV/AIDS (Goetghebeur et al., 2008; Paulden, Stafinski, Menon & McCabe, 2015; Schlander et al. , 2016; Sussex et al., 2013; Wagner, Khoury, Willet, Rindress & Goetghebeur, 2015; Youngkong, Teerawattananon, Tantivess & Baltussen, 2012), on the application of the EVIDEM evaluation framework for assessing interventions in ultra-rare diseases by health systems (Goetghebeur et al., 2011), such as the Catalan Health Service (Spain) (Gilabert-Perramon et al., 2017), on the incorporation of innovations in certain geographic areas, such as Lombardy (Italy) (Radaelli et al., 2014) and on the prioritization of health interventions in Norway (Defechereux et al., 2012).

The aim of this study is therefore to generate a framework for assessing health outcomes with greater relevance in opioid substitution treatment programs for patients with OUD in Spain, using MCDA methodology, which facilitates the objective assessment of these interventions from the point of view of clinical management.

Method

The MCDA process was carried out following international recommendations which define the necessary steps (Marsh et al., 2016; Thokala et al., 2016; Thokala et al., 2012). The study comprised three distinct phases based on the tasks to be performed: 1) a first phase in which concepts and criteria were defined for use in the assessment of opioid substitution treatment programs in patients with OUD; 2) a second phase in which these criteria were screened and weighted; 3) a deliberative process to reach a final conclusion on the entire process (Bobes et al., 2018).

A panel of 20 Spanish experts of national and international standing in the clinical management of mental health and addictive behaviours took part in the project, alongside representatives of scientific societies and healthcare policy administrators.

Phase 1: Definition of criteria and levels

The main aim of this phase was to establish the criteria with which to assess the suitability of the interventions in the treatment of OUD. To this end, we called on five experts in the treatment of OUD. First, they were sent a questionnaire with a series of criteria and outcome measures and a proposal with different patient profiles for consideration in choosing a program for OUD treatment. After completing and processing the responses to this first questionnaire, a consensus was established with the five experts during a face-to-face meeting on the criteria and levels to be considered. In this consensus, a performance matrix was drawn up for use in the next phase.

Phase 2: Screening and weighting of criteria

The main aim of this phase was the screening of those criteria considered important in decision-making and the weighting of each one. Thus, a questionnaire was designed based on Discrete Choice Experiment (DCE) methodology, in accordance with international recommendations for good practice (Bridges et al., 2011; Reed Johnson et al., 2013). This questionnaire was completed by 15 experts who participated exclusively in this phase, in addition to three experts from phase 1.

The questionnaire items comprised pairs of hypothetical interventions and patient profiles. The interventions were configured based on the combination of the levels of each of the criteria agreed on in phase 1 (Table 1). Based on these criteria, it was necessary to generate 72 intervention pairs to calculate the weighting of each of the criteria. To facilitate completion of the DCE, two versions of the questionnaire with 36 items each were generated. For the design of the interventions shown in the items, an orthogonal design was chosen using the "Support.Ces" package (Aizaki, 2012).

The patient profiles included in the questionnaire were designed on the basis of the characteristics considered relevant by the panel of experts in phase 1 with the aim of evaluating whether the characteristics of these patients influenced the assessment of the interventions, based on the established criteria. Twenty-one patient profiles were generated using a fractional factorial design algorithm with Fedorov optimization. To obtain the patient profiles, the "AlgDesign" package was used (Wheeler, 2004).

On obtaining the completed questionnaire, two statistical analyses were performed using multinomial logistic regression models, one to screen criteria and the other to estimate weights.

The selection criterion in the screening analysis required the coefficient to have a statistically significant value ($p < 0.05$). The screened variables were subject to a second multinomial logistic regression model to calculate the weight of the screened criteria. The following formula was used for weighting the criteria:

$$WD_i = \frac{e^{\beta_{Di}}}{\sum_{D1}^{Dn} e^{\beta_D}} * 100$$

D_i= Domain
WD_i= Domain i weight percentage
$ß_i$= Domain i model coefficient for

In addition, a qualitative analysis of the response pattern was also carried out to assess the influence that patient characteristics may have had on the choice of an intervention. The method of analysis is detailed in Appendix 1.

All statistical analyses were performed with R software, version 3.2.3.

Phase 3: Deliberative process

In this phase, the aim was to reflect on and interpret the screened criteria and their weights. Furthermore, we reviewed which patient profile characteristics had a notable influence on decision criteria in the choice of intervention. This phase involved the five experts from phase 1.

Results

Definition of criteria and levels

The criteria and levels agreed on by the experts for assessing opioid substitution treatment programs in patients with OUD, after the consensus meeting with the phase 1 experts, are shown in Table 1. In terms of *substance use*, it was assessed whether there was a remission (total or partial) after the intervention in the use of opioids, alcohol, tobacco, stimulants and cannabis, according to DSM-5 criteria (American Psychiatric Association, 2013). In the *mental disorders* section, it was considered whether the intervention led to an improvement in psychopathology based on DSM-5 criteria (American Psychiatric Association, 2013). Mental disorders considered were affective/anxiety disorder, psychosis, attention deficit hyperactivity

Table 1. *Criteria and levels assessed.*

Criteria		Levels
Substance use	Opioids	No remission Partial remission//early total remission (according to DSM-5 at least 3 months and less than 12 months) Prolonged total remission (according to DSM-5 more than 12 months)
	Alcohol	No remission Partial remission//early total remission (according to DSM-5 at least 3 months and less than 12 months) Prolonged total remission (according to DSM-5 more than 12 months)
	Tobacco	No remission Partial remission//early total remission (according to DSM-5 at least 3 months and less than 12 months) Prolonged total remission (according to DSM-5 more than 12 months)
	Stimulants	No remission Partial remission//early total remission (according to DSM-5 at least 3 months and less than 12 months) Prolonged total remission (according to DSM-5 more than 12 months)
	Cannabis	No remission Partial remission//early total remission (according to DSM-5 at least 3 months and less than 12 months) Prolonged total remission (according to DSM-5 more than 12 months)
Mental disorders	Affective / anxious disorders	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
	Psychosis	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
	Attention deficit and hyperactivity disorder	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
	Borderline personality disorder	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
	Antisocial personality	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
	Other compulsive behaviours (gambling ...)	No improvement in psychopathology determined according to DSM-5 criteria Improvement in psychopathology determined according to DSM-5 criteria
Level of disability		No improvement in social functioning assessed using the WHO_DAS II questionnaire Improvement of social functioning assessed using the WHO_DAS II questionnaire
Intervention adherence		Attending less than 70% of visits Attending more than 70% of visits
Medical diseases	Comorbidities: Clinical picture derived from substance use (or not).	No improvement in medical comorbidities Improvement in medical comorbidities
	Risk behaviour (sex, hygiene, etc.)	Reduction of risk behaviours No reduction of risk behaviours
	Infectious diseases (viral hepatitis, HIV)	Therapeutic benefits in the management of infectious diseases. No therapeutic benefits in the management of infectious diseases.
	Sexually transmitted diseases	Therapeutic benefits in the management of sexually transmitted diseases No therapeutic benefits in the management of sexual transmission
Psychosocial	Hostile and/or violent behaviour	No effect on hostile and violent behaviour Reduction of behaviour frequency
	Presence of work problems	No effect on work problems Reduction of work problems
Functional capacity	Quality of life	No improvement based on SF-36 questionnaire Improvement based on SF-36 questionnaire
	Satisfaction with treatment and service	No improvement based on Verona Service Satisfaction Scale (VSSS-32) Improvement based on Verona Service Satisfaction Scale (VSSS-32)
	Social functioning	No improvement based on Duke-UNC Social Support Scale Improvement based on Duke-UNC Social Support Scale

disorder, borderline personality disorder, antisocial personality disorders, gambling disorder, and other compulsive behaviours. Using the WHODAS II questionnaire (World Health Organization, 2010; Üstün et al., 2010), the extent to which the intervention produced a decrease in the *level of disability* was assessed. An additional important factor was *intervention adherence*, for which the criteria was attending 70% of visits.

Regarding *medical illnesses*, the question was whether the intervention could have beneficial effects on the awareness regarding the care of other comorbidities (whether linked to substance use or not), on the reduction of risk behaviours (sex, hygiene, etc.), improvement in the management of infectious diseases (viral hepatitis and HIV), as well as in the adoption of preventive behaviours to avoid sexually transmitted diseases (STDs). Hostile and/or violent behaviour (measured by the reduction in the frequency of this type of behaviour) and the presence of work problems (decrease in work problems) were considered under *psychosocial aspects*.

Functional disability was assessed in terms of quality of life (improvement based on the SF-36 questionnaire (Fernández Miranda, 2003; Fernández Miranda, González Gª-Portilla, Saiz Martínez, Gutiérrez Cienfuegos & Bobes García, 1999; Fernández Rodríguez, Fernández Sobrino & López Castro, 2016; Iraurgi Castillo, 2008; Ware & Sherbourne, 1992)), satisfaction with treatment and service (improvement based on the Verona Service Satisfaction Scale (Pérez de los Cobos et al., 2004)). Whether or not there was a post-intervention improvement in social functioning was also considered (based on the Duke-UNC Social Support Scale (Ayala et al., 2012; Bellón Saameño, Delgado Sánchez, Luna del Castillo & Lardelli Claret, 1996; de la Revilla et al., 1991)).

Characteristics of the patients

The patient profile characteristics to be taken into account when choosing an intervention were established by the experts participating in phase 1. An important characteristic was patient age, divided into 5 categories based on a recent study carried out in Spain (Carrera et al., 2016): children under 18 years of age, adults aged 18 to 24, 25 to 34, 35 to 44, and over 45. Other relevant characteristics were patient relapse (return to the habitual pattern of use) in a binary response (yes/no) and the length of addiction (< 1 year, 1-2 years, and > 2 years). The following were considered treatment-related variables: the number of previous treatments (none, 1, 2 or ≥ 3 treatments received), the type of treatment previously received (treatment with opioid antagonists, treatment with opioid agonists and drug-free treatment) and the location of administration of previous treatments (outpatient, day centre and residential withdrawal unit (therapeutic community)). Another important question for the experts was to find out if patients had a criminal history (crimes related to substance use, whether prosecuted or not).

Criteria screening

Table 2 shows the coefficients of the adjusted multinomial logistic regression model in the screening of criteria. In a first model including all criteria, the most important factor in choosing an intervention for the treatment of patients with OUD is remission (both total and partial) from opioid use. Likewise, total remission from alcohol and/or stimulant use was established as a relevant factor in the choice. Other general criteria with statistically significant coefficients were mental disorders (psychosis and borderline personality disorder), medical illnesses (comorbidities) and functional disability (social functioning).

Criteria weighting

Based on the screened criteria (with statistically significant coefficient values), a multinomial logistic regression model was fitted to estimate the weight of each criterion in deciding on an intervention for the treatment of OUD patients. The values of the resulting model are shown in Figure 1. The factor with the greatest weight was the remission from substance use, with 56.5% of the total weight in making the choice; the presence of mental disorders was second, with 21.9%; the presence of medical diseases was third, with 11.0% and functional disability was fourth, with 10.7%.

Analysis by patient profiles

These models and their weights are shown in Figure 2. In the analysis by profiles, it was found that an additional recommended criterion to consider in patients aged 25-34 years was that the intervention should reduce the appearance of sexually transmitted diseases.

In addition, the choice of an intervention for patients prosecuted for crimes related to substance use should take into account whether or not it reduces hostile and/or violent behaviour.

Discussion

MCDAs are very versatile tools since they allow the complexity of decision making to be dealt with in a transparent and reproducible way. Furthermore, they enable the integration of different profiles of decision-makers, clinicians, pharmacists, nurses, managers and directors, regional and national public administrations, and even patients. In this way, a dialogue framework can be established to integrate the different interests, facilitating decision-making based on the preferences of all the agents involved.

From the perspective of the clinical experts who participated in this study, the fundamental factor in the choice of an intervention and subsequent recovery of a patient with

Table 2. *Coefficients of the multinomial logistic regression screening model.*

Criteria			coef	exp(coef)	se(coef)	z	p
Substance use	Opioids	Partial remission	0.571	1.770	0.115	4.98	**< .001***
		Total remission	0.727	2.069	0.112	6.52	**< .001***
	Alcohol	Partial remission	0.184	1.202	0.107	1.72	.085
		Total remission	0.281	1.325	0.104	2.69	**.007***
	Tobacco	Partial remission	0.104	1.110	0.103	1.02	.309
		Total remission	0.012	1.012	0.105	0.12	.907
	Stimulants	Partial remission	0.038	1.039	0.108	0.35	.725
		Total remission	0.262	1.299	0.104	2.53	**.012***
	Cannabis	Partial remission	0.097	1.101	0.103	0.93	.351
		Total remission	0.052	1.053	0.104	0.49	.622
Mental disorders	Affective / anxious disorders		0.057	1.059	0.084	0.68	.496
	Psychosis		0.211	1.235	0.085	2.50	**.013***
	Attention deficit and hyperactivity disorder		0.134	1.144	0.084	1.59	.111
	Borderline personality disorder		0.165	1.180	0.084	1.96	.049*
	Antisocial personality		-0.002	0.998	0.084	-0.03	.979
	Other compulsive behaviours (gambling ...)		0.046	1.047	0.084	0.55	.583
Level of disability			0.121	1.129	0.084	1.44	.150
Intervention adherence			0.062	1.064	0.084	0.74	.461
Medical diseases	Comorbidities		0.183	1.201	0.085	2.17	**.030***
	Risk behaviour		-0.118	0.889	0.084	-1.40	.163
	Infectious diseases		-0.056	0.946	0.084	-0.66	.510
	Sexually transmitted diseases		0.150	1.161	0.084	1.77	.076
Psychosocial	Hostile and/or violent behaviour		0.059	1.060	0.084	0.70	.485
	Presence of work problems		0.103	1.108	0.084	1.22	.224
Functional capacity	Quality of life		0.010	1.010	0.084	0.11	.910
	Satisfaction with treatment and service		0.061	1.063	0.084	0.73	.468
	Social functioning		0.175	1.192	0.084	2.08	**.037***

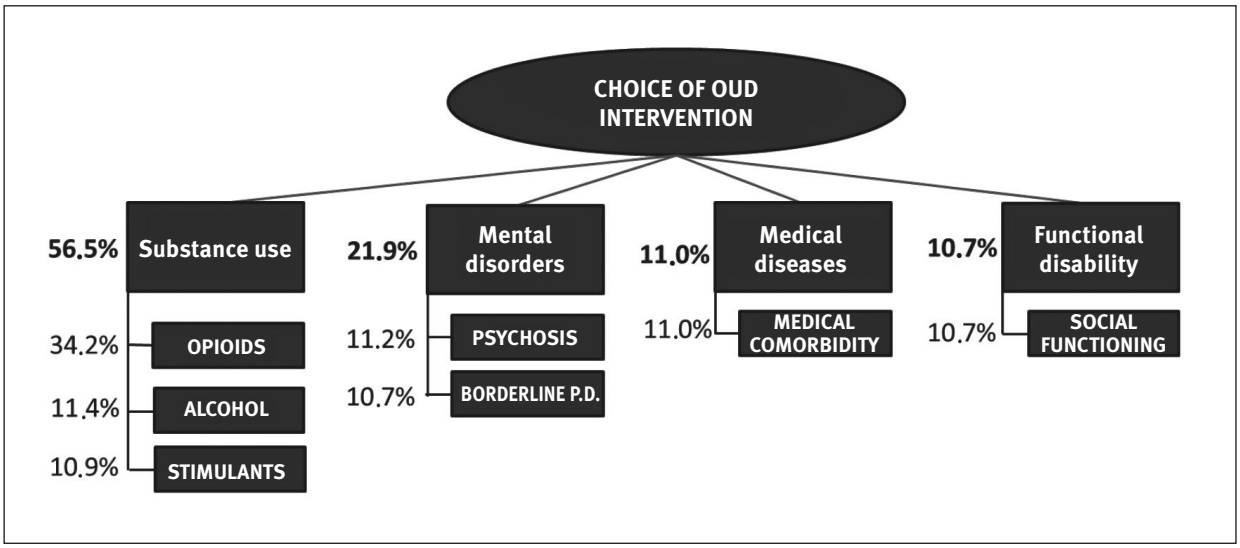

Figure 1. Results of screened criteria weighting.

OUD was confirmed to be the remission from opioid use behaviour. Other relevant factors were remission from alcohol and stimulant use behaviour. This could be the result of multiple substance use behaviour by this type of patient, so the aim of the intervention would be the cessation of addictive behaviour.

Other key factors in this study essential for the recovery of patients with OUD were improvement in psychiatric comorbidities, in the management of medical comorbidities, and in social function. The need to improve psychiatric comorbidities may be related to the fact that these patients commonly suffer some other comorbidity or relevant clinical condition in addition to opioid use disorder (Szerman et al., 2017).

Furthermore, interventions favouring an improvement in the medical comorbidities associated with this type of patients (HIV infection, HCV, etc.), would make the patients themselves adopt a greater awareness and degree of involvement in the self-care of their diseases and avoid behaviours that lead to possible complications or infection of other individuals. Lastly, the importance of an intervention offering improved social function should be highlighted, since the final objective of clinicians is the integration of these patients into society, ensuring their ability to progress without the handicaps imposed by addictive behaviour.

The analysis of patient profiles focused on the criteria to be considered based on the characteristics of these patients. Firstly, the analysis suggests that, in patients between the ages of 25 and 34, an important criterion was reducing the risk of sexually transmitted diseases. Secondly, in patients prosecuted for criminal behaviours linked to OUD, a desirable outcome for an intervention to achieve would be a reduction in hostile and/or violent behaviour. While it is true that these results are based on the qualitative review of the response patterns, the data were confirmed by the panel of experts in the deliberative process.

Comparing the results of this study with others is complicated due to the novelty of incorporating MCDA in the healthcare setting. To the authors' knowledge, the few experiences of applying MCDA in the field of addictions have been carried out in works such as that of Nutt, King, Phillips and the Independent Scientific Committee on Drugs (2010)

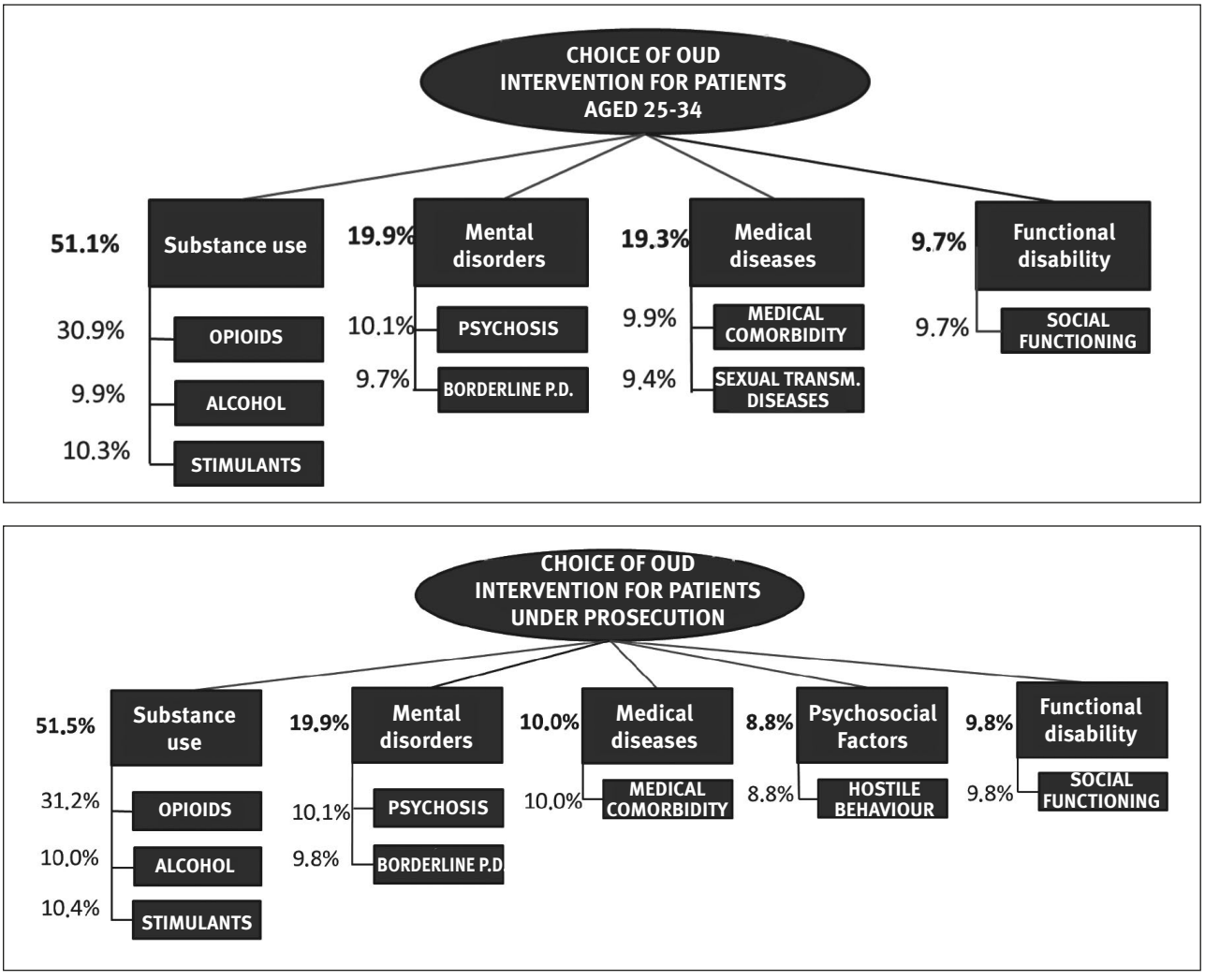

Figure 2. Alternative models according to patient profile.

in the United Kingdom, with the aim of weighting the harm arising from drug use for the user and other individuals.

One of the future strengths of MCDA is its potential use as a tool in the implementation of new forms of financing, such as results-based payment (Phelps & Madhavan, 2017; Sculpher, Claxton & Pearson, 2017). Thus, initiatives are already under way in various therapeutic areas, such as oncology, and promoted in healthcare systems (Clopes et al., 2017). A further example is the proposal developed by the United Kingdom government to measure results in the treatment of addictions and establish how results-based payment agreements could be used to pay for addiction treatment services (United Kingdom Government, 2013). In the case of our study, the results could serve as a starting point when establishing the fundamental criteria for assessing the incorporation of a new intervention for OUD patients.

A series of limitations should be noted on interpreting these results. When the results were analyzed based on patient profiles, only a qualitative analysis of the response pattern was performed given that the large number of criteria and possible profiles made it impractical to estimate the discrete choice models for each profile. Nevertheless, this analysis has allowed us to determine the situations in which the discrete choice model had worse predictive power and which factors could be involved.

Another possible limitation could be that the majority of experts on the panel had a fundamentally clinical and healthcare profile in the management of addictions. Methodologies which incorporate MCDA in the selection of health interventions favour the socio-health management of existing resources, incorporating information on health outcomes, pharmacoeconomic evidence and ethical criteria, involving all decision-makers from a multidisciplinary perspective. Therefore, future studies would be enriched by incorporating the perspective of other professionals involved in the management of OUD patients, such as psychologists, social workers and even representatives of patient associations, in order to facilitate systematic OUD-based decision-making so that better coordination of all the agents involved in the care and patient management process can be achieved.

The present study has established the bases for a bio-psycho-social assessment framework for health outcomes obtained with interventions for OUD patients, establishing a tool to systematically and transparently integrate and identify the health outcomes considered most relevant in the assessment and decision-making of opioid substitution treatment programs (OSP) in patients with OUD.

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Conflicts of interest

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Appendix 1

Statistical details of the analysis (Discrete Choice Experiment)

Given that the probability of choice between treatments is complementary and equal to 1, the probability of choosing treatment A would be:

$$P_{tA} = \frac{\Pr(A)}{\Pr(A) + \Pr(B)}$$

Taking into account that Pr(T) is calculated using the linear model indices of the categories contained in treatment n of item i with a total number of coefficients Ct and a number of coefficients included in the treatment of Cin, (cte is the intersection), then:

$$\Pr(A) = \frac{\sum_{cin=1}^{Cin} cin_i + cte}{\sum_{ct=1}^{Ct} ct + cte}$$

Example:

Suppose that the first treatment offers the options:

- partial remission of opioid consumption
- total remission of alcohol consumption.
- improvement in social functioning

Suppose the second treatment offers the options:

- total remission of opioid consumption
- improvement in social functioning

Since the rest are null or not significant categories for the model, the probability that a subject responds to each category is:

$$\Pr(A) = \frac{\sum_{cin=1}^{Cin} cin_i + cte}{\sum_{ct=1}^{Ct} ct + cte}$$

$$\Pr(T1) = \frac{1.63 + 2.49 + 1.47 + 1.58}{11.78} = 0.608$$

and

$$\Pr(T2) = \frac{1.63 + 1.35 + 3.26}{11.78} = 0.529$$

Thus the probability of selecting treatment 1 (T1) is:

$$P_{tA} = \frac{\Pr(A)}{\Pr(A) + \Pr(B)}$$

$$P_{tA} = \frac{0.608}{0.608 + 0.529} = 0.534$$

And the probability of selecting treatment 2, its complementary 1-T1 = 0.465.

