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Will changes in alcohol and tobacco use be seen during the COVID-19 lockdown?

¿Se observarán cambios en el consumo de alcohol y tabaco durante el confinamiento por COVID-19?

Leticia García-Álvarez *,**,***,****,*****, Lorena de la Fuente-Tomás*,**,***,****, Pilar Alejandra Sáiz *,**,***,****,******, Mª Paz García-Portilla*,**,***,****,******, Julio Bobes*,**,***,****,******

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Introduction

The coronavirus pandemic (COVID-19) of recent months has triggered a global emergency. Reactions of anxiety, worry or fear are estimated to be frequent across general population given the unknown and novel nature of the disease, and the social distancing measures resulting from the state of alarm. However, the potential psychological impact, not only of coronavirus per se but also of lockdown, is still unknown, as we are facing an exceptional and unprecedented situation.

Some studies focusing on the impact of Severe Acute Respiratory Syndrome (SARS), the first massive outbreak of an infectious disease in the 21st century, have shown significant repercussions on people's mental health and their level of well-being (Ko, Yen, Yen & Yang, 2006), even four years after the epidemic (Lam et al., 2009). People talk about "bio-disasters" capable of generating psychological impacts comparable to those of other catastrophes such as terrorist attacks, earthquakes, etc. (Chong et al., 2004; Wu et al., 2008). In the case of exposure to SARS, post-traumatic stress disorder and depressive disorders have been shown to be the most prevalent mental disorders during long-term follow-up (Mak, Chu, Pan, Yiu & Chan, 2009). However, during SARS, neither the measures implemented nor the level of global impact were as extreme as on this occasion, so the effects of the COVID-19 pandemic can be expected to be even greater.

During the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreak in 2015, which caused the confinement of almost 17,000 people exposed to it, an increased risk of post-traumatic stress symptoms was observed in health workers who had treated infected patients (Lee, Kang, Cho, Kim & Park, 2018), as well as symptoms of anxiety (7.6%), anger (16.6%) and depression (19.3%), even among those under isolation measures without having become infected themselves (Yoon, Kim, Ko & Lee, 2016); in many cases, these symptoms continued during the 4-6 month period after confinement (Jeong et al., 2016).

Studies published on the psychological impact of COVID-19 in China have observed emotional distress, with severe anxiety responses present in one third of the general population (Lima et al., 2020; Wang et al., 2020). However,

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a study carried out with a large general population sample in Spain showed how during the first weeks of lockdown (from March 19 to 26) the most frequently observed pathological psychological responses were depressive symptoms (46.7%), followed by avoidance behaviour (44.3%). Furthermore, contrary to expectations, anxiety responses were the least frequent, affecting 6.1% of the population (García-Álvarez et al., 2020). Likewise, the psychological effects of lockdown seem to increase as the days go by (García-Álvarez et al., 2020) and in certain vulnerable groups of the population, such as healthcare workers (Bai et al., 2004; Maunder et al., 2003), people with past somatic disease or those with or current mental disorder, more specifically, depression, anxiety or bipolar disorder (García-Álvarez et al., 2020). Similarly, people with substance use disorders could represent at-risk groups (Pfefferbaum & North, 2020).

At issue is how this public health emergency may generate not only negative dysfunctional responses but also a lack of compliance with public health directives and at the same time trigger unhealthy behaviours such as substance use abuse (Pfefferbaum & North, 2020). The following have been put forward as potentially the most frequent responses to lockdown: stress, depression, irritability, insomnia, fear, confusion, anger, frustration, boredom or stigma, while there is also a concern that these symptoms may persist long after the quarantine period (Brooks et al., 2020). Moreover, it has also been pointed out that such measures could have a notable impact in the form of increased suicide risk in the population (Reger, Stanley & Joiner, 2020).

In the face of such a radical change in our behaviour and habits (social distancing, teleworking, limits to sports and leisure activities outside our homes, etc.), the search for alternative activities is not surprising. While the importance of expressing negative emotions, keeping in touch with family and friends, doing regular activities, leisure activities, etc. is acknowledged (Park & Park, 2020), other activities such as drinking, smoking and the use of other substances could also increase, not only as a form of distraction or a behavioural avoidance strategy but also as a result of the stress, anxiety or depressive symptoms that are being experienced.

Alcohol

Exposure to situations capable of generating post-traumatic stress disorders, such as terrorist attacks, natural disasters (earthquakes, volcanic eruptions) or accidents, has been associated with increased rates of alcohol abuse and dependence in some studies (Boscarino, Adams & Galea, 2006; Lebeaut, Tran & Vujanovic, 2020). However, results have shown the opposite tendency in others (North, Kawasaki, Spitznagel & Hong, 2004; Shimizu et al., 2000). It is therefore essential to analyze which factors are able to determine the differences found in these studies and estimate the extent to which these behaviours may be on the increase during this period of lockdown.

In the case of SARS, alcohol abuse or dependence was linked to working in health care during the epidemic, even three years after the outbreak (Wu et al., 2008). A higher degree of exposure to the virus and having to be isolated as a consequence were identified as risk factors. However, having family members affected or killed by SARS, or being exposed to news about the epidemic, were not related to alcohol abuse and dependence. In addition, a dose-response relationship was identified between intensity of virus exposure and symptoms of long-term alcohol abuse and dependence (Wu et al., 2008).

Regarding the COVID-19 pandemic, there are still no data on substance abuse disorders, or studies assessing the possible increase in consumption as a consequence of lockdown.

Tobacco

The use of alcohol, tobacco, and marijuana often occurs together (Degenhardt, Hall & Lynskey, 2001). It has been shown that smoking increases in the face of various environmental stressors, such as armed conflicts, natural disasters, etc. However, as in the case of alcohol (Sánchez-Autet et al., 2018), the possibility has been raised that this use is mediated by depressive symptoms or post-traumatic stress disorders (Ben-Zur & Zeidner, 2009; Jiménez-Treviño et al., 2019; Gross, Bastian, Smith, Harpaz-Rotem & Hoff, 2020). Differences based on gender have also been observed; specifically, it seems that women resort to smoking more frequently than men to regulate negative affect (Japuntich et al., 2016).

Regarding the COVID-19 pandemic, people who smoke or use vapers have been identified as a group more vulnerable to infection and its associated complications (Cai, 2020) since pathologies such as cardiovascular or comorbid respiratory diseases, which are more prevalent in chronic smokers, have been linked to a worse prognosis in patients infected with COVID-19 (Volkow, 2020). Therefore, special attention should be paid to this group given the increased risk of infection and the serious consequences they face.

It is also necessary to establish the extent to which changes in smoking patterns (new users, increased frequency, intensity of consumption, etc.) are taking place as a consequence of emotional distress, or as an avoidance strategy or alternative to boredom during lockdown and the pandemic.

Assessment and intervention

For all the above reasons, an assessment of emotional disturbances and behavioural changes is necessary, not only for the present moment in time, but also prospec-

tively, especially in people with persistent dysfunctional responses, with the aim of creating specific interventions adapted to current needs. To this end, it is necessary to determine what the vulnerability factors as well as the protective factors are, and to design adapted programs.

Among the psychological support measures proposed in China to address COVID-19 is a multidisciplinary approach which includes, among others, psychologists, psychiatrists, and mental health specialists, and which aims to provide reliable and up-to-date information on the pandemic and to establish different services to provide psychological support, which may include internet-based treatment programs (Xiang et al., 2020).

In Spain, in addition to the standard mental health approach, currently being applied whenever possible by telephone, there are helplines staffed by psychologists providing support to health professionals, family members of people hospitalized by COVID-19 or in cases in which a death has occurred (informing the relatives, asking for consent for sedation, facilitating a final contact and reporting the death as it occurs) (Arango, 2020).

Conclusions

While the coronavirus pandemic (COVID-19) and lockdown could trigger dysfunctional responses such as anxiety or depression, it could also lead to an increase in unhealthy behaviours such as excessive drinking or smoking.

It is necessary to develop psychological support measures for the entire population and, in particular, for the most vulnerable groups as well as for those who develop disorders as a consequence.

Moreover, it should be remembered that people subjected to situations of stress and isolation such as the current scenario could resort more frequently to substance use to alleviate negative emotions. Those with a substance use disorder in remission could also have to cope with tension and more intense cravings, leading to an increased risk of relapse. Therefore, primary care physicians and mental health specialists should pay special attention to this possibility, assessing their patients' situation and examining them to ensure they are free of any signs of substance abuse.

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Conflict of interests

The authors declare no conflicts of interest.

References

Arango, C. (2020). Lessons learned from the coronavirus health crisis in Madrid, Spain: How COVID-19 has changed our lives in the last two weeks. *Biological Psychiatry*. Advance publication online. doi:10.1016/j.biopsych.2020.04.003.

Bai, Y., Lin, C. C., Lin, C. Y., Chen, J. Y., Chue, C. M. & Chou, P. (2004). Survey of stress reactions among health care workers involved with the SARS outbreak. *Psychiatry Service, 55*, 1055-1057. doi:10.1176/appi.ps.55.9.1055.

Ben-Zur, H. & Zeidner, M. (2009). Threat to life and risk-taking behaviors: a review of empirical findings and explanatory models. *Personality and Social Psychology Review, 13*, 109–128. doi:10.1177/1088868308330104.

Boscarino, J. A., Adams, R. E. & Galea, S. (2006). Alcohol use in New York after the terrorist attacks: a study of the effects of psychological trauma on drinking behavior. *Addictive Behaviors, 31*, 606-621. doi:10.1016/j.addbeh.2005.05.035.

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N. & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet, 395*, 912-920. doi:10.1016/S0140-6736(20)30460-8.

Cai, H. (2020). Sex difference and smoking predisposition in patients with COVID-19. *The Lancet Respiratory Medicine, 8*, e20. doi:10.1016/S2213-2600(20)30117-X.

Chong, M. Y., Wang, W. C., Hsieh, W. C., Lee, C. Y., Chiu, N. M., Yeh, W. C., . . . Chen, C. L. (2004). Psychological impact of severe acute respiratory syndrome on health workers in a tertiary hospital. *The British Journal of Psychiatry, 185*, 127-133. doi:10.1192/bjp.185.2.127.

Degenhardt, L., Hall, W. & Lynskey, M. (2001). The relationship between cannabis use and other substance use in the general population. *Drug and Alcohol Dependence, 64*, 319–327.

García-Alvarez, L., de la Fuente-Tomás, L., García-Portilla, M. P., Saiz, P. A., Moya-Lacasa, C., dal Santo, F., …Bobes, J. (2020) Early impact of the 2019 coronavirus disease (COVID-19) pandemic and lockdown in a large Spanish sample. *Psychological Medicine*. Manuscript submitted for publication.

Gross, G. M., Bastian, L. A., Smith, N. B., Harpaz-Rotem, I. & Hoff, R. (2020). Sex differences in associations between depression and posttraumatic stress disorder symptoms and tobacco use among veterans of recent conflicts. *Journal of Womens Health (Larchmt)*. Advance publication online. doi:10.1089/jwh.2019.8082.

Japuntich, S. J., Gregor, K., Pineles, S. L., Gradus, J. L., Street, A. E., Prabhala, R. & Rasmusson, A. M. (2016). Deployment stress, tobacco use, and postdeployment posttraumatic stress disorder: Gender differences. *Psychological Trauma*, 8, 123-126. doi:10.1037/tra0000093.

Jeong, H., Yim, H. W., Song, Y. J., Ki, M., Min, J. A., Cho, J. & Chae, J. H. (2016). Mental health status of people isolated due to Middle East respiratory syndrome. *Epidemiology and Health, 38*, e2016048. doi:10.4178/epih.e2016048.

Jiménez-Treviño, L., Velasco, A., Rodriguez-Revuelta, J., Abad, I., De la Fuente-Tomás, L., González-Blanco, L., … Saiz, P. A. (2019). Factors associated with tobacco consumption in patients with depression. *Adicciones, 31,* 298-308. doi:10.20882/adicciones.1191.

Ko, C. H., Yen, C. F., Yen, J. Y. & Yang, M. J. (2006). Psychosocial impact among the public of the severe acute respiratory syndrome epidemic in Taiwan. *Psychiatry and Clinical Neurosciences, 60*, 397-403. doi:10.1111/j.1440-1819.2006.01522.x.

Lam, M. H., Wing, Y. K., Yu, M. W., Leung, C. M., Ma, R. C., Kong, A. P., . . . Lam, S. P. (2009). Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Archives of Internal Medicine, 169*, 2142-2147. doi:10.1001/archinternmed.2009.384.

Lebeaut, A., Tran, J. K. & Vujanovic, A. A. (2020). Posttraumatic stress, alcohol use severity, and alcohol use motives among firefighters: The role of anxiety sensitivity. *Addictive Behaviors, 106*, 106353. doi:10.1016/j.addbeh.2020.106353.

Lee, S. M., Kang, W. S., Cho, A. R., Kim, T. & Park J.K. (2018). Psychological impact of the 2015 MERS outbreak on hospital workers and quarantined hemodialysis patients. *Comprehensive Psychiatry, 87*, 123-127. doi:10.1016/j.comppsych.2018.10.003.

Lima, C. K. T., Carvalho, P. M. M., Lima, I., Nunes, J., Saraiva, J. S., de Souza, R. I., . . . Neto, M. L. R. (2020). The emotional impact of Coronavirus 2019-nCoV (new Coronavirus disease). *Psychiatry Research, 287*, 112915. doi:10.1016/j.psychres.2020.112915.

Mak, I. W., Chu, C. M., Pan, P. C., Yiu, M. G. & Chan, V. L. (2009). Long-term psychiatric morbidities among SARS survivors. *General Hospital Psychiatry, 31*, 318-326. doi:10.1016/j.genhosppsych.2009.03.001.

Maunder, R., Hunter, J., Vincent, L., Bennett, J., Peladeau, N., Leszcz, M., . . . Mazzulli, T. (2003). The immediate psychological and occupational impact of the 2003 SARS outbreak in a teaching hospital. *Canadian Medical Association Journal , 168,* 1245-1251.

North, C. S., Kawasaki, A., Spitznagel, E. L. & Hong, B. A. (2004). The course of PTSD, major depression, substance abuse, and somatization after a natural disaster. *The Journal of Nervous and Mental Disease, 192*, 823-829. doi:10.1097/01.nmd.0000146911.52616.22.

Park, S. C. & Park, Y. C. (2020). Mental health care measures in response to the 2019 novel coronavirus outbreak in Korea. *Psychiatry Investigation, 17*, 85-86. doi:10.30773/pi.2020.0058.

Pfefferbaum, B. & North, C. S. (2020). Mental health and the Covid-19 pandemic. *The New England Journal of Medicine*. Advance publication online. doi:10.1056/NEJMp2008017.

Reger, M. A., Stanley, I. H. & Joiner, T. E. (2020). Suicide mortality and coronavirus disease 2019-A perfect storm? *JAMA Psychiatry*. Advance publication online. doi:10.1001/jamapsychiatry.2020.1060.

Sánchez Autet, M., Garriga, M., Zamora, F.J., González, I., Usall, J., Tolosa, L., …Arranz, B. (2018). Screening of alcohol use disorders in psychiatric outpatients: influence of gender, age, and psychiatric diagnosis. *Adicciones, 30,* 251-263. doi:10.20882/adicciones.885.

Shimizu, S., Aso, K., Noda, T., Ryukei, S., Kochi, Y. & Yamamoto, N. (2000). Natural disasters and alcohol consumption in a cultural context: the Great Hanshin Earthquake in Japan. *Addiction, 95*, 529-536. doi:10.1046/j.1360-0443.2000.9545295.x.

Volkow, N. D. (2020). Collision of the COVID-19 and addiction epidemics. *Annals of Internal Medicine*. Advance publication online. doi:10.7326/m20-1212.

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S. & Ho, R. C. (2020). Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *International Journal of Environmental Research and Public Health, 17*. Advance publication online. doi:10.3390/ijerph17051729.

Wu, P., Liu, X., Fang, Y., Fan, B., Fuller, C. J., Guan, Z., . . . Litvak, I. J. (2008). Alcohol abuse/dependence symptoms among hospital employees exposed to a SARS outbreak. *Alcohol and Alcoholism, 43*, 706-712. doi:10.1093/alcalc/agn073.

Xiang, Y. T., Yang, Y., Li, W., Zhang, L., Zhang, Q., Cheung, T. & Ng, C. H. (2020). Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiatry, 7*, 228-229. doi:10.1016/S2215-0366(20)30046-8.

Yoon, M. K., Kim, S. Y., Ko, H. S. & Lee, M. S. (2016). System effectiveness of detection, brief intervention and refer to treatment for the people with post-traumatic emotional distress by MERS: a case report of community-based proactive intervention in South Korea. *International Journal of Mental Health Systems, 10,* 51. doi:10.1186/s13033-016-0083-5.

For most fully alcohol-attributable diagnoses in the ICD, the etiological specification should be removed

La CIE debería de eliminar la especificación etiológica en la mayoría de diagnósticos atribuibles al alcohol

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The International Classification of Diseases (ICD) is the international standard for defining and reporting diseases and health conditions, with the purpose of providing a foundation for the identification of health statistics and trends globally, as well as evidence-based decision-making (World Health Organization, n.d.). There are more than 40 diseases which are 100% attributable to alcohol (Rehm et al., 2017) in the current versions of the ICD (10th revision [ICD-10] and 11th revision [ICD-11]) (World Health Organization, 2018a). The practice of specifying alcohol, alcoholic or alcohol-induced in the name of a disease in the ICD has been occurring since the 1920s. However, it is time to reconsider this practice for the majority of these disease and injury categories, with the exception of disorders due to use of alcohol (ICD-11: 6C40) or alcohol poisoning (ICD-11: NE61, PD00, PH50), as it often does not lead to a specific clinical intervention, but rather has a number of negative consequences. In this contribution, it is argued that the etiological specification should be removed from the names of most fully alcohol-attributable diagnoses in the ICD using two specific examples to outline the consequences of this practice: alcoholic liver disease (ICD-11: DB94) and foetal alcohol syndrome (FAS; ICD-11: LD2F.00).

Alcoholic liver disease

First, diagnoses of all disease categories with alcohol in the name are considerably underestimated in both the health-care system, as well as on death certificates. Consider the classic study of Puffer and Griffith (1967), which included data from 12 cities in ten countries, and compared data on death certificates with data from hospital records and interviews of attending physicians or family members. This led to more than a doubling of the number of deaths deemed to be due to alcoholic liver cirrhosis, with the majority of new cases having been recorded originally under other categories of cirrhosis, none of which referred to alcohol as the causal agent. This kind of underreporting has persisted in current times and is not restricted to alcoholic liver disease, but rather extends to other chronic diseases fully attributable to alcohol (see examples in Rehm, Hasan,

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Imtiaz & Neufeld, 2017). It has been demonstrated using various comparison standards, autopsies, clinical markers, interviews with family members, as well as indirect measures. One of the main reasons for underreporting is this: diagnoses with alcohol are associated with a high level of stigmatization, over and above the stigma of mental disorders (Schomerus et al., 2011). Heavy drinkers and people with alcohol use disorders are not only seen as responsible for their disorder, but are also thought to be aggressive and disruptive. This stigma may lead to heavy drinkers avoiding the health-care system and, ultimately, a failure to disclose their alcohol use (Probst, Manthey, Martinez & Rehm, 2015).

For the treatment of liver disease itself, most treatment interventions are the same irrespective of the etiology–that is to say, interventions for the liver do not necessarily differ, and alcohol use should always be assessed, minimized or avoided. Assessment of alcohol use can be done via modern biomarkers such as phosphatidylethanol (PEth) (Carvalho, Heilig, Perez, Probst & Rehm, 2019; Andresen-Streichert, Müller, Glahn, Skopp & Sterneck, 2018), thus avoiding potential underreporting as a result of stigmatization. The reason for assessing alcohol use and intervening when it is reported is that for people affected by liver cirrhosis, even relatively small amounts consumed regularly may lead to death (Fuster & Samet, 2018). Unfortunately, alcohol use is often not addressed when it is not considered to be the etiology of the disease. This is problematic, as a recent study of all French patients over a five-year period showed that 71.8% (95% confidence interval [CI]: 66.0% to 76.8%) of 17,669 liver-related complications, 67.4% (95% CI: 61.6% to 72.4%) of 1,599 liver transplantations, and 68.8% (95% CI: 63.4% to 73.5%) of 6,677 deaths in people with chronic hepatitis C virus infections were due to alcohol use, and a large part could have been avoided if alcohol use had been addressed (Schwarzinger, Baillot, Yazdanpanah, Rehm & Mallet, 2017). The above numbers may even be an underestimate for the reasons mentioned above: alcohol use is not regularly assessed and reported in French hospital settings, and disorders used to identify heavy alcohol use in this study were likely underreported. This reasoning is even true for the so-called non-alcoholic fatty liver disease (ICD-11: DB92), where alcohol use plays a role in worsening as well (Fuster & Samet, 2018).

Finally, the reliance on alcoholic liver disease as a category severely impedes the estimate of the true impact of alcohol, as people are classified based on their presumed original etiology, and not on the impact of alcohol as a risk factor. For example, an analysis that relied on the diagnosis of alcoholic liver cirrhosis to estimate the proportion of liver cirrhosis mortality and burden of disease attributable to alcohol (GBD 2016 Alcohol Collaborators, 2018) estimated about 50% lower mortality and 60% lower burden of disease than an analysis that used all liver cirrhosis and estimated the contribution of alcohol via the usual epidemiological attributable fraction methodology in the World Health Organization Global Status Report (World Health Organization, 2018b). Furthermore, the differentiation of alcoholic vs. non-alcoholic liver disease is often made based on the reported alcohol intake of the patient. The threshold varies between 20-40 grams of pure ethanol per day; however, aside from the fact that most people are not able to report their alcohol intake accurately, or are simply being dishonest, this threshold seems arbitrary and does not consider the multifactorial etiology of liver diseases (Pimpin et al., 2018; Roerecke et al., 2019). Again, the use of biomarkers such as PEth would be advisable for both clinical practice and research.

This is not to say that alcohol is not one of the leading risk factors for liver diseases, but identifying an "alcoholic" liver disease ignores the contribution of other risk factors, and conversely, the contribution of alcohol is ignored in the so-called "non-alcoholic" liver diseases.

Foetal alcohol syndrome

As with other fully alcohol-attributable diagnoses, individuals prenatally exposed to alcohol often feel judged by others, which prevents them, or their family members, from seeking diagnostic services and interventions that could contribute to an improved quality of life, in order to avoid being labeled with a stigmatizing diagnosis. Stigma is an important clinical risk factor as it is known to delay treatment-seeking, worsen course and outcome, reduce compliance, and to increase the risk of relapse, causing further disability, discrimination and isolation even in individuals who have accessed services (Shrivastava, Bureau, Rewari & Johnston, 2013). It is for this reason that women also tend to deny or underreport their alcohol use during pregnancy (Lange, Shield, Koren, Rehm & Popova, 2014), which ultimately leads to the misdiagnosis of FAS. The purpose of a classification system is to provide disorder categorizations that are independent (Lecrubier, 2008); however, the coexistence of FAS with other neurodevelopmental disorder diagnoses (such as, attention deficit hyperactivity disorder [ICD-11: 6A05]) appears to be the norm (Lange, Rehm, Anagnostou & Popova, 2018). In fact, it was recently found that children with foetal alcohol spectrum disorder, the umbrella term used to encompass a number of alcohol-related diagnoses including FAS, are neurodevelopmentally and behaviorally indistinguishable from children with other neurodevelopmental disorders (Lange, Shield, Rehm, Anagnostou & Popova, 2019). This finding is a demonstration of the insignificance of specifying alcohol as the cause of the neurodevelopmental impairments with respect to clinical practice, especially given that there is no evidence to support such differentiation with respect to treatment effectiveness (Premji, Benzies, Serrett & Hayden, 2007).