Using these probabilities, it can be calculated whether the selection of treatments by the subjects can be considered random or based on the characteristics of the subjects.

Detection of alcohol use disorders using the camouflaged CAGE questionnaire in three population groups

Detección de trastornos por uso de alcohol mediante la aplicación del cuestionario CAGE camuflado en tres grupos poblacionales

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Abstract

The objective was to evaluate the risk of presenting an alcohol use disorder (AUD) in outpatient psychiatric units and compare it with drug addiction outpatient units and with healthy controls in the same administrative health area. An observational, descriptive, multicenter study was carried out in which a total of 1054 participants were evaluated. Data were obtained by means of the camouflaged CAGE questionnaire, which consists of 4 basic questions camouflaged with 8 other questions about healthy lifestyle habits. Cut-off points 1 and 2 were considered.

Of the total number of participants, 588 were psychiatric outpatients, 153 outpatients from addiction centers and 313 healthy individuals. The mean age of the total sample was 45.8 years and the percentage of men was 53.2%. Of the total sample, 38.3% scored ≥1, as did 34.2% of psychiatric patients, 72.5% of drug addicts and 29.4% of healthy people. The ≥2 cut-off was reached by 26.6% of the total sample, 22.6% of psychiatric patients, 64.7% of drug addicts and 15.3% of healthy subjects. The participants with the highest percentage of ≥1 scores were men (48.8%), those younger than 30 years (50%), those with a diagnosis of alcohol use disorder (95.9%) and ADHD (83.3%). Psychiatric patients are at a higher risk of having an AUD than the healthy subjects, although lower than those who are drug addicts, and the CAGE questionnaire is a simple and useful tool to detect the risk patients have to suffer the condition under study.

Keywords: Alcohol use disorder; CAGE questionnaire; Drug dependent outpatients; Dual pathology; Psychiatric outpatients.

Resumen

El objetivo fue evaluar el riesgo de presentar un trastorno por uso de alcohol (TUA) en las consultas psiquiátricas ambulatorias y compararlo con las consultas de drogodependencias y con individuos sanos de la misma zona de salud. Se realizó un estudio observacional, descriptivo, multicéntrico, en el que fueron incluidos un total de 1054 participantes. Se utilizó el cuestionario CAGE camuflado para la obtención de los datos, que consta de 4 preguntas básicas camufladas con otras 8 preguntas sobre hábitos de vida saludables. Se consideraron los puntos de corte de 1 y 2.

Del total de participantes, 588 eran pacientes psiquiátricos ambulatorios, 153 de los centros de drogodependencias ambulatorios y 313 sanos. La edad media de la muestra fue de 45,8 años y el porcentaje de hombres fue del 53,2%. El 38,3% de los participantes presentaron una puntuación ≥1, el 34,2% en las consultas psiquiátricas, el 72,5% en las de drogodependencias y el 29,4% en sanos. El 26,6% presentaron una puntuación ≥2, el 22,6% en las consultas psiquiátricas, el 64,7% en las de drogodependencias y el 15,3% en sanos. Los que presentaron mayor porcentaje de puntuación ≥1 fueron los hombres (48,8%), los menores de 30 años (50%), y los que tenían un diagnóstico de trastorno por uso de alcohol (95,9%) y de TDAH (83,3%).

Los pacientes psiquiátricos presentan un mayor riesgo de presentar un TUA que los individuos sanos, aunque menor que los drogodependientes, siendo el cuestionario CAGE una herramienta sencilla y útil para detectar el riesgo de presentarlos.

Palabras clave: Trastornos por uso de alcohol; Cuestionario CAGE; Pacientes drogodependientes ambulatorios; Patología dual; Pacientes psiquiátricos ambulatorios.

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Alcohol is one of the main preventable causes of premature mortality, illness and disability. It is the most widely used psychoactive drug in Spain (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2017), where it also presents a significant burden of death and disease. Ten percent of the total mortality of the population aged 15 to 64 in 2011 was potentially attributable to alcohol, mostly due to habitual excessive use, with the probability of death or alcohol-related harm being much higher in men than in women (Pulido et al., 2014). Currently, the total social cost of alcohol consumption in Spain may be around 1% of GDP (more than €10,000 million) (Rehm, Rehm, Shield, Gmel & Gual, 2013).

In Spain, no clear data on the prevalence of alcohol use disorders (AUD) are available. A prevalence of between 4.0% and 8.7% of the general population screening positive was obtained in different studies carried out in different Spanish autonomous communities between 1992 and 2010 using the CAGE questionnaire with a cut-off point ≥ 2 (Alvarez & del Rio, 1994; Alvarez, Fierro & del Rio, 2006; Anitua, Aizpuru & Sanzo, 1998; Dirección General de Atención Primaria, 2001; Dirección General de Atención Primaria, 2006; Dirección General de Atención Primaria, 2011; Pérez et al., 2010; Servicio de Estudios e Investigación Sanitaria, 2004); this prevalence ranged in men from 6.1% to 13.6% and in women from 1.2% to 5.3%. Using the AUDIT test (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2017), 5.1% of Spaniards aged 15 to 64 were classified in the high-risk alcohol use group (7.6% of men and 2.6% of women) and 0.2% as having a possible addiction (0.3% of men and 0.1% of women). In the 2015 EDADES survey (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2015), the proportion of those with high-risk consumption was 5% of Spaniards aged 15 to 64 (5.8% of men and 4% of women), this time the criterion being the amount of alcohol drunk per week.

Users of other substances have higher alcohol consumption than the general population. Among smokers, 84.3% had drunk alcohol in the last 12 months, a figure which rose to 91.7% in users of cannabis, 94.4% in cocaine and 96.3% in ecstasy users (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2017). Patients with alcohol abuse/addiction also frequently use other psychoactive drugs and suffer from other mental health disorders with a high prevalence (Gual A, 2007; Segui et al, 2001).

Psychiatric patients also present a higher frequency of toxic consumption than the general population, with the psychiatric population observed as having a risk twice as high of presenting an AUD than the general population (Mansell, Spiro, Lee & Kazis, 2006; Regier et al., 1990). Patients with dual pathology are those who simultaneously suffer from a psychiatric illness and a substance abuse disorder, such as AUD itself (Luoto, Koivukangas, Lassila & Kampman, 2016; Sánchez-Autet et al., 2018; Torrens, Mestre-Pintó, Montanari, Vicente & Domingo-Salvany, 2017). These patients with mental disorder and an AUD have worse treatment adherence, worse prognosis, worse quality of life, more social complications, higher suicide rates and longer hospital stays; this has been observed in almost all mental illnesses such as anxiety (Vorspan, Mehtelli, Dupuy, Bloch & Lépine, 2015), depression (Sullivan, Fiellin & O'Connor, 2005; Worthington et al., 1996), bipolar disorder (Coryell et al., 1998; Feinman & Dunner, 1996; Sonne, Brady & Morton, 1994; Winokur et al., 1998; Zamora-Rodríguez, Sánchez-Waisen, Guisado & Vaz, 2018) and schizophrenia (Soyka, Albus, Immler, Kathmann & Hippius, 2001; Urbanoski, Cairney, Adlaf & Rush, 2007).

Different questionnaires for detecting AUD or high-risk drinkers are available, the most commonly used being AUDIT (Alcohol Use Disorders Identification Test; Saunders, Aasland, Babor, de la Fuente & Grant, 1993) and CAGE (Fiellin, Reid & O'Connor, 2000). AUDIT was more effective in identifying subjects with risky or dangerous consumption (sensitivity, 51%-97%; specificity, 78%-96%), while the CAGE questionnaire was superior in detecting alcohol abuse and dependence (sensitivity, 43%-94%; specificity, 70%-97%) (Fiellin et al., 2000).

The CAGE questionnaire is an instrument for detecting alcohol use disorders which is simple, brief and easy to apply. It was developed by Ewing (1984) and validated by Mayfield, McLeod and Hall (1974). It consists of four questions regarding alcohol use. In general, the greater the number of affirmative answers, the more serious the dependency (Ewing, 1984; Malet, Schwan, Boussiron, Aublet-Cuvelier & Llorca, 2005; O'Brien, 2008).

The "camouflaged" CAGE questionnaire was developed to make the interview less intimidating (Castells & Furlanetto, 2005; Masur, Capriglione, Monteiro & Jorge, 1985). The four questions of the original CAGE are mixed with eight further questions about healthy lifestyle habits. Although they lack discriminatory value, these intermediate questions are useful in introducing the topic of alcohol use, thereby, as already mentioned, making the interview less intimidating for the interviewee.

Regarding scoring and the most appropriate cut-off point in the CAGE questionnaire, there is some controversy about whether this should be 1 or 2 positive responses (Sánchez-Autet et al., 2018) since this could affect both its sensitivity and its diagnostic specificity. We found studies in favor of using ≥ 1 positive response as the cut-off point (Agabio, Marras, Gessa & Carpiniello, 2007; Bradley, Bush, McDonell, Malone & Fihn, 1998; Bush, Shaw, Cleary, Delbanco & Aronson, 1987; Liskow, Campbell, Nickel & Powell, 1995), while others argue that the most appropriate cut-off is ≥ 2 positive responses (Castells et al., 2005; Fiellin et al., 2000; Hearne, Connolly & Sheehan, 2002; Mayfield et al., 1974; Paz Filho et al., 2001). It has been estimated that

the sensitivity and general specificity for clinical populations of the CAGE questionnaire is 71% and 90% respectively (Dhalla & Kopec, 2007; Mitchell, Bird, Rizzo, Hussain & Meader, 2014). A cut-off point of 1 seems to provide high sensitivity at the same time as maintaining sufficient specificity, while, despite implying lower sensitivity, a cut-off point of 2 does improve specificity (Corradi-Webster, Laprega & Furtado, 2005; Dervaux et al., 2006).

In the first part of our study (Sánchez-Autet et al., 2018), in which we analyzed the prevalence of AUD in outpatient psychiatric patients with a modified CAGE, we found that the male patients with bipolar or personality disorder presented a higher risk of AUD.

The objectives of our study were: 1) to obtain the prevalence of AUD in outpatient psychiatric services, in outpatient drug addiction centers and in a sample of healthy subjects by using the camouflaged CAGE questionnaire; 2) to compare the prevalence of the three samples; 3) to analyze the impact of rurality, a variable not used in the previous literature, on the results obtained.

Material and methods

Recruitment of participants

An observational, descriptive and multicenter study was carried out. The sample was obtained from different outpatient services in Spain in the Autonomous Community of Extremadura (provinces of Badajoz and Cáceres) and the Autonomous Community of Catalonia (only the province of Barcelona); a total of 30 outpatient psychiatrists and 10 doctors from drug addiction centers participated in data collection.

The methodology was the same as in the previous study published by our group (Sánchez-Autet et al., 2018), but in this second part, data were collected for three groups of participants: patients who were being treated by their outpatient mental health unit, as in the initial study, plus those who we could not include in the first analysis, patients who were being treated in their outpatient drug addiction center and healthy subjects. The sample of outpatient drug addicts could only be obtained from the Autonomous Community of Extremadura.

The inclusion criteria were: aged 18 years of age or over, having the cognitive ability to answer the questionnaire (at the discretion of the interviewer), and giving their consent to participate in the study. For the control group of healthy subjects, those with a personal history of having received any type of pharmacological or psychotherapeutic treatment by mental health or drug centers were excluded, although other medical illnesses were accepted.

Patients were included consecutively as they arrived at their treatment center, both at the outpatient mental health unit and their outpatient drug addiction service, depending on their diagnosis, and provided they met the inclusion criteria. The sample of healthy subjects was obtained from health workers, family members and other people in the researchers' environment. All participants gave their written consent. The study was approved by the different local ethics committees.

Study design

The recruitment period was from May 2015 to August 2015 for the sample from outpatient mental health and drug addiction centers, extended until December of the same year for the collection of the sample of healthy subjects. All procedures performed for this study were carried out in a single visit within the usual care provided for these patients and by specifically contacting healthy controls for a study visit. After signing written consent, sociodemographic data (age and sex) were collected and the patient's diagnosis was recorded, based on DSM-V criteria (Diagnostic and Statistical Manual of Mental Disorders, 5th ed.) (American Psychiatric Association, 2013). The "camouflaged" CAGE questionnaire (Appendix) was then administered. Each affirmative answer for any of the four items on the original CAGE questionnaire scored 1 point. The reason for choosing this AUD detection questionnaire against the AUDIT or other similar questionnaires was its greater brevity and ease of application, in addition to being a self-administered test, thus permitting the least possible interruption of consultation time (Ewing, 1984). Another advantage we considered important for this choice was that by being "camouflaged" within eight other questions about healthy lifestyle habits, patients did not even know that they were completing a questionnaire on alcohol use detection, which made the interview less intimidating and the answers more reliable (Castells et al., 2005).

Although in the first article published (Sánchez-Autet et al., 2018) we decided to use the cut-off point of ≥ 1 positive response for a positive screening, given the existing controversy over whether it should be ≥ 1 or ≥ 2 (Agabio et al., 2007; Bradley et al., 1998; Bush et al., 1987; Castells et al., 2005; Fiellin et al., 2000; Hearne et al., 2002; Liskow et al., 1995; Mayfield et al., 1974; Paz Filho et al., 2001), for our second article we decided to use both cut-off points for statistical analysis, i.e. a score of both ≥ 1 and ≥ 2 on the CAGE questionnaire.

Patients from outpatient mental health centers were classified into the following diagnostic categories: depressive disorders, psychotic disorders, anxiety disorders, personality disorders, bipolar disorders, borderline intellectual capacity (BIC), dementia, and attention deficit hyperactivity disorders (ADHD). Patients with BIC and dementia were included as long as their intellectual and cognitive capacity was sufficient to understand the study and respond adequately to the questions in the questionnaire. Outpatient drug addiction patients were classified according to dependence to each of the following substances: alcohol, canna-

bis, cocaine, heroin, cocaine plus heroin, and a final group which included other addictive behaviors (gambling, compulsive shopping, tobacco). If they used more than one substance, they were classified according to the main drug treatment problem.

To analyze the differences in the CAGE questionnaire scores by age, we decided to divide the sample into four subgroups (18-30 years, 31-45 years, 46-60 years and over 60 years).

Having samples from two geographical areas of the Spanish territory which are very far apart and have very different indices of rurality, Extremadura (the provinces of Cáceres and Badajoz) and Catalonia (Barcelona province), we decided to compare them in the search for possible differences. The index of rurality, or people living in municipalities with less than 5,000 inhabitants or with a maximum density of 300 inhabitants per km^2 (Goerlich & Cantarino, 2015), was 6.5% for the province of Barcelona, where the whole Catalonia Community sample was taken from, while in the provinces of Badajoz and Cáceres it was 44.5% and 51.2%, respectively (Goerlich et al., 2015).

Statistical analysis

After creating the database with all variables collected, statistical analysis was carried out with version 15.0 of SPSS (Statistical Package for the Social Sciences).

The three groups described were compared: outpatient psychiatric patients, outpatient drug addiction patients and healthy subjects. The same comparison was also carried out excluding patients with an AUD diagnosis from the group of outpatient drug addicts. A comparison was also made between the two autonomous communities in the healthy groups and psychiatric population, since a sample of drug-dependent patients could not be obtained from the Autonomous Community of Catalonia.

Statistically significant differences when testing hypotheses were considered when the associated p-value was below 0.05. For descriptive statistics, qualitative variables were expressed as frequencies and numbers, and quantitative variables as means and standard deviations.

The chi-square test was used to compare the qualitative variables. For the comparison of qualitative variables with quantitative variables, we compared means between the different qualitative variables by one-way analysis of variance (ANOVA) when the qualitative variables were non-dichotomous and by Student's t when they were dichotomous. Age, as a quantitative variable, is presented as mean ± standard deviation.

Results

Sample descriptives

A total of 1,054 participants were included in the study. The characteristics of the sample are described in Table 1, and the diagnoses and their percentages are shown in Table 2.

CAGE questionnaire scores

The average CAGE questionnaire score in the three groups was 0.88 ± 1.3. The average score for those attending psychiatric units was 0.74 ± 1.2; those with drug addiction 2.12 ± 1.55 and for the control group 0.55 ± 0.99 ($F = 97.33$; $p < 0.001$). Excluding patients with AUD among those attending drug addiction units, the average score for this group drops to 1.34 ± 1.48 ($F = 14.7$; $p < 0.001$). Table 3 shows the percentage of participants with each of the CAGE scores.

The CAGE score was higher in men than in women (1.21 ± 1.44 vs 0.50 ± 1.01; $F = 42.67$; $p < 0.001$). Analysis by age groups yielded the following results: from age18 to 30 the score was 1.01 ± 1.25; from 31 to 45 years 0.86 ± 1.33; from 46 to 60 years 1.00 ± 1.36; and in people over 60 years 0.56 ± 1.08 ($F = 4.62$; $p = 0.003$). By diagnoses, we found that the highest CAGE scores were obtained in

Table 1. *Characteristics of the sample of participants: age and sex.*

Baseline characteristics		PSYCHIATRY		ADDICTION		HEALTHY		TOTAL	
		N	%	N	%	N	%	N	%
		588	55.8	153	14.5	313	29.7	1054	100
Age: mean-min-max (SD)		49.92	18-92 (14.06)	42.71	18-72 (12.35)	39.92	19-73 (10.89)	45.87	18-92 (13.72)
Age groups	18-30	58	10	28	18.4	46	14.7	132	12.6
	31-45	160	27.6	54	35.5	190	60.7	404	38.7
	46-60	234	40.4	58	38.2	56	17.9	348	33.3
	>60	127	21.9	12	7.9	21	6.7	160	15.3
Sex	Men	274	46.6	127	83.0	194	52.4	565	53.6
	Women	314	53.4	26	17.0	149	47.6	489	46.4

Note. Excluding patients with AUD (73 in total) from the addiction group, the average age of the remaining 80 patients is 36.81 ± 11.3 years.

patients with ADHD with 2.00 ± 1.26 within the psychiatric group, and 1.79 ± 1.48 for patients with heroin addiction within the drug dependence group (F = 19.64; p < 0.001) if we excluded patients with AUD, who scored 2.99 ± 1.11 (Figs. I and II).

Within each of the four questions of the CAGE questionnaire, the question answered most frequently in the affirmative was question 1 and the least was question 4; this happened in the three groups and therefore also in the total sample (Table 4).

Positive results in the CAGE questionnaire

Taking a score ≥ 1 as a cut-off point in the CAGE questionnaire, 38.3% of the total sample screened positive, 34.2% of the patients in psychiatric units, 72.5% of those with addictions and 29.4% of the control group (χ^2 = 90.64; p < 0.001). Taking ≥ 2 positive questions as the cut-off, these percentages fell to 26.6% in the total sample, to 22.6% in psychiatric units, to 64.7% in addictions and 15.3% in the control group (χ^2 = 139.02; p < 0.001) (Table 5). Excluding patients with AUD from those attending drug addiction units, 51.3% of the remaining subjects with addictions had a score ≥ 1 in the CAGE questionnaire (χ^2 = 13.568; p = 0.001) and 41.3% had a score ≥ 2 (χ^2 = 25.64; p < 0.001) (Table 5).

Table 2. *Diagnoses included in the study and percentage of the total participants.*

Diagnosis	N	% of psychiatric patients	% of total sample
Depressive disorders	239	40.6	22.7
Psychotic disorders	133	22.6	12.6
Anxiety disorders	94	16	8.9
Personality disorders	51	8.7	4.8
Bipolar disorders	41	7.0	3.9
BIC	8	1.4	0.8
Dementia	6	1	0.6
ADHD	6	1	0.6
TOTAL PSYCHIATRIC	588	100	55.8
		% of addiction patients	
Alcohol	73	47.7	6.9
Cannabis	24	15.7	2.3
Cocaine (CC)	18	11.8	1.7
Heroin (H)	14	9.2	1.3
H + CC	14	9.2	1.3
Other addictive behaviors	9	5.9	0.9
TOTAL ADDICTIONS	153	100	14.5
HEALTHY	313	-	29.7
TOTAL SAMPLE	1054	-	100

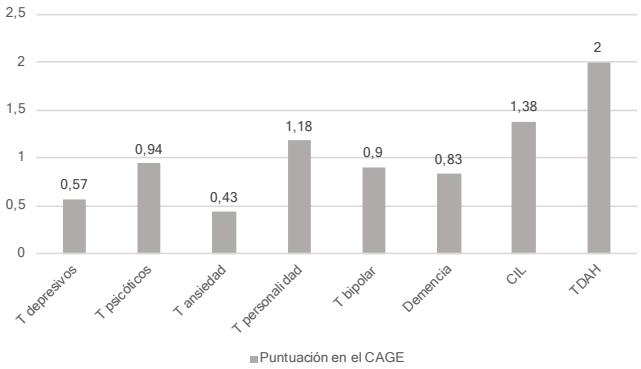

Figure I. CAGE questionnaire scores by diagnostic group in psychiatry units.

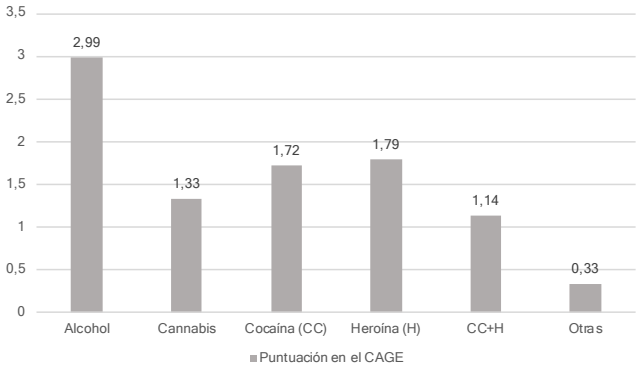

Figure II. CAGE questionnaire scores by diagnostic group in drug addiction units.

Table 3. *Percentage of participants with each of the CAGE scores.*

	PSYCHIATRY		ADDICTION		HEALTHY		TOTAL	
CAGE score	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	588	55.8	153	14.5	313	29.7	1054	100
0	387	65.8	42	27.5	221	70.6	650	61.7
1	69	11.7	12	7.8	44	14.1	125	11.9
2	51	8.7	21	13.7	18	5.8	90	8.5
3	57	9.7	41	26.8	28	8.9	126	12
4	24	4.1	37	24.2	2	0.6	63	6

Note. χ^2= 182.17; p<0.001.

By sex, 48.8% of men had a score ≥ 1 in the CAGE questionnaire, compared with 25.4% of women (χ^2 = 66.31; p < 0.001). The percentage of men with a score ≥ 2 was 37.4% and women 13.8% (χ^2 = 74.33; p < 0.001). Table 5 describes the differences according to sex and the diagnosis on the CAGE scale for each study group. The diagnoses with a higher percentage of patients with positive screening for AUD were: ADHD, at both cut-off points, in psychiatric units; and heroin addiction at the ≥ 1 cut-off point and cocaine addiction at ≥ 2 in drug addiction units after excluding alcohol addiction from the latter (Table 5). The differences between the different diagnoses were significant, at both the ≥ 1 cut-off point (χ^2 = 138.41; p < 0.001) and ≥ 2 (χ^2 = 177.55; p < 0.001).