Prenatal alcohol exposure is associated with a wide range of symptoms and a diagnosis of FAS is not an indication of a specific set of those symptoms. Even worse, a diagnosis of FAS does not lead to an established treatment plan (Price & Miskelly, 2015), as there is no specific therapeutic strategy for FAS (Murawski, Moore, Thomas & Riley, 2015).

Discussion

It is clear from the two examples presented above that specifying "alcohol" in the name of a disease has limited clinical relevance, and can even lead to delayed care and mistreatment. Such a specification can lead to inappropriate reporting, which has significant implications for research, public health policy, and health-care planning, especially given that, as all evidence indicates, conditions containing "alcohol" in their name will be underreported.

It can certainly be argued that the specification of alcohol in a disease name is necessary to maximize prevention efforts. In fact, the incidence and prevalence of a condition are indicators of the respective conditions' public health burden and provide a basis for resource allocation for health care and prevention initiatives. However, if such estimates are flawed because they are based on a system that inherently leads to misdiagnosis, then it should be deduced that the system itself is flawed. Given that, as the international diagnostic classification standard for clinical and research purposes, maximizing prevention efforts is not the purpose of the ICD (World Health Organization, n.d.), and that other methodology exists to determine the correct incidence and prevalence of conditions that would not exist without the contribution of alcohol (Rehm et al., 2004), successful prevention initiatives are not contingent on specifying alcohol, alcoholic or alcohol-induced in the name of a disease in the ICD. Consider tobacco use as an example: prevention of tobacco-attributable disease burden was certainly possible without creating disease categories such as tobacco-induced lung cancer.

Further, one of the major aims for classifying patients as having one disorder or another is to link them with the best possible therapeutic intervention (Lecrubier, 2008). If the treatment approach does not differ from that of other conditions with the same symptomatology, whether idiopathic or not, then specifying alcohol in the name of such health conditions is simply not necessary.

One could argue that the root of the problem is stigmatization, and in fact, contrary to other mental disorders, stigmatization of harmful alcohol use and alcohol use disorders has not improved over the past couple decades (Schomerus, Matschinger & Angermeyer, 2014). As such, efforts are urgently needed to address the stigma surrounding fully alcohol-attributable conditions, and thus, in this day and age having disease names which promote stigmatization is unacceptable. We currently have a system that results in inaccurate conclusions for clinical care, health policy and research with respect to most fully alcohol-attributable conditions, which can easily be fixed. Therefore, it is time for the ICD to remove the etiological specification of alcohol in disease names when it comes to diseases causally linked to alcohol.

Conflict of interest

The authors have no conflicts of interest to declare.

References

Andresen-Streichert, H., Müller, A., Glahn, A., Skopp, G. & Sterneck, M. (2018). Alcohol biomarkers in clinical and forensic contexts. *Deutsches Arzteblatt International, 115,* 309-315. doi:10.3238/arztebl.2018.0309.

Carvalho, A. F., Heilig, M., Perez, A., Probst, C. & Rehm, J. (2019). Alcohol use disorders. *The Lancet, 394,* 781-792. doi:10.1016/S0140-6736(19)31775-1.

Fuster, D. & Samet, J. H. (2018). Alcohol use in patients with chronic liver disease. *New England Journal of Medicine, 379,* 1251-1261. doi:10.1056/NEJMc1814129.

GBD 2016 Alcohol Collaborators. (2018). Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet, 392,* 1015-1035. doi:10.1016/S0140-6736(18)31310-2.

Lange, S., Rehm, J., Anagnostou, E. & Popova, S. (2018). Prevalence of externalizing disorders and Autism Spectrum Disorders among children with Fetal Alcohol Spectrum Disorder: systematic review and meta-analysis. *Biochemistry and Cell Biology, 96,* 241-251. doi:10.1139/bcb-2017-0014.

Lange, S., Shield, K., Koren, G., Rehm, J. & Popova, S. (2014). A comparison of the prevalence of prenatal alcohol exposure obtained via maternal self-reports versus meconium testing: a systematic literature review and meta-analysis. *BMC Pregnancy and Childbirth, 14,* 127. doi:10.1186/1471-2393-14-127.

Lange, S., Shield, K., Rehm, J., Anagnostou, E. & Popova, S. (2019). Fetal alcohol spectrum disorder: Neurodevelopmentally and behaviorally indistinguishable from other neurodevelopmental disorders. *BMC Psychiatry, 19,* 322. doi:10.1186/s12888-019-2289-y.

Lecrubier, Y. (2008). Refinement of diagnosis and disease classification in psychiatry. *European Archives of Psychiatry and Clinical Neuroscience, 258(Supl. 1),* 6-11. doi:10.1007/s00406-007-1003-0.

Murawski, N. J., Moore, E. M., Thomas, J. D. & Riley, E. P. (2015). Advances in Diagnosis and Treatment of Fetal Alcohol Spectrum Disorders: From Animal Models to Human Studies. *Alcohol Research: Current Reviews, 37,* 97-108.

Pimpin, L., Cortez-Pinto, H., Negro, F., Corbould, E., Lazarus, J. V., Webber, L.,… EASL HEPAHEALTH Steering Committee. (2018). Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. *Journal of Hepatology, 69,* 718-735. doi:10.1016/j.jhep.2018.05.011.

Premji, S., Benzies, K., Serrett, K. & Hayden, K. A. (2007). Research-based interventions for children and youth with a Fetal Alcohol Spectrum Disorder: revealing the gap. *Child: Care, Health and Development, 33,* 389-397; discussion 398-400.

Price, K. J. & Miskelly, K. J. (2015). Why Ask Why? Logical Fallacies in the Diagnosis of Fetal Alcohol Spectrum Disorder. *Ethics & Behavior, 25,* 418-426. doi:10.1080/10508422.2014.946031

Probst, C., Manthey, J., Martinez, A. & Rehm, J. (2015). Alcohol use disorder severity and reported reasons not to seek treatment: a cross-sectional study in European primary care practices. *Substance Abuse Treatment, Prevention, and Policy, 10,* 32. doi:10.1186/s13011-015-0028-z.

Puffer, R. R. & Griffith, G. W. (1967). *Patterns of urban mortality: report of the Inter-American Investigation of Mortality.* Scientific Publication no. 151. Washington, D.C.: Pan American Health Organization.

Rehm, J., Gmel, G. E. Sr., Gmel, G., Hasan, O. S. M., Imtiaz, S., Popova, S.,… Shuper, P. A. (2017). The relationship between different dimensions of alcohol use and the burden of disease—an update. *Addiction, 112*, 968-1001. doi:10.1111/add.13757.

Rehm, J., Hasan, O. S. M., Imtiaz, S. & Neufeld, M. (2017). Quantifying the contribution of alcohol to cardiomyopathy: a systematic review. *Alcohol, 61,* 9-15. doi:10.1016/j.alcohol.2017.01.011.

Rehm, J., Room, R., Monteiro, M., Gmel, G., Graham, K., Rehn, N.,… Jernigan, D. (2004). Alcohol use. In: M. Ezzati, A. D. Lopez, A. Rodgers & C. J. L. Murray (Eds.), *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors.* (pp. 959-1108). Geneva, Switzerland: World Health Organization.

Roerecke, M., Vafaei, A., Hasan, O. S. M., Chrystoja, B., Cruz, M., Lee, R.,… Rehm, J. (2019). Alcohol consumption and risk of liver cirrhosis: a systematic review and meta-analysis. *American Journal of Gastroenterology, 114,* 1574-1586. doi:10.14309/ajg.0000000000000340.

Schomerus, G., Lucht, M., Holzinger, A., Matschinger, H., Carta, M. G. & Angermeyer, M. C. (2011). The stigma of alcohol dependence compared with other mental disorders: a review of population studies. *Alcohol and Alcoholism, 46,* 105-112. doi:10.1093/alcalc/agq089.

Schomerus, G., Matschinger, H. & Angermeyer, M. C. (2014). Attitudes towards alcohol dependence and affected individuals: persistence of negative stereotypes and illness beliefs between 1990 and 2011. *European Addiction Research, 20,* 293-299. doi:10.1159/000362407.

Schwarzinger, M., Baillot, S., Yazdanpanah, Y., Rehm, J. & Mallet, V. (2017). Contribution of alcohol use disorders on the burden of chronic hepatitis C in France, 2008–2013: A nationwide retrospective cohort study. *Journal of Hepatology, 67,* 454-461. doi:10.1016/j.jhep.2017.03.031.

Shrivastava, A., Bureau, Y., Rewari, N. & Johnston, M. (2013). Clinical risk of stigma and discrimination of mental illnesses: Need for objective assessment and quantification. *Indian Journal of Psychiatry, 55,* 178-182. doi:10.4103/0019-5545.111459.

World Health Organization. (2018a). *Classifications ICD-11 2018.* Geneva, Switzerland: WHO. Retrieved at https://www.who.int/classifications/icd/en/

World Health Organization. (2018b). *Global status report on alcohol and health 2018.* Geneva, Switzerland: WHO. Retrieved at https://www.who.int/substance_abuse/publications/global_alcohol_report/en/

World Health Organization. (n.d.). *International Classification of Diseases (ICD) Information Sheet.* Retrieved at https://www.who.int/classifications/icd/factsheet/en/

Birth-sex cohort alcohol use transitions in the general population: the cross-sectional PEGASUS-Murcia project

Las transiciones en el uso de alcohol en una cohorte de nacimiento-sexo en la población general: el proyecto transversal PEGASUS-Murcia

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Abstract

To examine the potential impact of prevalence of alcohol use in a birth-sex cohort on subsequent initiation and progression of alcohol use in the PEGASUS-Murcia project, a cross-sectional survey of a representative sample of non-institutionalized adults in Murcia (Spain). Data on lifetime history of alcohol use, DSM-IV use disorders, and remission were collected from 1,459 adults using face-to-face interviewers based on the Composite International Diagnostic Interview (CIDI 3.0). Life-table estimates based on survival functions for alcohol use age-of-onset and remission were used as time-varying predictors of subsequent individual-level alcohol use in discrete-time survival models. Nearly nine out of ten adults had a lifetime alcohol use history at time of interview. Of these lifetime users, 84.3% became regular users (>12 drinks a year) and 5.5-1.6% went on to meet criteria for DSM-IV alcohol abuse or dependence, respectively. By the age of 18, 70.9% of respondents had used alcohol, and one half (50.2%) had used regularly. Regular use sharply increased during early adulthood to reach 90.8% by age 22. Birth-sex cohort alcohol use was significantly and positively associated with increased odds of all subsequent transitions examined except for the transition from use to abuse. The findings highlight sensitive periods with rapid transitions to higher levels of alcohol use and emphasize the importance of cohort experiences in the full spectrum of stages of alcohol use. These results may contribute to predicting population-levels trends in alcohol-related problems in Spain.

Keywords: Alcohol; Abuse; Cohort-use; Dependence; Remission.

Resumen

Examinar el impacto potencial de la prevalencia de uso de alcohol en una cohorte de nacimiento-sexo en el inicio y progresión del uso de alcohol en el proyecto PEGASUS-Murcia, encuesta transversal en una muestra representativa de adultos no institucionalizados de Murcia (España). Se entrevistaron personalmente a 1.459 adultos sobre consumo de alcohol a lo largo de la vida, trastornos por uso de alcohol (criterios DSM-IV) y remisión utilizando la Entrevista Diagnóstica Internacional Compuesta (CIDI 3.0). Se calcularon estimaciones de tablas de vida basadas en las funciones de supervivencia para la edad de inicio en el uso de alcohol y su remisión en modelos de supervivencia de tiempo discreto. Casi nueve de cada diez adultos tuvieron una historia de uso de alcohol a lo largo de la vida. Entre ellos, 84,3% desarrolló un uso regular (> 12 bebidas por año) y 5,5% y 1,6% cumplieron criterios DSM-IV de Abuso y Dependencia de alcohol, respectivamente. A los 18 años, 70,9% había usado alcohol, 50,2% de forma regular, con un aumento brusco en adultos jóvenes (90,8% a los 22 años). El uso de alcohol de la cohorte de nacimiento-sexo se asoció significativamente con mayores probabilidades para todas las transiciones examinadas, excepto en la transición uso-abuso. Se detectan períodos sensibles con transiciones rápidas a niveles más altos de uso de alcohol. Las experiencias de cohortes en todas las etapas del consumo de alcohol son importantes. Estos resultados podrían contribuir a la predicción de las tendencias poblacionales de los problemas con el alcohol en España.

Palabras clave: Alcohol; Abuso; Cohorte; Dependencia; Remisión.

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According to the Spanish Observatory on Drugs and Drug Abuse (Observatorio Español de la Droga y las Toxicomanías, 2017), more than 90% of Spanish citizens had used alcohol at least once in their life between 2009-2015 with daily alcohol consumption among 9.3% of the population (Gual et al., 2016). Alcohol consumption per capita among individuals 15 years and above in Spain is estimated at 11.2 liters per year (World Health Organization, 2014) and alcoholism is considered to be a major public health problem (Pérez, 2002). Since the mid 1970's, overall alcohol consumption decreased due mostly to a decrease in wine consumption. As of 2010, 50% of recorded alcohol consumption was beer, followed by spirits (28%) and wine (20%). As is the case in Spain, most adults living in Western cultures have used alcohol at some point in their life (Degenhardt et al., 2008), however only a small portion develops an alcohol use disorder (AUD) (Demyttenaere et al., 2004). Considering the severity of alcohol-related burden of disease (Rehm, Gmel & Gual, 2013; Rehm et al., 2009), there has been extensive research to identify factors associated with the risk of transitioning from earlier to later stages of alcohol use.

Male sex, lower education level, ethnicity, exposure to traumatic events, prior mental disorders, and age of first alcohol use have been associated with greater risk of transitioning from alcohol use to alcohol use disorders (DeWit, Adlaf, Offord & Ogborne, 2000; Flórez-Salamanca et al., 2013; Grant, 1997; Kalaydjian et al., 2009; Lee et al., 2009; Lev-Ran, Imtiaz, Rehm & Le Foll, 2013; Lopez-Quintero et al., 2011; Oberleitner, Smith, Weinberger, Mazure & McKee, 2015; Probst, Moyo, Purshouse & Rehm, 2015; Silveira et al., 2011; Suliman, Seedat, Williams & Stein, 2010; Werner et al., 2016). In addition, contextual factors including peer substance use, period, birth-sex cohort and age have been shown to affect both a given population's use of alcohol (Degenhardt, Stockings, Patton, Hall & Lynskey, 2016; Grant, 1997; Rehm et al., 2015) and transitions from use to disorders (Grant, 1997). Yet, the role of birth-sex cohort use in the full spectrum of transitions from use to AUDs and from AUDs to remission remains unclear. Studies that have examined factors associated with the full trajectory of alcohol use have provided evidence of differential risk of contextual factors as a function of the stage of progression (Abdin, Subramaniam, Vaingankar & Chong, 2013; Carballo, Fernandez-Hermida, Secades-Villa & García-Rodríguez, 2008; Carballo et al., 2008; Kalaydjian et al., 2009; Lee et al., 2009; Silveira et al., 2011), reinforcing the need to include the full spectrum of alcohol transitions when examining specific risk factors.

The study seeks to examine the role of cohort use in the natural history of alcohol use and use disorders in a representative sample of the general population of Murcia, one of 17 autonomous regions of Spain. The specific objectives are to identify the age of onset and time to transition between various stages of alcohol use in the general population of Murcia, and to estimate the association of birth-sex cohort alcohol use with the probability of transitioning to regular alcohol use, use disorder, and remission from abuse.

Method

Procedure and participants

The Psychiatric Enquiry to General Population in Southeast Spain-Murcia (PEGASUS-Murcia) project is a cross-sectional general population survey that is part of the World Mental Health (WMH) Survey Initiative (http://www.hcp.med.harvard.edu/wmh/). The study was carried out between 2010 and 2012 and was designed to collect data on the prevalence, age of onset, burden, treatment, and correlates of common mental disorders in a representative sample of the general population of adults residing in the Murcia region (Navarro-Mateu et al., 2013b; Navarro-Mateu et al., 2015). The overall response rate was 67.7%. After obtaining written consent for participation, face-to-face computer-assisted interviews were conducted by trained lay-interviewers with 2,621 adults 18 or older. As described in detail previously (Navarro-Mateu et al., 2013b), interviews were divided into two parts to reduce participant burden: Part 1 and Part 2. Part 1 was administered to all participants and included the core diagnostic assessment of mood and anxiety disorders. Part 2 comprised the assessment of additional mental disorders including alcohol use disorders and was administered to respondents who had endorsed mood and anxiety symptoms, and to a probability subsample of those who had not endorsed such symptoms. The present study is based on the Part 2 sample (n=1,459) for which data on alcohol use and alcohol use disorders were collected. The protocol was approved by the Clinical Ethics Research Committee of the University Hospital Virgen de la Arrixaca of Murcia. The present study has been written in accordance with the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) statement guidelines (von Elm et al., 2007).

Measures: Alcohol use and stages of use

The Spanish adaptation (Navarro-Mateu et al., 2013a) of the CAPI (Computer Assisted Personal Interviewing) version of the WHO Composite International Diagnostic Interview 3.0 (hereafter referred to as the CIDI) (Kessler & Ustun, 2004) was used to ascertain the presence of Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) (American Psychiatric Association, 2000) alcohol use disorders (AUDs). Alcohol use was defined as having ever consumed a standard alcoholic beverage, including beer, wine, wine coolers, or hard liquor. Regular use was defined as having 12 alcoholic drinks or

more in a one-year period. Questions regarding alcohol abuse and dependence were asked of all persons who, in the year they drank most, either consumed alcohol at least once per week, or drank five or more drinks per day on the days they drank. Remission was defined as the absence of disorder-related symptoms for more than 12 months prior to the interview. In addition, retrospective age-of-onset reports were provided regarding each stage of alcohol use.

Data Analysis

All analyses were based on weighted data, accounting for stratification and clustering, as described in detail elsewhere (Navarro-Mateu et al., 2013b). Briefly, sampling weights were applied to account for differential probabilities of selection at each sampling stage, and post-stratification weights were applied to ensure the data were representative of the regional general population based on available census data from the Murcia region in 2010. Part 2 individuals were additionally weighted in order to adjust for differential sampling of individuals with mental health problems and ensure data representativeness of the Part 2 subsample. Lifetime prevalence was estimated as the proportion of all respondents who had ever met criteria for a given disorder in their lifetime up to the age at interview. Life-table (actuarial) estimates of the survival functions for age of onset and remission were produced using the PROC LIFETEST procedure in SAS Version 9.4.

The association between transitions across alcohol stages and birth-sex cohort-level lifetime prevalence of use controlling for basic socio-demographics were assessed using odds ratios and confidence interval estimates from multivariable discrete-time survival models in the PROC SURVEYLOGISTIC procedure in SAS, with person-year as the unit of analysis and a logistic link function. Person-years were defined from six years of age for modelling commencement of use, from age of onset of abuse for remission from abuse, and all other models from age of onset of the first stage to age of onset of the second (depending on the model) or age at interview (for censored cases). There was an insufficient number of dependence cases to analyze transitions to, or from, alcohol dependence.

A contextual variable was defined to represent the level of alcohol use in an individual's birth and sex cohort to estimate the effect of changes in use over time. Birth cohort was defined as an individual's year of birth +/- 5 years, creating an 11-year wide sex-specific cohort around each year of birth. The cohort widths were reduced for those aged below 23 years to as close as possible ensure symmetry around birth year, and were top-coded from age 65 and above. The covariate modelled was a time-varying estimate of the proportion of people (/10) in the individual's birth cohort who has used alcohol by the prior person year.

Other variables considered in all use/use disorder transition models were sex, age of commencing use (except in modelling commencement of use) defined as early, mid or late tertile time-varying education levels and age of person year (<=14, 15-17, 18-20, 21-24, 25-29 and 30+). In addition to these, the remission from abuse models also included speed of transition from use to abuse and years with the disorder, as well as alternate person year age groupings (<=18, 19-20, 21-22, 23-24, 25-29, 30-39 and 40+). Multivariate significance tests were made with Wald χ^2 tests using Taylor series design-based coefficient variance-covariance matrices to account for complex sampling design. All significance tests were evaluated at the .05 level with two-sided tests.

Results

Prevalence of alcohol use, alcohol use disorders and remission

The great majority of respondents (89.4%) consumed alcohol at least once in their lifetime, with 75.4% respondents having used alcohol regularly (≥12 drinks a year) (Table 1). The lifetime prevalence of DSM-IV alcohol abuse (without dependence) was 4.9% and of alcohol dependence 1.5%. Once conditioning on use, while the great majority of adults used alcohol regularly (84.3%), only a small portion developed alcohol abuse (5.5%) or dependence (1.6%). Most respondents with lifetime abuse

Table 1. *Prevalence of alcohol use, DSM-IV alcohol use disorders and remission in Murcia.*

	n	% [a]	SE
Lifetime prevalence			
Use	1459	89.4	1.3
Using ≥12 drinks a year	1459	75.4	2.4
Abuse W/O dependence	1459	4.9	0.7
Dependence	1459	1.5	0.5
Remission from abuse	1459	4.2	0.8
Remission from dependence	1459	1.2	0.5
Conditional prevalence			
Using ≥12 drinks a year | use	1272	84.3	1.9
Abuse W/O dependence | use	1272	5.5	0.7
Dependence | use	1272	1.6	0.6
Remission from abuse | LT abuse W/O dependence	73	85.3	7.6
Remission from dependence | LT dependence	20	79.4	13.5

Note. SE - standard error. W/O – without. LT – lifetime. n = The total unweighted number of respondents who answered alcohol use questions for lifetime prevalence, and the total unweighted number of respondents in the conditional cohort for conditional prevalence. [a] Prevalence estimates are based on weighted data.

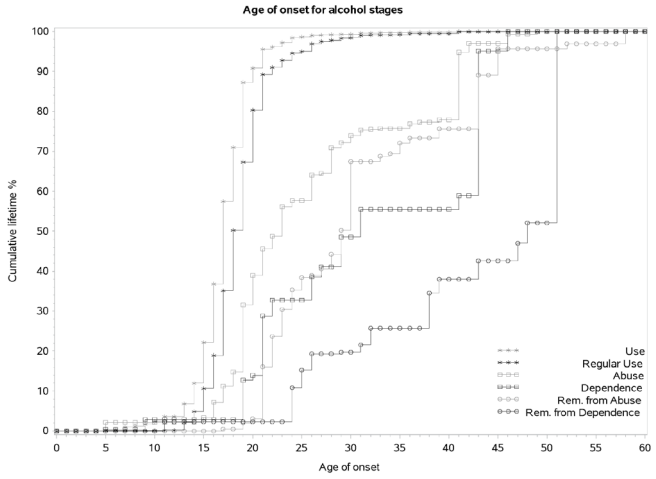

Figure 1. Age of onset curves for alcohol stages in the PEGASUS-Murcia projecta,b

Note. [a] Life-table estimates of the survival functions are based on weighted Part II data (total sample of 1,459 respondents) and include respondents with and without the specific diagnosis, where age of onset for the latter is censored at age of interview. Estimates scaled up to reach 100%. [b] Respondents with missing age of onset of remission from abuse (n=10) were excluded from the remission from abuse curve.

(85.3%) or dependence (79.4%) had remitted by the time of interview.

Age of onset for alcohol use stages

The cumulative age of onset (AOO) curves for all alcohol use stages are presented in Figure 1. By the age of 18, 70,9% of alcohol users had and one half (50.2%) of regular users had started in those stages. Regular use sharply increases during early adulthood to reach 90.8% by age 22. The median AOO for alcohol abuse (23 years) is reached within 5 years of the median AOO for regular use (18 years). Three out of four cases of alcohol abuse (75.3%) are observed by age 31. One third of alcohol dependence cases are observed prior to age 22, reaching 55.4% by age 31 and 95.0% by age 43. Remission AOO curves show that

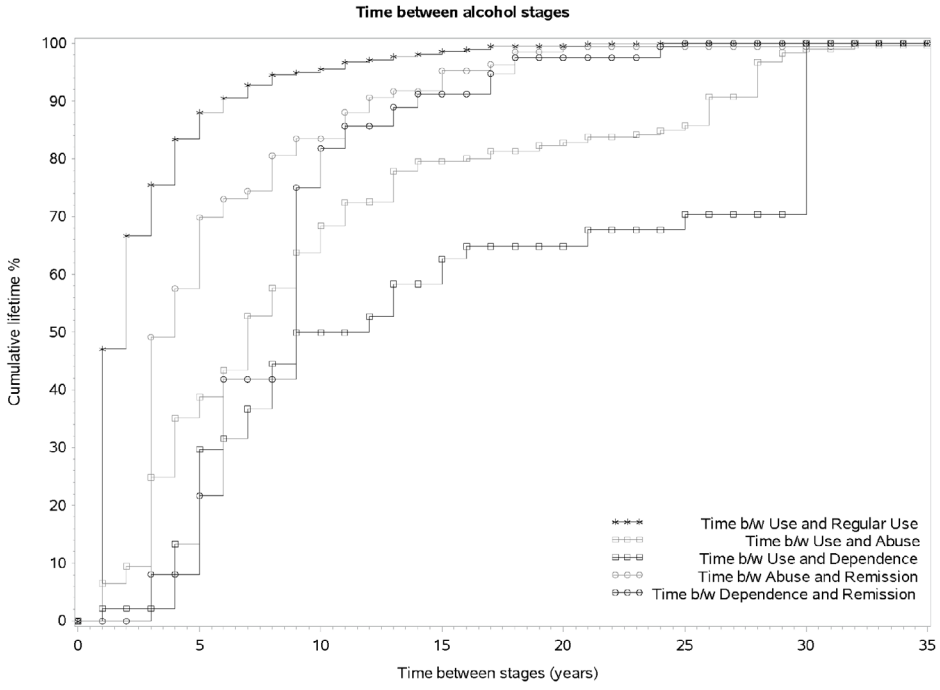

Figure 2. Time between alcohol stages in the PEGASUS-Murcia project[a,b]

[a] Life-table estimates of the time between stages are based on weighted Part II data and each curve only includes respondents with a diagnosis of the second stage. [b] Respondents with missing age of onset of remission from abuse (n=10) were excluded from the time between abuse and remission curve.

50% of remissions from alcohol abuse occurred by age 29 while 50% of remissions from alcohol dependence occurred by age 48 and 100% by age 51.

Time to transition across stages of involvement with alcohol use

The most rapid transition is found in the transition from initial use to regular use (Figure 2). Within one year of their first drink, 47.1% of users had become regular users and within three years 75.5% had become regular users. The transition from first use to AUD is slower; 52.7% of the transitions from use to abuse occur within 7 years, and 52.7% of transitions from use to dependence occur within 12 years. The transition from AUD onset to remission was more rapid for alcohol abuse than for alcohol dependence. Within three years of disorder onset, 49.1% of alcohol abuse cases and only 8.1% of alcohol dependence had remitted. Within 9 years of disorder onset, the majority of abuse (83.5%) and dependence (75.0%) cases had remitted.

Transitions across alcohol use stages

Table 2 presents multivariate discrete-time survival analyses examining covariates of transitioning from non-use to use, use to regular use, use to abuse, and regular use to abuse in a given year. The transitions from use to abuse and from regular use to abuse were significantly more common in male respondents. Birth-sex cohort alcohol use was significantly associated with increased odds for all transitions examined with the exception of the transition from use to abuse. Later commence of alcohol use, relative to other respondents, was associated with higher odds of transitioning from use to regular use. Education was also significantly associated with transitions from use to abuse and regular use to abuse with students or persons with a low-average education level at increased odds of transitioning to the disorder compared to those with a low education level.

Transition to remission from alcohol abuse

Table 3 presents multivariate discrete-time survival analyses examining covariates of remission from alcohol abuse including sex, education, age tertile of first onset, birth-sex cohort alcohol use, number of years with the dis-

Table 2. *Multivariate associations of socio-demographic variables with transitions between stages of lifetime alcohol use/use disorders in Murcia.*

Variable	Category	Commencing Use		Use to using ≥12 drinks a year		Use to abuse (without prior dependence)		Regular use to abuse (without prior dependence)[e]	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sex (Ref: Female)	Male	1.21	(0.92-1.58)	1.00	(0.78-1.28)	3.62*	(1.53-8.54)	4.08*	(1.28-13.03)
	X^2_1 [p]	1.92	[0.165]	<0.10	[0.998]	8.62**	[0.003]	5.63**	[0.018]
Percentage of individual's birth-sex cohort already using[a]	Cohort use	1.50*	(1.44-1.57)	1.16*	(1.09-1.24)	1.43	(0.98-2.10)	1.46*	(1.06-2.01)
	X^2_1 [p]	333.94**	[<0.001]	19.32**	[<0.001]	3.38	[0.066]	5.50**	[0.019]
Education level (Ref: High)	Student	0.67	(0.14-3.26)	0.41*	(0.19-0.87)	2.80	(0.66-11.85)	2.63	(0.63-11.02)
	Low	0.53	(0.12-2.34)	0.38*	(0.16-0.92)	0.65	(0.25-1.66)	0.67	(0.27-1.68)
	Low-average	0.66	(0.11-3.92)	0.37*	(0.18-0.73)	2.98	(0.68-13.04)	2.81	(0.65-12.18)
	High-average	0.60	(0.10-2.97)	0.32*	(0.14-0.72)	1.23	(0.32-4.67)	1.22	(0.32-4.69)
	X^2_4 [p]	8.13	[0.087]	8,58	[0.072]	45.12**	[<0.001]	20.27**	[<0.001]
Age tertile of commencing alcohol use[b, c] (Ref: Late)	Early	-		0.34*	(0.22-0.51)	2.00	(0.61-6.87)	1.63	(0.45-5.83)
	Mid	-		0.49*	(0.38-0.64)	1.24	(0.41-3.72)	1.10	(0.36-3.32)
	X^2_2 [p]	-		37.78**	[<0.001]	1.71	[0.425]	1.00	[0.609]
Sample Size	Total n[d]	1 459		1 272		1 272		1 055	

Note. OR - odds ratios; CI - confidence interval. All discrete time logistic regression analyses are based on weighted Part II person-year data controlling for person-year age groups of <=15, 16-17, 18-20, 21-24, 25-29 and 30+ (Ref). */** Significant at the 0.05 level, two-sided test. [a] Percentage (/10) of +/-5-yr sex-specific cohort who had used alcohol by the prior person year. e.g. For a female born in 1975 the cohort would be females born between 1970 and 1980. A context OR of 1.5 in commencement of use would be interpreted as, for a 10% increase of people in the age-sex cohort having commenced use by the previous person year (controlling for all other variables in the model), the odds of commencing use increases by 50%. [b] Age tertile of commencing alcohol use was included in all models except transition to initial use. [c] Individuals' age of commencing alcohol use is split into survey-specific tertiles among all those who ever used alcohol. The earliest (first) tertile is age <= 15, the 2nd tertile age 16-17 and the 3rd tertile aged 18+. [d] n = The total unweighted number of respondents included in model conditioning on initial stage. [e] Respondents were excluded from the modelling of this transition if onset of regular use was after the onset of abuse (n=4). Respondents were excluded from the modelling of the transition if the onset of the initial stage was after the onset of the second stage.

order, and speed tertile of transitioning from use to disorder. Remission from alcohol abuse was significantly associated with level of cohort alcohol use. Being female and having a low-average to high-average education level were both associated with an increased likelihood of remitting from alcohol abuse. Time with the disorder, transition speed from use to abuse, and age tertile of alcohol use initiation were not significantly associated with remission.

Discussion

The present study sought to examine the age of onset and transition time between various stages of alcohol use in a representative sample of the general population of Region of Murcia, in the South East of Spain, and to estimate the association of cohort use with the probability of transitioning to alcohol use, use disorder, and remission. Several noteworthy findings were obtained. First, the results indicate that three quarters of the population have used alcohol regularly (≥12 drinks a year), a behavior that is largely in place by age 20. Second, the findings point to the role of birth-sex cohort use as a factor associated with the transition from one stage of alcohol use to the next. Finally, remitting from alcohol abuse was associated with female sex, cohort use and education level.

Consistent with existing data regarding the ubiquitous nature of alcohol use in western civilizations (Degenhardt et al., 2008) and with data from the Spanish Observatory on Drugs and Drug Abuse (Observatorio Español de la Droga y las Toxicomanías, 2017), lifetime alcohol use was reported in close to nine in ten residents. By age 16, one third of the population had had their first drink, sharply

Table 3. *Multivariate associations of socio-demographic variables with transitions from alcohol abuse to remission in Murcia*

Variable	**Category**	**Abuse (without dependence) to remission from abuse[e]**	
		OR	**95% CI**
Sex (Ref: Female)	Male	0.23*	(0.13-0.38)
	X^2_1 *[p]*	31.22**	[<0.001]
Percentage of individual's birth-sex cohort already using[a]	Cohort use	2.02*	(1.00-4.07)
	X^2_1 *[p]*	3.88**	[0.049]
Education level (Ref: High)	Student	1.49	(0.26-8.42)
	Low	3.14	(0.91-10.80)
	Low-average	5.42*	(2.33-12.59)
	High-average	2.65*	(1.22-5.77)
	X^2_4 *[p]*	92.25**	[<0.001]
Age tertile of commencing alcohol use[b] (Ref: Late)	Early	0.63	(0.32-1.25)
	Mid	1.10	(0.28-4.64)
	X^2_2 *[p]*	3.31	[0.192]
Speed to transition from use to disorder[c] (Ref: Late)	Early	0.93	(0.40-2.21)
	Mid	1.12	(0.52-2.42)
	X^2_2 *[p]*	0.14	[0.931]
Time with disorder	Years	0.99	(0.95-1.03)
	X^2_2 *[p]*	*0.37*	*[0.545]*
Sample Size	Total (N[d])	63	

Note. OR - odds ratios; CI - confidence interval. All discrete time logistic regression analyses are based on weighted Part II person-year data controlling for person-year age groups of <=18, 19-20, 21-22, 23-24, 25-29, 30-39 and 40+ (Ref). */** Significant at the 0.05 level, two-sided test. [a] Percentage (/10) of +/-5-yr sex-specific cohort who had used alcohol by the prior person year. e.g. For a female born in 1975 the cohort would be females born between 1970 and 1980. A context OR of 1.5 in commencement of use would be interpreted as, for a 10% increase of people in the age-sex cohort having commenced use by the previous person year (controlling for all other variables in the model), the odds of commencing use increases by 50%. [b] Individuals' age of commencing alcohol use is split into survey-specific tertiles among all those who ever used alcohol. The earliest (first) tertile is age <= 15, the 2nd tertile age 16-17 and the 3rd tertile aged 18+. [c] Individuals' speed of transition from alcohol use to disorder is split into survey-specific tertiles. When predicting remission from abuse, tertiles were calculated for transition from use to abuse: the fastest at 0-3 years, the middle tertile 4-9 years and late transitions were 10+ years. [d] n = The total unweighted number of respondents included in the model conditioning on the initial stage. [e] Remission is defined as having reported more than 12 months, or at least two birthdays, since the last disorder related problem. In cases where the reported time since last problem was less than two years and the exact age of remission could not be defined, remission age of onset was set to missing (n=10). These respondents were excluded from the modelling of transition to remission.

increasing to over two thirds by age 18, the legal drinking age in Spain. A rapid transition was found from first use to regular use with one half of users having become regular users within one year of their first drink. Three quarters of the population has used alcohol regularly which may complicate preventive efforts aimed at delaying age of first use despite its important role in the transition to AUDs (e.g., (DeWit et al., 2000; Kalaydjian et al., 2009; Silveira et al., 2011). Indeed, alcohol is available in homes and current drinking laws are not systematically enforced in Southern European establishments that sell alcoholic beverages. Easy access to alcohol might be associated with the finding that one-third of the cases of alcohol abuse and over one in ten cases of dependence occurred by age 19. Beyond the availability of alcohol to young people, these findings highlight the need for targeted prevention efforts as youth with mental disorders have been shown to have a greater risk of transitioning to higher levels of alcohol use (Conway, Swendsen, Husky, He & Merikangas, 2016).

Despite the commonality of regular alcohol use defined as 12 or more drinks a year, the lifetime prevalence of alcohol abuse without dependence (4.9%) and alcohol dependence (1.5%) are relatively low and well within the range of what is found in other western European countries (Alonso et al., 2004). In these studies, prevalence rates are largely driven by the prevalence of AUDs among men (8.6% and 2.5% for alcohol abuse and dependence, respectively) as compared to women (1.1% and 0.1%) (Navarro-Mateu et al., 2015). In the present study, male sex was strongly associated with an increased risk of transitioning from use to abuse and from regular use to abuse which is consistent with findings from other regions of the world (Cheng, Chandra, Alcover & Anthony, 2016; DeWit et al., 2000; Grant, 1997; Kalaydjian et al., 2009; Lee et al., 2009; Lopez-Quintero et al., 2011; Silveira et al., 2011; Suliman et al., 2010). However, sex was not significantly associated with the risk of transitioning from use to regular use nor was it associated with alcohol use initiation, which may in part reflect a closing male–female gap in substance use observed in recent years (Slade et al., 2016).

Recent evidence regarding the importance of peer consumption (Degenhardt et al., 2016) was confirmed in our study, where birth-sex cohort alcohol use was found to be significantly associated with commencing use and of the transition from alcohol use to regular use, and from regular use to abuse. This finding suggests that preventive measures targeting cohorts may prove helpful in reducing progression into later stages of alcohol use. Birth-sex cohort alcohol use was also significantly associated with remission from abuse, underlining the importance of shared societal norms related to substance use (Pollard, Freeman, Ziegler, Hersman & Goss, 2000). Combined with findings related to the speed at which individual transition into the earlier stages of alcohol use, cohort use effects suggest that preventive efforts should be geared towards youth. Such efforts may involve school settings, colleges but should not be limited to the latter, as substance use and mental health problems are at least as prevalent if not more among young adults who are no longer in school (Blanco et al., 2008; Degenhardt et al., 2016; Kovess-Masfety et al., 2016). Finally, while the overall total alcohol consumption per capita has been cut in half in recent decades going from close to 20 liters per year in 1975 to 11.2 liters in 2010 (World Health Organization, 2014), changes in drinking patterns with a drastic reduction in wine consumption and an increase in beer consumption may point to additional venues for prevention in Spain (Mateos, Páramo, Carrera & Rodríguez-López, 2002; Paschall, Grube & Kypri, 2009; Robledo de Dios, 2002).

In contrast with a significant amount of evidence in the literature showing the importance of early age of first use in the risk of transitioning to alcohol abuse (Abdin et al., 2013; DeWit et al., 2000; Grant, Stinson & Harford, 2001; Kalaydjian et al., 2009), early age of first use was not associated with the transition from use or regular use to abuse nor was it associated with remission from abuse. In fact, it was inversely associated with the risk of transitioning from use to regular use. As mentioned previously, certain risk factors have a differential effect on the full spectrum of alcohol use stages (Kalaydjian et al., 2009; Lee et al., 2009; Silveira et al., 2011; Suliman et al., 2010). Prior studies have in fact also reported that early age of alcohol use was associated with some but not all stages of alcohol use (Silveira et al., 2011), and that it may not affect rapid transition to alcohol disorders among male adolescents or young adults (Cheng et al., 2016) . Additional research is needed to document the differential role of key factors associated with greater risk of transition to AUDs in Spain including the role of early age of alcohol use initiation.

Several limitations should be noted when interpreting the findings. First, there were insufficient rates of alcohol dependence in the present sample (1.5%) to examine associations of the transition from use to dependence, or from dependence to remission. Data was available to model the transition to remission from abuse though findings are based on a small number of abuse cases (N=63) and care should be taken in interpreting these results. That being said, the rates of alcohol use and abuse were sufficient to allow examination of the respective onsets. Second, age of onset for stages of alcohol use was based on retrospective self-reporting and may have been subject to forward telescoping (Johnson & Schultz, 2005; Shillington, Woodruff, Clapp, Reed & Lemus, 2012). However, the structured design of the diagnostic instrument combined with the strategy used in the WMH surveys have been shown to reduce this recall bias (Knäuper, Cannell, Schwarz, Bruce & Kessler, 1999). Finally, as the study was conducted in a representative sample of a single region of Spain, additional

research is needed to replicate the findings in samples of other geographic areas.

The present study documented the age of onset of the full spectrum of stages of alcohol use from first ever use to dependence and remission in the general population of the autonomous region of Murcia. To the best of our knowledge, the present findings are the first to document the timing of the natural course of alcohol use in the general population of a Southern European region. The findings highlight sensitive periods with rapid transitions to higher levels of alcohol use. The study further emphasizes the importance of cohort use in the full spectrum of stages of alcohol use which contributes important data to policy makers focused on the prevention of alcohol-related problems in Spain.

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Conflict of interests

The PEGASUS-Murcia project is carried out in conjunction with the WHO-World Mental Health (WMH) Survey Initiative. WMH Coordinating Center staff at Harvard and Michigan Universities provided assistance with the instrumentation, fieldwork and data analysis. These latest activities were partially supported by Ortho-McNeil Pharmaceutical, Inc., GlaxoSmithKline, Bristol-Myers Squibb and Shire. In the past three years, Dr. Kessler has been a consultant for Hoffman- La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. Dr. Kessler has served on advisory boards for Mensante Corporation, Plus One Health Management, Lake Nona Institute, and U.S. Preventive Medicine. Dr. Kessler is a co-owner of DataStat, Inc. There are no patents, products in development or marketed products to declare.

References

Abdin, E., Subramaniam, M., Vaingankar, J. A. & Chong, S. A. (2013). The role of sociodemographic factors in the risk of transition from alcohol use to disorders and remission in singapore. *Alcohol and Alcoholism, 49*, 103-108. doi:10.1093/alcalc/agt126.

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H.,… Vollebergh, W. (2004). Prevalence of mental disorders in europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica, 109*, 21-27. doi:10.1111/j.1600-0047.2004.00327.x.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (Fourth edition - Text revision)*. Washington, DC: American Psychiatric Association.

Blanco, C., Okuda, M., Wright, C., Hasin, D. S., Grant, B. F., Liu, S.-M. & Olfson, M. (2008). Mental health of college students and their non–college-attending peers: Results from the national epidemiologic study on alcohol and related conditions. *Archives of General Psychiatry, 65*, 1429-1437. doi:10.1001/archpsyc.65.12.1429.

Carballo, J. L., Fernandez-Hermida, J. R., Secades-Villa, R. & García-Rodríguez, O. (2008). Determinants of recovery from alcohol problems in treated and untreated individuals in a spanish sample. *Adicciones, 20*, 49-58.

Carballo, J. L., Fernández-Hermida, J. R., Sobell, L. C., Dum, M., Secades-Villa, R., García-Rodríguez, O.,… AlHalabí-Diaz, S. (2008). Differences among substance abusers in spain who recovered with treatment or on their own. *Addictive Behaviors, 33*, 94-105. doi:10.1016/j.addbeh.2007.07.013.

Cheng, H. G., Chandra, M., Alcover, K. C. & Anthony, J. C. (2016). Rapid transition from drinking to alcohol dependence among adolescent and young-adult newly incident drinkers in the united states, 2002–2013. *Drug*

& Alcohol Dependence, 168, 61-68. doi:10.1016/j.drugalcdep.2016.08.015.

Conway, K. P., Swendsen, J., Husky, M. M., He, J.P. & Merikangas, K. R. (2016). Association of lifetime mental disorders and subsequent alcohol and illicit drug use: Results from the national comorbidity survey–adolescent supplement. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*, 280-288. doi:10.1016/j.jaac.2016.01.006.

Degenhardt, L., Chiu, W.-T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M.,… Huang, Y. (2008). Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health surveys. *PLoS Medicine, 5*, e141. doi:10.1371/journal.pmed.0050141.

Degenhardt, L., Stockings, E., Patton, G., Hall, W. D. & Lynskey, M. (2016). The increasing global health priority of substance use in young people. *Lancet Psychiatry, 3*, 251-264. doi:10.1016/S2215-0366(15)00508-8.

Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J. P., . . . WHO World Mental Health Survey Consortium. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health surveys. *Journal of the American Medical Association, 291*, 2581-2590. doi:10.1001/jama.291.21.2581.

DeWit, D. J., Adlaf, E. M., Offord, D. R. & Ogborne, A. C. (2000). Age at first alcohol use: A risk factor for the development of alcohol disorders. *American Journal of Psychiatry, 157*, 745-750. doi:10.1176/appi.ajp.157.5.745.

Flórez-Salamanca, L., Secades-Villa, R., Hasin, D. S., Cottler, L., Wang, S., Grant, B. F. & Blanco, C. (2013). Probability and predictors of transition from abuse to dependence on alcohol, cannabis, and cocaine: Results from the national epidemiologic survey on alcohol and related conditions. *The American Journal of Drug and Alcohol Abuse, 39*, 168-179. doi:10.3109/00952990.2013.772618.

Grant, B. F. (1997). Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: Results of the national longitudinal alcohol epidemiologic survey. *Journal of Studies on Alcohol, 58*, 464-473. doi:10.15288/jsa.1997.58.464.

Grant, B. F., Stinson, F. S. & Harford, T. C. (2001). Age at onset of alcohol use and DSM-IV alcohol abuse and dependence: A 12-year follow-up. *Journal of Substance Abuse, 13*, 493-504. doi:10.1016/S0899-3289(01)00096-7.

Gual, A., Arbesú, J. Á., Zarco, J., López-Pelayo, H., Miquel, L. & Bobes, J. (2016). Alcoholism and its treatment approach from a citizen perspective. *Adicciones, 28*. 163-173. doi:10.20882/adicciones.742.

Johnson, E. O. & Schultz, L. (2005). Forward telescoping bias in reported age of onset: An example from cigarette smoking. *International Journal of Methods in Psychiatric Research, 14*, 119-129. doi:10.1002/mpr.2.

Kalaydjian, A., Swendsen, J., Chiu, W.-T., Dierker, L., Degenhardt, L., Glantz, M.,… Kessler, R.C. (2009). Sociodemographic predictors of transitions across stages of alcohol use, disorders and remission in the national comorbidity survey-replication. *Comprehensive Psychiatry, 50*, 299-306. doi:10.1016/j.comppsych.2008.09.012.

Kessler, R.C. & Ustun, T. B. (2004). The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Compositve International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research, 13*, 93-121. doi:10.1002/mpr.168.

Knäuper, B., Cannell, C. F., Schwarz, N., Bruce, M. L. & Kessler, R. C. (1999). Improving accuracy of major depression age-of-onset reports in the U.S. National Comorbidity Survey. *International Journal of Methods in Psychiatric Research, 8*, 39-48. doi:10.1002/mpr.55.

Kovess-Masfety, V., Leray, E., Denis, L., Husky, M., Pitrou, I. & Bodeau-Livinec, F. (2016). Mental health of college students and their non-college-attending peers: Results from a large french cross-sectional survey. *BMC Psychology, 4*. doi:10.1186/s40359-016-0124-5.