By age group, the following results were obtained: from 18 to 30 years of age 50% had a score of ≥ 1, from 31 to 45

Table 4. *Affirmative responses to the different CAGE questionnaire items by groups.*

CAGE question	Psychiatry (n=588)	Addictions (n=153)	Healthy (n=313)	Total (n=1054)	Test	P
CAGE 1: Have you ever felt you needed to cut down on your drinking (n, % "yes")	136 (23.1%)	103 (67.3%)	66 (21.1%)	305 (28.9%)	χ^2 =128.64	‹0.001
CAGE 2: Have people annoyed you by criticizing your drinking? (n, % "yes")	126 (21.4%)	79 (51.6%)	54 (17.3%)	259 (24.6%)	χ^2 =72.64	‹0.001
CAGE 3: Have you ever felt guilty about drinking? (n, % "yes")	123 (20.9%)	92 (60.1%)	46 (14.7%)	261 (24.8%)	χ^2 =124.41	‹0.001
CAGE 4: Have you ever felt you needed a drink first thing in the morning (eye-opener) to steady your nerves or to get rid of a hangover? (n, % "yes")	57 (9.7%)	51 (33.3%)	6 (1.9%)	114 (10.8%)	χ^2 =106.89	‹0.001

Table 5. *Percentage of participants with positive CAGE questionnaire screening for alcohol use disorder (cut-off points ≥ 1 and ≥ 2) by diagnosis and sex.*

Diagnosis		N	CAGE ≥ 1		P	CAGE ≥ 2		P
			N	%		N	%	
	T	239	69	28.9		39	16.3	
Depressive disorders	M	88	34	38.6	0.002	21	23.9	0.049
	W	149	33	22.1		18	12.1	
	T	133	53	39.8		41	30.8	
Psychotic disorders	M	80	45	56.3	‹ 0.001	36	45	‹ 0.001
	W	53	8	15.1		5	9.4	
	T	94	21	22.3		11	11.7	
Anxiety disorders	M	44	14	31.8	0.038	9	20.5	0.013
	W	50	7	14		2	4	
	T	51	24	47.1		19	37.3	
Personality disorders	M	17	10	58.8	NS	9	52.9	0.027
	W	32	12	37.5		8	25	
	T	41	18	43.9		12	29.3	
Bipolar disorders	M	23	12	52.2	NS	9	39.1	NS
	W	18	6	33.3		3	16.7	
	T	8	3	37.5		3	37.5	
BIC	M	6	2	33.3	NC	2	33.3	NC
	W	2	1	50		1	50	
	T	6	2	33.3		1	16.7	
Dementia	M	3	1	33.3	NC	0	0	NC
	W	3	1	33.3		1	33.3	
	T	6	5	83.3		4	66.7	
ADHD	M	4	3	75	NC	3	75	NC
	W	2	2	100		1	50	

Diagnosis		N	CAGE ≥ 1		P	CAGE ≥ 2		P
			N	%		N	%	
	T	588	201	34.2		133	22.6	
TOTAL PSYCHIATRY	M	270	124	45.9	‹ 0.001	91	33.7	‹ 0.001
	W	309	70	22.7		39	12.6	
	T	73	70	95.9		66	90.4	
Alcohol	M	61	59	96.7	NS	55	90.2	NS
	W	12	11	91.7		11	91.7	
	T	24	12	50		9	37.5	
Cannabis	M	19	9	47.4	NS	7	36.8	NS
	W	5	3	60		2	40	
	T	18	12	66.7		11	61.1	
Cocaine (CC)	M	16	10	62.5	NC	9	56.3	NC
	W	2	2	100		2	100	
	T	14	10	71.4		7	50	
Heroin (H)	M	14	10	71.4	-	7	50	-
	W	-	-	-		-	-	
	T	14	6	42.9		5	35.7	
H + CC	M	13	5	38.5	NC	4	30.8	NC
	W	1	1	100		1	100	
	T	9	1	11.1		1	11.1	
Other addictive behaviors	M	3	1	33.3	NC	1	33.3	NC
	W	6	0	0		0	0	
	T	153	111	72.5		99	64.7	
TOTAL DRUGS	M	127	94	74	NS	83	65.4	NS
	W	26	17	65.4		16	61.5	
	T	80	41	51.3		33	41.3	
TOTAL DRUGS EXCL. AUD	M	66	35	53	NS	28	42.4	NS
	W	14	6	42.9		5	35.7	
Diagnosis		**N**	**CAGE ≥ 1**		**P**	**CAGE ≥ 2**		**P**
			N	**%**		**N**	**%**	
	T	313	92	29.4		48	15.3	
HEALTHY	M	164	56	34.1	NS	36	22	0.001
	W	149	36	24.2		12	8.1	
	T	1054	404	38.3		280	26.6	
TOTAL SAMPLE	M	561	274	48.8	‹ 0.001	210	37.4	‹ 0.001
	W	484	123	25.4		67	13.8	

Nota. T: Total; M: Men; W: Women; AUD: Alcohol Use Disorder; NS: not significant; NC: not calculable.
P=significance of sex within each diagnosis, using the Pearson chi-square test (χ^2)

years 35.6%, from 46 to 60 years 40.8%, and in those over 60 years 27.5% (χ^2 = 17.68; p = 0.001). The percentage of those with a score ≥ 2 was 28.8% in participants aged 18 to 30, 24.8% aged 31 to 45, 32.2% aged 46 to 60, and 16.3% in people over 60 (χ^2 = 15.41; p = 0.001).

Within the healthy sample and separating them by age group, significant differences were obtained for the percentage of healthy subjects with positive screening for AUD at a score of ≥ 1 (χ^2 = 12.65; p = 0.005), but not at ≥ 2 (χ^2 = 5.17; p = 0.160), and differentiating by sex only at a score of ≥ 2 (Table 6).

Differences between autonomous communities

Of the 1,054 patients in the sample, 651 (61.8%) were from the Autonomous Community of Extremadura (provinces of Badajoz and Cáceres) and 403 (38.2%) from the Autonomous Community of Catalonia (province of Barcelona). Of the 588 from outpatient psychiatric units, 262

(44.6%) were from Extremadura and 326 (55.4%) from Catalonia. All 153 of those in drug addiction units were from Extremadura. Of the total healthy subjects (313), 236 (75.4%) were Extremaduran and 77 (24.6%) Catalan (Table 7).

The average age of Extremaduran and Catalan psychiatric patients was very similar: 49.85 ± 14.78 and 49.98 ± 13.5, respectively (F = 0.011; p = 0.915), as was the average age of healthy Extremaduran and Catalan subjects: 39.95 ± 11.14 and 39.82 ± 10.13, respectively (F = 0.008; p = 0.927).

Among those attending outpatient psychiatric units, the CAGE score in the sample from the Autonomous Community of Catalonia was 0.80 ± 1.21, and in the Autonomous Community of Extremadura sample it was 0.68 ± 1.18 (F = 1.41; p = 0.235). Meanwhile, the 77 healthy participants from Catalonia had an average CAGE score of 0.29 ± 0.60 and the 236 from Extremadura 0.64 ± 1.07 (F = 7.4; p = 0.007). Table 7 shows the percentage of psychiatric patients and healthy subjects who had ≥ 1 and ≥ 2 positive responses in the CAGE questionnaire separated by sex and autonomous community.

Discussion

Our study is the first that we have found in the literature which assesses the prevalence of AUD using the camoufla-

Table 6. *Percentage of healthy subjects screening positive on the CAGE questionnaire for alcohol use disorder (cut-off points ≥ 1 and ≥ 2) by age group and sex.*

HEALTHY		N	CAGE ≥ 1		P	CAGE ≥ 2		P
			N	%		N	%	
	T	46	23	50		12	26.1	
18-30 years	M	25	15	60	0.139	9	36.0	0.095
	W	21	8	38.1		3	14.3	
	T	190	52	27.4		27	14.2	
31-45 years	M	97	31	32	0.147	20	20.6	0.010
	W	93	21	22.6		7	7.5	
	T	56	12	21.4		7	12.5	
46-60 years	M	32	9	28.1	0.158	7	21.9	0.014
	W	24	3	12.5		0	0	
	T	21	4	19		2	9.5	
Over 60 years	M	10	0	0	0.034	0	0	0.156
	W	11	4	36.4		2	18.2	
	T	313	91	29.4		48	15.3	
Total	M	164	55	33.5	0.060	36	22	0.039
	W	149	36	24.2		12	8.1	

Nota. T: Total; M: Men; W: Women. P = significance of sex within each diagnosis, using the Pearson chi-square test (χ^2).

Table 7. *Number of participants and percentage of positive screenings at ≥ 1 and ≥ 2 with the CAGE Questionnaire and the differences between participants from Extremadura and Catalonia, in psychiatric and healthy patients, and separated by sex.*

Variable		PSYCHIATRIC		P	HEALTHY		P
		Extremadura	Cataluña		Extremadura	Cataluña	
	T	80 (30.5%)	121 (37.1%)	0.094	75 (31.8%)	16 (20.8%)	0.065
CAGE ≥ 1	M	51 (42.9%)	73 (48.3%)	0.369	49 (35.5%)	6 (23.1%)	0.218
	W	22 (16.4%)	48 (27.4%)	0.022	26 (26.5%)	10 (19.6%)	0.349
	T	52 (19.8%)	81 (24.8%)	0.150	42 (17.8%)	6 (7.8%)	0.034
CAGE ≥ 2	M	41 (34.5%)	50 (33.1%)	0.817	32 (23.2%)	4 (15.4%)	NC
	W	8 (6%)	31 (17.7%)	0.002	10 (10.2%)	2 (3.9%)	NC
	T	262	326		236	77	
TOTAL	M	124 (47.3%)	151 (46.3%)		138 (58.5%)	26 (33.8%)	
	W	138 (52.7%)	175 (53.7%)		98 (41.5%)	51 (66.2%)	

Nota. T: Total; M: Men; W: Women; NC= Not calculable. P = significance of autonomous community, using the Pearson chi-square test (χ^2).

ged CAGE questionnaire, not only in psychiatric patients, already described in the first article (Sánchez-Autet et al., 2018), but also compared with substance dependent patients and healthy subjects. When comparing these groups with the camouflaged CAGE questionnaire, we found that in our sample there is a higher percentage of positive screenings in substance dependent patients than in psychiatric patients, which is also higher in the latter than in healthy individuals (Table 5). Furthermore, the score on this questionnaire is higher in drug addiction than in psychiatric units, and higher in these than in healthy subjects. Even excluding patients diagnosed with AUD from the drug addiction unit totals, patients in addiction units maintained a higher percentage of positive screenings and a higher score, both statistically significant, than psychiatric patients and healthy controls.

In the sample of outpatient psychiatric patients, as described in the first part of our study (Sánchez-Autet et al., 2018), positive screening with CAGE in men and in those aged under 60 was more frequent. By diagnosis, we found that serious mental disorders were those which had higher rates of positive CAGE scores: personality disorders, bipolar disorders and psychotic disorders, with figures close to 50%, corresponding to findings in the literature (Mellos, Liappas & Paparrigopoulos, 2010; Mueser, Drake & Wallach, 1998; Mueser et al., 2000).

In the specific case of bipolar disorders, we found 43.9% of patients with a CAGE score ≥ 1, 52.2% in men and 33.3% in women. Epidemiological studies with large samples have found a similar proportion to this in subjects with type I bipolar disorder: in the RCT (Epidemiological Catchment Area Study, ECA; Regier et al., 1990), 46% had a history of alcohol abuse/addiction, and 45% in the Edmonton Study (Fogarty, Russell, Newman & Bland, 1994). In the ECA (Regier et al., 1990), the prevalence of alcohol use varied according to the different psychiatric diagnoses: the 46% referred to above for type I bipolar disorder, 39.2% for type II bipolar disorder and 33.7% for schizophrenia. Frye et al. (2003) found that alcohol abuse was more frequent in men with bipolar disorder than in women, with figures very similar to ours, 49% vs. 29%, respectively, who met criteria of lifetime alcoholism, although the relative risk of alcohol abuse compared to the general population was higher in bipolar women than in men, with an odds ratio of 7.35 vs 2.77, respectively. A study conducted in Badajoz, also within the Autonomous Community of Extremadura, on patients hospitalized with a bipolar disorder diagnosis (Zamora-Rodríguez et al., 2018), showed 28.8% of patients with alcohol abuse or addiction criteria.

On the other hand, anxiety and depressive disorders did not appear to be a risk factor for presenting AUD in our sample since they had very similar rates of screening positive with CAGE, even lower than those presented by the healthy sample, which contradicts previous articles (Anthenelli, 2012; Grant et al., 2004), although conflicting results have been obtained in the case of anxiety disorders (Goldstein, Smith, Dawson & Grant, 2015; Hasin & Kilcoyne, 2012; Sánchez-Autet et al., 2018). The diagnosis presenting the highest percentage of positive screenings with both cut-off points, ≥ 1 and ≥ 2, was ADHD, albeit with just six patients with this pathology; this ADHD-alcohol use ratio has already been described in the literature (Biederman et al., 1995; Weiss & Hechtman, 1993; Wilens, Biederman, Mick, Faraone & Spencer, 1997).

Regarding the sample of patients being treated in drug addiction centers, the fact that those who were being treated for alcohol addiction answered at least one question affirmatively in 95.9% of the cases indicates the high sensitivity of CAGE. This sensitivity dropped to 90.4% when the cut-off point was raised to two affirmative questions. We have already noted that the sensitivity of the CAGE questionnaire varied in different studies from approximately 70% to 90%, being higher for the cut-off point of one affirmative answer and decreasing when increased to two, although with increased specificity in this case (Berks & McCormick, 2008; Corradi-Webster et al., 2005; Dervaux et al., 2006; Dhalla et al., 2007; Mitchell et al., 2014).

In the rest of addictive substances (cannabis, cocaine, heroin, cocaine + heroin), we found a much higher percentage of positive results in the CAGE questionnaire than in healthy participants or in psychiatric patients. In these groups of substances, the percentage of positive screenings is very similar in men and women, in some cases being even higher for the latter. This association between the use of different substances and alcohol use has been described previously (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2017; Font-Mayolas, Gras & Planes, 2006; Font-Mayolas et al., 2013; Kandel & Yamaguchi, 1985), showing that the use of one of these substances is linked to the use of alcohol. Kandel et al. (1985) affirmed that the use of legal drugs could facilitate the subsequent use of marijuana, which in turn would open the door to the use of other illicit drugs in accordance with the escalation model. According to data from the EDADES (2017) survey, alcohol is present in more than 90% of polydrug use, with percentages close to 100% when the number of substances consumed was four or more (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2017).

It is noteworthy that in the control sample of healthy subjects (Table 6) we find almost one third (29.4%) with a CAGE score of ≥ 1 and almost one sixth (15.3%) with a score of ≥ 2, prevalences higher than those obtained in other national and international studies. In the aforementioned 2017 EDADES survey (Government Delegation for the National Drug Plan, 2017), the AUDIT test showed that 5.1% of Spaniards aged 15 to 64 were classified within the high-risk category of alcohol use (7.6% of men and 2.6% of women), figures much lower than ours. Other research

using the CAGE questionnaire with 2 affirmative answers as a cut-off point, carried out in Portugal on patients undergoing surgery (Sousa, Pinho, Santos & Abelha, 2017), in France on people attending hospital emergency departments (Richoux et al., 2011) or in Brazil on public transport workers (Cunha, Giatti & Assunção, 2016), also found a lower prevalence than ours.

The percentage of positive CAGE screenings in healthy individuals was higher the younger the sample, and in men compared to women (33.5% vs 24.2% with score ≥ 1 and 22% vs 8.1% with score ≥ 2); however, it can be noted that in women over 60 years of age it was higher than in men of the same age group, although it is also true that in this age group the percentage of participants was lower (Table 6). Another Brazilian article on 192 workers on the campus of the University of São Paulo (Amaral and Malbergiera, 2004) with a ≥ 2 cut-off point, a greater percentage was also observed in men than in women (22.1% vs 0 %, with only 20 women analyzed); these results are similar to ours, although they did not yield the same distribution by age groups (being much higher in people aged over 60), an issue that could be explained by the low number of participants in some groups, as well as socio-cultural differences, among others.

A study carried out in Singapore with 2,565 healthy people aged over 60 (Ong et al., 2016) found 4.2% with a CAGE score ≥ 2, compared to 9.5% in our healthy Spanish sample in the same age range. In their study, this frequency was higher in men, of Indian ethnicity and who were separated or divorced. Other articles even point to a lower percentage in people over 60, such as Almeida et al. (1997), in which only 1.42% of a total of 351 had a score ≥ 2. A recent study (Lycke et al., 2019) carried out in cancer patients with a mean age of 77.7 years found 6.3% of men and 1.2% of women with positive results (≥ 2) with CAGE.

Research carried out in three European countries (Bulgaria, Germany and Poland) with 2,103 university students (Mikolajczyk et al., 2016) also found a percentage of people with positive CAGE screening (score ≥ 2) which much lower than ours: 22.7%, 26.3% and 19% respectively in Bulgaria, Germany and Poland for men, and 9.6%, 9.3% and 8.5% for women, which contrasts with 36% for men and 14.3% for women in our sample of healthy 18-30-year-olds, which is the most similar by age group to that of university students. Similar studies on samples of young Italian adults aged 18 to 35 (Manzoli et al., 2009) or on Canadian medical students (Thakore et al., 2009) or other recent studies on samples of medical students in different countries of the world: Wales (Farrell et al., 2019), Portugal (Almeida, Kadhum, Farrell, Ventriglio & Molodynski, 2019), Morocco (Lemtiri Chelieh et al., 2019), Canada (Wilkes et al., 2019), Brasil (Castaldelli-Maia et al., 2019), Paraguay (Torales et al., 2019) and Jordan (Masri et al., 2019) also showed a lower prevalence of positive screening with CAGE (score ≥ 2), ranging from 5% of Moroccans to 25% of Brazilians, than healthy participants aged 18 to 30 in our study, reaching 26.1%, including both men and women.

Although our study focused on patients aged 18 or older, drinking among patients under 18 years of age is also noteworthy. A recent study (Teixidó-Compañó et al, 2019) using data from the Survey on drug use in Secondary Education in Spain (ESTUDES, 2014) with 14-18-year-old students (N = 34,259) obtained a total prevalence of binge drinking in the previous month of 33%, a prevalence which increased with age, and was mainly associated with the perception of easy access to alcohol, its consumption in open areas, having one of two parents who allows drinking and having more than €30 to spend per week.

These data should make us think about the high levels of alcohol use among the apparently healthy Spanish population, which is higher than shown by other studies, both in European countries and the rest of the world, and the possible repercussions on their health, with greater disability and mortality, leading to higher health and social costs (Pulido et al., 2014; Rehm et al., 2013).

Regarding the influence of rurality in our results, it should be noted that among the Catalan and Extremaduran samples of outpatient psychiatric units, comparable in mean age and sex, we found a certain tendency for greater positive screening with CAGE in the Catalan sample (a more urban sample), the difference being statistically significant in women. We also found significant differences between both autonomous communities in the samples of healthy individuals with the ≥ 2 cut-off, but in this case in favor of the (more rural) Extremadura sample. As previously noted, different studies carried out in different Spanish autonomous communities in the general population obtained a prevalence of positive screenings with the CAGE questionnaire at the ≥ 2 cut-off of between 4.0% and 8.7% (Alvarez et al., 1994; Alvarez et al., 2006; Anitua et al., 1998; Dirección General de Atención Primaria, 2001; Dirección General de Atención Primaria, 2006; Dirección General de Atención Primaria, 2011; Pérez et al., 2010; Servicio de Estudios e Investigación Sanitaria, 2004), figures below the Extremadura sample of healthy subjects (17.8%) and similar to the Catalan (7.8%).

The most important limitations of our study, already mentioned in the first published part (Sánchez-Autet et al., 2018), are mainly the absence of a structured diagnostic interview to confirm the positive screening obtained with CAGE and the non-collection of other sociodemographic, medical or substance use data. One of its main strengths is the large number of participants (1,054) and the inclusion of three different samples: healthy individuals, patients of outpatient psychiatric centers and patients of outpatient drug addiction units, which allows us to establish comparisons between individuals of the same health areas. The results obtained seem to be in line with expectations based

on previous experience and literature, which supports the theoretical validity of the questionnaire used.

In conclusion, the data found in our analysis speak of greater positive screening for alcohol use in patients attending drug addiction units compared to psychiatric patients, and in the latter compared to a sample of healthy subjects. Also noteworthy is the high rates of AUD in both psychiatric patients, especially those with severe mental disorders, as well as in healthy subjects; however, this is a frequently underdiagnosed pathology, and therefore not treated, with the consequences this implies in terms of worsening quality of life, higher rates of associated disease and greater mortality. It may therefore be worth considering the need to include specific screening elements for alcohol use, such as the simple and easy to use CAGE, both in psychiatric services and primary care, and even with hospital patients.

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Conflict of interests

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Appendix

Camouflaged CAGE questionnaire, adapted for Spanish patients.

1. Do you think you eat too many sweet things?
2. Have you ever been offered a joint or a dose of cocaine?
3. Have people annoyed you by criticizing your drinking?
4. Have you ever thought about exercising weekly?
5. Do you think you sleep enough hours to feel fit during the day?
6. Have you ever thought that you should cut down on your drinking?
7. Have you ever seriously considered that you should quit smoking?
8. Have people ever told you that you should eat more fruit and vegetables?
9. Have you ever felt guilty about drinking?
10. Have you ever been told that you should smoke less?
11. Have you ever felt you needed a drink first thing in the morning (eye-opener) to steady your nerves or to get rid of a hangover?
12. Have you ever considered swapping the habit of taking sleeping pills for relaxation techniques?

Nomophobia Questionnaire (NMP-Q): Factorial structure and cut-off points for the Spanish version

Cuestionario de Nomofobia (NMP-Q): Estructura factorial y puntos de corte de la versión española

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Abstract

Nomophobia is a situational phobia leading to a deep, irrational, and disproportionate fear of not being able to use the smartphone. An instrumental study on the Spanish version of the *Nomophobia Questionnaire* (NMP-Q) was carried out. The objectives were: 1) To analyse its factor structure and reliability; 2) to test for the invariance of sex and age groups, and 3) to obtain specific cut-off points by sex and age non-existent to date. Sampling was incidental and non-probabilistic with 5012 participants (57.9%, females) aged 12-24 years (M = 18.04, SD = 3.3). The confirmatory factor analysis revealed a hierarchical model with four correlated factors explained by a general second-order factor. The internal validity and reliability values of the NMP-Q dimensions are satisfactory, ranging between .78, .85, .86, and .92 (Omega ω). A multigroup analysis confirmed the invariance across sex and age groups. Building on the NMP-Q scores, we calculated 3 cut-off points using percentiles 15th, 80th and 95th (unnomophobic, at risk of nomophobia, and nomophobic). Females aged 12-15 years had the highest nomophobic scores. We can conclude that the proposed sex and age cut-off points will allow us to better identify nomophobic problems from a clinical point of view.

Keywords: Nomophobia; Cut-off points; Smartphone; Internet; Behavioural addiction.

Resumen

La nomofobia es una fobia situacional en la que se experimenta un miedo intenso, irracional y desproporcionado a no poder usar el smartphone. Se realizó un estudio instrumental de la versión española del cuestionario de Nomofobia (NMP-Q) con los objetivos de: 1) analizar su estructura factorial y fiabilidad; 2) analizar su invarianza con relación al sexo y la edad, y 3) obtener puntos de cortes específicos para distintas edades y sexo. El muestreo fue incidental y no probabilístico. Hubo 5012 participantes (57.9%, mujeres) de 12-24 años (M = 18,04, SD = 3,3). El análisis factorial confirmatorio mostró un modelo jerárquico de 4 factores correlacionados y explicados por uno general de segundo orden. Los índices de fiabilidad de las dimensiones del NMP-Q fueron satisfactorios oscilando entre ,78, ,85, ,86 y ,92 (Omega ω). Un análisis multigrupo confirmó la invarianza por sexo y edad. A partir de las puntuaciones del NMP-Q se calcularon 3 puntos de corte siguiendo los percentiles 15, 80 y 95 (sin nomofobia, riesgo de nomofobia, y nomofóbico). Las mujeres de 12-15 años tuvieron las puntuaciones más altas en nomofobia. Podemos concluir que el NMP-Q nos permite identificar problemas de nomofobia por sexo y edad desde un punto de vista clínico.

Palabras clave: Nomofobia; Puntos de corte; Smartphone; Internet; Adicción conductual.

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Introduction

The digitalization of society has profoundly transformed the way we socially interact, allowing us to communicate, obtain information, develop ideas, generate synergies, and maximize opportunities in forms we never before dreamed of. However, despite numerous advantages, these changes also entails challenges and risks, especially for young people, giving rise to new psychosocial pathologies (Kirwan, 2016). In this sense, it is unclear whether we are facing a new behavioral addiction or a problem of a psychosocial and environmental nature (Pedrero Pérez et al., 2018).

In particular, Spain, along with Asian countries, tops the list of worldwide countries that have greater access to Internet via their smartphones, more specifically 92% of the respondents (Google/TNS, 2017; Statista, 2017). In addition, 99% of young Spaniards access the Internet every day through their mobile phones (Ditrendia, 2017). On the other hand, people have their own mobile at increasingly early ages, with a current mean age between 10-12 years (Garmendia-Larrañaga, Jiménez-Iglesias, Casado & Mascheroni, 2016; González-Cabrera, Balea, Vallina, Moya & Laviana, 2017).