Lee, S., Guo, W. J., Tsang, A., He, Y. L., Huang, Y. Q., Zhang, M. Y.,… Kessler, R. C. (2009). Associations of cohort and socio-demographic correlates with transitions from alcohol use to disorders and remission in metropolitan China. *Addiction, 104*, 1313-1323. doi:10.1111/j.1360-0443.2009.02595.x.

Lev-Ran, S., Imtiaz, S., Rehm, J. & Le Foll, B. (2013). Exploring the association between lifetime prevalence of mental illness and transition from substance use to substance use disorders: Results from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). *The American Journal on Addictions, 22*, 93-98. doi:10.1111/j.1521-0391.2013.00304.x.

Lopez-Quintero, C., Cobos, J. P., Hasin, D. S., Okuda, M., Wang, S., Grant, B. F. & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence, 115*, 120-130. doi:10.1016/j.drugalcdep.2010.11.004.

Mateos, R., Páramo, M., Carrera, I. & Rodríguez-López, A. (2002). Alcohol consumption in a southern european region (Galicia, Spain). *Substance Use & Misuse, 37*, 1957-1976. doi:10.1081/JA-120016226.

Navarro-Mateu, F., Tormo, M., Vilagut, G., Alonso, J., Ruiz-Merino, G., Escamez, T.,… Navarro, C. (2013a). Epidemiology and genetics of common mental disorders in the general population: The PEGASUS-Murcia project. *BMJ Open, 3*. doi:10.1136/bmjopen-2013-004035.

Navarro-Mateu, F., Morán-Sánchez, I., Alonso, J., Tormo, M. J., Pujalte, M. L., Garriga, A.,… Navarro, C. (2013b). Cultural adaptation of the latin american version of the World Health Organization Composite International Diagnostic Interview (CIDI v 3.0) for use in Spain. *Gaceta Sanitaria, 27*, 325-331. doi:10.1016/j.gaceta.2012.06.005.

Navarro-Mateu, F., Tormo, M. J., Salmerón, D., Vilagut, G., Navarro, C., Ruíz-Merino, G.,… Kessler, R. C. (2015). Prevalence of mental disorders in the south-east of spain, one of the european regions most affected by the economic crisis: The cross-sectional pegasus-murcia project. *PLoS One, 10*. doi:10.1371/journal.pone.0137293.

Oberleitner, L. M., Smith, P. H., Weinberger, A. H., Mazure, C. M. & McKee, S. A. (2015). Impact of exposure to childhood maltreatment on transitions to alcohol dependence in women and men. *Child Maltreatment, 20*, 301-308. doi:10.1177/1077559515591270.

Observatorio Español de la Droga y las Toxicomanías. (2017). Edades 2015-2016. Encuesta sobre alcohol y drogas en españa. Madrid: Delegación del gobierno para el plan nacional sobre drogas. Retrieved at http://www.pnsd.msssi.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2015_EDADES__Informe_.pdf.

Paschall, M. J., Grube, J. W. & Kypri, K. (2009). Alcohol control policies and alcohol consumption by youth: A multi-national study. *Addiction, 104*, 1849-1855. doi:10.1111/j.1360-0443.2009.02698.x.

Pérez, B. (2002). El alcohol como problema de salud pública. La responsabilidad de los poderes públicos. *Adicciones, 14*, 291-301.

Pollard, J. W., Freeman, J. E., Ziegler, D. A., Hersman, M. N. & Goss, C. W. (2000). Predictions of normative drug use by college students. *Journal of College Student Psychotherapy, 14*, 5-12. doi:10.1300/J035v14n03_03.

Probst, C., Moyo, D., Purshouse, R. & Rehm, J. (2015). Transition probabilities for four states of alcohol use in adolescence and young adulthood: What factors matter when? *Addiction, 110*, 1272-1280. doi:10.1111/add.12985.

Rehm, J., Anderson, P., Barry, J., Dimitrov, P., Elekes, Z., Feijão, F.,… Kraus, L. (2015). Prevalence of and potential influencing factors for alcohol dependence in Europe. *European Addiction Research, 21*, 6-18. doi:10.1159/000365284.

Rehm, J., Gmel, G. & Gual, A. (2013). Alcohol consumption, alcohol dependence and related harms in Spain, and the effect of treatment-based interventions on alcohol dependence. *Adicciones, 25*, 11-18.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y. & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *The Lancet, 373*, 2223-2233. doi:10.1016/S0140-6736(09)60746-7.

Robledo de Dios, T. (2002). Políticas institucionales de prevención de los problemas de salud generados por el consumo de bebidas alcohólicas en España y Europa. *Adicciones, 14,* S303-S315.

Shillington, A. M., Woodruff, S. I., Clapp, J. D., Reed, M. B. & Lemus, H. (2012). Self-reported age of onset and telescoping for cigarettes, alcohol, and marijuana: Across eight years of the national longitudinal survey of youth. *Journal of Child & Adolescent Substance Abuse, 21*, 333-348. doi:10.1080/1067828X.2012.710026.

Silveira, C. M., Viana, M. C., Siu, E. R., de Andrade, A. G., Anthony, J. C. & Andrade, L. H. (2011). Sociodemographic correlates of transitions from alcohol use to disorders and remission in the Sao Paulo megacity mental health survey, brazil. *Alcohol and Alcoholism, 46*, 324-332. doi:10.1093/alcalc/agr007.

Slade, T., Chapman, C., Swift, W., Keyes, K., Tonks, Z. & Teesson, M. (2016). Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: Systematic review and metaregression. *BMJ Open, 6*. doi:10.1136/bmjopen-2016-011827.

Suliman, S., Seedat, S., Williams, D. R. & Stein, D. J. (2010). Predictors of transitions across stages of alcohol use and alcohol-use disorders in South Africa. *Journal of Studies on Alcohol and Drugs, 71*, 695-703. doi:10.15288/jsad.2010.71.695.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C. & Vandenbroucke, J.P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med, 4*: e296. doi:10.1371/journal.pmed.0040296.

Werner, K. B., Sartor, C. E., McCutcheon, V. V., Grant, J. D., Nelson, E. C., Heath, A. C. & Bucholz, K. K. (2016). Association of specific traumatic experiences with alcohol initiation and transitions to problem use in european american and african american women. *Alcoholism: Clinical and Experimental Research, 40*, 2401-2408. doi:10.1111/acer.13220.

World Health Organization. (2014). *Global status report on alcohol and health*. Geneva, Switzerland: World Health Organization.

Adolescent substance use and its association with risk and protective factors. An exploratory analysis of the large-scale school survey of Comunidades Que se Cuidan, Colombia

Uso de sustancias en adolescentes y su asociación con factores de riesgo y protección. Un análisis exploratorio de la encuesta escolar a gran escala de Comunidades Que se Cuidan, Colombia

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Abstract

Communities That Care (CTC) is a prevention system aimed at reducing antisocial behaviors in adolescents. In Colombia, this system has been developed and adapted under the name of Comunidades Que se Cuidan (CQC). Successful implementation of CQC depends on valid associations between measured risk and protective factors (RPFs) for substance use and substance use outcomes. This study assessed these associations using large-scale, school-based surveys of Colombian youth. A cross-sectional analysis was performed. Data from 23 communities in Colombia were collected between 2012 and 2016 from young people (N = 50,946) aged 10 to 19 years. Dichotomous alcohol, cigarette, cannabis, and other illegal drug use outcomes were assessed for past 30-day, past-year, and lifetime use. Logistic regression analyses, adjusting for age, gender, and age by RPF, and gender by RPF interactions, were performed for each RPF. All the associations of the 14 RPF evaluated were statistically significant ($p < .001$). Regarding observed effect sizes, 3.0% were considered very small (0.70 ≥ OR ≤ 1.43), 51.7% small (0.70 ≥ OR ≥ 1.43), 42.6% medium (0.40 ≥ OR ≥ 2.48) and 7.1% large (0.23 ≥ OR ≥ 4.27). Significant main effects for age and gender, and their interactions with RPFs were found for most RPFs. Findings from this study demonstrate the viability of RPFs for adolescent substance use as focal points for intervention planning, development, and evaluation of community-based prevention systems like CQC that rely on epidemiologic data for local decision making.

Keywords: Risk factors; Ssubstance use; Adolescents; Prevention.

Resumen

Communities That Care (CTC) es un sistema preventivo que busca disminuir comportamientos problemáticos en adolescentes. En Colombia, este sistema ha sido adaptado bajo el nombre de Comunidades Que se Cuidan (CQC). Este estudio validó las asociaciones entre los factores de riesgo y protección (FRP) para el uso de sustancias psicoactivas (SPA) medidos por CQC y las prevalencias de consumo de estas en adolescentes colombianos. Entre 2012 y 2016, se aplicó una encuesta a gran escala en jóvenes de 10 a 19 años (N = 50,946) pertenecientes a 23 comunidades de Colombia. Se analizó de forma transversal la asociación entre los FRP con el consumo de alcohol, cigarrillo, marihuana y otras drogas ilegales en los últimos 30 días, año y alguna vez en la vida. Se realizaron regresiones logísticas, ajustando por edad, sexo y sus interacciones con cada FRP. Todas las asociaciones de los 14 FRP evaluados fueron significativas ($p < .001$). De los efectos observados, 3,0% se consideraron efectos muy pequeños (0,70 ≤ OR ≤ 1,43), 51,7% pequeños (0,70 ≥ OR ≥ 1,43), 42,6% medianos (0,40 ≥ OR ≥ 2,48) y 7,1% grandes (0,23 ≥ OR ≥ 4,27). Se encontraron asociaciones significativas para edad, sexo y sus interacciones con los FRP para la mayoría de FRP. Los hallazgos demuestran la validez de los FRP estudiados para la planificación, el desarrollo y la evaluación futura de sistemas preventivos comunitarios como CQC, los cuales se basan en datos epidemiológicos para la toma de decisiones locales.

Palabras clave: Factores de riesgo; Consumo de SPA; Adolescentes; Prevención.

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Adolescence is a stage in which the vulnerability to engaging in high-risk behaviors, including the use of psychoactive substances (PAS) (Pérez & Scoppetta, 2009) is high. People at this life stage are still in a period of brain maturation; the use of PAS therefore implies an even greater risk (Gruber, Sagar, Dalhgren, Racine & Lukas, 2012; Scoppetta, Pérez & Lanziano, 2011). It has been found that adolescents are most vulnerable to the neurotoxic effects of alcohol and drugs, which produce negative consequences at the cognitive level (Guerri & Pascual, 2010; Zeigler et al., 2005). Similarly, alcohol abuse at a young age is linked to a lower volume in the hippocampus and in the pre-frontal cortex, which is associated with poor verbal, attentional and visuospatial performance (Bellis et al., 2000; Medina, Schweinsburg, Cohen-Zion, Nagel & Tapert, 2007). Given the attendant educational, legal, family, emotional and health problems, this phenomenon generates great concern (Espada, Griffin, Botvin & Méndez, 2003; Pérez & Scoppetta, 2009; Wills et al., 2013).

The latest study of PAS use among the Colombian school population conducted by the Ministry of Justice and Law, Ministry of National Education and Ministry of Health and Social Protection (2011) showed that the substance with the highest prevalence among young people is alcohol. Some of the core conclusions of this study are related to: (a) a concern about the early ages of onset of legal and illegal substance use found, (b) a need to take a preventive approach to reduce alcohol and tobacco use, and, (c) a need to increase effective strategies to prohibit the sale of alcohol to minors.

It is important to keep in mind that drug use is a heterogeneous phenomenon that changes over time (Glantz, Conway & Colliver, 2005; Sloboda, 2005; Scoppetta et al., 2011; Thatcher & Clark, 2008). Constant assessment of its prevalence and incidence, as well as of associated risk factors is therefore essential as it informs future prevention and intervention strategies to ensure their effectiveness (Clayton,1992; Hawkins, Catalano & Miller, 1992; Sloboda, Glantz & Tarter, 2012). In Colombia, prevention initiatives have unfortunately not been guided by epidemiological data, nor have they included systematic methodologies in their assessment. Therefore, there is a pressing need to identify the risk and protective factors associated with PAS use in Colombian adolescents from a scientific perspective.

In the early 1990's in the United States, Richard F. Catalano and J. David Hawkins developed the preventive system known as Communities That Care (CTC) (Hawkins et al., 2008a). CTC's main objective is to provide tools for communities to generate and use their own epidemiological data on risk and protective factors for PAS use, prioritize them, and implement effective evidence-based interventions in answer to specific factors established as priorities (Arthur, Hawkins, Pollard, Catalano & Baglioni, 2002; Hawkins, 2006). To determine the risk and protection profiles for communities, CTC developed the Communities That Care Youth Survey (CTCYS) instrument. This questionnaire allows a simple diagnostic assessment of the specific risk in adolescents (Arthur et al., 2002; Brown et al., 2009; Hawkins, 2006).

The original CTC youth survey assesses 25 risk factors and 13 protective factors in the domains: (a) community, (b) school, (c) family, and (d) individual and peers (Arthur et al., 2002; Hawkins, 2006). These risk factors respond to those which have been reported as predictors of various problematic behaviors, such as the use of PAS (Hawkins et al., 1992; Herrenkohl, Lee, Kosterman & Hawkins, 2012; Kenny & Schreiner, 2009; Kilpatrick et al., 2000). CTC has shown to be effective in reducing the incidence and prevalence of PAS use, violence and juvenile delinquency by addressing and reducing the associated factors of risk and protection (RPFs) (Feinberg, Greenberg, Osgood, Sartorius & Bontempo, 2007; Feinberg, Jones, Greenberg, Osgood & Bontempo, 2010; Hawkins et al., 2008a; Hawkins et al., 2008b; Hawkins, Oesterle, Brown, Abbott & Catalano, 2014; Hawkins et al., 2009; Hawkins et al. 2012; Oesterle et al., 2015). This has led to its implementation in other countries such as Germany, Chile, Croatia, Sweden, Australia and the Netherlands (Toumbourou, 1999; Jonkman et al., 2009).

For its part, Colombia began the process of adapting CTC under the name of Comunidades Que se Cuidan (CQC) (Pérez-Gómez, Mejía-Trujillo, Brown & Eisenberg, 2016) in 2012. The Nuevos Rumbos corporation was entrusted with implementing this task, and it has since been able to adapt the first Latin American instrument derived from CTC, which focuses on 18 risk factors and 8 protective factors, assessed by cut points specific to the country. As part of the implementation process it is necessary to carry out the validation of the associations between risk and protection factors (RPFs) for the use of PAS reported in the literature, and the prevalence of their use. For this reason, the present study aims to evaluate the association and the effect size between the RPFs measured by CQC and the use of PAS among Colombian adolescents in order to guarantee successful future adaptation and implementation of the CQC system.

Method

Participants

The sample consisted of students (N = 52,588) with low and middle socioeconomic backgrounds attending 6th through 11th grades (age range = 10 to 19 years) in 114 public and private schools in 23 communities of Colombia; all students at school on the day the questionnaire was administered were included in the sample. Of these, 52.8% were female and 48.2% male. Mean age was 14.2 years (SD

= 1.9, range 11 to 19). The level with most students participating was the sixth grade (19.9%), followed by seventh (19.1%), eighth (18.2%), ninth (15.7%), tenth (14.7%) and eleventh (12.4%).

Instrument

We used the adaptation of the Communities That Care Youth Survey (CTCYS) by Arthur et al. (2002) for Spanish, called Encuesta para Jóvenes de Comunidades Que Se Cuidan (EJCQC) (Mejía-Trujillo, Pérez-Gómez & Reyes-Rodríguez, 2015). The instrument is aimed at people aged between 10 and 19, and is designed to be applied in the school environment. The first part of the questionnaire collects demographic information and the prevalence of the last-month, last-year and lifetime use of alcohol, cigarettes, marijuana and other illegal drugs (cocaine, coca paste and cocaine base, inhalants, ecstasy, mushroom, acids, tranquilizers, poppers, amphetamines, heroin and dick). In the second part, 18 of 25 risk factors and 8 of 11 protection factors covered by CTC are assessed (Mejía-Trujillo et al., 2015; Pérez-Gómez et al., 2016).

The questionnaire has shown acceptable sensitivity and specificity in the US population and in five ethnic groups, including the Latino population (Arthur et al, 2007), as well as good predictive validity (Briney, Brown, Hawkins & Arthur, 2012). Internal consistency is high for the complete questionnaire ($\alpha = 0.82$) with the study population. In terms of the instrument's validity, Nuevos Rumbos corporation carried out a confirmatory factor analysis to assess construct validity, and the results have shown good and acceptable goodness of fit indices for most of the risk and protection factors (Mejía-Trujillo et al., 2015).

Procedure

Authorization was obtained from the relevant education authorities of the 23 communities located in different areas of Colombia. Informed consent was then obtained from the school directors, and data confidentiality was agreed and guaranteed. The survey was completely anonymous and students were informed that their participation was voluntary and that they could stop responding at any time they wished.

Subsequently, data was collected during the period from 2012 to 2016. The questionnaire was administered during the school day by previously trained experts from the Nuevos Rumbos corporation. In order to include more measures of risk in the survey, we used the missing data methodology known as 3-Form Design (Graham, 2012; Little & Rhemtulla, 2013). This method allowed us to distribute all the RPFs across three different versions of the survey. In this way, the number of valid cases for each RPF varied according to the version. Although the RPFs did not all have the same number of observations, only those that presented at least 70% of the cases in the total sample (n >36,800) were included in the analysis. Given that the present study focused on validating the existing associations between RPFs and behaviors through the interpretation of adjusted odds ratios, and because the sample was large, it was not considered necessary to take missing data into account.

Data analysis

The questionnaires were processed using optical readers, and the STATA 13 statistical package was used to perform a transversal analysis of the EJCQC. As part of the strategy to ensure the quality of the information, three questions were included in the instrument to identify answers of questionable validity. In this way, those students who reported the use of a fictitious drug were excluded from the sample, with the result that, of the 52,588 initial observations, 3.1% (n = 1,642) were eliminated from the subsequent analyses, so that the final sample consisted of 96.9% (n = 50,946) of the initial total.

The analysis was performed on 11 of the EJCQC's 18 risk factors and 3 of its 8 protective factors. This was because the factors not included were incorporated into the EJCQC after this analysis. The 14 RPFs (11 risk factors and 3 protective factors) were dichotomized (0 = low risk or low protection, 1 = high risk or high protection) using the cut-off points designed specifically for CQC and normalized for each school year (Mejía-Trujillo et al., 2015). Likewise, the means of each of the variables to be analyzed were centered in order to obtain a single measure of association for age, sex and their possible interactions and thereby facilitate the interpretation of the main effects. Logistic regression was used to assess the association between each RPF and the prevalence of alcohol, tobacco, marijuana and other illegal drug use in the last 30 days, last year and lifetime. Based on these considerations, in order to evaluate the individual association of each of the 12 prevalences of use and the 14 RPFs, the following logistic regression model was fitted:

$$log\ [\ p_i\ /\ (1 - p_i)] = \beta_O + \beta_1 FRPc + \beta_2 EDADc + \beta_3 SEXOc + \beta_4 FRPc_* EDADc + \beta_5 FRPc_* SEXOc$$

where pi is equal to the probability of use of the substance in question of the i-th person, RPFc is the centered variable of the type of risk or protection according to the factor assessed, AGEc is the centered age variable in years and SEXc the sex variable. RPFc* AGEc and RPFc* SEXc correspond to the centered variable of the type of risk or protection depending on exposure and their respective interactions with the centered variables of age and sex. Given the number of hypothesis tests, the analysis was performed with p-values adjusted by the Bonferroni method.

The proposed analysis matched the overall concept of CTC, which considers that risk factors can independently influence substance use behavior (Arthur et al., 2007).

Therefore, it was considered that analyzing this association in models with multiple risk factors could lead to a situation of multicollinearity among the covariates. In addition, the aim of the study was not to understand the variability of the use of each substance but to assess the associations and their directionality, and understand their strength of association through the main effect sizes of each RPF.

Ethical considerations

Informed consent was provided by the school directors, who informed the parents or legal representatives of the children using the passive consent method. Additionally, students gave their approval at the moment of survey administration. The consent and approval forms informed participants about the objectives of the study, its confidential, anonymous and voluntary nature, the procedures of anonymous data storage through codes, as well as the possible risks and benefits. Students were again informed in the classroom that the data provided in the survey were confidential, so they should not write any information that could identify them. It was also mentioned that participation was voluntary, so students could refuse to participate, withdraw at any time and/or request the destruction of the record if they did not wish it to be included in the study. The project has the endorsement of the Ethics Committee of the Nuevos Rumbos corporation, which guarantees compliance with the ethical principles of research enshrined in the law.

Results

Prevalences of use

Alcohol was the most frequently used substance (last 30 days 42.7%, last year 70.1%, and lifetime 73.7%), followed by cigarettes (last 30 days 10.5%, last year 21.3%, and lifetime 26.2%), marijuana (last 30 days 5.1%, last year 10.3%, and lifetime 12.1%) and the category of other illegal drugs (last 30 days 3.7%, last year 7.4%, and lifetime 10.3%). In general, men had higher prevalences of use than women, especially for cigarettes and marijuana (Table 1).

Analysis of RPFs and prevalences of use

The association of 11 risk factors and 3 protection factors for each of the 12 PAS use prevalences was evaluated. Figure 1 shows the main effects between each individual RPF and the prevalence of alcohol, cigarettes, marijuana and other illegal drugs (cocaine, basuco, inhalants, ecstasy, mushrooms, acids, tranquilizers, poppers, amphetamines, heroin and dick) in the time categories lifetime, year and month. The effect was reported in odds ratios (OR) adjusted for age, sex and their respective interactions for each RPF.

Figure 1 presents a categorization in grayscale (from white to black). The cells in dark gray scales and blank numerical values represent the possibilities of developing the associated risk behavior. Cells in light gray scales and numerical values in black indicate the buffering effects of the protective factors studied. The gray scales were determined through the conversion to OR of the cut points for the interpretation of the size of the effect (Cohen, 1988).

OR values from 0.71 to 1.42 were considered to be very small effects, as established by Sawilowsky (2009), and were thus not included in the color scales. This approach allowed us to observe and compare each of the 168 independent effects obtained for each substance and time category in terms of the specific strength of association of the effect. When the association was not statistically significant or the effect was considered very small, the OR value appears in white.

Although all 168 associations evaluated were highly significant ($p < .05$), the intensities of the gray color varied only for only for 97% since five (3.0%) effects belonging to protective factors were considered very small according to the established criteria (OR = [0.71-0.99]). It is important to note that these five effects are from associations with alcohol use (Figure 1). In terms of the observed effects, 3.0% were considered very small ($0.70 \leq OR \leq 1.43$), 51.7% small ($0.70 \geq OR \geq 1.43$), 42.6% medium ($0.40 \geq OR \geq 2.48$) and 7.1% large ($0.23) \geq OR \geq 4.27$). The domain with the highest odds ratios for the use of any substance was that of individual-peer, followed by family, school and community. In general, it was found that substance availability, low perception of substance use risk, favorable attitudes towards substance use, and substance use among friends were the most important predictors of PAS use.