In the light of these data, it is not surprising that nomophobia (acronym for no-mobile-phobia) is receiving increasing attention in Spain and globally. This is because it relates to a contemporary phenomenon that is characteristic of our societies, i.e., the need to connect online (Walsh, White & Young, 2010) or *digital connectedness*, which can be defined as the urge to be in constant contact with social networks through Internet and personal devices and laptops that allow us to be constantly connected with others. In addition, given the digital changes we are going through, the concept of the *extended self* proposed by James (1890) is also undergoing a profound transformation. In this sense, avatars, profiles, contacts, comments and messages circulating in the social networks, emails, etc., have become part of our inner "self" (Belk, 2016), changing the processes of self-presentation and self-monitoring implied by Internet. This online reality affects the establishment of one's self-concept and core identity (Carter & Grover, 2015; Davis, 2013; Walsh et al., 2010) in ways we are still trying to understand.

Therefore, Internet and smartphones have not only changed our socio-communicative needs, but also our habits and social behavior. The dysregulation of certain behavioral patterns can produce distress and anxiety in some individuals, generating harmful and dysfunctional outputs (Dongre, Inamdar & Gattani, 2017; King et al., 2013; Taneja, 2014). Among these behavioral problems, the conceptualization of nomophobia as an anxiety disorder has recently attracted attention. In the field of psychology and psychiatry, it is defined as a disorder resulting from people's interaction with the information and communication technologies, which produces anxiety and distress (King et al., 2013). More specifically, it is considered a situational and social phobia that makes individuals experience a deep, irrational, and disproportionate fear of not being able to use the mobile phone or of running out of coverage and/or battery and, therefore, having to temporarily relinquish their social identity, that is, the personality that communicates and expresses itself on the social network accessed through the mobile phone (Bragazzi & Del Puente, 2014; González-Cabrera, León-Mejía, Calvete & Pérez-Sancho, 2017; Han, Kim & Kim, 2017; King et al., 2013; Yildirim & Correia, 2015). It is also related to other mental problems, such as generalized anxiety disorder, panic, agoraphobia, depression, social phobia, obsessive compulsive disorder, post-traumatic stress, and anorexia (King, Guedes, Pedro Neto, Guimaraes & Nardi, 2017). Regardless of the lack of agreement on how we label or conceptualize the problematic use of smartphones (phobia vs. addictions), we need to better understand this phenomenon as well as to improve the way we psychosocially intervene to prevent and treat it (Ruiz-Ruano, López-Salmerón & López-Puga, 2020).

Assessment tools and at-risk groups

The existence of a technological generation gap allows us to differentiate between people who have experienced the digital communicative social change (and some of its possible pernicious effects) in their adult life –with their basic personality already formed–, and people who are already growing up and socializing as digital natives and early adopters of technology. This is of great interest for the study of nomophobia, as everything seems to indicate that adolescents and young people (especially young females) are at higher risk (González-Cabrera et al., 2017; Securenvoy, 2012). However, in order to reach valid conclusions about at-risk groups, it is essential to have data on scores that reliably indicate a nomophobic problem, and to determine whether these scores are really sensitive to individuals' sex and age.

Since nomophobia is a relatively new concept, we had no specific tools to evaluate it until the NMP-Q was proposed by Yildirim and Correia (2015). Afterwards, different linguistic adaptations have been made to Spanish, Italian, Persian or Chinese (Adawi et al., 2018; Bragazzi et al., 2016; González-Cabrera et al., 2017; Lin, Griffiths & Pakpour, 2018; Ma & Liu, 2018), and most surely others adaptations are ongoing. However, to date few studies have identified cut-off points to establish problematic levels of nomophobia (González-Cabrera et al., 2017), and due to the relative novelty of the construct, normative data on nomophobia is still needed. Consequently, our objectives are: 1) to obtain indicators of validity and reliability of the Spanish version of the Nomophobia Questionnaire (NMP-Q), including the confirmatory study of its factor structure; 2) to test whether the questionnaire works equally in both men and

women, as well as in adolescences and young adults of different ages, and 3) to obtain specific cut-off points by sex and age.

We formulated the following hypotheses: (a) Nomophobia will be higher in females than in males; (b) Regarding age, the scores will be higher in the younger groups, with the range of greatest concern between 14 and 18 years; (c) Confirmatory factor analysis (CFA) will confirm the four-dimension model that other authors have reported (Lin et al., 2018) and the original model of Yildirim and Correia (2015).

Material and methods

Participants

We conducted an instrument validation study (Montero & León, 2007) between November and December 2017 in Spain, the purpose of which was to confirm the factor structure of a tool already adapted to Spanish and to study in depth its psychometric properties. The initial sample comprised 5380 participants from the entire national territory, but the final sample was made up of 5012 people, after eliminating incomplete questionnaires (one or more unanswered items or containing response errors) as well as questionnaires that were completed in less than 4 minutes. Sampling procedure was non-probabilistic and incidental, but the sample included participants from the 17 regions of Spain, including Ceuta and Melilla (see Table 1).

Of these participants, 2902 (57.9%) were female and 2110 (42.1%) were male, with ages ranging between 12 and 24 years (mean= 18.04, SD= 3.3). Regarding the age of participants, there were 252 (5%) participants between 12-13 years of age, 1171 (23.4%) between 14-15 years, 1155 (23%) between 16-17 years, 727 (14.5%) between 18 and 19 years, 703 (14%) between 20-21 years, and 1004 (20%) between 21 and 24 years of age.

Table 1. *Distribution of participants according to their Region/city (n = 5012).*

Region/city	Frequency (%)	Region/city	Frequency (%)	Region/City	Frequency (%)
Andalucía	785 (15.7%)	Castilla la Mancha	186 (3.7%)	Madrid	1425 (28.4%)
Aragón	117 (2.3%)	Castilla y León	360 (7.2%)	Region of Murcia	128 (2.6%)
Principality of Asturias	112 (2.2%)	Cataluña	541 (10.8%)	Statutory Community of Navarre	51 (1%)
Balearic Islands	80 (1.6%)	Extremadura	100 (2%)	Basque Country	224 (4.5%)
Canary Islands	182 (3.6%)	Galicia	201 (4%)	Valencia Community	259 (7.2%)
Cantabria	80 (1.6%)	La Rioja	59 (1.2%)	Ceuta & Melilla	Ceuta 6 (.1%) Melilla 16 (.3%)

Note. Spain is composed of 17 regions and two cities with a special regimen (Ceuta and Melilla).

Assessment instrument

Initially, participants were asked about their sex (male/female), age (participant's age at the time of assessment) and region or city of residence. Subsequently, they completed the Spanish version of the Nomophobia Questionnaire (NMP-Q) adapted by González-Cabrera et al. (2017), who also conducted exploratory factor analyses (α-value of .95).This tool assesses four dimensions: 1) Not being able to access information (4 items): the hassle of losing immediate access to information through the smartphone and the possibility of finding what you want immediately. 2) Giving up convenience (5 items): feelings of comfort and psychological peace provided by having control of the smartphone, especially in relation to the battery, coverage, and credit. 3) Not being able to communicate (6 items): Feelings about loss of an immediate communication and about not being able to use the available services for that purpose. 4) Loss of connection (5 items): Emotions related to the loss of ubiquity after losing connectivity. This is related to the disconnection with one's online identity, especially on social networks. The response format follows a seven-point Likert scale, ranging from 1 *(strongly disagree)* to 7 *(strongly agree)*. There are no inverse items, and the total score ranges between 20 and 140 points, meaning that the higher the score, the higher nomophobia is.

Procedure

The application was made through the online Survey Monkey® Platform, where an online questionnaire was created specifically for this study. It was introduced in a well-known Spanish social media whose sphere of influence covers the entire national territory. The study was conducted with the approval of the Institution to whom the social media web belonged. Following ethical principles of the American Psychological Association (APA) for research (APA, 2017), in the first page of the online form participants were informed about the purpose of the research, including the advance in knowledge about the prevalence of nomophobia in Spain, expected duration, and content of the questionnaire. They were informed about their right to decline to participate and to withdraw from the survey anytime without

any consequence and about the confidentiality of the information, which was warranted due to the anonymous nature of the survey. Finally, they were informed about whom to contact for questions about the research. After reading this information, in case they agreed to participate, they should indicate their acceptance and then went to the survey. This study has been evaluated by the Research Ethics Committee of the International University of La Rioja (PI 009/2019). There were no exclusion criteria other than to own and use a smartphone with Internet.

Statistical Analyses

First, we calculated the descriptive statistics of the NMP-Q scores according to sex and age (recoded into three groups: 12-15, 16-20, and 21-24 years). We used these groups in order to be consistent with the psycho-evolutionary stages inherent in initial adolescence (12-15), mid and late adolescence (16-20) and early youth (21-24) (Salmera-Aro, 2011). Quantitative variables were expressed as mean and standard deviation (SD). The mean difference between the qualitative variables of two categories was analyzed with Student's T-test for independent samples. In the case of more than two categories, results were compared using ANOVA. Pairwise post hoc comparisons were examined using the Bonferroni test.

Cohen's *d* was also calculated to provide the effect size. Regarding internal validity, an analysis of the psychometric properties of each item was conducted, indicating the arithmetic mean, standard deviation, item-total correlation, skewness, and kurtosis (see Table 2). The structure of the NMP-Q was analyzed by means of CFA. We used the robust maximum likelihood (RML) method, which requires an estimate of the asymptotic covariance matrix of the sample variances and covariances and includes the Satorra-Bentler scaled χ^2 index (S-Bχ^2).

The hypothesized model consisted of a correlated four-factor structure: Not being able to access information (4 items); Giving up convenience (5 items); Not being able to communicate (6 items); and Loss of connection (5 items). This model was compared with several alternative models: (1) a one-dimensional model, in which all items were allowed to be explained by a single factor; (2) an uncorrelated four-factor model, where covariances between the four nomophobia factors were fixed to 0; and (3) a hierarchical model with one second-order factor explaining the four nomophobia factors. In all models, items were constrained to load on one factor only. Following the recommendations of Hu and Bentler (1999), goodness of fit was assessed by the comparative fit index (CFI; values of .95 or greater indicate that the model adequately fits the data), the root mean squared error of approximation (RMSEA; values of .06 or less indicate excellent fit and values up to .08 indicate moderate fit), and the standardized root-mean-square residual (SRMR; values of .08 or less indicate that the model adequately fits the data). To compare models, we used the corrected Chi-squared difference test (Crawford & Henry, 2003). To determine the internal consistency of the instrument, we estimated the Cronbach's alpha coefficient (Cronbach, 1951), the Ordinal alpha coefficient (Elosua & Zumbo, 2008), McDonald's Omega (1999), the GLB of Woodhouse and Jackson (1977), and the GLB algebraic algorithm (GLBa) of Moltner and Revelle (2015).

To examine if the NMP-Q can be used with both men and women, as well as with people of different ages, we tested the invariance of the structural model across sex and age groups (under and above 17). In the first step, we estimated the model separately in males, females, participants between 12 and 17 years, and participants between 18 and 24 years. Secondly, configural invariance was tested. This implies that the relations between each indicator and its construct have the same pattern of fixed and free loadings for each group. Thirdly, this model was compared with a more restrictive model (weak factorial invariance), in which first-order factor loadings within constructs were specified as equal for both groups. In the fourth step, we examined whether the intercepts were invariant across groups (strong factorial invariance). With this aim, the intercepts were added to the previous model. Finally, we examined whether second-order factor loadings were equivalent across groups. Given that Chi-Square is very sensitive to large samples and non-normality conditions, it is assumed that the model is invariant if the ΔCFI is not above 0.01 (Cheung Rensvold, 2002).

To classify the cut-off points, we used the 15th, 80th, and 95th percentiles, which correspond to: nonnomophobic, at risk of nomophobia, and nomophobic. This classification is based on other areas of research, such as pathological gambling or the problematic use of mobile phones, yet it has been adapted to the uniqueness of the nomophobic problem presented herein (González-Cabrera et al., 2017; López-Fernández, Freixa-Blanxart & Honrubia-Serrano, 2013). These cut-off points will be analyzed according to the variables sex and age, distributed in 3 age groups: 12-15, 16-20, and 21-24 years.

In order to perform the data analysis, we used the statistical package IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp.), LISREL 9.2 (Jöreskog & Sörbom, 2013), R version 3.5.0 (R Core Team, 2013) and psych package (Revelle, 2019). The graphic representation was performed with yEd-Graph©.

Results

Sex and age differences

There were significant sex differences in the total scores of the NMP-Q (males: $M = 52.37$ and $SD = 19.62$; females: $M = 59.66$ and $SD = 22.54$; $t = -11.931$, $p < .001$, $d = .34$), and these sex differences were observable in all dimensions of

the questionnaire: 1) Not being able to access information (males: M = 12.81 and SD = 4.86; females: M = 13.77 and SD = 5.09; t = -6.720, $p < .001$, d = .20); 2) Giving up convenience (males: M = 11.54 and SD = 5.46; females: M = 12.72 and SD = 6.26; t = -6.943, $p < .001$, d = .20); 3) Not being able to communicate (males: M = 14.68 and SD = 6.95; females: M = 17.75 and SD =7.96; t = -14.238, $p < .001$, d = .41) and 4) Loss of connection (males: M = 13.34 and SD = 5.44; females: M = 15.42 and SD = 6.09; t = -12.452, $p < .001$; d = .36).

In terms of age, the 12-15 age-group presented a mean and standard deviation of 57.76 and 22.50, respectively. The 16-20-year-olds obtained M = 55.14 and SD = 20.47; and the 21-24 age-group obtained M = 53.54 and SD = 20.80. There were significant differences between the three age groups in the total score, $F_{(5, 5006)}$ = 10.521, $p < .001$, η^2 = 0.01). The differences between the 16-20 and the 12-15 age-groups were statistically significant ($p < .001$). Scores were also higher and statistically significant in the groups of 21-24 and 12-15 ($p < .001$). The correlation between age and the total NMP-Q score was negative and statistically significant (r = -.091, p <.001).

Validity Evidence of the NMP-Q scores

Table 2 depicts various psychometric indicators for each of the items of the NMP-Q, specifically the mean, standard deviation, skewness, kurtosis and the item-total correlations. The lowest mean score (1.85) was found in Item 15 (dimension "Not being able to communicate"), which focuses on people's anxiety if constant connection to their family and friends were broken. Conversely, the items with the highest scores were found in the dimension "Not being able to access information," in Item 2, which asks the extent to which people would be annoyed if looking up information on the smartphone was not possible whenever they wanted (3.67), Item 4, which asks how annoyed people would be if it was impossible to use the smartphone when they so wished (3.59), and Item 1, which asks how uncomfortable people would be if they did not have constant access to information through the smartphone (3.43). Skewness and kurtosis values showed that, in general, the curve was asymmetrically negative, and the distribution was leptokurtic. Item 15 was the most anomalous. Discrimination indexes of all items were acceptable and above the critical value of .30, ranging from .48 and .76.

Table 2. *Mean, Standard Deviation, Item-Total Correlation, Kurtosis and Skewness for the 20 items of the NMP-Q (n = 5012).*

Item		M	SD	I-T	Kurt	Skew
1.	I would feel uncomfortable without constant access to information through my smartphone.	3.43	1.5	.68	-.406	.111
2.	I would be annoyed if I could not look information up on my smartphone when I wanted to do so.	3.67	1.48	.63	-.370	-.008
3.	Being unable to get the news (e.g., happenings, weather, etc.) on my smartphone would make me nervous.	2.53	1.45	.58	-.011	.737
4.	I would be annoyed if I could not use my smartphone and/or its capabilities when I wanted to do so.	3.59	1.52	.66	-.421	.088
5.	Running out of battery in my smartphone would scare me.	2.83	1.64	.62	-.501	.573
6.	If I were to run out of credits or hit my monthly data limit, I would panic.	2.17	1.39	.59	.843	1.152
7.	If I did not have a data signal or could not connect to Wi-Fi, then I would constantly check to see if I had a signal or could find a Wi-Fi network.	3.03	1.63	.65	-.517	.476
8.	If I could not use my smartphone, I would be afraid of getting stranded somewhere.	3.20	1.74	.48	-.825	.307
9.	If I could not check my smartphone for a while, I would feel a desire to check it.	2.98	1.61	.69	-.547	.441
10.	I would feel anxious because I could not instantly communicate with my family and/or friends.	2.85	1.59	.74	-.343	.324
11.	I would be worried because my family and/or friends could not reach me.	3.20	1.62	.64	-.618	.324
12.	I would feel nervous because I would not be able to receive text messages and calls.	2.64	1.54	.76	-.039	.754
13.	I would be anxious because I could not keep in touch with my family and/or friends.	2.92	1.54	.75	-.403	.494
14.	I would be nervous because I could not know if someone had tried to get a hold of me.	2.52	1.44	.74	.215	.824
15.	I would feel anxious because my constant connection to my family and friends would be broken.	1.85	1.26	.69	2.918	1.707
16.	I would be nervous because I would be disconnected from my online identity.	2.72	1.53	.73	-.196	.653
17.	I would be uncomfortable because I could not stay up-to-date with social media and online networks.	2.43	125	.66	.139	.894
18.	I would feel awkward because I could not check my notifications for updates from my connections and online networks.	2.18	1.44	.72	.927	1.212
19.	I would feel anxious because I could not check my email messages.	2.19	1.40	.60	.816	1.153
20.	I would feel weird because I would not know what to do.	2.5	1.54	.63	-.103	.818

Note. This table shows the 20 items of the NMP-Q along with their mean (M), standard deviation, (SD) the item-total correlations (IT), Kurtosis (Kurt) and skewness (Skew). The twenty items correspond to 4 dimensions: Not being able to access information (4 items, 1-4); Giving up convenience (5 items, 5-9); Not being able to communicate (6 items, 10-15) and Loss of connection (5 items, 16-20).

Table 3 presents the fit indexes for all the models. As can be seen, the hypothesized model consisting of four correlated factors obtained good fit indexes. We performed a second-order model, which also had adequate indexes.

Models 2 and 3 increased chi square significantly and presented poorer fit indexes. However, Model 4, although it also increased chi square significantly, presented very similar fit indexes. This hierarchical model has the advantage of estimating a total score for the NMP-Q, together with the partial scores of the subscales. The factor loadings of the first-order factors on the second-order factor were .84, .99, .79, and .95, respectively for Not being able to communicate, Loss of connection, Not being able to access information, and Giving up convenience.

Figure 1 presents hierarchical model (four first-order factors explained by one second-order factor), whose loadings

Table 3. *Fit Indexes for the Models (n = 5012).*

Model	S-Bχ^2	RMSEA	CI	CFI	NNFI	SRMR	Comparison with the hypothesized model
Four correlated factors (hypothesized model)	S-Bχ^2(163) = 4356	.072	(90% CI [.070, .073])	.980	.977	.062	
Model 2. Four uncorrelated factors	S-Bχ^2(169) = 14144	.128	(90% CI [.127, .130])	.935	.926	.379	ΔS-Bχ^2(6, n = 5012) = 9788, p < .001
Model 3. One factor	S-Bχ^2(169) = 13452	.125	(90% CI [.123, .127])	.938	.930	.071	ΔS-Bχ^2(6, n = 5012) = 7574, p < .001
Model 4. Hierarchical model (four first-order factors explained by one second-order factor)	S-Bχ^2(165) = 4387	.72	(90% CI [.070, .073])	.980	.977	.063	ΔS-Bχ^2(2, n = 5012) = 29, p < .001

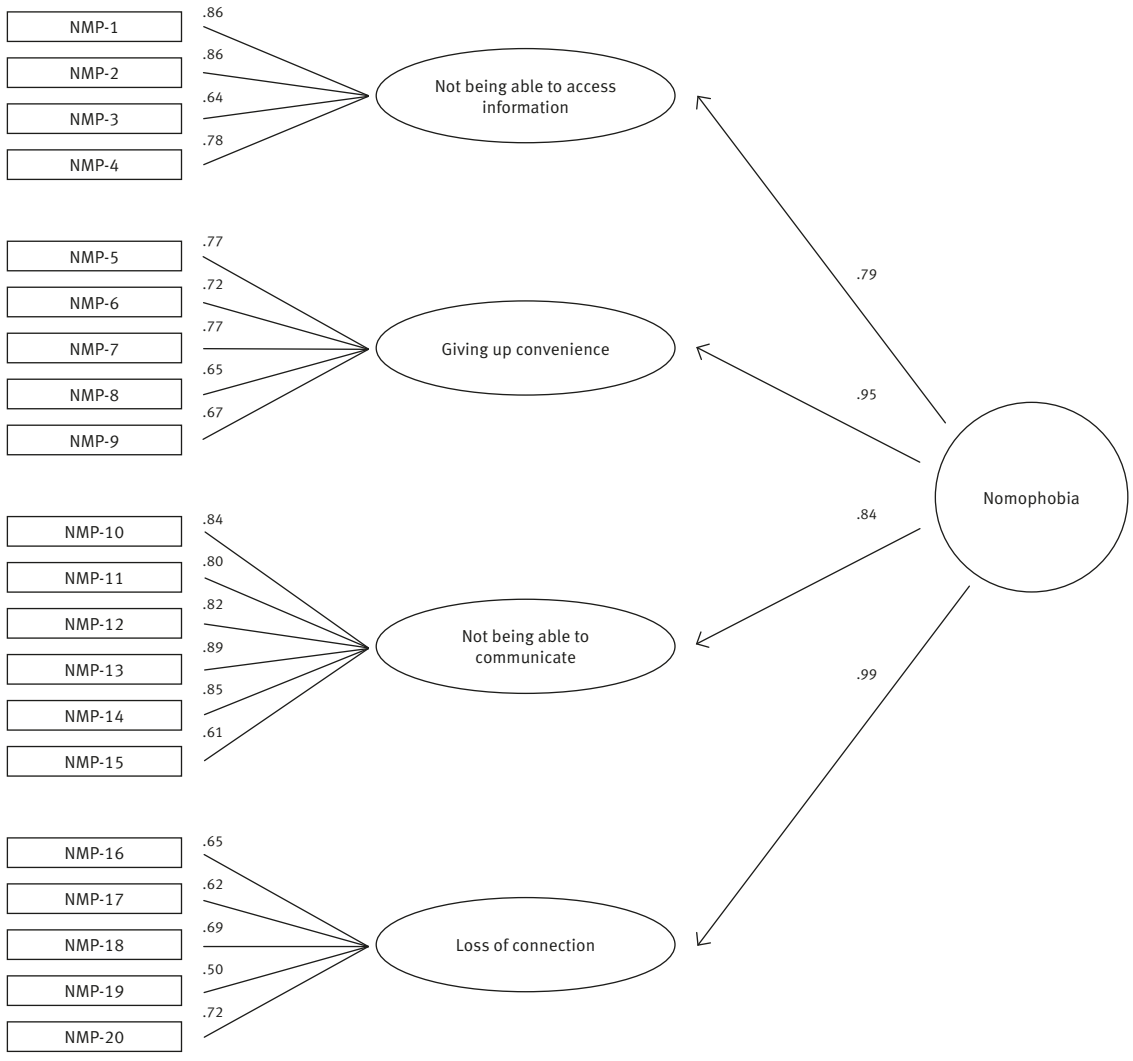

Figure 1. Hierarchical model (four first-order factors explained by one second-order factor) for the NMP-Q.