Associations in the community domain

At the community level, the effects on PAS use were analyzed for two risk factors: 1) substance availability; and

Table 1. *Substance use prevalences by sex and time period*

Substance	Last 30 days			Last 12 months			Lifetime		
	Female	Male	Both	Female	Male	Both	Female	Male	Both
Alcohol	41.9%	41.5%	41.7%	69.9%	70.3%	70.1%	73.3%	74.1%	73.7%
Cigarettes	8.6%	12.3%	10.5%	18.5%	24.0%	21.3%	23.3%	29.0%	26.2%
Marijuana	4.2%	6.0%	5.1%	8.8%	11.8%	10.3%	10.4%	13.7%	12.1%
Other illegal drugs	2.6%	2.8%	2.7%	7.0%	7.8%	7.4%	9.5%	11.2%	10.3%

Domain	Risk factor / Protective factor	Alcohol (OR)			Cigarettes (OR)			Marijuana (OR)			Oother illegal drugs (OR)		
		Last 30 days	Last 12 months	Lifetime	Last 30 days	Last 12 months	Lifetime	Last 30 days	Last 12 months	Lifetime	Last 30 days	Last 12 months	Lifetime
Community	Substance availability	1.57	1.70	1.75	2.92	2.59	2.56	5.06	4.17	4.02	3.03	2.65	2.65
	Laws and regulations favorable to use	1.56	1.55	1.56	1.87	1.74	1.75	2.01	1.84	1.82	2.10	1.70	1.76
School	Low school commitment	1.59	1.71	1.81	2.70	2.51	2.39	2.89	2.59	2.56	2.60	2.36	2.30
	Recognition at school for participation	0.75	0.67	0.62	0.57	0.62	0.60	0.55	0.60	0.58	0.55	0.57	0.54
Family	Problems with family management	1.66	1.64	1.59	3.09	2.71	2.57	3.51	3.08	2.93	2.80	2.52	2.50
	Parental attitudes favorable to use	2.93	3.62	3.86	2.48	2.27	2.22	2.81	2.41	2.32	2.35	2.19	2.12
	Parental attitudes favorable to antisocial beh.	1.66	1.86	2.01	2.71	2.54	2.53	3.11	2.90	2.80	2.62	2.73	2.61
	Family opportunities for involvement	0.74	0.75	0.75	0.51	0.54	0.56	0.47	0.53	0.55	0.58	0.59	0.59
	Family recognition for participation	0.74	0.69	0.68	0.50	0.54	0.55	0.46	0.49	0.52	0.54	0.56	0.56
Individuad-Peer	Low perception of substance use risk	2.93	1.70	1.76	2.37	2.07	2.02	4.25	3.40	3.17	3.12	2.57	2.49
	Favorable attitude to substances	2.41	2.82	2.91	4.45	3.64	3.53	5.59	4.47	4.27	4.16	3.57	3.31
	Favorable attitude to antisocial beh.	1.60	1.82	1.93	2.62	2.40	2.43	3.08	2.65	2.68	2.99	2.69	2.61
	Friends behave antisocially	1.81	2.02	2.07	2.97	2.74	2.61	3.39	3.24	3.16	3.10	3.06	2.92
	Friends use substances	2.89	3.78	4.12	6.33	5.51	5.03	8.64	7.41	7.05	5.25	4.55	4.25

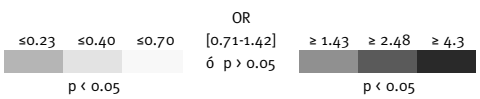

Figure 1. Heat map of adjusted odds ratios (OR) between risk and protective factors of the CQC youth survey by domain and use of alcohol, tobacco, marijuana and other illegal drugs for both sexes.

Note. OR: odds rations adjusted by age, sex, age x [risk factor or protective factor], sex x [risk factor or protective factor].

2) laws and regulations favorable to use. In general, substance availability was a more important risk factor than laws and regulations favorable to consumption. A median effect size was observed in 66.7% of the associations between availability of drugs and the use of PAS among young people, especially for cigarettes, marijuana and other illegal drugs. In contrast, 100% of the effects between laws and rules favorable to PAS use were considered small. The association that presented the largest effect size was that between substance availability and marijuana use, which raised the probability of substance use in the last 30 days by up to five times (OR = 5.06, 95% CI: 4.46, 5.74) among those young people who perceived its availability as high.

The likelihood of marijuana use in the last year among young people who reported high availability was 4.17 times as high as those who did not (OR = 4.17, 95% CI: 3.84, 4.54) and 4.02 times higher for lifetime use compared to those who perceived low availability (OR = 4.02, 95% CI: 3.72, 4.35). As for the other PAS, the set of other illegal substances had larger effect sizes for their use compared to the effect sizes observed for cigarettes and alcohol. No protective factors were included in this domain (Figure 1. Community Domain).

Associations in the school domain

In the school domain, the effects on PAS use were analyzed for the risk factor: 1) low school commitment, and the protective factor: 2) favorable parental attitudes towards substance use. A median effect size was observed in 50.0% of the associations between low school commitment and PAS use among young people. The other 50.0% was considered low. The strongest associations were observed among young people who reported low school commitment with consumption of marijuana in the last 30 days (OR = 2.89, 95% CI: 2.59, 3.22), cigarettes (OR = 2.70, 95% CI: 2.51, 2.90) and other illegal drugs (OR = 2.60, 95% CI: 2.29, 2.95). On the other hand, the protective factor of school recognition for participation generally showed small effects. The strongest protective effect was observed in the 46% decrease in the lifetime use of illegal substances

(OR = 0.54, 95% CI: 0.50, 0.59), 45% reduction in the use of other illegal drugs in the last month (OR = 0.55, IC95%: 0.48, 0.64) and marijuana in the last month (OR = 0.55, IC95%: 0.49, 0.62). School recognition had the lowest protective effect on alcohol use, in particular in the last 30 days (OR = 0.75, 95% CI: 0.71, 0.78), which was the least favorably affected by the presence of this protective factor (Figure 1. School Domain)

Associations in the family domain

Three risk factors were analyzed: 1) problems in family management; 2) favorable attitudes of parents towards the use of drugs; 3) favorable attitudes of parents toward problem behavior; and two protection factors: 1) family opportunities to get involved; 2) recognition in the family for participation. A median effect size was observed in 63.9% of the associations for the three risk factors and the use of PAS in the young. The other 36.1% was considered small. The most relevant associations were observed in young people who reported favorable attitudes of parents towards the use of drugs and alcohol consumption in the last year (OR = 3.86, 95% CI: 3.62, 4.11) and sometime in life (OR = 3.62; 95% CI: 3.42, 3.82). Another association to highlight was between family management problems and marijuana use in the last 30 days (OR = 3.51, 95% CI: 3.14, 3.93).

As for the protection factors, more than 83.3% were considered small and the remaining 16.7% was very small. The protection of individuals who reported family opportunities to engage in prosocial activities was considered as very low in the specific case of alcohol consumption. The same situation was observed for the association between family recognition of participation in prosocial activities and the consumption of alcohol in the last 30 days. The most relevant protective effects observed were the apparent decrease of 54.0% of the possibilities of marijuana use in the last 30 days (OR = 0.46, 95% CI: 0.42, 0.52) in young people with greater family opportunities and a 55.0% decrease (OR = 0.45, 95% CI: 0.41, 0.52) in the same type of consumption in young people who were recognized by their family given their involvement in prosocial activities (Figure 1. Family Domain)

Associations in the individual-peer domain

The following risk factors were analyzed: 1) low perception of substance use risk; 2) favorable attitudes towards substance use; 3) favorable attitudes toward problematic behavior; 4) problematic behaviors among friends; 5) substance use among friends. As previously mentioned, this was the domain with most and largest effect sizes. Of the effects analyzed, 18.3% were considered large (OR ≥ 4.27), 60.0% medium (OR ≥ 2.48) and only 21.7% small (OR ≥ 1.43). The largest associations for all substances and time categories, with the exception of alcohol in the last month, were observed among young people who reported substance use among friends and who had a favorable attitude toward their use. In particular, the highest ORs of all were observed between substance use among friends and the use of marijuana in the last month (OR = 8.64, 95% CI: 7.51, 9.24), year (OR = 7.41, 95% CI: 6.76, 8.11), and lifetime (OR = 7.05, 95% CI: 6.47, 7.68). The same risk factor was the most important in increasing the likelihood of cigarette smoking in the last month (OR = 6.33, 95% CI: 5.81, 6.90), year (OR = 5.51, 95% CI: 5.20, 5.82) and lifetime (OR = 5.03; 95% CI: 4.77, 5.30).

Other associations worth highlighting in connection with substance use among friends were the increases in the use of other illegal drugs in the last month (OR = 5.25, 95% CI: 4.53, 6.10), year (OR = 4.55, 95% CI: 4.17, 4.97) and lifetime (OR = 4.25, 95% CI: 3.95, 4.59). Regarding the other risk factors, the favorable attitude of young people towards substance use was highly associated with cigarette and marijuana use in the last month and the consumption of marijuana in the last year. It should be noted that problematic behavior among friends and a favorable attitude on the part of young people towards this type of behavior were in general weakly associated with alcohol use and averagely associated with the use of other substances (Figure 1. Individual-Peer Domain).

Table 2 shows the covariates that were observed as significant ($p < .05$) for the association between each RPF and the lifetime use of alcohol, cigarettes, marijuana and other illegal substances. This assessment allowed us to confirm the expected association of each covariate with respect to the use of each substance. Of the covariates evaluated, age was associated with all substances. Thus, the probability of the lifetime use of any substance was higher among older students. Likewise, age had a synergistic interaction effect with the majority of RPFs for all PAS, which increased its main effect. On the other hand, sex was associated with cigarettes and all illegal substances (marijuana and other illegal substances), with males presenting the greatest likelihood of lifetime use. However, despite its relevance as a predictor of cigarette and illegal substance use, sex was not associated with alcohol use. The interaction of sex with each risk factor were most evident for cigarette smoking. With regard to protective factors, it should be noted that all interactions between sex and the protective factor were significant and synergistic for all substances except alcohol.

Discussion

In line with the last national study of schoolchildren in Colombia, our research shows that the most frequently used substances were alcohol, cigarettes and marijuana. However, the prevalences of lifetime, last-year and last-month use of alcohol and cigarettes were higher than those at national level. In the specific case of marijuana, it was found that the use of this substance was twice the na-

tional average for the three prevalences (Ministry of Justice and Law, Ministry of National Education and Ministry of Health and Social Protection, 2011).

Perhaps the most important finding yielded by this study was the evidence in favor of the set of 14 selected RPFs in their four domains (family, community, school and individual-peer) as predictors of PAS use among Colombian adolescents, thereby concurrently validating the CQC RPFs with those of the present study and those validated in the literature in terms of directionality and strength (Arthur et al., 2007, Briney et al., 2012; Glaser, Van Horn, Arthur, Hawkins & Catalano, 2005; Hawkins et al., 1992). This finding provides relevant information for Latin America, since it allows us to assume that the RPFs for PAS use could be universal. This in turn implies that they are relevant and appropriate for the implementation of preventive-type initiatives aiming to reduce and monitor over time the prevalence of alcohol, cigarette, marijuana and other illegal substance use among adolescents.

In the community domain specifically, the risk factor substance availability was an appropriate predictor of high illegal substance use for both the last year and the last month; this is similar to the findings of the National Study of the Consumption of Psychoactive Substances in the School Population of Colombia, which reported that a greater perception of PAS being easy to obtain was linked to their use (Ministry of Justice and Law, Ministry of National Education, and Ministry of Health and Social Protection, 2011). This situation is of special interest in the Colombian context, since minors have a generalized perception that PAS are easily procured, which could be related to low controls nationally over the sale to minors, as well as the long tradition of substances such as alcohol being acceptable from an early age, leading to a potential increase in the use of other substances such as tobacco or illegal substances.

Similarly, the relationship between the factors in the family domain and the use of PAS found in this study was also found in the National Study of Consumption of Psychoactive Substances in the School Population of Colombia (Ministry of Justice and Law, Ministry of National Education, and Ministry of Health and Social Protection, 2011). This confirms that working with families is fundamental for prevention. Hawkins, Catalano & Miller (1992) support the premise that parents need adequate family management based on the ability to establish rules and limits, to assert discipline through negotiation and to maintain good relationships with family members. Likewise, the relationship between the parents influences the use of PAS by children, so that good relationships and communication reflected in opportunities and recognition in the family act as protective factors reducing the risk of substance use (Plenum-Sanz, Iraurgi, Martínez & Cosgaya, 2006; Mallick 2009).

In the individual-peer domain, results showed that the three risk factors favorable attitudes towards substance use, favorable attitudes towards problematic behavior, and substance use among friends were strongly associated with the frequent PAS use. This corresponds to findings in other studies which reported that these factors are perhaps the best predictors for substance use and can be exemplified by the selection of friends for substance use (Dishion & Owen, 2002), peers offering PAS, and persuasion by friends and environments of use (Moral & Ovejero, 2008). Moreo-

Table 2. *Statistically significant covariables and interactions ($p < 0.001$) by RPF and lifetime PAS use*

Risk factor / Protective factor	Alcohol	Cigarettes	Marijuana	Other illegal drugs
Substance availability	A	A, S, AxR	A, S, AxR,SxR	A, S
Laws and regulations favorable to use	A	A, S, AxR	A, S	A, S
Low school commitment	A, S, SxR	A, S, AxR	A, S	A, S
Recognition at school for participation	A	A, S	A, S	A, S
Problems with family management	A	A, S, SxR	A, S, SxR	A, S
Parental attitudes favorable to use	A	A, S	A, S	A, S
Parental attitudes favorable to antisocial beh.	A	A, S, SxR	A, S, SxR	A, S
Family opportunities for involvement	A	A, S, AxP,SxP	A, S, AxP	A, S, AxP
Family recognition for participation	A	A, S, SxP	A, S, AxP,SxP	A, S, AxP
Low perception of substance use risk	A	A, S, SxR	A, S	A
Favorable attitude to substances	A	A, S, AxR,SxR	A, S, AxR	A
Favorable attitude to antisocial beh.	A, SxR	A, S, SxR	A, S, SxR	A, S, SxR
Friends behave antisocially	A	A, S, SxR	A, S	A, S ,SxR
Friends use substances	A	A, S	A, S	A, AxR

Note. † RFP= risk and protective factors; PAS=psychoactive substances; A=Age; S= Sex; AxR= Interaction of age and risk factor; AxP= Interaction of age and protective factor; SxR= Interaction of sex and risk factor; SxP= Interaction of sex and protection factor; beh.= behavior.

ver, drinking alcohol tends to begin with increasing age, as shown by Pérez and Scoppetta (2008), and could occur with the aim of exploring, seeking recognition and acceptance of a peer group (Cicua, Méndez & Muñoz, 2008). Given this evidence, the adoption of approaches such as those proposed by CTC and now by CQC in Colombia is essential for communities so that they can prioritize risk factors and intervene on them individually in order to prevent problematic behaviors among young people.

The great variability in the effect sizes observed at a general level can be explained by the dynamism and heterogeneity of the phenomenon of PAS use, which, as previously mentioned, has been reported as changing over time (Glantz et al., 2005; Sloboda, 2005; Thatcher & Clark, 2008; Scoppetta et al., 2011) and in the specific case of our study, is found to change across the domains studied. Given this situation, instruments such as the EJCQC, which not only measures the prevalence of PAS use but also the exposure to the main risk factors that explain its variability, make it a tool to be applied continuously at a national level at least every two years, according to the CTC recommendations (Hawkins, Catalano & Arthur, 2002).

Limitations and recommendations

Finally, the main limitation of this study, in our opinion, is the type of design selected to evaluate associations, since its transversal nature implies a loss of explanatory power with regard to the relationships evaluated, and the inferences are subject to possible biases of reverse causality. However, given that these same factors have also been evaluated longitudinally in other contexts, we have assumed for the purposes of this paper that their proven universality also allows us to confirm the temporality of the relationship and therefore ignore the bias. Despite this, it is recommended to continue reporting future findings through the use of longitudinal measurements that allow a systematic, dynamic and continuous assessment of the communities, highlighting the changes or stability of the risk factors presented, and thereby making it possible to focus and implement prevention strategies even more effectively. Furthermore, it is important to mention that measurements were obtained by self-report of the subjects surveyed. However, thanks to the rigor with which the instruments were applied, it is considered that in this case the self-report was an adequate and direct method for the assessment of the cognitive responses and the subjective experiences of the individual.

Conclusions

This research is one of the few of its kind to inform about the risk profiles and behavior associated with PAS use in Colombia using an epidemiological approach based on risk indicators reported in the evidence and now validated for our country.

The findings of this study have show the validity of the RPFs studied as starting points for the planning, development and future assessment of interventions designed to reduce PAS use in Colombia. Likewise, the results highlight the importance of the use of preventive community systems such as CQC, which are based on epidemiological data for local decision making.

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Conflicts of interest

There are no conflicts of interest.

References

Arthur, M. W., Briney, J. S., Hawkins, J. D., Abbot, R. D., Brooke-Weiss, B. L. & Catalano, R. F. (2007). Measuring risk and protection in communities using the Communities That Care Youth Survey. *Evaluation and Program Planning*, *30*, 197–211. doi:10.1016/je.evalprogplan.2007.01.009.

Arthur, M. W., Hawkins, J. D., Pollard, J. A., Catalano, R. F. & Baglioni A. J., Jr. (2002). Measuring risk and protective factors for substance use, delinquency and other adolescent problems behaviors: The Communities That Care Youth Survey. *Evaluation Review*, *24*, 575–601. doi:10.1177/019384102237850.

De Bellis, M. D., Clark, D. B., Beers, S. R., Soloff, P. H., Boring, A. M., Hall, J., … Keshavan, M. S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, *157*, 737–744. doi:10.1176/appi.ajp.157.5.737.

Briney, J. S., Brown, E. C., Hawkins, J. D. & Arthur, M. W. (2012). Predictive validity of established cut points for risk and protective factor scales form the Communities That Care Youth Survey. *Journal of Primary Prevention*, *33*, 249–258. doi:10.1007/s10935-012-0280-1.

Brown, E. C., Graham, J. W., Hawkins, J. D., Arthur, M. W., Baldwin, M. M., Oesterle, S. & Abbott, R. D. (2009). Design and analysis of the Community Youth Development Study longitudinal cohort sample. *Evaluation Review*, *33*, 311–334.

Clayton, R. R. (1992). Transitions in drug use: Risk and protective factors. In M. D. Glantz & R. W. Pickens (Eds.), *Vulnerability to drug abuse* (pp. 15–51). Washington, DC: American Psychological Association. doi:10.1037/10107-001.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd Ed.). Hillsdale, NJ: Erlbaum Associates.

Crow, I., France, A., Hacking, S. & Hart, M. (2004). *Does Communities That Care work? An evaluation of a community-based risk prevention programme in three neighbourhoods*. York: Joseph Rowntree Foundation.

Dishion, T. J. & Owen, L. D. (2002). A longitudinal analysis of friendships and substance use: Bidirectional influence from adolescence to adulthood. *Developmental Psychology*, *38*, 480–491. doi:10.1037//0012-1649.38.4.480.

Espada, J. P., Botvin, G. J., Griffin, K. W. & Méndez, X. (2003). Adolescencia: Consumo de alcohol y otras drogas. *Papeles del Psicólogo*, *23*, 9–17.

Feinberg, M. E., Greenberg, M. T., Osgood, D. W., Sartorius, J. & Bontempo, D. (2007). Effects of the Communities That Care model in Pennsylvania on youth risk and problem behaviors. *Prevention Science*, *8*, 261–270.

Feinberg, M. E., Jones, D., Greenberg, M. T., Osgood, D. W. & Bontempo, D. (2010). Effects of the Communities That Care model in Pennsylvania on change in adolescent risk and problem behaviors. *Prevention Science*, *11*, 163–171.

Glantz, M. D., Conway, K. P. & Colliver, J. D. (2005). Drug abuse heterogeneity and the search for subtypes. In Z. Sloboda (Ed.). *Epidemiology of drug abuse* (pp. 15–28). New York, NY: Springer.

Glaser, R. R., Van Horn, M. L., Arthur, M. W., Hawkins, J. D. & Catalano, R. F. (2005). Measurement properties of the Communities That Care Youth Survey across demographic groups. *Journal of Quantitative Criminology*, *21*, 73–102.

Graham, J. W. (2012). *Missing data: Analysis and design*. New York, NY: Springer. doi:10.1007/978-1-46144018-5_1

Gruber, S. A., Sagar, K. A. Dahlgren, M. K., Racine, M. & Lukas, S. E. (2012). Age of onset of marijuana use and executive function. *Psychology of Addictive Behaviors*, *26*, 496–506. doi:10.1037/a0026269.

Guerri, C. & Pascual M. (2010). Mechanisms involved in the neurotoxic, cognitive, and neurobehavioral effects of alcohol consumption during adolescence. *Alcohol*, *44*, 15–26. doi:10.1016/j.alcohol.2009.10.003.

Hawkins, J. D. (2006). Science, social work, prevention: Finding the intersections. *Social Work Research*, *30*, 137–152.

Hawkins, J. D., Catalano, R. F. & Miller, J. Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention. *Psychological Bulletin*, *112*, 64–105.

Hawkins, J. D. Catalano, R. F. & Arthur, M. W. (2002). Promoting science-based prevention in communities. *Addictive Behaviors*, *27*, 951–976.

Hawkins, J. D., Catalano, R. F., Arthur, M. W., Egan, E., Brown, E. C., Abbott, R. D. & Murray, D. M. (2008a). Testing Communities That Care: The rationale, design and behavioral baseline equivalence of the Community Youth Development Study. *Prevention Science*, *9*, 178–190.

Hawkins, J. D., Brown, E. C., Oesterle, S., Arthur, M. W., Abbott, R. D. & Catalano, R. F. (2008b). Early effects of Communities That Care on targeted risks and initiation of delinquent behavior and substance use. *Journal of Adolescent Health, 43*, 15–22.

Hawkins, J. D., Oesterle, S., Brown, E. C., Arthur, M. W., Abbott, R. D., Fagan, A. A. & Catalano, R. F. (2009). Results of a type 2 translational research trial to prevent adolescent drug use and delinquency: A test of Communities That Care. *Archives of Pediatrics and Adolescent Medicine*, *163*, 789–798. doi:10.1001/archpediatrics.2009.141.

Hawkins, J. D., Oesterle, S., Brown, E. C., Monahan, K. C., Abbott, R. D., Arthur, M. W. & Catalano, R. F. (2012). Sustained decreases in risk exposure and youth problem behaviors after installation of the Communities That Care prevention system in a randomized trial. *Archives of Pediatrics Adolescent Medicine*, *166*, 141–148.

Hawkins, J. D., Oesterle, S., Brown, E. C., Abbott, R. D. & Catalano, R. F. (2014). Youth problem behaviors 8 years after implementing the Communities That Care prevention system: A community-randomized trial. *JAMA Pediatrics*, *168*, 122–129.

Herrenkohl, T. I., Lee, J. O., Kosterman, R. & Hawkins, J. D. (2012) Family influences related to adult substance use and mental health problems: A developmental analysis of child and adolescent predictors. *Journal of Adolescence Health*, *51*, 129–135. doi:10.1016/j.jadohealth.2011.11.003.

Jonkman, H. B., Haggerty, K. P., Steketee, M., Fagan, A. A., Hanson, K. & Hawkins, J. D. (2009). Communities That Care, core elements and context: Research of implementation in two countries. *Social Developmental Issues*, *30*, 42–57.

Kenny, D. T. & Schreiner, I. (2009). Predictors of high-risk alcohol consumption in young offenders on community orders: Policy and treatment implications. *Psychology, Public Policy, and Law*, *15*, 54–79. doi: 10.1037/a0015079.

Kilpatrick, D. G., Acierno, R., Saunders, B., Resnick, H. S., Best, C. L. & Schnurr, P. P. (2000). Risk factors for adolescent substance abuse and dependence: Data from a national sample. *Journal of Consulting and Clinical Psychology*, *68*, 19–30.