Table 4. *Cronbach Alpha (α), Ordinal, and Omega (ω) Coefficients for the four Dimensions and confidence interval (CI), the Greatest Lower Bound (GLB) and the GLB.algebraic (GLBa) of the NMP-Q.*

Dimensions	A (CI)	Ordinal (CI)	ω (CI)	GLB	GLBa	Number of items
Not being able to communicate	.91 [.91, .92]	.93 [.93, .94]	.92 [.92, .93]	.94	.94	6
Loss of connection	.85 [.84, .86]	.88 [.87, .88]	.85 [.84, .86]	.86	.86	5
Not being able to access information	.86 [.85, .87)	.88 [.87, .89]	.86 [.86, .0.87]	.87	.87	4
Giving up convenience	.77 [.76, .78)	.81 [.80, .81]	.78 [.76, .79]	.82	.81	5

Table 5. *Invariance analyses across sex and age (with strict comparisons using S-B χ^2).*

	Model	S-Bχ^2	df	RMSEA	RMSEA 90% CI	SRMR	NNFI	CFI	Compared models	ΔCFI
	Sex									
1	Men	2320	165	.067	[.065, .070]	.062	.977	.980		
2	Women	2213	165	.077	[.074, .079]	.066	.977	.980		
3	Configural model	4536	330	.071	[.070, .073]	.062	.977	.980		
4	First-order factor loadings invariance	4603	346	.070	[.068, .072]	.060	.977	.979	3-4	.001
5	Strong invariance	4664	362	.069	[.067, .071]	.060	.978	.979	4-5	.000
6	Second-order factor loadings invariance	4710	366	.069	[.067, .071]	.073	.978	.979	5-6	.000
	Age									
7	≤ 17 years	2418	165	.073	[.070, .075]	.066	.977	.980		
8	≥ 18 years	3444	165	.070	[.068, .073]	.061	.977	.980		
9	Configural model	4562	330	.072	[.070, .072]	.061	.977	.980		
10	First-order factor loadings invariance	4671	346	.071	[.069, .072]	.071	.977	.979	9-10	.001
11	Strong invariance	4733	362	.069	[.068, .071]	.071	.978	.979	10-11	.000
12	Second-order factor loadings invariance	4761	366	.069	[.068, .071]	.080	.978	.979	11-12	.000

Note. S-Bχ^2 = Satorra-Bentler χ^2; df = Degrees of freedom; RMSEA =Root Mean Square Error of Approximation; CI = Confidence Interval; SRMR= Standardized Root Mean Squared Residual; CFI: Comparative Fit Index; NNFI = Non-Normed Fit Index; ΔCFI = differences in Comparative Fit Index.

were higher than .50 in all cases. The Cronbach alpha, Ordinal, and Omega coefficients are shown in Table 4 along with the fit indexes. As shown, all values of each dimension were adequate, ranging from .78 to .92 (Omega ω).

Measuring invariance across sex and age

We estimated the hierarchical model in separate subsamples by sex and age. Fit indexes were adequate for each subsample. Tests of invariance indicated that both factor-loadings and intercepts could be assumed to be invariant because change in CFI was lower than .01 in all cases.

Cut-off points of the Spanish Version of the NMP-Q as a function sex and age

The mean score and standard deviation for the NMP-Q was of 55.44 and 21.21, respectively, within a range of 20-140. The 15th, 80th, and 95th percentiles correspond to nonnomophobic, at risk of nomophobia, and nomophobic, respectively. Following this criterion, the cut-off points are 34, 72 and 94 for the above-mentioned classifying categories. The distribution for males is 32, 68, and 87, and for females, it is 36, 78, and 100. Table 6 presents the different scores for the percentiles as a function of sex for the age groups of 12-15, 16-20, and 21-24 years.

Discussion

This work contributes to the knowledge and identification of nomophobia, a new problem that has not yet been explored in depth at the clinical level, due to its lack of recognition in the *Diagnostic and Statistical Manual of Mental Disorders-5th edition DSM-5* (American Psychiatric Association, 2013) and to the diversity of the theoretical approaches to this recent construct. Regarding the first objective of the manuscript, i.e., to assess the structure and reliability of the Spanish version of the Nomophobia Questionnaire (NMP-Q), we confirm the hypothesized four-factor correlated model (see Table 3) and provide evidence for the existence of a broader second-order factor that would explain the associations between the four dimensions of nomophobia. These data are consistent with those found in other adaptations, such as that of Lin et al. (2018), and they constitute a validation of previous exploratory works (González-Cabrera et al., 2017; Yildirim & Correia, 2015).

Table 6. *Scores for the Percentiles of the NMP-Q as a Function of Sex and Age (n = 5012)*

	Scores					
	Males			Females		
Percentiles	12-15 n = 809	16-20 n = 1276	21-24 n = 817	12-15 n = 614	16-20 n = 929	21-24 n = 567
1	20	20	20	21	21	21
5	25	25	23	29	27	25
10	31	30	27	34	32	29
15	34	33	30	38	37	32
20	36	36	32	41	40	37
25	39	39	36	44	43	41
30	41	41	39	47	46	44
35	43	43	41	50	49	47
40	45	45	44	53	53	50
45	48	48	47	57	55	53
50	51	50	49	60	57	57
55	54	53	52	65	59	60
60	58	55	55	67	62	63
65	61	58	58	70	66	64
70	65	61	61	73	69	68
75	68	64	63	77	73	72
80	71	67	66	82	77	75
85	*75*	*71*	71	87	82	80
90	82	76	76	94	88	85
95	92	84	86	107	101	95
99	121	110	103	129	126	124
M	54.27	52.11	50.90	62.37	59.29	57.33
DT	20.88	18.68	16.68	23.71	22.04	21.77

Note. Gray indicates the 15th (No Nomophobia), 80 (Risk of Nomophobia), and 95 (Nomophobia) percentiles.

Additionally, we provide a hierarchical model with four first-order factors and a general second-order factor, which allow us to provide both a total score and three cut-off points, making it possible not only to determine whether a nomophobic problem exists but also its severity.

There are currently few studies on the prevalence of nomophobia, and even fewer with a large and geographically representative sample of all the regions of the same country. To date, no work has established clear cut-off points to identify different levels of a nomophobic problem. The only work that suggests cut-off points was performed by González-Cabrera et al. (2017), using the 15th, 80th, and 95th percentiles according to sex and age of their participants. However, the sample of that study had major limitations due to the small size and its representativeness. In addition, the cut-off points were conceptualized as casual user (P15), at-risk user (P80), and problematic user (P95). In this manuscript, we adapted these categories coming from the game disorder literature to the singularity of the nomophobia construct, indicating absence of nomophobia (P15), being at risk of developing nomophobia (P80), and the existence of a nomophobic problem (P95). Besides, our present study was conducted with a large Spanish sample, general (not just students) and with representation of all regions of the country (see Table 1), whereas the former study of González-Cabrera et al. (2017) were done with smaller and student samples. The new cut-off points suggested here are, in general, lower than those of González-Cabrera et al. (2017), but they maintain the same tendency of the exploratory study, as females (at any age) presented greater levels of nomophobia and, among them, females of the 14-15 and 16-17 age groups presented the highest scores.

Regarding the hypotheses that sex and age nomophobic differences do exist (Arpaci, Baloglu, Kozan & Kesici, 2017; Dasgupta et al., 2017; Gezgin & Çakır, 2016; Gezgin, S¸umuer, Arslan & Yildirim, 2017; González-Cabrera et al., 2017; King et al., 2017; Prasad et al., 2017), this study has come to confirm that females score higher in the NMP-Q (and in all four dimensions) than males. However, other works have not reported these differences (Lin et al., 2018) or have indicated that they are nonsignificant (Farooqui, Pore & Gothankar, 2017; Madhusudan, Sudarshan, Sanjay, Gopi & Fernandes, 2017; Müge & Gezgin, 2016; Uysal, Özen & Madeno˘glu, 2016). Some works have even found males to have higher levels of nomophobia and mobile dependence (Dongre et al., 2017; Nawaz, Sultana, Amjad & Shaheen, 2017). These differences may be due to cultural or religious issues, which may have more explanatory value than the variable sex itself, as it has been suggested in other studies on problematic Internet use and mobile phone (Baron & Campbell, 2011; Yudes-Gómez, Baridon-Chauvie & González-Cabrera, 2018). In addition, data from the present study support the hypothesis that nomophobia scores decrease with age, more specifically after 18 years old. This is convergent with the work of Gezgin et al. (2017), who argue that, as age increases, the levels of nomophobia decrease, and it is somehow in line with the findings of Dasgupta et al. (2017), although in this latter study the age that makes a different it is not placed in the 18 years old but in the 21, being younger than this age a predictor of nomophobia. Similarly, age differences between those who are younger than 20 and those who are older have also been reported (Adawi et al., 2018; Yildirim, Sumuer, Adnan & Yildirim, 2015). Finally, some other works have also provided different age ranges for at-risk groups, being the more problematic groups those of 18-29 years (King et al., 2017) and 22-24 years (Sharma, Sharma, Sharma & Wavare, 2015).

This study also presents some methodological limitations. Firstly, the NMP-Q is a self-reporting questionnaire, so there may be response and desirability biases. For this reason, some participants may have answered some questions untruthfully, under-reporting the severity or frequency of nomophobia symptoms to minimize their problems. Albeit more unlikely, they may also have exaggerated their answers to make their mobile problems seem worse. Despite the fact that, due to the characteristics of this research, we did not use any mechanism to detect dishonesty, participants were given their nomophobia scores. Therefore, it is reasonable to assume that the online question-

naire was only answered by readers who were interested in the topic and in knowing their scores. We believe that this incentive, which is not so common in research, served to reduce the aforementioned problems associated with self-reports. Also, the short time that it took to complete the 20-item questionnaire (7 minutes on average), along with the fact that there were no reverse items, may have reduced problems related to poor attention or boredom. We also eliminated the questionnaires that were completed in less than 4 minutes. This study could be improved in the future by using complementary measures to self-report.

Secondly, sampling was not random, although the sample size ensures that the participants come from in all the Spanish regions and cities, and there was high sociodemographic diversity. More importantly, extrapolating these results should be done with caution, and they should be understood as a first approximation carried out with a large sample and as a first attempt of providing normative criteria for interpreting the NMP-Q scores in Spain. We recommend replicating these results following the cut-off points established herein for sex and age in randomized samples. We also encourage intercultural comparative studies among Spanish-speaking countries. In addition, we consider that the use of this tool with diagnostic purposes should be employed alone with a clinic interview or with any other complementary clinical assessment, but we do not recommend using it as a single measure. We did not evaluate additional nomophobia-related problems, such as time spent online and/or on the phone, FoMO (fear of missing out), etc., precluding us from conducting other statistical analyzes aimed at evaluating the diagnostic accuracy of the NMP-Q. This was not possible due to circumstances beyond our research design control and the requirements of the media that posted the online questionnaire. Also, this study has not examined the relationship between nomophobia and other constructs to analyze the external and internal validity of the NMP-Q, but this has been done in other works, particularly in the Spanish adaptation of González-Cabrera et al. (2017), as well as in other adaptation studies (Adawi et al., 2018; Lin et al., 2018; Yildirim & Correia, 2015). Finally, we did not explore sociodemographic variables such as ethnicity, type of degree, socio-economic status, time spent using the mobile, etc., which would be worth studying in future research.

In conclusion, this study confirms the factor structure of the Spanish version of the NMP-Q of Gonzalez-Cabrera et al. (2017) and the original four-factor model of Yildirim and Correia (2015). In addition, we also show that there is a broader second-order factor that would explain the associations between the four dimensions of nomophobia and that provides a first standardization of nomophobia scores according to sex and age (between 12 and 24 years). This work can be useful for pediatric and psychological care units, as well as for those in charge of school orientation in schools. All the above information is also of special interest to parents, since education and parental supervision can play a very important role in the prevention of the problems associated with the information and communication technologies.

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Obsession and compulsion in mobile phone use/abuse: OCDUS-ICT

Obsesión y compulsión en el uso/abuso del móvil: el OCDUS-TIC

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Abstract

Compulsiveness has been considered one of the core characteristics of addictive behaviours. One of the abusive behaviours that has acquired importance in recent times involves the use of mobile phones. The aim of this study is to obtain a version of the Obsessive-Compulsive Drug-Use Scale (OCDUS) to study the compulsivity associated with mobile phone abuse, its basic psychometric properties and the results of its application. The OCDUS-ICT was created and administered over the Internet, through instant messaging programs, social networks and e-mail, and anonymous and voluntary participation was requested. Additionally, MULTICAGE-ICT and the Inventory of Prefrontal Symptoms were administered. A sample of n=748 subjects, 33% males and 94% born and resident in Spain was obtained. The test obtained adequate values of internal consistency, applying different estimators. Confirmatory factor analysis of the theoretical scales yielded adequate fit indices. Obsessive-compulsive components were observed to become stronger as mobile phone use increased and approached abuse levels. OCDUS-ICT scales showed large correlations with prefrontal malfunction symptoms, especially Thoughts-Interference (r>0.80). In conclusion, OCDUS-ICT explores with psychometric accuracy the obsessive-compulsive components of mobile use/abuse, which are closely related to malfunctions in daily life attributable to the prefrontal cortex. If impulsivity has so far been the focus in the study of mobile phone abuse, the data from the present study suggest that greater attention should be paid to compulsivity as a factor in maintaining abuse.

Keywords: opioids, Compulsivity; Smartphone Addiction; OCDUS; Prefrontal symptoms in daily life; Behavioural addictions.

Resumen

La compulsividad ha sido considerada una de las características nucleares de las conductas adictivas. Uno de los comportamientos abusivos que ha adquirido importancia en tiempos recientes es el uso del teléfono móvil. El objetivo del presente trabajo es obtener una versión de la Escala de Uso Obsesivo-Compulsivo de Drogas (OCDUS) para estudiar la compulsividad asociada al abuso del móvil, conocer sus propiedades psicométricas básicas y resultados de su aplicación. Se creó y administró el OCDUS-TIC por Internet, mediante mensajería instantánea, redes sociales y correo electrónico, solicitándose la participación anónima y voluntaria. Adicionalmente se administraron el MULTICAGE-TIC y el Inventario de Síntomas Prefrontales (ISP). Se obtuvo una muestra de n=748 sujetos, 33% varones y 94% nacidos y residentes en España. El test obtuvo adecuados valores de consistencia interna, aplicando diferentes estimadores. Se realizó un análisis factorial confirmatorio sobre las escalas teóricas, alcanzando adecuados estimadores de ajuste. Se observó que los componentes obsesivo-compulsivos son de mayor magnitud a medida que se incrementa la implicación en el uso y su progresión al abuso del móvil. Las escalas del OCDUS-TIC mostraron correlaciones de gran magnitud con los síntomas de mal funcionamiento prefrontal, especialmente la de Pensamiento-Interferencia (r>0,80). En conclusión, el OCDUS-TIC explora con garantías psicométricas los componentes obsesivo-compulsivos del uso/abuso del móvil, que se relacionan estrechamente con fallos cotidianos de origen prefrontal. Si la impulsividad ha centrado el interés en el estudio del abuso del móvil, los datos del presente estudio aconsejan prestar mayor atención a la compulsividad como factor de mantenimiento del abuso.

Palabras clave: Compulsividad; Adicción al Móvil; OCDUS; Sintomatología prefrontal; Adicciones comportamentales.

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Introduction

Although in everyday usage they are often treated as synonyms, the terms "impulsivity" and "compulsivity" present important differences at the conceptual level which are crucial in the context of addictive behaviours. Impulsivity was initially defined as the tendency to act quickly when triggered by both internal and external stimuli, without assessing all available information before carrying out an action and, therefore, without calculating its consequences (Eysenck & Eysenck, 1978). Impulsive behaviour is maintained by positive reinforcement, oriented towards the achievement of a hedonic goal, and ego-syntonic to the extent that these goals are in harmony with or acceptable to the needs of the individual and consistent with his or her self-image. Compulsive behaviour, meanwhile, is maintained by negative reinforcement, is aimed at reducing distress and is ego-dystonic since the subject knows that he or she should not perform it but feels compelled to do so (Cabrini et al., 2009; Koob, 2013).

While impulsivity is linked to initial consumption and drug abuse episodes, compulsivity seems to be the central element of addiction maintenance (Baker, Piper, McCarthy, Majeskie & Fiore, 2004). Everitt and Robbins (2005) outlined the issue as follows in their neuropsychological model of transition between impulsivity and compulsive habits: "*Drug addiction is increasingly viewed as the endpoint of a series of transitions from initial drug use—when a drug is voluntarily taken because it has reinforcing, often hedonic, effects—through loss of control over this behavior, such that it becomes habitual and ultimately compulsive (…) We hypothesize that the change from voluntary drug use to more habitual and compulsive drug use represents a transition at the neural level from prefrontal cortical to striatal control over drug seeking and drug taking behavior as well as a progression from ventral to more dorsal domains of the striatum, involving its dopaminergic innervation. These neural transitions may themselves depend on the neuroplasticity in both cortical and striatal structures that is induced by chronic self-administration of drugs.*" (p. 1481). This starting hypothesis has been further refined by important accumulated empirical evidence (Everitt & Robbins, 2016).

Impulsivity has been widely studied in its relationship with the development of addictive behaviours (Verdejo-García, Lawrence & Clark, 2008), although compulsivity has not been the subject of the same volume of research, mainly due to the lack of evaluable theories and instruments. The existence of an axis has been posited with an impulsive and a compulsive pole, and addictive behaviours playing out between these two extremes. This would allow subjects to be classified at some point on the continuum and treatments to be adjusted to their needs (Fernández Serrano et al., 2012). It has been found that impulsivity precedes and predicts compulsivity in samples of people with addictive behaviours (Baker et al., 2004; Belin-Rauscent et al., 2016).

However, with the emergence and rise of so-called behavioural addictions, new challenges have appeared. As noted above, Everitt and Robbins (2016) attribute the changes in behavioural control to *"chronic self-administration of drugs"*, but with these behavioural addictions there is no substance to be held responsible. And yet, prefrontal hypofunction has been identified, both at the structural level (e.g., Zsidó et al., 2019) and in performance in neuropsychological tests (p. ej., Brand, Young & Laier, 2014; Van Timmeren, Daams, Van Holst & Goudriaan, 2018), and also in activities of daily living (e. g., Pedrero-Pérez et al., 2018). Tthey also have in common the compulsive nature of the behaviour, so that, although the term "addiction" has not been officially accepted, except in the case of pathological gambling, the literature usually refers to these problems as compulsive Internet use (Gmel, Khazaal, Studer, Baggio & Marmet, 2019), compulsive shopping (de Mattos, Kim, Filomensky & Tavares, 2019) or compulsive sexual behaviour (Efrati & Mikulincer, 2018), among others, with instruments for the measurement of each of the disorders being developed, as in the case of the works cited. However, if compulsivity is indeed a type of behaviour associated with addiction, it should be possible to measure it in all addictive modalities, with or without substances, as the basic substrate of addictive behaviour, regardless of the phenomenology associated with each modality.

One of the addictions or compulsive behaviours which has grown in importance over recent years is the use of the smartphone (mobile phone with Internet connection), precisely because this device permits access to sources with stimulants which facilitate the development of multiple addictive behaviours, be it to shopping, sex, gambling, video games or the Internet itself (Pedrero-Pérez, Rodríguez-Monje & Ruiz-Sánchez de León, 2012). Avoidance in this case also seems to largely explain compulsive use and maintenance over time (Ruiz-Ruano, López-Salmerón & López, 2020). Although there are a large number of instruments proposed for the assessment of mobile addiction or problematic use, no studies have been found which explore the compulsivity which underlies this behaviour in terms comparable to its presence in other addictive modalities involving substances.

The Obsessive Compulsive Drug Use Scale (OCDUS) was initially validated for the measurement of the obsession-compulsion cycle in people dependent on heroin (Franken, Hendriks & van den Brink, 2002). Simply by modifying the drug mentioned in each item, it was subsequently adapted and validated for users of cocaine (Lievaart et al., 2015) and cannabis (Machielsen et al., 2012; Machielsen, Veltman, van den Brink & de Haan, 2018). The OCDUS is one of the tests put forward by a committee of international experts to measure the compulsive dimension in addictive behaviours

within the neuroscientific scope of the RDoC project (Yücel et al., 2018). However, no research has been found which applies this test with a behavioural addiction focus. The objective of this study is to develop an OCDUS-ICT version to investigate compulsivity associated with the abuse of information and communication technologies, to reveal its basic psychometric properties and the results of its application, as well as provide evidence of concurrent and discriminant validity.

Method

Participants

A sample of n = 764 subjects was obtained. After an outlier detection analysis, 16 subjects with atypical scores were excluded, leaving a reduced final sample of n = 748 subjects. Table 1 presents the descriptive analysis of the final sample, of which 93.6% were born and resident in Spain.

Table 1. *Descriptive variables of the sample.*

	Men	Women	Total
n	**245**	**503**	**748**
Age			
18 - 24	28	90	118
25 - 30	38	67	105
31 - 45	67	133	200
46 - 60	86	158	244
› 60	26	55	81
Education			
Primary or less	8	10	18
Compulsory secondary	13	5	18
Higher secondary	52	57	109
University student	18	55	73
University graduate	154	376	530

Process

Since the target population was one of regular ICT users, a survey was prepared through Google Docs® (available on https://goo.gl/Y3t3rr), and anonymous and voluntary participation was requested through instant messaging programs (WhatsApp®), social networks (Facebook®, Instagram®) and email. At the same time, a chain sampling technique was employed by asking participants to forward the survey to contacts. Data collection began on January 2 and stopped on February 12, 2019.

Tools

The Obsessive-Compulsive Drug Use Scale (OCDUS) is a 12-item self-report questionnaire. The validation study (Franken et al., 2002) found three factors: thoughts and interference (6 items), desire and control (4 items) and resistance to thoughts and intention (2 items). Responses are given on a 7-point analogue scale (typically ranging from Not at all to All the time). Items 6 and 12 will have to be reversed to ensure that all items point in the same direction. For the present study, a version called OCDUS-ICT was created following the usual translation-back translation procedure from the original version (Franken et al., 2002), and replacing the name of the drug with "the mobile phone or its applications" without changing the rest of the question in any way. Studies with previous versions showed adequate evidence of internal consistency and validity (Lievaart et al., 2015; Machielsen et al., 2012; Machielsen, Veltman, van den Brink & de Haan, 2018). Since the OCDUS-ICT is a new version, it has been validated.

The MULTICAGE-ICT is a 20-item questionnaire consisting of 5 scales designed to investigate problems related to the use of the Internet, mobile phone, videogames, instant messaging and social networks (Pedrero-Pérez et al., 2018). It is based on MULTICAGE CAD-4, a compulsive behaviour screening questionnaire, with and without substances (Pedrero-Pérez et al., 2007), which has been used in primary care (Garrido-Elustondo, Reneses, Navalón, Martín, Ramos & Fuentes, 2016; Reneses et al., 2015; Rodríguez-Monje, Pedrero-Pérez, Fernández-Girón, Gallardo-Alonso & Sanz-Cuesta, 2009), behavioural addictions (Estevez, Herrero-Fernández, Sarabia & Jauregui, 2015; Estévez Gutiérrez, Herrero Fernández, Sarabia Gonzalvo & Jáuregui Bilbao, 2014; Megías et al., 2018) and substance addiction (Martínez-González, Munera-Ramos & Becoña-Iglesias, 2013; Navas, Torres, Cándido & Perales, 2014; Navas, Verdejo-García, Lopez-Gomez, Maldonado & Perales, 2016; Pedrero-Pérez, 2010). A mobile phone use/abuse scale was subsequently included (Rodríguez-Monje et al., 2019). The MULTICAGE-ICT asks four questions with a dichotomous answer (yes/no) for each problem behaviour, focusing on: item 1, estimated time of own excessive use; item 2, estimated time of excessive use by significant others; item 3, difficulty in not performing the behaviour; item 4, difficulties in voluntarily interrupting the behaviour. The psychometric study yielded adequate internal consistency of all scales ($0.74 < \omega < 0.93$) and evidence of structural validity.

The screening version of the Prefrontal Symptom Inventory (PSI-20; Pedrero-Pérez, Ruiz-Sánchez de León, Morales-Alonso, Pedrero-Aguilar & Fernández-Méndez, 2015) explores symptoms of malfunction in daily life related to neuropsychological disorders attributable to the prefrontal cortex. This is a 20-item scale with a 5-point Likert-type response format (0: never or almost never; 1: rarely; 2: sometimes yes and sometimes no; 3: many times; 4: always or almost always). Factorial analysis revealed a three-factor solution: problems in behavioural control, problems in emotional control and problems in social behaviour. Adequate internal consistency of all subscales was reported in validation both in the general population and in addicts under treatment reported ($0.87 < \alpha_s < 0.89$); this was also the case in clinical validity tests (Ruiz-Sánchez de León,

Pedrero-Pérez, Gálvez, Fernández-Méndez & Lozoya-Delgado, 2015), ecological (Pedrero-Pérez et al., 2016) and cross-cultural validity (González Roscigno, Mujica Díaz, Terán Mendoza, Guerrero Alcedo & Arroyo Alvarado, 2016; Mendoza, Cuello & López, 2016). In the sample of the present study, the multivariate consistency of the complete test was $\alpha_s = 0.91$ and that of the scales $0.81 < \alpha_s < 0.90$.

Data analysis

The Mahalanobis distance was applied for outlier detection, considering a probability of $p < 0.001$ as a limit; sixteen subjects were thus excluded (2.09% of the total sample). Descriptive statistics of the items and their distributions were obtained. A confirmatory factor analysis with unweighted least squares was performed on the theoretical three-factor model proposed for previous versions. To analyze the fit of the theoretical model to the data we used absolute (Goodness-of-fit statistic GFI, Adjusted goodness-of-fit statistic AGFI and Root mean square residual RMR), incremental (Normed fit index NFI and Relative fit index RFI) and parsimonious indices (Parsimony Goodness-of-Fit Index PGFI and Parsimonious Normed Fit Index PNFI), comparing their values in two alternative models and applying the currently accepted values for their interpretation (Schreiber, Nora, Stage, Barlow & King, 2006). Several indicators were reported for internal consistency (regular and standardized Cronbach's alpha, and McDonald's omega), as recommended for dichotomous or Likert-type scales (Trizano-Hermosilla & Alvarado, 2016). For multivariate comparisons, multivariate analysis of variance was used, applying omega squared (ω^2) as an estimator of effect size; to interpret this, Cohen's rule of thumb was observed, where 0.01 is considered a low effect, 0.03 a moderate effect and 0.6 a large effect (Cohen, 1988). In the correlational analysis, the Bonferroni correction was applied to avoid committing Type I error. The AMOS 18.0 program was used for the confirmatory factor analysis, and the SPSS 17.0 statistical package for the rest (ω^2 was calculated manually from the ANOVA table).

Results

Univariate descriptions

Table 2 shows the descriptive data for OCDUS-ICT items.

Tabla 2. *Descriptivos univariados de los ítems del OCDUS-TIC.*

Item	Mean	CI 95%	Variance	Asymmetry	Kurtosis (centred at 0)
1	2.08	(1.97 - 2.20)	1.50	1.34	1.42
2	2.01	(1.90 - 2.12)	1.36	1.45	2.07
3	1.85	(1.73 - 1.96)	1.42	1.74	2.95
4	1.61	(1.52 - 1.70)	1.01	2.06	4.54
5	1.81	(1.70 - 1.92)	1.42	1.77	3.00
6	3.44	(3.22 - 3.65)	5.18	0.47	-1.31
7	2.90	(2.76 - 3.03)	2.05	0.48	-0.39
8	2.91	(2.77 - 3.04)	2.07	0.57	-0.26
9	2.96	(2.81 - 3.11)	2.63	0.52	-0.72
10	2.21	(2.08 - 2.33)	1.73	1.17	0.97
11	2.55	(2.42 - 2.69)	2.10	0.81	-0.17
12	3.11	(2.94 - 3.27)	3.21	0.59	-0.66

Confirmatory Factor Analysis

Figure 1 shows the structure yielded by the application of confirmatory factor analysis on the theoretically proposed scales for OCDUS-ICT. This structure generally produced adequate fit indices. We also studied the hypothetical structure of two factors (obsession and compulsion, merging factors 2 and 3 of the three-factor model the latter), but the fit indices did not improve significantly (Table 3).

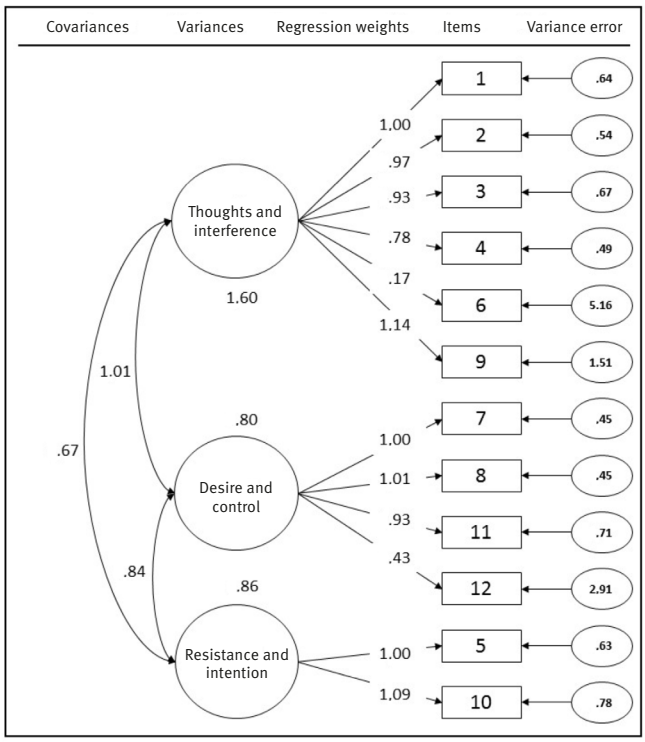

Figure 1. Confirmatory factor analysis of the OCDUS-ICT.

Table 3. *Fit indices of OCDUS-ICT three-factor and two-factor models.*

	GFI	AGFI	NFI	RFI	RMR	PGFI	PNFI
Better fit	**› 0.95**	**› 0.90**	**› 0.95**	**› 0.90**	*	**› 0.50**	**› 0.50**
3 factors	0.96	0.95	0.94	0.92	0.19	0.63	0.72
2 factors	0.96	0.95	0.93	0.92	0.19	0.65	0.75

Note. * The closer to 0 the better.

The thoughts and interference scale showed adequate consistency (α= 0.69; ω= 0.87; α_s= 0.84), as did desire and control (α= 0.89; ω= 0.86; α_s= 0.84) and resistance and intention (α= 0.71).

Scores obtained on the OCDUS-ICT scales

Table 4 shows the means and scatter of the scores obtained on the OCDUS-ICT by the total sample and by sex. The differences were not significant in any of the cases (λ= 0.99; p= 0.18).

Table 5 shows the scores obtained by each age group on the OCDUS-ICT scales. This variable did show an interaction effect (λ= 0.87; p< 0.01; ω^2=0.13) and in this case the differences were significant in all three scales (thoughts and interference F_4= 6.4; ω^2= 0.03; desire and control F_4= 16.1; ω^2= 0.08; resistance and intention F_4= 24.6; ω2= 0.12; p< 0.001 in all three cases). As can be seen, the scores on all three scales fall as age increases.

OCDUS-ICT and MULTICAGE-ICT

The correlations between the scales of both questionnaires are shown in Table 6. After applying the Bonferroni correction, all correlations are significant, although the effect size is larger with the desire/control scale and all the MULTICAGE-ICT scales, except for videogames.

Table 7 shows the scores obtained on the OCDUS-ICT in each of the mobile phone use categories. It is clear that as the use of mobile phones becomes more problematic, scores on all OCDUS-ICT scales increase, with a small effect size, except in the case of desire/control, in which effect size is moderate.

Table 4. *Average scores and standard deviation of scores obtained on the OCDUS-ICT scales.*

OCDUS-ICT	Men	Women	Total	F_1	p
Thoughts/interference	7.30 (3.6)	6.92 (3.4)	7.05 (3.5)	1.96	0.16
Desire/control	11.18 (4.6)	11.60 (4.8)	11.46 (4.7)	1.27	0.26
Resistance/intention	4.01 (2.0)	4.01 (2.3)	4.01 (2.2)	0.00	0.99

Table 5. *Means (and confidence interval) on the OCDUS-ICT scales by age.*

	OCDUS-ICT					
	Thoughts/interference		Desire/control		Resistance/intention	
Age	M	CI95%	M	CI95%	M	CI95%
18 - 25	8.33	(7.7 - 8.9)	13.46	(12.6 - 14.3)	5.47	(5.1 - 5.9)
25 - 30	7.17	(6.5 - 7.8)	12.35	(11.5 - 13.2)	4.54	(4.1 - 4.9)
30 - 45	6.98	(6.5 - 7.5)	11.91	(11.3 - 12.5)	3.90	(3.6 - 4.2)
45 - 60	6.75	(6.3 - 7.2)	10.65	(10.1 - 11.2)	3.51	(3.2 - 3.8)
›60	6.09	(5.3 - 6.8)	8.80	(5.3- 6.8)	3.00	(2.6 - 3.5)

Tabla 6. *Correlaciones entre las escalas del OCDUS-TIC y del MULTICAGE-TIC.*

	OCDUS-ICT		
MULTICAGE-ICT	Thoughts/interference	Desire/control	Resistance/intention
Internet	0.18*	0.63*	0.44*
Mobile phones	0.19*	0.58*	0.41*
Video games	0.13*	0.19*	0.14*
Instant messaging	0.13*	0.51*	0.40*
Social networks	0.23*	0.46*	0.38*
PSI-20			
Problems in the control of social behaviour	0.31*	0.17*	0.06
Problems in the control of emotions	0.56*	0.27*	0.17*
Problems in executive control	0.87*	0.24*	0.20*
Total prefrontal symptoms	0.86*	0.29*	0.21*

Note. * Significant correlations after Bonferroni correction (p< 0.0033).

Table 7. *Scores obtained on the OCDUS-ICT in each of the mobile use categories.*

	MULTICAGE-ICT (Mobile)					
OCDUS-ICT	Non-problematic use	Risky use	Problematic use			
	M (SD)			F_2	p	ω^2
Thoughts/interference	6.45 (3.4)	7.20 (3.3)	7.87 (3.5)	10.760	‹ 0.001	0.03
Desire/control	8.84 (3.6)	12.05 (4.1)	15.24 (4.4)	157.420	‹ 0.001	0.30
Resistance/intention	3.15 (1.7)	4.25 (2.1)	5.20 (2.5)	61.550	‹ 0.001	0.14

OCDUS-ICT and PSI-20

Table 6 shows the correlations found between the OCDUS-ICT scales and those of the PSI-20, as well as with their total prefrontal symptom score. In this case, it is the thoughts/interference scale which presents the strongest correlations, in particular with the problems in executive control scale and total prefrontal symptoms. Scale items showing extreme correlations are shown in Figure 2.

Discussion

The present study has adapted a questionnaire measuring the components of obsession and compulsion in substance use and abuse in order to investigate the use/abuse of mobile phones. Hypothetically, since these behavioural components are involved in the maintenance of addictive behaviours involving substances (Yücel et al., 2018), they should also be core components of so-called behavioural addictions. The structure of the questionnaire we have named OCDUS-ICT largely matches that used in previous versions of the scale, and is therefore applicable to the study of behavioural addictions. Factorially derived scales have adequate internal consistency values, especially when multivariate estimators are applicable, which are appropriate to the uneven distribution of items.

No differences by sex were observed in the scores obtained on the different scales of the questionnaire, a result which is not comparable with previous studies, given their usually exclusively (Mokri, 2016; Yang et al., 2016) or predominantly male samples, where gender differences were not analyzed (Dekker et al., 2012; Dijkstra, De Jong, Bluschke, Krabbe & Van Der Staak, 2007; Franken et al., 2002; Franken, Kroon & Hendriks, 2000; Lievaart et al., 2015). However, there were some differences according to age groups, with the strength of obsession-compulsion components decreasing as age increased, although the effect size of these differences is very low.

When the scores on the OCDUS-ICT scales are compared to those of the MULTICAGE-ICT, it can be seen that there is a significant relationship between all of them, that

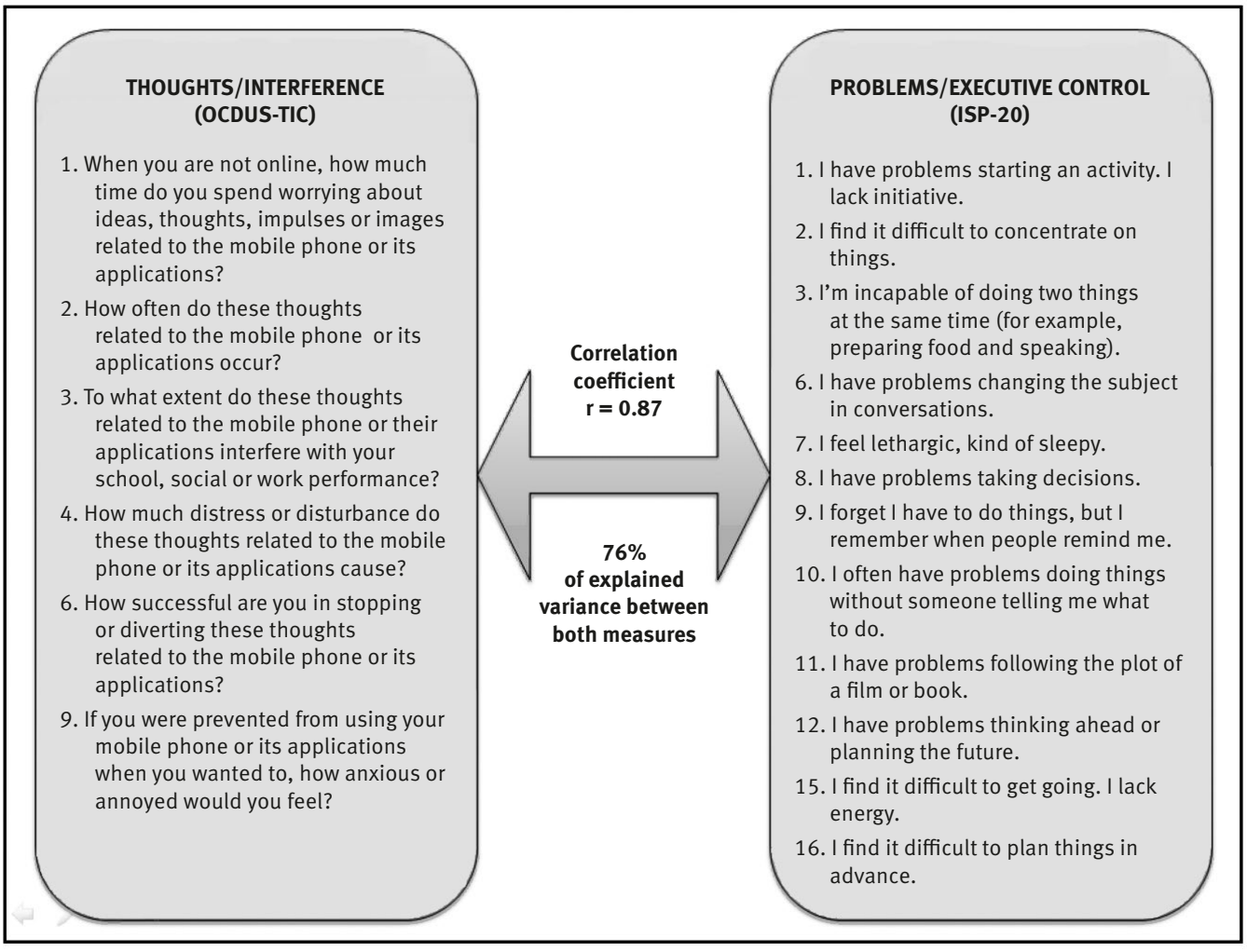

Figure 2. Items of the OCDUS-ICT Thoughts/Interference scale presenting extreme correlations with items of the PSI-20 Executive Control Problems scale.

is, all the behaviours explored in the different ICT use/abuse scales have a significant relationship with the obsessive-compulsive components. However, the effect size of these relationships is noticeably larger with the compulsive components and less so with the interference of obsessive thoughts. This difference is likely the result of the ease with which these devices and applications can be accessed; obsessive ideas are thus rapidly neutralised because the user can trigger a neutralising response before such ideas reach high levels of anxiety. All this is valid for access to the Internet, mobile phones or instant messaging applications and social networks, although the effect size is much smaller in the case of video games, probably because the involvement in this type of activity requires greater levels of preparation, concentration and involvement.

A revealing finding is the fact that obsessive-compulsive components are stronger as the degree of use of the smartphone becomes greater and moves towards abuse. The MULTICAGE-ICT allows subjects to be classified according to the negative consequences of their use, from non-problematic to problematic use, with a range of risk levels in between (Pedrero-Pérez et al., 2018). The values on all OCDUS-ICT scales are at their lowest when use is non-problematic, rise with risky use and reaches maximum levels for those people who can be classified as problematic mobile phone users. Once again, however, the strongest association is presented by the scale for desire and control, so that this seems to be the main component linking mobile phone abuse with the obsession-compulsion cycle. Again it seems that neutralising behaviours are triggered by low levels of intrusive thoughts, pointing to the ease of use of mobile phones and access to their applications, unlike the findings in studies of drug abuse behaviours (Kuo-Lun, 2017).

When comparing the scores of the OCDUS-ICT scales to those of prefrontal symptoms in daily life (PSI-20), significant correlations are found in almost all cases. However, the strength of these correlations is greatest in the case of the thoughts/interference scale, which presents an index of mutual determination with the scale of problems in the control of social behaviour (r^2= 0.10), the problems in emotional control scale (r^2= 0.31) and, surprisingly, with the problems in executive control scale (r^2= 0.76), as well as with the total prefrontal symptoms score (r^2= 0.74). Figure 2 shows the extremely strong relationship between the presence of intrusive thoughts or obsessions (items 1, 2, 3, 4, 6 and 9 of OCDUS-ICT) and executive problems as measured with PSI-20 combining motivational problems (items 1, 7, 10 and 15), selective, sustained, alternating and divided attention (items 2, 11, 6 and 3, respectively), as well as decision-making (item 8), prospective memory (item 9) and planning in activities of daily living (items 12 and 16).

Previous studies have shown that the distribution of prefrontal symptomatology in general and problems with executive control in particular in the general population has a classic normal curve (Pedrero-Pérez et al., 2011; Ruiz Sánchez de León et al., 2012) and that this deficit is closely related to addictive phenomena (Méndez Gago et al., 2018; Pedrero-Pérez et al., 2015). What the results suggest in this case is that, at the same time, individuals with weaker executive capacity tend to present obsessive ideas and that such obsessive ideas tend to block executive functioning, but it is difficult to determine cause and effect in what appears to be a characteristic dysfunctional loop. This is fully congruent with the conclusions of a recent meta-analysis (Norman et al., 2018) which notes that the brains of patients with obsessive compulsive disorder (OCD) get stuck in an "error" loop, in which they cannot stop even when they know they should. It is clear that this OCD formulation is fully applicable to compulsive substance use and also to behavioural addictions.

Given the parallelism proposed by Everitt and Robbins (2005, 2016) of addiction as a special form of OCD, perhaps this population could provide a finding similar to that of the present study. However, in OCD, executive dysfunctions - in general - do not seem to be linked to the presence of obsessions, which depend exclusively on cognitive inhibition; on the other hand, there does seem to be a relationship between compulsions and a global deficit in executive functions (Harsányi et al., 2014). Moreover, the study of executive functions in patients with obsessive-compulsive disorder is characterized by the variety of inconclusive results, from research showing their relative conservation to that showing significant deficits or even adding an amnestic picture to dysexecutive syndrome (Abramovitch & Cooperman, 2015; Aycicegi et al., 2003).

Since the study of OCD does not provide conclusive results in this field, the study of obsessions as behavioural components involved in the maintenance of addiction, either to substances or behaviours, is of special interest in the syndromic description in light of results. The OCDUS in its different substance-centred versions and the OCDUS-ICT used in this paper are tools of clinical and research utility to describe the three related factors: thoughts and interference, desire and control, and resistance to thoughts and intention.

The main limitation of this study is, without doubt, the sampling method. Diffusion via social networks does not allow the quality of participation, the motivation, or the sincerity of the participants to be controlled, nor, of course, the generalizability of results. The only way to control response quality, at least globally, is to obtain a large enough sample so that the percentage of inappropriate responses has a lower specific weight in the overall results. The ratio of the number of participants and the number of items

APPENDIX I

OCDUS-ICT

1	When you are not online, how much time do you spend worrying about ideas, thoughts, impulses or images related to the mobile phone or its applications?						
	NOT AT ALL						ALL THE TIME
	1	2	3	4	5	6	7
2	How often do these thoughts related to the mobile phone or its applications occur?						
	NOT AT ALL						ALL THE TIME
	1	2	3	4	5	6	7
3	To what extent do these thoughts related to the mobile phone or their applications interfere with your school, social or work performance?						
	NOT AT ALL						ALL THE TIME
	1	2	3	4	5	6	7
4	How much distress or disturbance do these thoughts related to the mobile phone or its applications cause you?						
	NONE						A GREAT DEAL
	1	2	3	4	5	6	7
5	How much effort do you make to resist these thoughts related to your mobile phone or its applications, or try to ignore or divert your attention from these thoughts?						
	NONE						A GREAT DEAL
	1	2	3	4	5	6	7
6	How successful are you in stopping or diverting these thoughts related to the mobile phone or its applications?						
	NOT AT ALL						COMPLETELY
	1	2	3	4	5	6	7
7	If you are not connected, how often do you feel the need or the urge to use your mobile phone or its applications?						
	NOT AT ALL						CONSTANTLY
	1	2	3	4	5	6	7
8	If you are not connected, how much time a day do you feel the need or the urge to use your mobile phone or its applications?						
	NONE						ALL THE TIME
	1	2	3	4	5	6	7
9	If you were prevented from using your mobile phone or its applications when you wanted to, how anxious or annoyed would you feel?						
	NOT AT ALL						EXTREMELY
	1	2	3	4	5	6	7
10	How much effort do you make to resist the use of mobile phones or their applications?						
	NONE						A GREAT DEAL
	1	2	3	4	5	6	7
11	How intense was the impulse to use the mobile phone or its applications last week?						
	NOT AT ALL						EXTREMELY
	1	2	3	4	5	6	7
12	How much control do you have over your mobile phone use or its applications?						
	NONE						TOTAL
	1	2	3	4	5	6	7

(764/12=63.7/1) is much greater than the most restrictive demands of a 10/1 ratio. In addition, detection of atypical scores was carried out so that random responses or inconsistent completion could be eliminated. In any case, the chain sampling technique is recommended in cases where the target population is difficult to reach or when very large samples are required, but, like all sampling methods, it presents risks which must be taken into account (Bowling,

2005). The internal consistency of the evidence, at both item and scale levels, is the main proof that the data was obtained, at least to a large extent, in a manner suitable for the realization of a structural study and correlational analysis. Future studies should look for sampling methods which allow generalizability of results.

Consequently, the OCDUS version for the study of obsessive-compulsive components of mobile phone use/abuse, which we have called OCDUS-ICT, is shown to be a consistent test with adequate structural validity for clinical application. The size of the correlations found with mobile use/abuse categories makes it possible to affirm that obsessive-compulsive components are central to this behaviour, as is likely to be the case in all addictive behaviours. It is possible that a great deal of attention has been paid to impulsivity as a predictor of abuse and much less to compulsivity as a factor in maintaining abuse and addiction. The use of exposure therapy with response prevention, which is difficult to apply in substance addictions, has shown its usefulness in the treatment of OCD (Hezel & Simpson, 2019) and in behavioural addictions, such as pathological gambling (Echeburúa, Fernández-Montalvo & Báez, 1999) and could be part of the therapeutic menu, thereby avoiding more aggressive interventions such as pharmacological ones, a crucial argument especially in the case of adolescents and young people. The present study offers an instrument to explore these and related issues.

Conflicts of interest

The authors declare no conflict of interest.

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Cognitive functioning in patients with alcohol use disorder who start outpatient treatment

Funcionamiento cognitivo en pacientes con trastorno por uso de alcohol que inician tratamiento ambulatorio de deshabituación alcohólica

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Abstract

The main objective of the present study is to analyze the presence of cognitive impairment associated with alcohol consumption in patients with moderate or severe alcohol use disorder seeking outpatient treatment for their dependence. To do this, we compared a sample of 111 patients with active alcohol use disorder who initiated ambulatory treatment with 100 healthy controls. We compared sociodemographic and clinical variables associated with alcohol consumption, such as alcohol craving and impulsivity. A systematized battery of cognitive tests was also used in the comparison, which allowed the evaluation of the following functions: Attention, anterograde memory, processing speed, verbal fluency, executive function and implicit attitude towards alcoholic beverages. Compared with healthy controls, patients with moderate or severe alcohol use disorder performed significantly worse in all tests used, and therefore in all cognitive functions evaluated, but for two tests, the *Iowa Gambling Test* and the *Implicit Association Test*. The analysis through a correlation matrix of the patient group indicates that patients who report more impulsivity and more chronic alcohol abuse and with more addiction are those who suffer greater deterioration in their cognitive function. Cognitive damage associated with alcohol consumption was distributed heterogeneously among patients. The present study confirms the presence of cognitive deterioration associated with alcohol consumption in patients seeking outpatient treatment.

Keywords: Alcoholism; Alcohol use disorder; Impulsivity; Alcohol related brain damage; Executive function.