Little, T. D., Rhemtulla, M., Gibson, K. & Schoemann, A. M. (2013). Why the items versus parcels controversy needn't be one. *Psychological Methods*, *18*, 285–300.

Mallick, J. (2009). Parent drug education: A participatory action research study into effective communication about drugs between parents and unrelated young people. *Drugs: Education, Prevention, and Policy*, *14*. 247–260. doi:10.1080/09687630601022416.

Medina, K., L. Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J. & Tapert, S. F. (2007). Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicology*, *29*, 141–152.

Mejia-Trujillo, J., Pérez-Gómez A. & Reyes-Rodríguez, M. (2015). Implementación y adaptación en Colombia del sistema preventivo Communities That Care. *Adicciones*, *27*, 253–264.

Ministerio de Justicia y del Derecho, Ministerio de Educación Nacional, y Ministerio de Salud y Protección Social. (2012). *Estudio Nacional de Consumo de Sustancias Psicoactivas en Población Escolar*. Retrieved at http://www.unodc.org/documents/colombia/Documentostecnicos/Estudio_Consumo_Escolares.pdf.

Moral-Jiménez, M. d. l. V. & Ovejero, A. (2008). Experimentación con sustancias psicoactivas en adolescentes españoles: perfil de consumo en función de los niveles de edad. *Revista Latinoamericana de Psicología*, *41*, 533–553.

Navarro Cicua, D. C., Méndez, M. & Muñoz, L. (2008). Factores en el consumo de alcohol en adolescentes. *Pensamiento Psicológico*, *4*, 115–134.

Oesterle, S., Hawkins, J. D., Kuklinski, M. R., Fagan, A. A., Fleming, C., Rhew, I. C., … Catalano, R. F. (2015). Effects of Communities That Care on males' and females' drug use and delinquency 9 years after baseline in a community-randomized trial. *American Journal of Community Psychology*, *56*, 217–228.

Pérez-Gómez, A., Mejía-Trujillo, J., Brown, E. C. & Eisenberg, N. (2016). Adaptation and implementation of a science-based prevention system in Colombia: Challenges and achievements. *Journal of Community Psychology*, *44*, 538–545. doi:10.1002/jcop.21781.

Pérez, A. & Scopetta, O. (2009). *Consumo de alcohol en menores de 18 años en Colombia 2008: Estudio en 7 capitales y dos municipios pequeños*. Bogotá: Nuevos Rumbos/Dupligráficas.

Sanz, M., Iraurgi, I., Martínez-Pampliega, A. & Cosgaya, L. (2006). Conflicto marital y consumo de drogas en los hijos. *Adicciones*, *18*, 39–48.

Sawilowsky, S. S. (2009). New effect size rules of thumb. *Journal of Modern Applied Statistical Methods*, *8*, 467–474.

Scoppetta, O., Pérez-Gómez, A. & Molano, C. M. (2011). Perfiles asociados al consumo de alcohol en adolescentes escolarizados mediante análisis de correspondencias múltpiles. *Acta Colombiana de Psicología*, *14*, 139–146.

Sloboda, Z, Glantz, M. D. & Tarter, R. E. (2012) Revisiting the concepts of risk and protective factors for understanding the etiology and development of substance use and substance use disorders: Implications for prevention. *Substance Use & Misuse*, *47*, 944–962. doi:10.3109/10826084.2012.663280.

Sloboda, Z. (2005). Implications of epidemiologic information for effective drug abuse prevention strategies. In Z. Sloboda (Ed.), *Epidemiology of Drug Abuse* (pp. 211-223). New York, NY: Springer.

StataCorp. (2013). *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Thatcher, D. L. & Clark, D. B. (2008). Adolescents at risk for substance use disorders: Role of psychological dysregulation, endophenotypes, and environmental influences. *Alcohol Research and Health*, *31*, 168–176.

Toumbourou, J. W. (1999). Implementing Communities That Care in Australia: A community Mobilisation approach to crime prevention. *Trends & Issues in Crime and Criminal Justice*, *122*, 1–6.

Wills, T. A., Bantum, E. O., Pokhrel, P., Maddock, J. E., Ainette, M. G., Morehouse, E. & Fenster, B. (2013). A dual-process model for early substance use: Tests in two diverse populations of adolescents. *Health Psychology*, *32*, 533–542. doi:10.1037/a0027634.

Zeigler, D. W., Wang, C. C., Yoast, R. A., Dickinson, B. D., McCaffree, M. A., Robinowitz, C. B., … Council on Scientific Affairs, American Medical Association. (2005). The neurocognitive effects of alcohol on adolescents and college students. *Preventive Medicine*, *40*, 23–32. doi:10.1016/j.ypmed.2004.04.04.

Experiential avoidance and excessive smartphone use: a Bayesian approach

Evitación experiencial y uso abusivo del smartphone: un enfoque bayesiano

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Abstract

The smartphone is a common tool in our everyday lives. However, recent research suggests that using the smartphone has both positive and negative consequences. Although there is no agreement on the concept or the term to label it, researchers and clinical practitioners are worried about the negative consequences derived from excessive smartphone usage. This study aims to analyse the relationship between smartphone addiction and experiential avoidance. A sample of 1176 participants (828 women) with ages ranging from 16 to 82 (M = 30.97; SD = 12.05) was used. The SAS-SV scale was used to measure smartphone addiction and the AAQ-II to assess experiential avoidance. To model the relationship between variables, Bayesian inference and Bayesian networks were used. The results show that experiential avoidance and social networks usage are directly related to smartphone addiction. Additionally, the data suggests that sex is playing a mediating role in the observed relationship between these variables. These results are useful for understanding healthy and pathological interaction with smartphones and could be helpful in orienting or planning future psychological interventions to treat smartphone addiction.

Keywords: Experiential avoidance; Smartphone; Addiction; Social networks; Bayesian inference.

Resumen

El uso del teléfono móvil se ha convertido en una actividad cotidiana en nuestro entorno más cercano. Dicho uso, según investigaciones recientes, tiene tanto aspectos positivos como negativos. Aunque hay controversia en cuanto a la denominación del fenómeno, se aprecia cierta preocupación por las consecuencias negativas que tiene el uso excesivo del teléfono móvil. Este estudio analiza la relación que se establece entre el uso abusivo del teléfono móvil y la evitación experiencial. Se utilizó una muestra compuesta por 1176 participantes (828 fueron mujeres) con edades comprendidas entre los 16 y los 82 años (M = 30.97; DT = 12.05). Se empleó la escala SAS-SV para valorar el uso problemático del móvil y el AAQ-II para la evitación experiencial. Para modelar la relación que se establece entre las variables se hizo uso de inferencia bayesiana y redes bayesianas. Los resultados muestran una relación directa entre el uso abusivo, la evitación experiencial y las redes sociales. Además, los datos sugieren que el sexo juega un papel mediador entre estas variables. Estos resultados son útiles para entender el uso saludable y patológico del teléfono móvil así como para orientar el tratamiento de los trastornos que pueden surgir de un mal uso de estos dispositivos.

Palabras clave: Evitación experiencial; Smartphone; Adicción; Redes sociales; Inferencia bayesiana.

The use of mobile phones in today's society has gone from being an isolated phenomenon to forming an almost essential activity in our lives (Odgers, 2018). Thus, authors such as Buchinger, Kriglstein, Brandt & Hlavacs (2011) qualify the mobile phone as an indispensable tool for current social and working life. Mobile phones, or so-called smartphones, offer a series of advantages such as allowing us to be more connected, promoting heightened group identity or being an easy means of communicating emotions (Tresáncoras, García-Oliva & Piqueras, 2017). Their use also has effects on the levels of autonomy and social prestige; it is a source for leisure and represents a way of promoting and establishing social relationships (Chóliz, Villanueva & Chóliz, 2009). Moreover, smartphones can be used as tools for interventions in certain pathologies and for data collection with applications focused on health (eg, Capon, Hall, Fry & Carter, 2016; Gustafson et al., 2014; Kuhn et al., 2017; Seoane & Álvarez, 2012). However, despite these positive aspects (Odgers, 2018), a wide range of studies indicate possible adverse effects that may arise from their misuse.

Nevertheless, there is no consensus on how the pernicious effects mobile phones have on health are described (Carbonell, Fúster, Chamorro & Oberst, 2012; Simó, Martínez, Ballester & Domínguez, 2017). Some authors advocate the terminology of excessive use (eg, Chóliz et al., 2009), problematic use (eg, Marín, Carballo & Coloma-Carmona, 2018; Pedrero-Pérez et al., 2018; Simó et al., 2017; Tresáncoras et al., 2017), maladaptive use (eg, Gil, del Valle, Oberst & Chamarro, 2015), or even addiction (eg, Carbonell et al., 2012). In any case, it seems that most studies attempt to locate this phenomenon within the so-called behavioural addictions. However, given how the diagnostic manuals deal with addictions, especially if we take the current DMS-5 (American Psychiatric Association [APA], 2013) as a reference point, to use the term mobile phone addiction may be both legitimate and questionable since there is a lack of consensus on the subject (Simó et al., 2017).

In any case, there are certain studies that emphasize the harmful consequences of such excessive or problematic use of mobile phones, pointing out physical and psychological consequences (stress or anxiety) in social, family, school or work contexts (eg, Babín, 2009; Echeburúa & Corral, 2010; Hardell, Carlbert & Hansson, 2011; Klawer et al., 2014; Lee, Kang & Shin, 2015; Marín et al., 2018; Zarghami, Khalilian, Setareh & Salehpour, 2015). Within these negative consequences, the emergence of new maladaptive behaviours linked to mobile phone use has also been described (eg, Bragazzi & Puente, 2014; Gil et al., 2015; Karadağ et al., 2015; Krasnova, Abramova, Notter & Baumann, 2016; McDaniel & Coyne, 2016; Mendoza & Cuñarro, 2016; Roberts & David, 2016; Rodríguez, 2015; Wang, Xie, Wang, Wang & Lei, 2017).

From a theoretical point of view, it appears that women may be more prone to problematic use of smartphones (Veissière & Stendel, 2018), given their greater tendency towards prosocial behaviour compared to men. Similarly, Karadağ et al. (2015) point out that women make more use of smartphones than men because of their greater desire to be liked and to share their experiences. In addition, there is a series of studies showing that women spend more time using smartphones, instant messaging and social networks (eg, Chóliz, 2012; Chóliz et al., 2009; De-Sola, Rodríguez & Rubio, 2016; Gil et al., 2015; Pedrero-Pérez et al., 2018, Tresáncoras et al., 2017). Another relevant aspect found in some of these studies is that, in some cases, women state that the use of mobile phones helps them deal with unhappy moods (Chóliz et al., 2009; De-Sola et al., 2016), and even to "overcome boredom, deal with anxiety, or at times when they are sad or alone" (Chóliz et al., 2009, p.84). Finally, a review by Carbonell et al. (2012) of Spanish studies has found that women have more problems with the use of smartphones and also consider their use more problematic than do men.

Furthermore, the smartphone is one of the most, if not the most, frequently used tools to access social networks. Some studies show that social networks allow the development of positive aspects in people (eg, Pedrero, Rodríguez & Ruiz, 2012) and have transformed how social relationships are established (eg, Echeburúa & Corral, 2010; Orozco, 2015). However, despite the clear advantages provided by this type of technology, negative aspects are also linked to its use. For example, using social networks is considered a risk factor for excessive smartphone use (Deursen, Bolle, Hegner & Kommers, 2015; Griffiths, 2000; Zhitomirsky-Geffet & Blau, 2016), mental health problems or stress (Pedrero-Pérez et al., 2018) and especially for the adolescent population (Arab & Díaz, 2015; Chóliz et al., 2009; Tresáncoras et al., 2017).

From a psychological point of view, a possible explanation of the maladaptive use of the mobile phone in the field of social networks could be linked to the tendency to flee from aversive feelings provoked by non-virtual reality, especially in the case of women, as mentioned above (Carbonell et al., 2012; Chóliz et al., 2009). The concept of experiential avoidance or experiential avoidance disorder was coined precisely to allude to the maladaptive avoidance tendency linked to different mental disorders (Hayes, Wilson, Gifford, Follete & Strosahl, 1996). Within this paradigm, it is understood that certain psychological disorders are the result of a persistent pattern of maladaptive avoidance oriented towards negative internal events that produce chronic and generalized discomfort. It is understood that this pattern of dysfunctional functioning is based on verbal regulation processes (eg, Hayes, Brownstein, Zettle, Rosenfard & Korn, 1986; Hayes, Strosahl & Wilson, 1999; Hayes, Zettle & Rosenfarb, 1989; Wulfert, Greenway, Far-

kas, Hayes & Dougher, 1994), the person involved consequently experiencing social, personal and/or work-related limitations, which are transferred to different life contexts at a high personal cost (Wilson & Luciano, 2012).

In the context of addictions, it has been observed that the inappropriate or excessive use of chemical substances such as tobacco or alcohol is related to experiential avoidance. For example, in 2016, Levin et al. reported that people who drank excessively scored higher on experiential avoidance. Garey, Farris, Schmidt & Zvolensky (2016) suggest that smoking could be explained by an experiential avoidance mechanism conditioned by the usual stressors of everyday life. Furthermore, Watson, Heffner, McClure & Bricker (2017) provide evidence suggesting that smokers with high levels of social anxiety also present greater experiential avoidance. Bahrami & Asghari (2017), on the other hand, observed that experiential avoidance and inappropriate coping styles could explain therapeutic failure with methamphetamine-dependent patients. In addition, they concluded that the use of Acceptance and Commitment Therapy as a technique aimed at reducing experiential avoidance (Hayes et al., 1999) optimized the prospects for improvement for these patients. Buckner & Zvolensky (2014) also obtained evidence that a pattern of avoidance conditioned the social anxiety shown by cannabis users.

There are fewer studies that link experiential avoidance to behavioural addictions. In fact, the only disorder most directly linked to the idea of addiction is pathological gambling, and it is pointed out (criterion A.5 of DSM-5) that problematic behaviour appears as a consequence of unpleasant sensations such as restlessness, helplessness, depression or anxiety (APA, 2013). Moreover, internet gaming disorder is included in DSM-5 under conditions needing further study and if it were to be recognized as a disorder per se in the future, we would be dealing with the first disorder derived from the use of new technologies. According to the APA (2013), one of the diagnostic criteria for internet gaming disorder is directly related to experiential avoidance: criterion 8 states that pathological behaviour appears in order to "escape problems or alleviate negative emotions" (p. 795). A recent study by García-Oliva & Piqueras (2016) points out that there is a relationship between experiential avoidance and the use of information and communication technologies (ICTs). Specifically, they indicate that ICTs are used as a way of escaping from aversive internal stimuli.

Thus, given that experiential avoidance is associated with some addictive disorders (eg, Hayes et al., 1996), a link between this variable and excessive smartphone use could also be expected. Since social networks play a very important role in the use of mobile devices, as indicated above, it would not be surprising that the use of these tools for social interaction could be partially explained by high levels of experiential avoidance. In addition, one might also expect that problematic use of the mobile phone is related to sex since some authors link this variable to maladaptive smartphone use (eg, Chóliz, 2012; Choliz et al., 2009; Gil et al., 2015; Pedrero-Pérez et al., 2018; Tresáncoras et al., 2017). To study these hypothesised relationships between mobile phone abuse, preference for social network applications and experiential avoidance, we will use the automatic structural learning algorithms of Bayesian networks (eg, Nagarajan, Scutari & Lèbre, 2013; Ruiz-Ruano, 2015; Scutari, 2010). Bayesian networks are multivariate statistical tools that allow the probabilistic relationships established between a set of variables to be graphically modelled (Cowell, Dawid, Lauritzen & Spiegelhalter, 1999; Edwards, 1998; Puga, Krzywinski & Altman, 2015). Despite its potential usefulness, the automatic structural learning of Bayesian networks has been relatively little used in psychology compared to other applications used with this type of tool (eg, López, García, De la Fuente & De la Fuente, 2007; Ruiz-Ruano, 2015). If the data point in the same direction as the hypotheses, our work could be useful from the clinical or applied point of view when planning interventions to prevent or approach problems related to excessive mobile phone use.

Method

Participants

The non-probabilistic sample selected by means of a snowball-type method consisted of 1176 participants in total, with 348 men (29.6%) and 828 women (71.4%). Ages ranged from 16 to 82 (M = 30.97, SD = 12.05). Participants who lived with a partner (38.4%) or were married (21.3%) made up 59.7%, followed by those were single (36.3%), divorced (2.5%), widowed (0.3%), and 1.1% who indicated that they had a different marital status to those listed above. Regarding the level of education, most of the sample indicated that they had a university degree (64.8%), 0.4% indicated that they had no schooling, and the rest stated that they had completed higher secondary schooling or vocational training, lower secondary or primary schooling. Regarding professional status, 44.5% of participants said they were workers, 37.8% students, 9.9% were unemployed, 2.4% were retired, and 2% indicated that they were housewives.

Instruments

A questionnaire was developed using Google Forms® to gather sociodemographic information (age, sex, marital status, educational level and employment status) as well as information relating to smartphone use (most used application, time of use, reasons for use and number of phones). The questionnaire included a question about the application that was most frequently used on the mobile device, and the responses were recoded to represent the participant's

preference for social networks over other applications available on their phones. The questionnaire also included a scale to assess the level of addiction to the smartphone and a questionnaire to assess the level of experiential avoidance.

The smartphone addiction scale used (SAS-SV) is the short version of the smartphone addiction scale (SAS) originally created by Kwon et al. (2013a). The internal consistency of this reduced version designed by Kwon, Kim, Cho & Yang (2013b) is α = .91. In this study we have used the adaptation to Spanish by López-Fernández (2015), which obtained a Cronbach's α of .88 in the corresponding adaptation study. The scale consists of ten items based on substance dependence and the pathological gambling disorder described in DSM-IV (APA, 1994, 2000). The response format is presented on a 6-point Likert scale, where 1 corresponds to "strongly disagree" and 6 to "strongly agree". Scores range from 10 to 60, with higher scores representing greater risk of smartphone addiction. The internal consistency indices obtained in this study for the SAS-SV scale are: α = .87, 95% CI: .86, .89, and ω = .88.

To measure experiential avoidance, or cognitive inflexibility, we used the version of the Acceptance and Action Questionnaire (Acceptance and Action Questionnaire II or AAQ-II) presented by Ruiz, Langer, Luciano, Cangas & Beltrán (2013). The first version of this test was developed by Hayes et al. (2000) and Hayes et al. (2004); this was based on different clinical experiences and obtained an internal consistency alpha of .7. Bond et al. (2011) developed the second version of the test, which achieved higher internal consistency levels (.97) and contained fewer items. The test consists of seven items with Likert-type responses on a 7-point scale to reflect the degree of truthfulness that the participant attributes to each item according to their experience. In our application of the test, the observed values of internal consistency were: α = .89, 95% CI: .89, .90, y ω = .90.

Procedure

The electronic questionnaire was made available to participants via the WhatsApp® instant messaging application, social networks (Facebook® and Twitter®) and email. To begin data collection, we asked university students to complete the form and then distribute it among their contacts on social networks. The questionnaire began with an outline of the study's objectives, a data anonymity and confidentiality guarantee, and a request to share the form among their social network contacts. The dissemination of the form and collection of data began on November 24, 2016 and ended on January 30, 2017.

Data analysis

The analytical strategy used is in line with the proposal of Cohen, Cohen, West & Aiken (2003), which takes correlational models as a general framework for studying behaviour. For example, the correlations between quantitative and dichotomous variables (such as having more than one mobile phone or not) were estimated as standardized coefficients in the corresponding linear regression models which would explain the quantitative variable depending on group membership in the dichotomous variable. To obtain the matrix of correlations between the study variables and the Bayes factors favouring the alternative to the null hypothesis (BF_{10}), we used version 0.9 of the JASP statistical software (JASP Team, 2018).

The resulting Bayes factor expresses how much more true or probable the alternative hypothesis is against the null hypothesis (Kass & Raftery, 1995). A Bayes factor equal to one would indicate that the alternative hypothesis is just as likely as the null hypothesis, given the observed data. A Bayes factor greater than one would indicate how much more likely the alternative hypothesis is against the null hypothesis. For example, a BF_{10} equal to two indicates that the alternative hypothesis is twice as likely as the null hypothesis, while a BF_{10} of 100 means that the alternative hypothesis is 100 times more likely than the null hypothesis. The default Cauchy distribution ($r = 1$) suggested by Rouder, Speckman, Sun, and Morey (2009) was used to estimate the Bayes factors. Simulation studies carried out so far (Jeon & De Boeck, 2017) have shown that such a distribution offers a balanced option regarding the key elements involved in statistical decision making.

The structural models of Bayesian networks were estimated with version 4.2 of the "bnlearn" package (Scutari, 2010) for R. Six different algorithms were used to find the model that best fitted the data. Two of the algorithms used restricted model methods (*Grow-Shrink and Incremental Association*), two were based on fit (*Hill-Climbing and Tabu Search*), while the remaining two were mixed (*Max-Min Hill-Climbing and Restricted Maximization*). We used two different methods to study the goodness of fit of the models estimated by each algorithm. First, the sample was divided into an estimation set containing 70% of the observations, with the remaining 30% (test subset) being used to assess the degree to which the data fit the models established in the estimation phase. Goodness of fit was validated by means of log likelihood, the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC) (Scutari & Denis, 2014). In each case, the higher the values, the better the model-to-data fit. The second validation procedure consisted of randomly dividing the data set into equal parts 2000 times to measure the log-likelihood differences from one estimate to another (Koller & Friedman, 2010). In this case, lower log-likelihood loss values would mean a better fit. Finally, to calculate the strength of association of each link in the Bayesian network, the changes in log likelihood, the AIC and the BIC were analysed by deleting the corresponding edge from the model (Scutari & Denis, 2014). In this case, the smaller the log likelihood, AIC or BIC values when a link is removed from the model, the

more relevant or influential that link is considered to be for the network tested. Thus, the goodness-of-fit statistics assess the degree to which the model weakens when a link is eliminated from it. The smaller the value of this statistic, the more the model is thought to weaken if the link in question is deleted.

Results

As can be seen in Table 1, the variables which are most closely and positively associated are the number of hours in which the smartphone is used and the time spent on the preferred application. The second largest positive correlation is that between the experiential avoidance score measured with the AAQ-II and the smartphone addiction score on the SAS-SV scale. Experiential avoidance also correlates positively and significantly with the time users spend on their preferred application and the hours of mobile phone use. There is also a positive relationship of the same strength between the SAS-SV addiction score and the hours of mobile phone use, as well as with the time spent on the preferred application. As can be seen in Table 1, the estimated Bayes factors for these correlations suggest that the observed data could be considered as decisive evidence ($BF_{10} > 100$) in favour of the correlations between these variables being genuinely different from zero (Jeffreys, 1948). In other words, given the Bayes factors associated with these correlations, we could say that the hypothesis of genuine correlation between these variables is at least 600 million times more probable (Bayes factor associated with the correlation observed between experiential avoidance and hours of smartphone use) than the null hypothesis.

The results show (Table 1) that the hours spent on the smartphone, the time dedicated to the preferred application and the preferred use of social networks are linked to the female sex. Although the estimated correlations are of a small magnitude, the Bayes factors obtained suggest that the observed data provide very strong evidence in favour of the relationship between these variables. In all three cases, the Bayes factors estimated in favour of the alternative hypothesis are greater than 100, and following the proposal of Jeffreys (1948), this suggests that the observed data provide decisive evidence in favour of the idea of genuine correlation between the variables. On the other hand, there are no significant correlations between the number of years of smartphone use, the preferred use of social networks, and experiential avoidance. There is also no noticeable correlation between years of use and the use of social networks.

Table 2 shows the goodness-of-fit results for the estimated graphical models with each of the algorithms used,

Table 1. *Correlation coefficients adapted to variable type (Cohen et al., 2003), classical p-value of statistical contrast, classical 95% confidence interval (lower left triangle) and Bayes factor favouring the alternative hypothesis or BF10 (upper right triangle).*

	SEX	NA	HM	YM	MOM	TPA	EA	SAS	SN
SEX	—	35377	2780	0.259	4414	1246	0.165	0.067	2.34×10^{7}
NA	.11 < .001 [.05, .17]	—	0.327	4.24×10^{7}	0.905	0.065	0.071	12510	0.041
HM	-.09 0.003 [-.14, -.03]	.06 0.036 [.004, .12]	—	0.039	0.294	9×10^{99}	6.11×10^{8}	5.97×10^{26}	122162
YM	-.06 .048 [-.12, -.001]	.16 < .001 [.10, .21]	.009 0.747 [-.05, .07]	—	10132	0.038	0.037	0.210	0.037
MOM	.09 .002 [.03, .15]	.07 .011 [.02, .13]	.06 0.041 [.002, .12]	.10 < .001 [.04, .16]	—	0.110	0.039	0.066	3436
TPA	-.08 .008 [-.14, -.02]	.03 .284 [-.03, .09]	.82 < .001 [.80, .84]	-.007 .808 [-.07, .05]	.04 .138 [-.01, .10]	—	5.84×10^{12}	2.86×10^{27}	3077
EA	-.05 0.083 [-.11, .01]	-.03 .253 [-.09, .02]	.20 < .001 [.14, .25]	.000 .987 [-.06, .06]	.01 .733 [-.05, .07]	.24 < .001 [.18, .29]	—	1.22×10^{31}	0.042
SAS	-.03 0.276 [-.09, .03]	.10 < .001 [.04, .16]	.33 < .001 [.27, .38]	.06 .062 [-.003, .11]	.03 .279 [-.03, .09]	.33 < .001 [.28, .38]	.35 < .001 [.30, .40]	—	403.9
SN	-.15 < .001 [-.21, -.09]	-.01 .641 [-.07, .04]	.12 < .001 [.06, .17]	.004 .891 [-.05, .06]	-.09 .003 [-.15, -.03]	.14 < .001 [.08, .20]	-.02 .604 [-.07, .04]	.13 < .001 [.07, .18]	—

Note. SEX: sex (1 = male, 0 = female), NA: number of applications installed on smartphone, HM: hours per day spent using mobile phone, YM: years of experience using mobile phones, MOM: owning more than one mobile phone (0 = no, 1= yes), TPA: time spent daily on preferred application, EA: score on experiential avoidance scale AAQ-II, SAS: score on smartphone addiction scale SAS-SV, and SN: considering social networks to be preferred application type (0 = no, 1 = yes). All contrasts are bilateral.

applying the 70/30 partition of the data as described above. The *tabu* and *hc* algorithms generate identical graphs, in the same way that the *rsmax2* and *mmhc* algorithms agree in their estimates. However, as shown in Table 2, the *tabu* and *hc* algorithms obtain the best goodness-of-fit indices when the models are estimated with 70% of the data. The *IAMB* algorithm is the one yielding the worst goodness-of-fit indices. When the remaining 30% of data are used to assess model overfitting, it can be seen that the *gs* algorithm is slightly better. The *mmhc* and *rsmax2* algorithms take second place while *hc-tabu* come third. Again, the *IAMB* turns out to be the worst of the algorithms. However, as shown in Figure 1, when cross-validation is performed using 2000 random partitions of the data, the best algorithms for estimating the structure of dependency contained in the data are *hc* and *tabu*.

The estimated graphical model with the *hc* and *tabu* algorithms, which can thus be considered the most accep-

Table 2. *Goodness-of-fit indices for each algorithm using 70% of the data for the estimation and the remaining 30% to assess overfitting.*

Algorithm	TABU	HC	RSMAX2	MMHC	GS	IAMB
ABF	1.44	1.44	1.1	1.1	1.22	0.78
Number of tests	288	140	245	220	212	292
Nodes	9	9	9	9	9	9
Arcs	13	13	10	10	11	7
Parameters	22	22	19	19	20	16
LL-70	-15843.82	-15843.82	-15855.34	-15855.34	-15862.58	-16340.11
AIC-70	-15865.82	-15865.82	-15874.34	-15874.34	-15882.58	-16356.11
BIC-70	-15917.5	-15917.5	-15918.98	-15918.98	-15929.56	-16393.7
LL-30	-6911.77	-6911.77	-6914.6	-6914.6	-6917.08	-7085.75
AIC-30	-6933.77	-6933.77	-6933.6	-6933.6	-6937.08	-7101.75
BIC-30	-6985.46	-6985.46	-6978.23	-6978.23	-6975.6	-7132.57

Note. ABF: average branching factor, TABU: *tabu search* algorithm, HC: *hill-climbing* algorithm, RSMAX2: *restricted maximization* algorithm, MMHC: *max-min hill-climbing* algorithm, GS: *grow-shrink* algorithm, IAMB: *incremental association* algorithm, LL: log-likelihood algorithm, AIC: Akaike Information Criterion, and BIC: Bayesian Information Criterion.

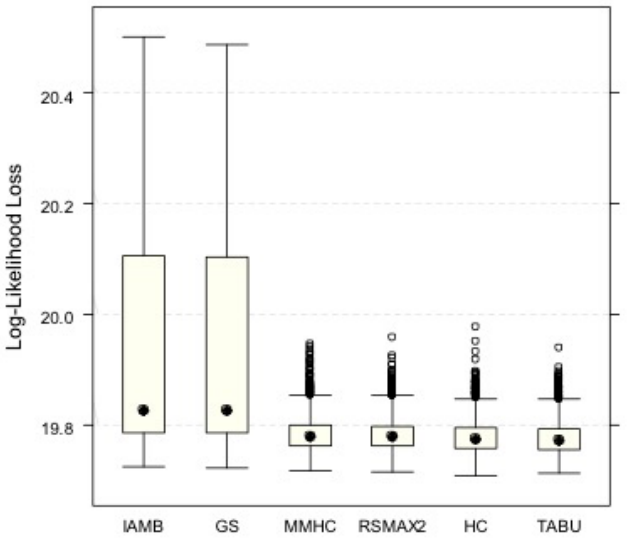

Figure 1. Results of cross-validation analyses.

Note. Log-likelihood loss for each of the 2000 partitions made in the database. The box plots are arranged in descending order by median.

table, is shown in Figure 2. As can be seen, the variables sex and years of mobile phone use are the only ones that do not depend on any other variable. The smartphone addiction score on the SAS-SV scale depends on experiential avoidance, social networks being the preferred application type, and the number of applications installed on the mobile device. The graph also shows that the number of hours spent on the mobile phone depends on the levels of experiential avoidance, the preference for the use of social networks and the score on the mobile phone addiction scale.

In order to assess the relevance of the graph's edges, the impact of deleting each one was estimated. Table 3 shows the weakening that occurs in the main goodness-of-fit indices of the new model when a particular link is eliminated from the estimated graph (Figure 2). The greater the reduction in the BIC and related statistics on removing a link, the more relevant that link can be considered in the model obtained. Thus, the most relevant link of the model presented in Figure 2, and the one that weakens all goodness-of-fit indices when eliminated from the model, is between the hours per day of mobile phone use and the hours per day spent on the preferred application (see Table 3). The second strongest link identified in the model is between experiential avoidance and the score on the smartphone addiction scale. These two links, together with that linking the SAS-SV score and the number of hours spent on the mobile phone would be the most relevant arcs of the

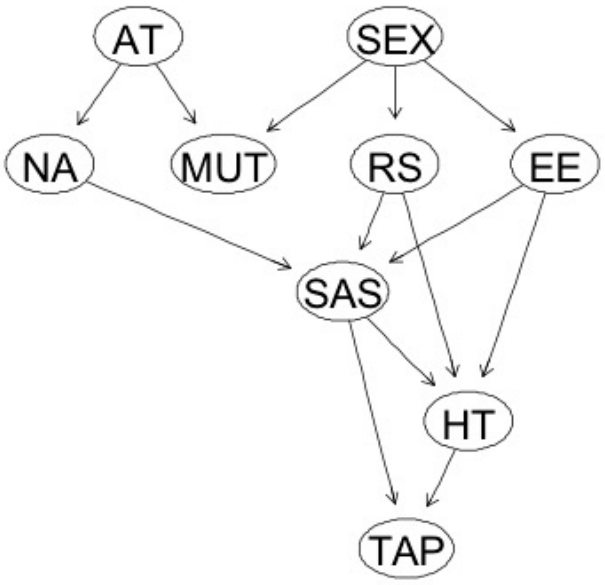

Figure 2. Estimated Bayesian network model with *tabu* and *hc* algorithms.

Note. AT: YM: years of experience using mobile phones, SEX: sex, NA: number of applications installed on smartphone, MUT: MOM: owning more than one mobile phone, RS: SN: considering social networks to be preferred application type, EE: EA: score on experiential avoidance scale AAQ-II, SAS: score on smartphone addiction scale SAS-SV, HT: HM: hours per day spent using mobile phone, and TAP: TPA: time spent daily on preferred application.

Table 3. *Change in goodness-of-fit on removing a directed link from the Bayesian network.*

From	To	LL	AIC	BIC
HM	TPA	-587.06	-586.06	-583.71
EA	SAS	-80	-79	-76.66
SAS	HM	-42.72	-41.72	-39.37
SEX	SN	-13.41	-12.41	-10.06
YM	NA	-14.01	-13.01	-10.66
SN	SAS	-12.02	-11.02	-8.67
NA	SAS	-8.79	-7.79	-5.44
SAS	TPA	-7.77	-6.77	-4.42
SEX	MOT	-5.5	-4.5	-2.15
EA	HM	-6.17	-5.17	-2.82
SN	HM	-4.58	-3.58	-1.23
YM	MOT	-6.33	-5.33	-2.99
SEX	EA	-1.51	-0.51	1.84

Note. SEX: sex, NA: number of applications installed on smartphone, HM: hours per day spent using mobile phone, YM: years of experience using mobile phones, MOM: owning more than one mobile phone, TPA: time spent daily on preferred application, EA: score on experiential avoidance scale AAQ-II, SAS: score on smartphone addiction scale SAS-SV, SN: considering social networks to be preferred application type, LL: log-likelihood, AIC: Akaike Information Criterion, and BIC: Bayesian Information Criterion.

model. If these links were eliminated from the model, the goodness-of-fit indices would weaken. In other words, these are the most strongly established relationships among the variables included in the model. Conversely, the link between sex and experiential avoidance is the least strong and could be eliminated from the model without drastic repercussions on the estimated goodness-of-fit indices.

Discussion

The aim of this study was to investigate the relationship between a range of variables which can be linked to smartphone addiction or problematic use of the same and of social networks. The first idea to be tested was whether a relationship between the experiential avoidance variable and the excessive use of mobile phones existed. Results show that this is indeed the case, both when analysing the correlations obtained between them, and in the Bayesian network which was generated. This result raises the possibility that the smartphone is used as an escape route for negative emotions and thoughts. These outcomes are consistent with some of the recent work published by Chóliz et al. (2009) and Carbonell et al. (2012), who point out that women use it to cope with unpleasant moods or to alleviate emotional distress, which is also noted by García-Oliva & Piqueras (2016). If the pattern of mobile phone use is conditioned by the avoidance of internal negative sensations, it could lead to long-term problems. The directional relationship observed between experiential avoidance and mobile addiction suggests that the latter depends on the former, as also seems to be the case in other addictive disorders (eg, Buckner & Zvolensky, 2014; Garey et al., 2016; Hayes et al., 1996; Levin et al., 2016; Watson et al., 2017). However, as this is an exploratory correlational study, these dependency relationships must be interpreted with caution and investigated with other research methodologies which allow us to more accurately approach causal explanations. In any case, our data suggest that a non-adaptive use of the mobile is related to experiential avoidance, and it would therefore be desirable to pay attention to this fact both from a clinical and scientific point of view.

Although we expected to find a link between levels of experiential avoidance and the use of social networks, the existence of a direct relationship between these variables was not observed. It should be taken into account, however, that mobile addiction is a convergence variable (a potentially common effect) with respect to social network use and experiential avoidance. Therefore, given the formalism of the Bayesian networks, experiential avoidance and social networks become conditionally dependent when the level of mobile addiction is known. In any case, the estimated Bayesian network model suggests that the relationship observed between these variables is mediated by sex. In this sense, as predicted and as stated, for example, by Chóliz et al. (2009), Gil et al. (2015) and Tresáncoras et al. (2017), there is a relationship between sex and excessive smartphone use. However, according to results obtained, this relationship may also be conditioned by the use of

social networks (Figure 2). In this as in previous studies, it has been observed that women use smartphones more than men in terms of time spent on social networks, which usually also happens to be their most preferred application type. Looking at it graphically, we see that the relationship between sex and hours of mobile phone use is mediated by considering social networks to be the preferred application type (Figure 2).

From a theoretical point of view, our results are consistent with the hypernatural monitoring model of smartphone addiction (Veissière & Stendel, 2018). This theory holds that there is not something intrinsically addictive in the mobile phone. Rather, Veissière and Stendel (2018) suggest that mobile addiction is a consequence of social expectation in terms of the rewards obtained by connecting with other people. This social component could explain both the onset and maintenance of smartphone addiction, as well as the neurophysiological dimension observed in addictions to substances and other behavioural addictions (eg, Bohbot, Del Balso, Conrad, Konishi & Leyton, 2013; Sussman, Harper, Stahl & Weigle, 2018). Our results provide support for this theory since the levels of smartphone addiction can be explained, partially at least, by the interaction with social networks and as a consequence of the systematic avoidance of unpleasant internal experiences. In any case, although this theory needs to be tested empirically, especially regarding neurophysiological correlates, our results are consistent with its postulates.

Except for gambling addiction, DSM-5 (APA, 2013) does not include behavioural addictions. However, despite the positive consequences that may arise from the use of information technologies, for example, the smartphone, it is noted that there are also negative consequences of their excessive or non-functional use. Thus, Potenza, Higuchi & Brand (2018) advocate continuity in the study of behavioural addictions in order to improve intervention strategies; the focus here should not only be on pathological gambling, but also on other types of behaviour that can lead to addictions. As this study has shown, it seems that experiential avoidance plays some role in relation to excessive mobile phone use. We therefore suggest further research into whether interventions for this type of problem should aim at favouring greater contact with oneself, and, as part of all mindfulness-based interventions, pay greater attention to internal states regardless of whether they are positive or negative. If, as can be deduced from our results, some people use the mobile to escape or avoid negative emotions by looking for a certain type of immediate relief, negative consequences could result for the individual in the long term, presumably leading to behavioural addiction.

One of the limitations of our work is that it is a correlational and exploratory study (Nosek, Ebersole, DeHaven & Mellor, 2018). While these types of study are useful, longitudinal and even experimental studies would be necessary to really analyse the impact of some variables on others. Although our results suggest the existence of a relationship between experiential avoidance and the maladaptive use of the mobile, it could be interesting to carry out studies comparing people with a clinical diagnosis of this disorder to the general population and observing the behavioural patterns in both groups. Another limitation of the study has to do with the data collection procedure. Despite allowing access to a broad spectrum of participants, certain variables cannot be controlled, such as social desirability in questionnaire responses. Moreover, there have not been any studies by age investigating differences between age groups or different life stages. It must be remembered that the age range of the participants studied is very wide, and this dispersion could have affected the results obtained in some way. Future research could have an impact on these aspects given that, as suggested by Odgers (2018), the consequences of technology use are not the same for each person or the developmental stage in which they find themselves.

We urge that one of the future lines of research should investigate whether or not excessive behaviours regarding the use of information technologies can be classified as addictive. As noted by Potenza et al. (2018), the understanding of the biological, psychological and social processes which are at the root of behavioural addiction can improve both prevention and treatment strategies. In any case, we should advocate good use of smartphones or technology in general to make our lives in society more beneficial. It is not a matter of prohibiting or rejecting technologies because they are misused, but rather, as Abelson (1997) suggests in the context of statistical data analysis, of education regarding their proper use.

Conflict of interest

The authors declare no conflicts of interest.

References

Abelson, R. P. (1997). On the surprising longevity of flogged horses: why there is a case for the significance test. *Psychological Science, 8,* 12-15. doi:10.1111/j.1467-9280.1997.tb00536.x.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).* Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).* Barcelona: Masson.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* Barcelona: Panamericana.

Arab, E. & Díaz, A. (2015). Impacto de las redes sociales e internet en la adolescencia: aspectos positivos y negativos. *Revista Médica Clínica Las Condes, 26*, 7-13.

Babín, F. A. (2009). Estudio del uso problemático de las tecnologías de la información, la comunicación y el juego entre los adolescentes y jóvenes de la ciudad de Madrid. *Trastornos Adictivos*, *11*, 151-163. doi:10.1016/S1575-0973(09)72407-9.

Bahrami, S. & Asghari, F. (2017). A controlled trial of acceptance and commitment therapy for addiction severity in methamphetamine users: Preliminary study. *Archives of Psychiatry and Psychotherapy, 19*, 49-55. doi:10.12740/APP/68159.

Bohbot, V. D., Del Balso, D., Conrad, K., Konishi, K. & Leyton, M. (2013). Caudate nucleus-dependent navigational strategies are associated with increased use of addictive drugs. *Hippocampus, 23*, 973-984. doi:10.1002/hipo.22187.

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., ... Zettle, R. D. (2011). Preliminary Psychometric Properties of the acceptance and action questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. *Behaviour Therapy*, *42*, 676-688.

Bragazzi, N. L. & Puente, G. (2014). A proposal for including nomophobia in the new DSM-5. *Psychology Research and Behavior Management, 7*, 155-160.

Buchinger, S., Kriglstein, S., Brandt, S. & Hlavacs, H. (2011). A survey on user studies and technical aspects of mobile multimedia applications. *Entertainment Computing*, *2*, 175-190. doi:10.1016/j.entcom.2011.02.001.

Buckner, J. D. & Zvolensky, M. J. (2014). Social anxiety and coping motives for cannabis use: the impact of experiential avoidance. *Psychology of Addictive Behaviors, 28*, 568-574.

Capon, H., Hall, W., Fry, C. & Carter, A. (2016). Realising the technological promise of smartphone in addiction research and treatment: an ethicall review. *International Journal of Drug Policy*, 36, 47-57.

Carbonell, X., Fúster, H., Chamarro, A. & Oberst, U. (2012). Adicción a internet y móvil: una revisión de estudios empíricos españoles. *Papeles del Psicólogo*, *33*, 83-89.

Chóliz, M. (2012). Mobile-phone addiction in adolescence: the test of mobile phone dependence (TMD). *Progress in Health Sciences, 2*, 33-44.

Chóliz, M., Villanueva, V. & Chóliz, M. C. (2009). Ellos, ellas y su móvil: uso, abuso (¿y dependencia?) del teléfono móvil en la adolescencia. *Revista Española de Drogodependencias*, *34*, 74-88.

Cohen, J., Cohen, P., West, S. G. & Aiken, L. S. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3ª ed). Mahwah, NJ: Laurence Erlbaum.

Cowell, R. G., Dawid, A. P., Lauritzen, S. L. & Spiegelhalter, D. J. (1999). *Probabilistic networks and expert systems*. Harrisonburg, VA: Springer.

De-Sola, J., Rodríguez, F. & Rubio, G. (2016). Cell-phone addiction: A review. *Frontiers in Psychiatry, 7*. doi: 10.3389/fpsyt.2016.00175.

Deursen, A. J., Bolle, C. L., Hegner, S. M. & Kommers, P. A. (2015). Modeling habitual and addictive smartphone behavior: the role of smartphone usage, types, emotional intelligence, social stress, self-regulation, age and gender. *Computers in Human in Behavior, 45*, 411-420. doi:10.1016/j.chb.2014.12.039.

Echeburúa, E. & Corral, P. (2010). Adicción a las nuevas tecnologías y a las redes sociales en jóvenes: un nuevo reto. *Adicciones*, *22*, 91-96.

Edwards, W. (1998). Hailfinder. Tools for and experiences with Bayesian normative modeling. *American Psychologist*, *53*, 416-428.

García-Oliva, C. & Piqueras, J. A. (2016). Experiential avoidance and technological addictions in adolescents. *Journal of Behavioral Addictions*, *5*, 293-303. doi:10.1556/2006.5.2016.041.

Garey, L., Farris, S. G., Schmidt, N. B. & Zvolensky, M. J. (2016). The role of smoking-specific experiential avoidance in the relation between perceived stress and tobacco dependence, perceived barriers to cessation, and problems during quit attempts among treatment-seeking smokers. *Journal of Contextual Behavioral Science, 5*, 58-63.

Gil, F., del Valle, G., Oberst, U. & Chamarro, A. (2015). Nuevas tecnologías - ¿Nuevas patologías? El smartphone y el fear of missing out. *Aloma. Revista de Psicologia, Ciències de l'Educació i de l'Esport*, *33*, 77-83

Griffiths, M. (2000). Does Internet and computer "addiction" exist? Some case study evidence. *Cyberpsychology & Behavior, 3*, 211-218.

Gustafson, D. H., McTavish, F. M., Chih, M. I., Atwood, A. K., Johnson, R. A., Boyle, M. G., ...Shah, D. (2014). A smartphone application to support recovery from alcoholism a randomized clinical trial. *JAMA Psychiatry, 71*, 566-572.

Hardell, L., Carlberg, M. & Hansson, K. L. (2011). Pooled analysis of case-control studies malignant brain tumors and the use of mobile and cordless phones including living and deceased subjects. *International Journal of Oncology, 38*, 1465-1474. doi:10.3892/ijo.2011.947.

Hayes, S. C., Bissett, R. T., Strosahl, K., Wilson, K., Pistorello, J., Toamino, D., …Follete, W. C. (2000). *Psicometric properties of the acceptance and action questionnaire (AAQ).* Manuscrito inédito, Departamento de Psicología, Universidad de Nevada, Reno.

Hayes, S. C., Brownstein, A. S., Zettle, R. D., Rosenfard, I. & Korn, Z. (1986). Rule-governed behavior and sensitivity

to changing consequences of responding. *Journal of the Experimental Analysis of Behavior, 45*, 237-256.

Hayes, S. C., Strosahl, K. D. & Wilson, K. G. (1999). *Acceptance and commitment therapy*. New York: The Guilford Press.

Hayes, S. C., Strosahl, K., Wilson, K. G., Bissett, R. T., Pistorello, J., Toarmino, D., … McCurry, S. M. (2004). Measuring experiential avoidance: a preliminary test of a working model. *The Psychological Record, 54*, 553-578.

Hayes, S. C., Wilson, K. G., Gifford, E. V., Follete, V. M. & Strosahl, K. (1996). Experiential avoidance and disorder: a functional dimensional approach to diagnosis and treatment. *Journal of Consulting and Clinical Psychology, 64*, 1152-1168.

Hayes, S. C., Zettle, R. D. & Rosenfarb, I. (1989). Rule following. En S. C. Hayes (Ed.), *Rule-governed behavior cognition, contingencies and instructional control* (pp. 191-220). New York: Plenum Press.

JASP Team (2018). JASP (Version 0.8.5) [Computer software].

Jeffreys, H. (1948). *Theory of probability* (2ª Ed.). Oxford: Oxford University Press.

Jeon, M. & De Boeck, P. (2017). Decision qualities of Bayes Factor and p value-based hypothesis testing. *Psychological Methods, 22,* 340-360. doi: 10.1037/met0000140.