Resumen

El objetivo principal del presente estudio es analizar la presencia del deterioro cognitivo asociado al consumo de alcohol en los pacientes con trastorno por uso de alcohol moderado o grave que demandan tratamiento de deshabituación alcohólica ambulatorio. Para ello, se comparó una muestra de 111 pacientes con trastorno por uso de alcohol activo que iniciaban tratamiento ambulatorio versus 100 controles sanos. Se compararon variables sociodemográficas y clínicas asociadas al consumo de alcohol, como el *craving* de alcohol y la impulsividad. También se empleó en la comparación una batería sistematizada de pruebas cognitivas que permitía valorar las siguientes funciones: atención, memoria anterógrada, velocidad de procesamiento, fluidez verbal, función ejecutiva y actitud implícita ante las bebidas alcohólicas. En comparación con los controles sanos, los pacientes con trastorno por uso de alcohol moderado o grave presentaban un rendimiento significativamente inferior en todas las pruebas utilizadas, y por ello en todas las funciones cognitivas evaluadas, con la excepción de dos pruebas, el *Iowa Gambling Test* y el *Implicit Association Test*. El análisis a través de una matriz de correlaciones del grupo de pacientes indica que los pacientes que refieren más impulsividad y un consumo abusivo de alcohol más cronificado y con más adicción son los que presentan un mayor deterioro en su función cognitiva. El daño cognitivo asociado al consumo de alcohol se distribuyó de forma heterogénea entre los pacientes. El presente estudio confirma la presencia del deterioro cognitivo asociado al consumo de alcohol en los pacientes que demandan tratamiento ambulatorio.

Palabras clave: Alcoholismo; Trastorno por uso de alcohol; Impulsividad; Daño cerebral asociado al consumo de alcohol; Función ejecutiva.

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It is beyond doubt that chronic abusive alcohol consumption damages brain tissue and thereby impairs cognitive function (Draper, Karmel, Gibson, Peut & Anderson, 2011; Erdozain et al., 2014; Florez, Espandian, Villa & Saiz, 2019; Hayes, Demirkol, Ridley, Withall & Draper, 2016; Laramee et al., 2015; Ridley, Draper & Withall, 2013; Sachdeva, Chandra, Choudhary, Dayal & Anand, 2016; Stavro, Pelletier & Potvin, 2013; Wollenweber et al., 2014). Such alcohol-related brain damage (ARBD) originates from two toxic mechanisms acting in combination (Moretti, Caruso, Dal Ben, Gazzin & Tiribelli, 2017): on the one hand, the direct neurotoxic effect of ethanol, mainly mediated by a glutamatergic excitotoxicity (Stavro et al., 2013; Wollenweber et al., 2014); and, on the other hand, the damage associated with thiamin deficiency, which gives rise to Wernicke-Korsakoff syndrome (Galvin et al., 2010; Maharasingam, Macniven & Mason, 2013; Stavro et al., 2013). These two mechanisms combine in patients with ARBD in a dimensional way, that is, the brain damage, and with it the cognitive deterioration, that they produce, can range from mild to entering the dementia spectrum (Moretti et al., 2017; Ridley et al., 2013; Zahr & Pfefferbaum, 2017). Among patients with alcohol use disorder, ARBD is very widespread, with detection rates of up to 78% in the autopsies performed on such patients (Ridley et al., 2013). ARBD is characterized by marked, generalized brain atrophy caused by neuronal destruction and damage to the white matter (Ridley et al., 2013; Stavro et al., 2013). The following brain areas seem to be particularly affected by ARBD (Zahr & Pfefferbaum, 2017): the white matter of the prefrontal cortex, the corpus callosum and the cerebellum, as well as the gray matter in the prefrontal cortex, the hypothalamus and the cerebellum.

This brain damage is accompanied by the presence of especially intense impairment in the following cognitive functions (Aharonovich et al., 2018; Hagen et al., 2016; Hayes et al., 2016; Horton, Duffy, Hollins Martin & Martin, 2015; Maharasingam et al., 2013): anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks. Working memory and response time are generally impaired. The cognitive deterioration profile of ARBD will differ in each patient in extent and intensity depending on different variables. The key element is the duration and intensity of alcohol use, especially binge drinking episodes, which will result in a specific combination of direct damage and thiamine deficiency (Golpe, Isorna, Barreiro, Brana & Rial, 2017; Hagen et al., 2016; Hayes et al., 2016; Horton et al., 2015). But the way in which this cognitive deterioration manifests itself will also be modulated by other variables (Hayes et al., 2016; Ridley et al., 2013; Sachdeva et al., 2016): women are more vulnerable to the neurotoxic effects of ethanol, while deterioration is counteracted by the level of education attained; and the presence of other psychiatric disorders (some, such as depression, involving high comorbidity with alcohol use disorder (Briere, Rohde, Seeley, Klein & Lewinsohn, 2014; Shoval et al., 2014)), with consumption of other toxins and vascular or trauma damage exacerbating deterioration.

It is important to emphasize that the effects of ARBD on the brain areas which control impulses, attention and memory will mean that affected patients are more vulnerable to alcohol addiction because they are less able to control the urge to drink alcohol despite its negative consequences. (Carmona-Perera, Sumarroca-Hernandez, Santolaria-Rossell, Perez-Garcia & Reyes Del Paso, 2019; Koob, 2003; Koob & Volkow, 2010; Mujica-Parodi, Carlson, Cha & Rubin, 2014; Volkow, Koob & McLellan, 2016)

Overall, the cognitive deterioration produced by ARBD and its implications for the daily activities of affected patients is less than that produced by degenerative processes or vascular damage in the brain, especially at the language level (Horton et al., 2015). Moreover, deterioration stops with abstinence, and is even partially reversed, again in a variable manner for each patient, if such abstinence is consolidated. It is estimated that at least one year of abstinence is required to consolidate improvement, with the impairment in anterograde memory being the most resistant to improvement (Sachdeva et al., 2016).

Despite the high prevalence of ARBD, studies carried out to date indicate that neither primary care services nor specific care units for patients with alcohol use disorder routinely assess cognitive impairment associated with alcohol use. (Aharonovich et al., 2018; Draper et al., 2011; Hagen et al., 2016; Rehm et al., 2015a; Rehm et al., 2015b; Rehm, Rehm, Shield, Gmel & Gual, 2013; Rehm, Shield, Gmel, Rehm & Frick, 2013). This clinical scenario is especially troubling since the affected cognitive functions are of vital importance if patients wish to complete alcohol detoxification/cessation successfully (Litten et al., 2015). If attention, memory, and planning capacity are affected, patients will find it difficult to follow the medical and therapeutic guidelines in outpatient treatment without support. In addition, significant improvements in these cognitive functions take time and will not be present during the critical initial moments to consolidate abstinence (Sachdeva et al., 2016).

The aim of the present study is to improve current knowledge regarding the cognitive impairments which patients with alcohol use disorder present when they seek treatment to stop drinking. For this purpose, a group of such patients will be compared with another group from the normative population without alcohol problems. Our main hypothesis is that, when compared with the control group, the group of patients will manifest severe cognitive dysfunctions which diminish the possibilities of success in outpatient alcohol withdrawal programs.

Material and methods

Participants

The final sample consisted of 100 healthy controls and 111 patients with active alcohol use disorder at the time of recruitment. Participants were recruited in three health care units: the La Calzada Mental Health Centre in Gijón (health area 5 of Asturias), the Addictive Behavior Unit at the psychiatry department of the Ourense Hospital Complex, and the Institute of Neuropsychiatry and Addictions at the Parc de Salut Mar, in Barcelona

The inclusion criteria for the patients were: being over 18 years of age, meeting DSM-5 criteria for moderate or severe alcohol use disorder, having an alcohol consumption over the past month of more than 60 grams of ethanol per day in men and 40 grams of ethanol per day in women, expressing a clear desire to control drinking, having no history of suicide attempts and no history of depressive episodes (uni or bipolar), scoring below 5 on the Hamilton Depression Rating Scale (HMDRS) at the time of assessment, agreeing to participate in the study and signing the corresponding informed consent.

The inclusion criteria for the control group were: aged over 18, no personal history of any mental disorder, no family history of alcohol use disorder, major depression and/or attempted suicide/completed suicide, alcohol consumption over the last month not exceeding 30 grams of ethanol per day, agreeing to participate in the study and signing the corresponding informed consent.

The exclusion criteria for both groups were being under 18, presenting organic or psychiatric pathology (according to the DSM-5) which, in the opinion of the researchers, would impede participation in the present study (including substance use disorders with the exception of alcohol in the patient group and smoking for both groups), refusing to participate in the study or sign the corresponding informed consent. Qualified researchers interviewed all candidates for participation in the study to verify that inclusion and exclusion criteria were met.

The controls were obtained through the staff at the centers and the people accompanying the patients. They were matched to patients by sociodemographic criteria.

All participants were thoroughly informed about the nature and characteristics of the study and gave their consent to participate in writing. All were presented with a 50 euro gift card for their participation in the study. The study was carried out following the ethical and legal guidelines regarding the protection of personal data and studies with humans, and fulfilling the Helsinki Declaration guidelines (Rickham, 1964). The study was approved by the following Research Ethics Committees: Pontevedra – Vigo – Ourense (2016-313), Principado de Asturias (2017-06), and Parc de Salut Mar (2017/7221/I).

Process

The design is transversal with a case-control comparison. The first step was to assess all participants to verify that they met the inclusion and exclusion criteria. Next, sociodemographic and clinical variables were collected. Finally, the battery of cognitive tests was completed. To complete the entire protocol, an average of 3 sessions not separated by more than 72 hours was necessary.

Variables

Using an ad-hoc questionnaire, the following sociodemographic and substance use variables were collected: sex, age, marital status, living arrangements, educational level, employment status, age of onset of drinking and smoking, alcohol and tobacco consumption during the previous month, age of onset of alcohol dependence (cases), family history of alcoholism.

The following questionnaires were used to collect clinical variables: to assess the presence of depression as an exclusion criterion, the Hamilton Depression Rating Scale-17 items (HDRS-17) (Bech, 1990); to assess impulsivity, the Barratt Impulsiveness Scale – 11 (BIS-11) (Patton, Stanford & Barratt, 1995); and to assess alcohol use disorder, the Obsessive Compulsive Drinking Scale (OCDS) (Anton, 2000).

The cognitive battery used to obtain neuropsychological variables is shown in Table 1. The tests used were: to measure overall IQ, the WAIS-III Symbol Search and Arithmetic subtests (Hagen et al., 2016); to measure attention, the D2 Attention Test (Steinborn, Langner, Flehmig & Huestegge, 2018); to measure memory, the California Verbal Learning Test (CVLT) (Elwood, 1995) and WAIS Digit Symbol and Digit Span tests (Hagen et al., 2016); to measure executive function, the FAS and semantic category of animals (del Ser Quijano et al., 2004), the Stroop Color Word Test (SCWT) (Scarpina & Tagini, 2017), Wisconsin Card Sorting Test (WCST) (Nyhus & Barcelo, 2009), and the Iowa Gambling Test (IGT) (Steingroever, Wetzels, Horstmann, Neumann & Wagenmakers, 2013); and to measure automatic processing, the Implicit Association Test (IAT) adapted for alcohol use (Ostafin, Marlatt & Greenwald, 2008).

Data analysis

Comparing the continuous variables of the two groups under study was done by means of Student's t-test, while the analysis of differences between both groups in the distribution of categorical variables was carried out with the chi-square test. Clinical and cognitive variables were also compared using a correlation matrix. The level of significance was set at $p < 0.05$.

Results

Table 2 shows the distribution of the sociodemographic and clinical variables of the sample, indicating the varia-

Table 1. *Battery of neuropsychological tests.*

Neuropsychological test	Main function evaluated	Characteristics
Symbol search (from WAIS-III)	Processing speed (**IQ**)	Measures the ability to quickly identify the presence of figures in a series. Non verbal.
Arithmetic (from WAIS-III)	Abstract reasoning (**IQ**)	Measures the mental solving of arithmetic problems given a time limit. Verbal.
Attention Test D2	Sustained attention / inhibition of response (**Attention**)	Measures the ability to focus on relevant visual stimuli and ignore irrelevant ones. Non verbal.
California Verbal Learning Test (CVLT)	Immediate recall, deferred and identification (**Memory**)	Measures the ability to remember lists of words over several attempts, with and without interference. Verbal.
Digit Symbol (from WAIS-III)	Working memory (**Memory**)	Measures speed in converting numbers into symbols according to an established sequence. Non verbal.
Digit Span (from WAIS-III)	Short-term memory (**Memory**)	Measures the ability to remember and follow a sequence of numbers. Verbal.
FAS and semantic category of animals	Verbal fluency (**executive function**)	Measures the ability to generate word lists by categories. Verbal.
Stroop Test (SCWT)	Divided attention and interference resistance (**Executive function**)	Measures the ability for color recognition. Non verbal.
Wisconsin Card Sorting Test (WCST)	Abstract Reasoning and Cognitive Flexibility (**Executive Function**)	Measures the ability to select cards based on categories. Non verbal.
Iowa Gambling Test (IGT)	Decision making and cognitive flexibility (**executive function**)	Measures the ability to select stimuli based on short and long term rewards. Non verbal.
Implicit Association Test (IAT)	Implicit attitude to a stimulus (**Automatic processing**)	Measures speed of matching words based on implicit attitudes related to alcohol. Non verbal.

bles in which there are significant differences between patients and healthy controls.

Sociodemographic variables (Table 2)

There are no significant differences with respect to the variables which may exert a bias in terms of cognitive assessment and cognitive impairment associated with alcohol consumption: age, sex and completed years of schooling. Nevertheless, alcohol use disorder does imply the presence of significant differences with respect to the following clinical and sociodemographic variables: controls are more frequently found to have a partner ($X^2 = 4.48$, $p = 0.035$), to live with a relative ($X^2 = 12.385$, $p = 0.002$) and to be in active employment ($X^2 = 36.828$, $p < 0.001$).

Variables related to drinking, smoking and impulsivity (Table 2)

Alcohol use disorder was involved in the significant differences found in the following variables: greater impulsivity measured through the BIS (BIS-11 cognitive) ($t = -3.60$, $p < 0.001$), BIS-11 motor ($t = -3.02$, $p = 0.003$), BIS-11 non-planning ($t = -3.35$, $p = 0.001$), BIS-11 total ($t = -4.04$, $p < 0.001$)); higher scores for pathological alcohol use as measured by OCDS - Obsessive ($t = -14.18$, $p < 0.001$), OCDS – Impulsive ($t = -22.95$, $p < 0.001$), OCDS – Total ($t = -21.23$, $p < 0.001$); earlier smoking onset age ($t = 3.96$, $p < 0.001$) and greater daily consumption of cigarettes ($t = -5.10$, $p < 0.001$); greater daily alcohol consumption (SDUs) ($t = -14.8$, $p < 0.001$); higher number of family members affected by alcohol use ($t = -4.73$, $p < 0.001$).

Cognitive variables (Table 3)

Table 3 shows the results yielded by the different cognitive tests in each group with respect to neuropsychological variables. In all tests, significant results were obtained which indicated better cognitive function in the control group, with the exception of IGT and IAT, in which no significant differences between the groups were found.

A correlation study was also carried out to study how variables related to alcohol use and impulsivity influence cognitive tests in the patient group. Table 4 shows the significant correlations. It was found that variables linked to chronic alcohol use (years of alcohol dependence, percentage of lifespan with alcohol dependence, OCDS and BIS) correlated more closely with worse cognitive function compared to the variables linked to severe alcohol use (SDUs, GOT, GPT, GGT and MCV).

Table 5 presents a matrix of correlations between variables related to alcohol use and impulsivity in the baseline assessment. A significant positive correlation was observed between BIS and OCDS, and between the analytical variables linked to alcohol use (GOT, GPT, GGT and MCV) and with SDUs.

Table 2. *Sociodemographic variables and related to alcohol consumption.*

	Controls (100)		Cases (111)		Total (211)		
	mean	DS	mean	DS	mean	DS	p
Age	48.66	9.569	49.07	8.405	48.88	8.956	0.741
Onset age, alcohol use	18.21	6.414	17.21	4.226	17.56	5.114	0.274
SDUs per day, previous month	0.53	0.688	9.613	6.426	5.308	6.521	‹0.001
Onset age, smoking	18.1	4.687	14.16	7.541	15.42	6.996	‹0.001
Cigarettes per day, previous month	3.75	6.722	9.811	10.338	6.938	9.3	‹0.001
Education, completed years	12.76	2.417	13.3	2.881	13.04	2.679	0.142
Family members affected by alcohol	0.27	0.566	0.973	1.449	0.6398	1.172	‹0.001
BIS11- Cognitive	14.85	5.809	18.58	9.038	16.81	7.885	‹0.001
BIS11- Motor	13.82	6.327	16.59	7.03	15.28	6.833	0.003
BIS11- Non-planning	16.28	6.482	19.72	8.379	18.09	7.717	0.001
BIS-Total	44.99	15.54	55.09	20.67	50.3	19.06	‹0.001
OCDS- Obsessive	0.06	0.371	6.5135	4.78	3.455	4.74	‹0.001
OCDS-Impulsive	0.72	1.349	10.703	4.356	5.972	5.98	‹0.001
OCDS-Total	0.79	1.559	17.207	7.981	9.427	10.101	‹0.001
Onset age, alcohol dependence			33.362	9.148			
GOT			38.53	25.44			
GPT			37.02	20.37			
GGT			130.4	167.5			
VCM			95	6.363			
Sex (% males)		74%		78.37%		76.30%	0.4551
Marital status (% married - de facto couple)		56%		41.44%		48.34%	0.035
Living arrangements (% single)		20%		24.32%		22.27%	0.002
Employment situation (% active)		80%		39.63%		58.76%	‹0.001

Note. SD: standard deviation; SDU: standard drink unit; BIS: Barratt Impulsiveness Scale; OCDS: Obsessive Compulsive Drinking Scale; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: mean corpuscular volume.

Discussion

The present study uses a systematized battery of verbal and non-verbal tests to compare the cognitive performance of a group of patients with alcohol use disorder seeking cessation treatment to that of a group of healthy volunteers, matched by the main sociodemographic variables influencing cognitive capacity (age, sex and completed years of schooling). As expected, and confirming the main hypothesis, the patient group displayed significant deficits compared to healthy volunteers in almost all tests. Both attention and processing speed, anterograde and working memory, as well as executive function (verbal fluency, resistance to interference, abstract reasoning and cognitive flexibility) were significantly affected in patients. Indeed, only two tests, IGT and IAT, revealed no significant differences. These findings confirm the results previously obtained in neuroimaging and neuropathology studies indicating the presence of diffuse damage throughout the brain, but with more severe involvement of the prefrontal cortex, the hypothalamus and the cerebellum (Erdozain et al., 2014; Hayes et al., 2016; Zahr & Pfefferbaum, 2017), and are similar to those obtained by other studies in which cognitive function was analyzed in patients with alcohol use disorder compared to a control population (Aharonovich et al., 2018; Romero-Martinez, Vitoria-Estruch & Moya-Albiol, 2020).

As a group, patients were aware of their greater impulsiveness and inability to plan, as reflected in the results obtained with BIS-11. In addition, these cognitive disorders, together with the negative consequences of alcohol intoxication, affect the patient's capacity for socio-familial integration. Results indicate that patients more often tend to lack a stable partner, to live alone and be unemployed. As if this were not enough, their physical health is more

Table 3. *Comparison of neuropsychological tests between controls and patients at baseline assessment.*

	Controls (SD) N = 100	Cases (SD) N= 111	P
IQ			
SYMBOL SEARCH Correct	30.78 (8.33)	23.95 (7.45)	‹ 0.001
SYMBOL SEARCH Error	0.95 (1.30)	1.54 (1.88)	0.008
SYMBOL SEARCH Raw Score	29.57 (9.31)	22.00 (7.69)	‹ 0.001
SYMBOL SEARCH Standard score	10.46 (3.12)	8.10 (2.83)	‹ 0.001
ARITHMETICS Raw score	13.79 (3.93)	11.32 (3.21)	‹ 0.001
ARITHMETICS Standard score	10.70 (3.53)	8.43 (3.06)	‹ 0.001
Attention			
D2	163.7 (43.2)	113.0 (44.5)	‹ 0.001
Memory			
CVLT-A1 first attempt	6.91 (2.75)	5.77 (1.92)	0.001
CVLT-A5 fifth attempt	13.38 (2.51)	11.26 (2.93)	‹ 0.001
CVLT-AToT total attempts	53.20 (9.80)	45.8 (11.6)	‹ 0.001
CVLT- Free immediate	12.31 (2.82)	9.77 (3.32)	‹ 0.001
CVLT- Free delayed	12.98 (2.90)	10.32 (3.35)	‹ 0.001
CVLT- Guided	13.64 (2.70)	11.42 (2.38)	‹ 0.001
CVLT- Recognition	15.34 (1.08)	14.20 (2.12)	‹ 0.001
DIGIT SYMBOL Correct	63.10 (19.10)	46.4 (15.8)	‹ 0.001
DIGIT SYMBOL Standard score	10.26 (3.26)	7.34 (2.86)	‹ 0.001
DIGITS Direct	9.33 (2.10)	8.11 (2.21)	‹ 0.001
DIGITS Reverse	8.07 (2.18)	6.71 (2.01)	‹ 0.001
DIGITS Cumulative	8.19 (2.33)	6.64 (2.27)	‹ 0.001
DIGITS Total	25.54 (5.39)	21.42 (5.57)	‹ 0.001
Executive Function			
FAS Direct score correct	36.5 (11.7)	27.3 (11.3)	‹ 0.001
FAS Perseveration errors	0.81 (1.28)	0.78 (1.53)	0.893
FAS Intrusion errors	0.23 (0.633)	0.64 (1.03)	0.001
FAS Derivation errors	0.48 (1.14)	0.577 (0.949)	0.507
ANIMALS Direct Score	21.56 (6.23)	17.14 (4.77)	‹ 0.001
SCWT prop correct	0.9466 (0.0705)	0.887 (0.115)	‹ 0.001
SCWT mean RTCC	1972 (1288)	2654 (1610)	0.001
SCWT mean RTCI	1874 (1170)	3033 (2635)	‹ 0.001
SCWT mean RTCCO	2349 (1921)	3179 (2958)	0.016
SCWT PROPCC	1776 (188)	1459 (1822)	0.133
SCWT_PROPCI	0.9857 (0.0861)	0.846 (0.255)	‹0.001
SCWT_PROPCCO	0.883 (0.179)	0.846 (0.255)	0.255
SCWT mean RT	49 (351)	1181 (1633)	‹ 0.001
WCST Completed categories	4.59 (1.98)	3.08 (2.04)	‹ 0.001
WCST Correct	70.7 (11.3)	67.2 (13.4)	0.042
WCST Error	36.1 (23.3)	54.0 (21.0)	‹0.001
WCST SUMPE	6.77 (3.08)	7.3 (11.0)	0.641
WCST PE	30.2 (21.2)	17.0 (18.2)	‹ 0.001
WCST PR	9.48 (4.41)	9.3 (13.6)	0.882
WCST SFMS	0.90 (1.22)	1.03 (1.28)	0.462

WCST			
TRIAL FIRST	22.6 (26.7)	30.3 (34.3)	0.07
WSCT CI	18.4 (16.8)	22.6 (19.4)	0.096
WCST FI	25.4 (16.2)	33.2 (20.1)	0.002
WSCT NI	28.5 (22.9)	31.6 (26.3)	0.36
WSCT C2	15.8 (15.3)	32 (176)	0.348
WSCT DIFFC1F1	-1315 (13095)	-9.5 (30.3)	0.321
WSCT DIFFF1N1	-1.7 (28.3)	1.5 (36.4)	0.466
WSCT DIFFN1C2	12.2 (24.7)	16.7 (29.1)	0.234
WSCT DIFFC2F2	-0.2 (21.4)	1.7 (22.8)	0.527
IGT Total	2039 (964)	1836 (822)	0.104
IGT CA	49.9 (16.1)	46.5 (15.5)	0.125
IGT CDA	50.1 (16.1)	53.5 (15.5)	0.125
IGT NET 5 AD	10.56 (4.85)	9.72 (4.60)	0.2
IGT NET 5DIS	9.44 (4.85)	10.28 (4.60)	0.2
Automatic processing			
IAT	-0.569 (0.515)	-0.483 (0.480)	0.215

Note. SD: Standard deviation; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

compromised, due not only to excessive drinking but also to smoking more and over a greater number of years. It is clear that not only impulsivity and lack of executive function play a role in maintaining tobacco addiction among patients with alcohol use disorder; other genetic, neurobiological and environmental factors are also involved and without doubt contribute significantly (Koob, 2003; Koob & Volkow, 2010; Volkow et al., 2016).

It was not observed that any variable related to the IGT permitted discrimination between patients and healthy controls. Although several studies initially found significant differences in this test measuring cognitive functions such as cognitive flexibility and decision making, most recent research in fact predominantly indicates that this test has little discriminative capacity when distinguishing between patients with alcohol use disorder and healthy controls (Hagen et al., 2016). In essence, performing the test correctly requires excellent cognitive function. This is why the results obtained by a representative control group well-matched to a group of patients like ours are poor. The analysis of variables reflecting the results of the last 20 trials of the test confirm this; Table 3 shows that in these IGT variables (IGT 5 NET AD, showing the number of correct responses in the last 20 trials, and IGT 5 NET DIS, measuring the opposite) the control group obtains results approaching the mark which shows that the necessary learning to correctly perform the test did not take place. Thus, if the control group obtains poor results, there can only be significant differences if the results of patients are catastrophically bad; this may be the case in patients with severe brain damage or suffering dementia, but is not applicable to patients participating in this study. It must be remembered that these are non-institutionalized outpatients with sufficient cognitive capacity to sign informed consent and participate in the study. The study assessment protocol was carried out at a time when this test had not yet been questioned by the most recent research and was therefore included.

With regard to the other test which did not achieve significant results in the comparison between patients and controls, the IAT, the results yielded by the study of correlations with clinical variables (Table 4) explain this lack of significance. The IAT measures the automatic and implicit preference of a person towards a particular category, in this study alcoholic beverages. When this automatic preference exists, response times when matching words related to the study category with words having positive or negative valence are modified compared with a neutral response. In this study, we expected to see response times indicating a preference of patients over controls for alcoholic beverages, but this was not initially observed. However, significant differences were observed in the patient group when

Table 4. *Significant correlations between variables related to alcohol use and impulsivity and cognitive variables in the patient group.*

Alcohol use / impulsivity variables	**Cognitive variables with significant correlation**
Years of alcohol dependence	D2 (-0.2. p= 0.032) CVLT A5 (-0.28. p = 0.0029) CVLT AToT (-0.23. p = 0.013) CVLT Free immediate (-0.27. P = 0.004) CVLT Free delayed (-0.21. P = 0.0027) Symbol Search correct (-0.31. P = 0.0007) Symbol Search total score (-0.28. P = 0.0024) Arithmetic standard score (-0.25. P = 0.0063) WCST SUMPE (0.23. P = 0.012).
Percentage of lifespan with alcohol dependence	CVLT A5 (-0.19. p = 0.004) CVLT Free immediate (-0.19. p = 0.036) Symbol Search correct (-0.23. p = 0.014) Symbol Search total score (-0.22. p = 0.018) Symbol Search standard score (-0.19. p = 0.046) WCST SUMPE (0.19. p = 0.036) IAT (0.21. p = 0.025)
SDUs	Arithmetic standard score (-0.20. p = 0.033)
GOT	No significant correlation found
GPT	SWCT PROPCC (-0.21. p = 0.024)
GGT	No significant correlation found
MCV	Arithmetic raw score (-0.19. p = 0.038) Arithmetic standard score (-0.20. p = 0.0036)
OCDS-Obsessive	Animals raw score (0.18. p = 0.049) WCST correct (-0.18. p = 0.049)
OCDS-Impulsive	Symbol Search standard score (-0.29. p = 0.0019) WCST completed categories (-0.20. p = 0.027) WCST correct (-0.26. p = 0.0046) WCST error (0.26. p = 0.0048) WCST DIFF2N2 (-0.22. p = 0.019
OCDS-Total	Symbol Search standard score (-0.25. p = 0.0075) IGT CA (0.20. p = 0.03) IGT CDA (-0.26. p = 0.03) WCST correct (-0.26. p = 0.0054) WCST error (0.25. p = 0.0084) WCST DIFF2N2 (-0.21. p = 0.023) IAT (0.18. p = 0.048)
BIS-Cognitive	CVLT guided (0.19. p = 0.038) SCWT mean RTCC (-0.29. P = 0.001) SCWT mean RTCI (-0.23. p = 0.012) SCWT PROPCI (0.23. p = 0.012) SCWT mean RT (-0.3. p = 0.0012) FAS correct raw score (-0.2. p = 0.032) Digits reverse (-0.24. p = 0.009) Digits cumulative (-0.31. p = 0.0008) Digits total (-0.24. p = 0.01) WCST completed categories (-0.31. p = 0.0009) WCST correct (-0.39. p <0.001) WCST error (0.36. p <0.001)
BIS-Motor	SCWT mean RTCI (-0.25. p = 0.007) SCWT PROPCI (0.19. p = 0.042) SCWT mean RT (-0.38. p <0.001) FAS correct raw score (-0.2. p = 0.032) WCST completed categories (-0.24. p = 0.0088) WCST correct (-0.26. p = 0.0056) WCST error (0.35. p = 0.0065) WCST FI (-0.3. p = 0.0011) WCST DIFF1N1 (-0.22. p = 0.019)
BIS-Non-planning	SWCT mean RTCC (-0.33. p = 0.0004) SWCT mean RTCI (-0.31. p = 0.0008) SCWT PROPCI (0.23 p = 0.011) SCWT mean RT (-0.38. p <0.001) Digits cumulative (-0.18. p= 0.047)

	WCST completed categories (-0.38. p<0.001) WCST correct (-0.45. p <0.001) WCST error (0.40. p <0.001) WCST C1 (-0.25 p = 0.008) WCST F1 (-0.28 p = 0.002) WCST C2 (-0.2 p = 0.033) WCST DIFF1N1 (-0.23. p = 0.019) WCST DIFF2N2 (-0.18. p = 0.0029) IAT (0.20. p = 0.047).
BIS-Total	SCWT mean RTCC (-0.31. p = 0.0007) SWCT mean RTCI (-0.30. p = 0.001) SCWT mean RT (-0.30. p <0.001 FAS correct raw score (-0.21. p = 0.024) Digits inverse(-0.19. p = 0.044) Digits cumulative (-0.25. p = 0.0065) Total digits (-0.22. p = 0.02) WCST completed categories (-0.36. p <0.001) WCST correct (-0.45. p <0.001) WCST error (0.40. p <0.001) WCST C1 (-0.20. p = 0.0034) WCST F1 (-0.27. p = 0.003) WCST DIFFF1N1 (-0.23. p = 0.014) WCST DIFFF2N2 (-0.18. p = 0.047) IAT (0.20. p = 0.031)

Note. SDUs: Standard drink units; BIS: Barratt Impulsiveness Scale; OCDS: Obsessive Compulsive Drinking Scale; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: medium corpuscular volume; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for correct congruent responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of correct congruent responses; PROPCI: Proportion of incongruous correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of times an incorrect letter is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: Percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

Table 5. *Matrix of correlations between the variables related to alcohol consumption and impulsivity in the baseline assessment of patients.*

	Years	**%**	**UBEs**	**GOT**	**GPT**	**GGT**	**VCM**	**BIS 11 C**	**BIS 11 M**	**BIS 11 N**	**BIS 11 T**	**OCDS O**	**OCDS C**	**OCDS T**
Years	**1**	0.904**	-0.034	-0.016	-0.057	0.080	0.207*	-0.158	-0.183	0.002	-0.121	-0.034	0.008	-0.009
%		**1**	0.0161	-0.019	-0.040	0.053	0.175	-0.091	-0.091	0.118	-0.011	-0.003	0.097	0.055
UBEs			**1**	0.246*	0.144	0.232*	0.149	0.146	0.192*	0.222*	0.200*	0.213*	0.298*	0.288*
GOT				**1**	0.710**	0.535**	0.248*	-0.133	-0.082	-0.109	-0.152	0.117	0.258*	0.215*
GPT					**1**	0.307*	0.112	-0.070	-0.059	-0.067	-0.084	-0.016	0.168	0.077
GGT						**1**	0.354*	-0.122	-0.122	0.014	-0.102	0.058	0.100	0.093
VCM							**1**	0.014	-0.047	0.102	0.037	0.139	0.073	0.133
BIS11 C								**1**	0.606**	0.562**	0.865**	0.404**	0.194*	0.341*
BIS11 M									**1**	0.585**	0.824**	0.338*	0.234*	0.318*
BIS11 N										**1**	0.846**	0.252*	0.219*	0.271*
BIS 11 T											**1**	0.388**	0.247*	0.361*
OCDS O												**1**	0.510**	0.884**
OCDS C													**1**	0.849**
OCDS T														**1**

Note. Years: Years of alcohol dependence; %: Percentage of life with alcohol dependence; SDU: Standard Drink Unit; BIS: Barratt Impulsiveness Scale (C: cognitive, M: motor, N: non-planning, T: total); OCDS: Obsessive Compulsive Drinking Scale (O: obsessive, C: Compulsive, T: Total); GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: medium corpuscular volume.
*p < 0.05; **p < 0.0001

taking into account the percentage of years of alcohol dependence, total OCDS, non-planning BIS and total BIS. These results indicate that the IAT is discriminative when the alcohol craving of patients is consolidated, intense and related to impulsivity. Alcohol is a psychoactive substance with low addictive power compared to tobacco, cocaine or morphine derivatives. Our group of patients presents moderate alcohol dependence, with daily consumption of about 90 grams of ethanol and an average period alcohol dependence of 13 years, with large standard deviations, as can be seen in Table 1. That is to say, it is not a group with extreme dependence and alcohol craving, which makes the sample more heterogeneous and leads to a substantial percentage of patients not yielding significant results in the IAT. In summary, the results seem to indicate that the IAT is discriminative in those patients with severe and prolonged alcohol dependence and craving, accompanied by significant impulsiveness.

It is important for health care staff in their daily work involving alcohol detoxification and cessation to know which variables related to alcohol use have a significant relationship with cognitive deterioration produced by ARBD. These variables, easily gathered in the initial diagnostic interviews, act as risk markers, the presence of which would indicate the need to perform a more exhaustive neuropsychological analysis. The SDUs consumed daily during the last month is a marker of recent consumption, alongside the parameters measuring the negative consequences of abusive alcohol consumption in blood tests (GOT, GPT, GGT and MCV). Of the latter, hepatic transaminases (GOT, GPT and GGT) are related to the alcohol drunk over the previous month, thus coinciding with the SDUs, while the parameter related to red blood cells, MCV, is linked to lower specificity than GGT and SDUs, to alcohol consumption over the three months prior to the assessment (Niemela, 2016). As indicated by the correlation study (Table 4), these markers of recent consumption are not strongly related to the cognitive functioning of patients, and appear to be only weakly related to the arithmetic test.

However, the variables related to long-term alcohol use (years of alcohol dependence, alcohol percentage of lifespan with alcohol dependence, OCDS and BIS-11) are more significantly related to cognitive function. The longer the alcohol dependence, the worse the attention, anterograde memory, processing speed and abstract reasoning. Higher scores on the OCDS, which indicate the presence of a more intense and consolidated alcohol craving, are related to declining processing speed, verbal fluency, abstract reasoning and cognitive flexibility. Higher scores in BIS-11, indicating the presence of greater impulsivity, are particularly associated with worsening executive function (verbal fluency, resistance to interference, divided attention, abstract reasoning and cognitive flexibility) and short term memory.

The results obtained in the correlation matrix with respect to BIS-11 are highly significant, conspicuous among them the strong correlation with worse executive functioning. It should be remembered that this test measures impulsivity in a global way, that is, it does not differentiate between the impulsiveness which may have caused the cognitive deterioration associated with alcohol use and the impulsiveness which patients may have had previously and which contributed to their developing alcohol dependence. Previous evidence confirms that both scenarios are possible and compatible. Patients with greater alcohol dependence whose problematic use started earlier display an increased tendency to impulsivity at both the individual and family levels (Bernstein et al., 2015; Jakubczyk et al., 2013), and patients in this study have a significantly greater family tendency to problematic alcohol use (Table 2).

What our study clearly shows is that the BIS-11 correlates especially well with the OCDS (Table 5), highlighting a close relationship between impulsivity and alcohol craving. It is these two psychopathological dimensions which are most closely related to cognitive impairment in this study (Table 4). This relationship is most likely bidirectional, with greater impulsivity and craving leading to more drinking and therefore greater cognitive impairment; the greater the cognitive impairment, the worse the executive function and therefore the greater the impulsivity and alcohol craving.

Our data confirm previous research indicating that the intensity of cognitive impairment associated with alcohol use is determined by the lifetime history of drinking, and not by the most recent use, however intense this may have been (Hayes et al., 2016; Horton et al., 2015).

The results of the present study therefore indicate that compared to healthy controls, patients with alcohol use disorder have worse planning capacity and less cognitive flexibility, added to which are attentional and anterograde memory impairments. These disorders would clearly pose serious problems for the patients when following a program of planned alcohol cessation, in which they would have to adhere to psychopharmacological guidelines and structured psychotherapeutic interventions. In addition, these cognitive impairments would favor relapses in alcohol use. Our results thus confirm the findings of previous research (Evren, Durkaya, Evren, Dalbudak & Cetin, 2012; Romero-Martinez et al., 2020). It is important to remember, as is confirmed in our study, which found no cut-off point to differentiate patients from healthy controls at an individual level in any of the cognitive tests, that cognitive deterioration associated with alcohol use is dimensional, and, therefore, the deterioration each patient may present will be variable. This deterioration can be predicted through the alcohol use history obtained in the initial clinical interview, but its intensity and possible prognostic repercussions can be only clearly known by performing a battery of systematized cognitive tests.

The present study has limitations which should be noted, the most important of which being the transversal nature of the design. This transversality does not allow the exact relationship between impulsivity measured with the BIS-11 and alcohol use disorder to be clarified, nor the influence on the evolution and prognosis of the cognitive disorders detected to be determined. A further issue associated with the cross-sectional design is the difficulty in retrospectively measuring alcohol use to great detail. The cognitive deterioration of patients with a history of alcohol use disorder of equal duration may have been produced by different patterns of alcohol use. Given the heterogeneity of patients in terms of their history of alcohol use (Table 2), a larger sample size would have provided stronger confirmation of the results obtained. Finally, the inclusion and exclusion criteria used in this study meant that patients with alcohol use disorder of low severity were excluded, and the conclusions of this study are therefore only applicable to patients with moderate or serious alcohol use disorder.

Despite these limitations, we can affirm that the present study substantiates the presence of cognitive deterioration in patients with moderate or severe alcohol use disorder starting outpatient alcohol cessation treatment. Such deterioration causes cognitive impairment which affects these patients' attentional capacity, anterograde memory and cognitive function, and, depending on the intensity of the cognitive deterioration presented by each patient, jeopardizes their chances of achieving abstinence and consolidating it by avoiding relapse. We found cognitive deterioration to be related to the duration of dependence, rather than recent consumption, and to the presence of impulsivity. Moreover, these two factors determine the presence of a more favorable implicit attitude towards alcoholic beverages, which also implies a higher risk of relapse. Given the heterogeneity in the history of alcohol use shown by patients with alcohol use disorder who start outpatient treatment, it is advisable to assess the presence of cognitive impairment individually with a battery of systematized cognitive tests.

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Conflict of interests

The authors declare no conflicts of interest in relation to the study, its authorship, and/or the publication of this manuscript.

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Smoking cessation in severe mental illness: challenges and opportunities in the COVID-19 times

Dejar de fumar en el trastorno mental grave: desafíos y oportunidades en tiempos de la COVID-19

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Currently, global public health is threatened by the coronavirus disease (COVID-19), which has spread rapidly from the Chinese region of Wuhan to the rest of the planet. Although most cases recover without sequelae, in the most severe patients it is associated with a pro-inflammatory reaction that leads to high morbidity and mortality rates (Yi, Lagniton, Ye, Li & Xu, 2020).

Available evidence suggests that tobacco use and previous history of metabolic, cardiovascular, and respiratory diseases are independently associated with an increased risk of lung failure, ICU admission, and death (Wang, Ruobao, Zhong & Huang, 2020; Vardavas & Nikitara, 2020). Because of this, the pandemic threatens to hit vulnerable populations with greater intensity, including individuals with severe mental illness (SMI).

Indeed, people with an SMI already have a high risk of premature morbidity and mortality, reducing their life expectancy by 10 to 20 years. In this population, cardiovascular and respiratory diseases are 2-3 times more frequent and have an earlier onset and more severe outcomes (De Hert et al., 2011). Of note, smoking is the major preventable risk factor for both comorbidities (Rüther et al., 2014).

Smoking with high levels of dependency, in a population with a higher level of social isolation and a lower opportunity for preventive care, further perpetuates this problem. Urgent measures of social and medical awareness are needed, which may ease access to safe and effective treatments aimed at smoking cessation.

Pandemic-related confinement has been associated with substantial changes in lifestyle behaviors, including smoking and substance misuse (Balanzá-Martínez, Atienza-Carbonell, Kapczinski & De Boni, 2020; García-Álvarez, de la Fuente-Tomás, Sáiz, García-Portilla & Bobes, 2020). After progressive de-escalation, the priority is now focused on preventive measures. This can be a golden opportunity to more strongly promote messaging regarding smoking cessation. The challenge now is to ensure that pandemic response and treatment represent an opportunity to include people with an SMI, who are more vulnerable due to their social position and unequal access to health services.

Although the patients with a SMI are usually less aware of the health risks associated with long-term tobacco use, up to 70% of this population has ever considered the need to quit (Prochaska et al., 2011). As with the majority of smokers, simply asking the patient about their smoking habits mobilizes motivation to quit. In multi-component approaches, the level of motivation to quit smoking achieved is decisive in significantly reducing consumption, as a previous step to abstinence (Sarramea et al., 2019a;

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Sarramea Crespo et al., 2019b). Moreover, specific and individual information about respiratory risks and chances for prevention could help increase a smoker's willingness to quit (Sarramea et al., 2019c).

With health services overwhelmed due to the pandemic, mental health professionals will need to adapt to new healthcare models, an increase in patient demand, and new patient needs. In this context, a paramount risk consists of constraining again the therapeutic approaches for SMI to clinical stability and preventing admissions, thus leaving apart among others, a more overarching aim of addressing the mental and physical health of patients with an SMI. In turn, this approach takes into account the prevention of environmental risk factors, such as smoking, which are major determinants of high rates of premature morbidity and mortality worldwide.

In sum, the current pandemic may be an opportunity to value both health and disease prevention. A major challenge is to identify the most vulnerable groups and protect their healthcare needs despite current, pressing emergencies due to COVID-19. In order to prevent premature morbidity and mortality, a comprehensive and coordinated approach to mental and physical health is more necessary than ever. This is especially important for patients with SMIs, who are ready to receive a clear message regarding the risk factors for smoking and available solutions to help them quit.

Conflict of interest

Author VBM has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini; Ferrer; Lundbeck; Nutrición Médica; and Otsuka.

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Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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

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

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

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

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

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

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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.
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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

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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.

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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.

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100 mg	350 mg
150 mg	525 mg

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

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

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

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de paliperidona de liberación prolongada, se debe iniciar la administración diaria de los comprimidos 3 meses después de la última dosis de TREVICTA y continuar el tratamiento con los comprimidos de paliperidona de liberación prolongada según se describe en la tabla siguiente. La tabla siguiente indica las pautas recomendadas de conversión de las dosis para que los pacientes previamente estabilizados con diferentes dosis de TREVICTA obtengan una exposición a paliperidona similar con los comprimidos de paliperidona de liberación prolongada.

Dosis de los comprimidos de paliperidona de liberación prolongada para los pacientes que cambian desde TREVICTA*

	Tiempo transcurrido desde la última dosis de TREVICTA		
	de la semana 12 a 18, incluida	de la semana 19 a la 24, incluida	desde la semana 25 y en adelante
Última dosis de TREVICTA (semana 0)	Dosis diaria de los comprimidos de paliperidona de liberación prolongada		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

*Todas las dosis de los comprimidos de paliperidona de liberación prolongada diarios se debe adaptar siempre al paciente individual, teniendo en cuenta variables como los motivos del cambio, la respuesta al tratamiento previo con paliperidona, la gravedad de los síntomas psicóticos y/o la tendencia a presentar efectos adversos.

Dosis omitidas. *Margen de administración.* TREVICTA se debe inyectar una vez cada 3 meses. Para no omitir una dosis de TREVICTA se puede administrar a los pacientes la inyección hasta 2 semanas antes o después del momento en que se cumple el trimestre.

Dosis omitidas

Si se ha omitido la dosis programada y el tiempo transcurrido desde la última inyección es de	Medida
> 3 meses y medio a 4 meses	Se administrará la inyección lo antes posible y a continuación se reanudará el calendario de inyecciones trimestrales.
de 4 meses a 9 meses	Se seguirá la pauta de reanudación recomendada que se indica en la tabla siguiente.
> 9 meses	Se reanudará el tratamiento con palmitato de paliperidona inyectable mensual según se describe en la ficha técnica del producto. Se podrá reanudar la administración de TREVICTA después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más.

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

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

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

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en Insuficiencia renal las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides (y viceversa) en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se facilitan en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se facilitan en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos o profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso <90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dada la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones**. Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo**. Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos $<1 \times 10^9$/l) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. Excipientes. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis; esto es, esencialmente "exento de sodio". **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiacinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vitro ni in vivo de que esas isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de $C_{máx}$ y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP a la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de $C_{máx}$ y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conducientes a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, difícultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. No se debe utilizar TREVICTA durante el embarazo a menos que sea claramente necesario. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas**. La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas**. Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en ≥5% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimada en los ensayos clínicos realizados con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1.000 a <1/100), *raras* (≥1/10.000 a <1/1.000), *muy raras* (<1/10.000) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	Frecuencia no conocida[a]
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, onicomicosis, celulitis	infección oftálmica, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, aumento del recuento de eosinófilos	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, pérdida de peso, apetito disminuido	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnia[a]	agitación, depresión, ansiedad	trastornos del sueño, manía, disminución de la líbido, nerviosismo, pesadillas	catatonía, estado de confusión, sonambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[c], acatisia[c], sedación/somnolencia, distonía[c], mareo, discinesias[c], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotriz, mareo postural, trastornos de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, falta de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones[c], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

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

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP).* En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y miodistonía), distonía (incluye distonía, espasmo cervical, emprostótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetanía, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurotótonos, espasmo lingual y trismus) y temblor. *Aumento de peso.* En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de +0,94 kg y -1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia.* Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de +7,48 ng/ml para 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%]).

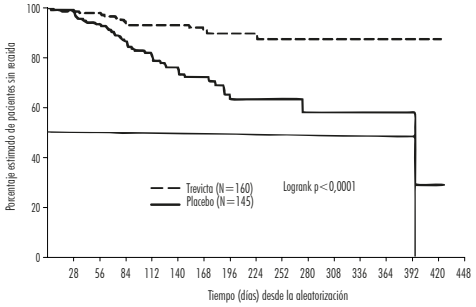


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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.

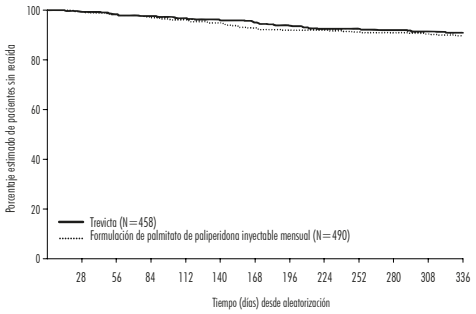


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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_{ss} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{ss}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas in vivo, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe 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_{ss}) 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 inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

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

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Medidas para evitar la omisión de dosis.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. *Omisión de la segunda dosis de iniciación (<4 semanas desde la primera inyección).* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: *Para los pacientes estabilizados con dosis de 25 a 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada > 65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥ 50 a < 80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada 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 raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos < $1x10^9$/l) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma 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-adenérgico, 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 períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. Uso concomitante de Xeplion y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10); *frecuentes* (≥1/100 a <1/10); *poco frecuentes* (≥1/1.000 a <1/100); *raras* (≥1/10.000 a <1/1.000); *muy raras* (<1/10.000); y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

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

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

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

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

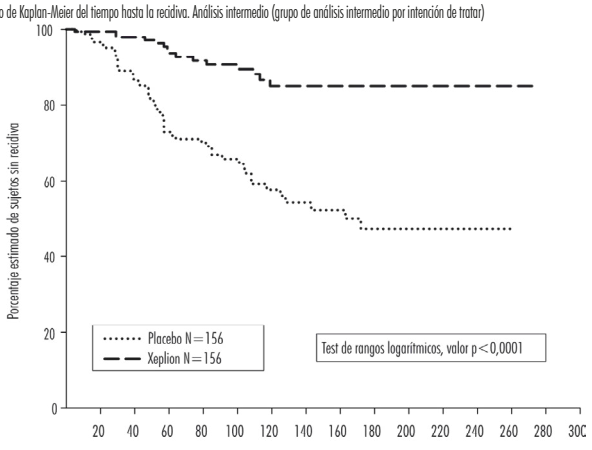
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (ClCr=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (ClCr=10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{∞}) 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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