Karadağ, E., Tosuntaş, Ş. B., Erzen, E., Duru, P., Bostan, N., Şahin, B. M., Çulha, I. & Babadağ, B. (2015). Determinants of phubbing, which is the sum of many virtual addictions: A structural equation model. *Journal of Behavioral Addictions, 4*, 60-74. doi:10.1556/2006.4.2015.005.

Kass, R. E. & Raftery, A. E. (1995). Bayes factors. *Journal of the American Statistical Association, 90*, 773-795. doi: 10.1080/01621459.1995.10476572.

Klawer, S. G., Guo, F., Simons-Morton, B. C., Ouimet, M. C., Lee, S. E. & Dingus, T. A. (2014). Distracted driving and risk of road crashes among novice and experienced drivers. *The New England Journal of Medicine, 370,* 54-59 doi:10.1056/NEJMsa1204142.

Koller, D. & Friedman, N. (2010). *Probabilistic graphical models. Principles and techniques*. Cambridge, MA: MIT Press.

Krasnova, H., Abramova, O., Notter, I. & Baumann, A. (2016). *Why phubbing is toxic for your relationship: Understanding the role of smartphone jealousy among "Generation Y" users*. Comunicación presentada en el Twenty-Fourth European Conference on Information Systems (ECIS), Estambul, Turquía.

Kuhn, E., Kanuri, N., Hoffman, J. E., Garvert, D. W., Ruzek, J. L. & Tailor, C. B. (2017). A randomized controlled trial of a smartphone app for postraumatic stress disorders symptoms. *Journal of Consulting and Clinical Psychology, 85*, 267-273. doi:10.1037/ccp0000163.

Kwon, M., Kim, D-J, Cho, H. & Yang, S. (2013b). The Smartphone Addiction Scale: Development and Validation of Short Version for Adolescents. *PLoS One, 8*, e83558. doi:10.1371/journal.pone.0083558.

Kwon, M., Lee, J-Y., Won, W-Y., Park, J-W., Min, J-A., Hahn, C., ... Kim, D. J. (2013a). Development and Validation of a Smartphone Addiction Scale (SAS). *PLoS One, 8*, e56936. doi:10.1371/journal.pone.0056936.

Lee, S., Kang, H. & Shin, G. (2015). Head flexion angle while using a smartphone. *Ergonomis 58*, 220-226. doi:10.1080/00140139.2014.967311.

Levin, M. E., Lillis, J., Seeley, J., Hayes, S. L., Pistorello, J. & Biglan, A. (2016). Exploring the relationship between experiential avoidance, alcohol use disorders, and alcohol-related problems among first-year college students. *Journal of American College Health, 60*, 443-448.

López, J., García, J., De la Fuente, L. & De la Fuente, E. I. (2007). Las redes bayesianas como herramientas de modelado en psicología. *Anales de Psicología, 23*, 577-581.

López-Fernández, O. (2015). Short version of the Smartphone addiction scale adapted to Spanish and French: Towards a cross-cultural research in problematic mobile phone use. *Addictive Behaviors, 64*, 275-280. doi:10.1016/j.addbeh.2015.11.013.

Marín, M., Carballo, J. L. & Coloma-Carmona, A. (2018). Rendimiento académico y cognitivo en el uso problemático de Internet. *Adicciones, 30*, 101-110. doi:10.20882/adicciones.844.

McDaniel, B. T. & Coyne, S. M. (2016). "Technoference": The interference of technology in couple relationships and implications for women's personal and relational well-being. *Psychology of Popular Media Culture, 5*, 85-98. doi:10.1037/ppm0000065.

Mendoza, M. I. & Cuñarro, L. (2016). Celular e intersubjetividad. *Omnia, 22*, 20-31.

Nagarajan, R., Scutari M. & Lèbre, S. (2013). *Bayesian networks in R with applications in systems biology*. Nueva York: Springer.

Nosek, B., Ebersole, C., DeHaven, A. & Mellor, D. (2018). The preregistration revolution. *Proceedings of the National Academy of Sciences, 115,* 2600-2606. doi:10.1073/pnas.1708274114.

Odgers, C. (2018). Smartphone are bad for some teens, not all. *Nature, 554*, 432-434. doi:10.1038/d41586-018-02109-8.

Orozco, G. O. (2015). Televisión y producción de significados (tres ensayos). *Revista Comunicación y Sociedad, 1*, 20-36.

Pedrero, E. J., Rodríguez, M. T. & Ruiz, J. M. (2012). Adicción o abuso del teléfono móvil. Revisión de la literatura. *Adicciones, 24*, 132-152.

Pedrero-Pérez, E. J., Ruiz-Sánchez de León, J. M., Rojo-Mota, G., Llanero-Luque, M., Pedrero-Aguilar, J., Morales-Alonso, S. & Puerta-García, C. (2018). Tecnologías de la Información y la Comunicación (TIC): uso problemático de internet, videojuegos, teléfonos móviles, mensajería instantánea y redes sociales mediante el

MULTICAGE-TIC. *Adicciones, 30*, 19-32. doi:10.20882/adicciones.806.

Potenza, M. N., Higuchi, S. & Brand, M. (2018). Broaden behavioural addiction research. *Nature, 555,* 30. doi: 10.1038/d41586-018-02568-z.

Puga, J. L., Krzywinski, M. & Altman, N. (2015). Bayesian networks. *Nature Methods, 12*, 799-800. doi:10.1038/nmeth.3550.

Roberts, J. A. & David, M. E. (2016). My life has become a major distraction from my cell phone: Partner phubbing and relationship satisfaction among romantic partners. *Computers in Human Behavior, 54*, 134-141. doi:10.1016/j.chb.2015.07.058.

Rodríguez, A. (2015). *Hábitos y problemas del sueño en la infancia y adolescencia en relación al patrón de uso del teléfono móvil: estudio transversal.* Tesis doctoral. Departamento de Pediatría, Obstetricia y Ginecología, Universidad de Valencia. Retrieved at http://hdl.handle.net/10550/50055.

Rouder, J. N., Speckman, P., Sun, D. & Morey, R. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychonomic Bulletin & Review, 16*, 225-237.

Ruiz, F. J., Langer, A. I., Luciano, C., Cangas, A. J. & Beltrán, I. (2013). Measuring experiential avoidance and psychological inflexibility: The Spanish version of the Acceptance and Action Questionnaire – II. *Psicothema, 25*, 123-129. doi:10.7334/psicothema2011.239.

Ruiz-Ruano, A. M. (2015). *Aprendizaje estructural de redes bayesianas para modelar el emprendimiento académico de base sostenible y tecnológica.* Tesis doctoral no publicada, Facultad de Ciencias de la Salud, Universidad Católica San Antonio de Murcia. Retrieved at http://hdl.handle.net/10952/1556.

Scutari, M. (2010). Learning Bayesian Networks with the bnlearn R package. *Journal of Statistical Software, 35*, 1-22. doi:10.18637/jss.v035.i03.

Scutari, M. & Denis, J. B. (2014). *Bayesian networks: with examples in R.* Boca Raton, FL: CRC Press.

Seoane, A. & Álvarez, G. (2012). Nuevas tecnologías aplicadas al tratamiento del tabaquismo: Doctor Fum. *Revista Española de Drogodependencias, 37*, 319-332.

Simó, C., Martínez, A., Ballester, M. L. & Domínguez, A. (2017). Instrumentos de evaluación del uso problemático del teléfono móvil/smartphone. *Health and Addictions, 17*, 5-14.

Sussman, C. J., Harper, J. M., Stahl, J. L. & Weigle, P. (2018). Internet and video game addictions. Diagnosis, epidemiology, and neurobiology. *Child and Adolescent Psychiatric Clinics of North America, 27*, 307-326. doi:10.1016/j.chc.2017.11.015

Tresáncoras, A. G., García-Oliva, C. & Piqueras, J. A. (2017). Relación del uso problemático del Whatsapp con la personalidad y la ansiedad en adolescentes. *Health and Addictions, 17*, 27-36.

Veissière, S. P. & Stendel, M. (2018). Hypernatural monitoring: A social rehearsal account of smartphone addiction. *Frontiers in Psychology, 9,* 1118. doi:10.3389/fpsyg.2018.00141.

Wang, X., Xie, X., Wang, Y., Wang, P. & Lei, L. (2017). Partner phubbing and depression among married Chinese adults: The roles of relationship satisfaction and relationship length. *Personality and Individual Diferences, 110*, 12-17. doi:10.1016/j.paid.2017.01.014.

Watson, N., Heffner, J., McClure, J. & Bricker, J. (2017). Relationships Between Social Anxiety and Smoking-Specific Experiential Avoidance. *Journal of Dual Diagnosis, 13*, 1-5. doi: 10.1080/15504263.2016.1248310.Wilson, K. G. & Luciano, M. C. (2012). *Terapia de Aceptación y Compromiso (ACT). Un tratamiento conductual orientado a los valores.* Madrid, España: Pirámide.

Wulfert, E., Greenway, D. E., Farkas, P., Hayes, S. C. & Dougher, M. J. (1994). Correlation between self-reported rigidity and rule-governed insensitivity to operant contingencies. *Journal of Applied Behavior Analysis, 27*, 659-671.

Zarghami, M., Khalilian, A., Setareh, J. & Salehpour, G. (2015). The impact of using cell phones after light-out on sleep quality, headache, tiredness, and distractibility among students of a university in North of Iran. *Iranian Journal of Psychiatry and Behavioral Sciences, 9*, e2010. doi:10.17795/ijpbs.2010.

Zhitomirsky-Geffet, M. & Blau, M. (2016). Cross generational analysis of predictive factors of addictive behavior in smartphone usage. *Computers in Human Behavior, 64*, 682-693.

Association between negative mood states, psychoactive substances consumption and bullying in school-aged adolescents

Asociación entre el estado de ánimo negativo, el consumo de sustancias psicoactivas y el *bullying* en adolescentes escolarizados

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Abstract

Objective: mental health problems during adolescence lead to increased morbidity and mortality. We intend to test the hypothesis that bullying and addictive substance use is related to negative mood states.

Methods: We carried out a cross-sectional study among high school students in Burela (Northern Spain) (n=238). "Negative mood state" was defined as experiencing the following: feeling tired, sad, out of place, bored, hopeless, nervous or lacking sleep. Independent variables were binge drinking, having smoked tobacco or cannabis, and the corresponding perceived risk of using them. The variable bullying was also measured. Poisson regression models with robust variance were estimated, and Prevalence Ratios were obtained.

Results: 10.5% [CI 95% (7.2-15.2)] of the students reported suffering negative mood states. Students declaring low perceived risk of cannabis use [PR = 2.6 (1.2-5.5)], having tried this addictive substance at some point [PR = 3.1 (1.1-8.9)] and having suffered bullying [PR = 4.8 (2.4-9.6)] increased the risk of experiencing negative mood states.

Conclusion: It would be advisable to design and implement interventions aimed at improving mental health during adolescence which account for the use of addictive substances and being a victim of bullying.

Key Words: negative mood states, substance use, adolescents, bullying.

Resumen

Antecedentes: los problemas de salud mental durante la adolescencia suponen un aumento de la morbimortalidad y la discapacidad. Se pretende testar la hipótesis de que el *bullying* y el consumo de sustancias psicoactivas están asociados al estado de ánimo negativo.

Métodos: estudio transversal entre estudiantes de Educación Secundaria Obligatoria (ESO) (n=238) de los institutos de Burela (Lugo). El "estado de ánimo negativo" se definió a partir de los siguientes ítems: sentirse cansado/a, triste, desplazado/a, aburrido/a, desesperanzado/a, nervioso/a o insomne. Como variables independientes se consideraron: el *binge drinking*, el haber fumado alguna vez tabaco o cannabis, así como sus correspondientes percepciones de peligrosidad. Además, se midió la variable *bullying*. Se estimaron modelos de regresión de Poisson con varianza robusta y se obtuvieron Razones de Prevalencia (RP).

Resultados: el 10,5% [IC95% (7,2-15,2)] de la población encuestada presentaba estado de ánimo negativo. La nula o baja percepción de peligrosidad para el cannabis [RP=2,6 (1,2-5,5)], haber probado alguna vez esta sustancia adictiva [RP=3,1 (1,1-8,9)] y haber sufrido *bullying* [RP=4,8 (2,4-9,6)] se asociaban al estado de ánimo negativo.

Conclusiones: sería recomendable crear intervenciones para la mejora de la salud mental durante la adolescencia que tengan en cuenta el consumo de sustancias adictivas y el hecho de haber sufrido *bullying*.

Palabras clave: estado de ánimo negativo, consumo de sustancias, adolescentes, *bullying*.

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During adolescence, emotional processes taking place over longer periods of time such as despair, sadness, loneliness or nervousness comprise negative mood states, which can predict major affective disorders (Monteagudo et al., 2013) with repercussions both on the health of the individual and on their social and family environment. In the last Spanish Survey of National Health, one in ten people aged 15 and over stated that they had been diagnosed with a mental health problem (Instituto Nacional de Estadística, 2018). A significant number of adolescents have thus reported different emotional and behavioral symptoms. Specifically, 22.6% of a sample of Spanish students reported feeling nervous, and 10.8% felt sad or discouraged, with differences in terms of sex and age (Ortuño-Sierra, Fonseca-Pedrero, Paíno & Aritio-Solana, 2014).

Negative mood and poor mental health during adolescence have been associated with bullying (Mello et al., 2017; Moore et al., 2017; Singham et al., 2017), defined as abuse or victimization occurring in school contexts among students. Spanish school pupils who have suffered bullying have lower scores on the *Strengthts and Difficulties Questionnaire* (SDQ) mental health scale (Garcia-Continente, Pérez-Giménez, Espelt & Nebot Adell, 2013; Mangot-Sala et al., 2018). In recent years, a stable trend has been observed in Spain, with 4.3% of students aged 13 to 16 reporting being bullied (Sánchez-Queija, García-Moya & Moreno, 2017).

Adolescence is a period during which numerous risky behaviors such as the use of addictive substances begin. In Spain, 38.5% of adolescents have smoked tobacco, 31.3% have used cannabis and 76.9% have drunk alcohol at least once in their lives (Plan Nacional Sobre Drogas, 2016). A variety of studies have reported links between the use of psychoactive substances and poor mental health, with greater evidence in the case of cannabis (Fonseca-Pedrero, Ortuño-Sierra, Paino & Muñiz, 2016; Mangot-Sala et al., 2018), the use of which could also increase the risk of attempted suicide in this population (Carvalho et al., 2018). Bullying and substance use may thus be associated with mood states during adolescence (Gaete et al., 2017; Garcia-Continente et al., 2013; Monteagudo et al., 2013; Moore et al., 2017). Some studies have found a relationship between bullying and substance use with problems of anxiety, low self-esteem, depressive tendencies or suicidal ideation in the adolescent population (Moore et al., 2017), as well as with negative mood states (Ahonen, Nebot & Giménez, 2007).

As far as we know, no studies have analyzed the possible interrelation between substance use, bullying and negative mood in small populations. For this reason, it would be interesting to examine this relationship in a multicultural population of less than 10,000 inhabitants in which more than fifty nationalities coexist and where immigrant and indigenous populations are found to use similar substances (Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018).

The aim of this study is then to analyze the associations between psychoactive substance use, bullying and negative mood state in high school students.

Methods

Study design and population

This is a cross-sectional study in which all students of the 2nd, 3rd and 4th years of compulsory secondary education (ESO) in the two high schools (IES) of Burela: IES O Perdouro and Monte Castelo (n=262).

Data collection

Data collection was implemented using the FRESC questionnaire (Risk Factors in High School Students), designed by the Barcelona Public Health Agency (ASPB) to show emerging risk behaviors among secondary-school students. Two models of the questionnaire were used: one for 2nd and 3rd year pupils (13-15 years of age) and another for the 4th grade (15-16 years). To access the study population, school management was contacted and the pertinent parental authorization was obtained. Data collection took place in the classrooms during school hours, in the presence of a teacher and a member of the research team in December 2015. The questionnaire was anonymous and self-completed so that data confidentiality was guaranteed at all times.

Variables

- Dependent variables

Negative mood states: negative mood state was measured with the following items: feeling too tired to do things; having problems falling asleep; waking up too early; feeling out of place; feeling sad or depressed; feeling hopeless about the future; feeling tense and nervous, and feeling bored. Answers were ordered on a five-point Likert scale from 0 = never, to 4 = always. The variable was then dichotomized, with "never", "almost never" and "sometimes" taking the value 0; and "frequently" and "always" represented by 1. Participants who answered "frequently" or "always" on at least three of the items were classified as having a negative mood state (Ahonen et al., 2007).

- Independent variables

In terms of main independent variables, those relating to substance use, their perceived risk and bullying were analyzed.

Regarding substance use, we took into account:

a) *Alcohol - binge drinking* was defined as having drunk four or more alcoholic beverages on the same occasion.
b) *Smoking* - having smoked cigarettes at some point.
c) *Cannabis* - having used cannabis at some point.

Low risk perception has been positively associated with drug use (Ojeda, Patterson & Strathdee, 2008; Tortajada Navarro et al., 2008), so we estimated the proportion of adolescents believing alcohol, tobacco and cannabis to be very risky.

Regarding the bullying variable, three items were considered to contribute: Have you been laughed at or insulted at school or on your way there? Have you been hit, attacked or threatened at school or on your way there? Do you sometimes get excluded by your classmates? Five possible answers were given for the three questions: never, once, twice, three times, more than three times. Subjects were considered as suffering or having suffered bullying when answering at least one of these questions "three times" or "more than three times", or answering "once" or more to all three items in the last twelve months (Garcia-Continente et al., 2013).

Other variables selected as potential confounding variables were:

a) *Self-reported educational level.* This variable was measured through the question "In relation to your classmates, how would you rate your educational level?"
b) *Place of origin.* The nationality of the father and the mother determined whether the respondent was indigenous or immigrant. Students whose parents were both born outside Spain were considered immigrants.
c) *Family Affluence Scale (FAS).* Respondents were asked whether their family had a car or a van, whether they had their own room, how many computers they had and the number of times they had been on vacation with their family in the previous year. The answers to the questions were added and classified into: low FAS (considered as having disadvantaged socioeconomic status) for a score of 0-3 points; average FAS (average socioeconomic status) if the score was 4-5 points; and high FAS (socioeconomically advantaged) with 6-7 points.

Age and sex were also taken as independent variables.

Statistical analysis

A descriptive statistical analysis was performed for the overall sample and itemized according to the presence/absence of negative mood state. The prevalences of negative moods were calculated for each of the independent variables.

For the analysis of the association between the independent variables and negative mood, univariate and multivariate Poisson regression models with robust variance were estimated, and prevalence ratios (PR) were obtaining with their respective confidence intervals at 95% (CI 95%) (Espelt, Mari-Dell'Olmo, Penelo & Bosque-Prous, 2017). The percentage of missing data ranged from 0.42% for the negative mood variable to 2.5% for the cannabis use variable. Analyses were performed using the STATA 15.0 statistical package.

Results

Our final sample comprised 238 students, representing a 91% survey of the 2nd, 3rd and 4th years of Burela's two high schools (n=238).

Table 1 shows the characteristics of the sample by mood state. Girls made up 46.8% of the sample, immigrants 20.7%, students aged 15 years or over 47.3%, average or low educational level 74.3%, and those reported having high FAS 39.6%. Finally, 10.5% [CI 95% (7.2-15.2)] of the surveyed population had negative mood states.

The prevalence of negative mood varied according to the different independent variables (Table 2), affecting 13.5% of girls [CI 95% (8.3-21.3)], and 7.9% of boys [CI 95% (4.2-14.2)]. Furthermore, it was slightly higher among those who used addictive substances. Among students who had experienced binge drinking, the prevalence of negative mood was 12.2% [CI 95% (5.1-26.4)] as against 10.2% [CI 95% (6.6-15.3)] among those who had not. For the adolescent population that had smoked cigarettes at some time, the prevalence of negative mood states reached 20% [CI 95% (8.4-40.6)] compared to 9.7% [CI 95% (4.9-18.4)] in those who had not smoked. Finally, among pupils who had used cannabis at some point, the prevalence of negative mood rose to 30% [CI 95% (9.3-64.2)] compared to 9.5% [CI 95% (6.2% -14.2)] in those who had never done so. As regards bullying, the prevalence of negative mood states was also higher among those who had suffered it, 34.5% [CI 95% (19.3-53.3)], compared to those who had not, 7.2% [CI 95% (4.3-11.6)].

Table 2 shows the prevalence ratios (PR) of negative mood by independent variable, with the corresponding 95% CI. Thus, the risk of experiencing negative mood state was higher among students who perceived cannabis as being not or moderately risky [$PR_{unadjusted}$ = 2.6; CI 95% (1.2-5.5); $PR_{adjusted}$ = 2.3; CI 95% (1.1-4.9)], among those who had used this substance at some point [$PR_{unadjusted}$ = 3.1; CI 95% (1.1-8.9)], and among those who had been bullied [$PR_{unadjusted}$ = 4.8; CI 95% (2.4-9.6); $PR_{adjusted}$ = 4.4; CI 95% (2.2-9.0)].

As for the other variables of substance use analyzed, no statistically significant association was observed either in the bivariate or in the multivariate analysis; even when point estimates suggested associations in the same direction as those found for cannabis.

Discussion

Negative mood state is associated with cannabis use, low perceived risk of the use of this substance and having been the victim of bullying. Our results suggest that 10.5% [(CI

Table 1. *Sociodemographic characteristics by mood states in students aged 13 to 16 (Burela, 2015).*

	Negative mood states		Non-negative mood states		Total		
	n	%	n	%	n	%	p-valor
Sex							
Female	15	60	96	45,3	111	46,8	0,136
Male	10	40	116	54,7	126	53,2	
Nationality							
Spanish	20	80	168	79,2	188	79,3	0,930
Immigrant	5	20	44	20,8	49	20,7	
Age							
‹15 years	10	40	115	54,2	125	52,7	0,177
›=15 years	15	60	97	45,8	112	47,3	
Self-reported educational level							
Low-average	21	84	155	73,1	176	74,3	0,239
High	4	16	57	26,9	61	25,7	
FAS							
Low	4	16	42	20,3	46	19,8	0,843
Medium	10	40	84	40,6	94	40,5	
High	11	44	81	39,1	92	39,6	
Alcohol							
Yes	5	20	36	17,0	41	17,3	0,706
No	20	80	176	83,0	196	82,7	
Tabaco							
Yes	5	20,8	20	9,6	25	10,8	0,093
No	19	79,2	188	90,4	207	89,2	
Cannabis							
Yes	3	12,5	7	3,4	10	4,3	0,038
No	21	87,5	200	96,6	221	95,7	
Alcohol perceived risk							
Moderately or not risky	18	72	168	79,3	186	78,5	0,404
Very risky	7	28	44	20,7	51	21,5	
Smoking perceived risk							
Moderately or not risky	16	66,7	133	64,3	154	65,3	0,878
Very risky	8	33,3	74	35,7	82	34,7	
Cannabis perceived risk							
Moderately or not risky	8	32	28	13,4	36	15,4	0,015
Very risky	17	68	181	86,6	198	84,6	
Bullying							
Yes	10	40	19	9,0	29	12,2	0,000
No	15	60	193	91,0	208	87,8	

95% 7.2-15.2)] of Burela high school students suffer from negative mood states.

Before discussing results, there are some limitations of the study which should be noted. First, the study is of a transversal design, which prevents causal relationships from being established. In addition, alcohol, tobacco and cannabis use of adolescents was self-reported. Nevertheless, there is evidence that the use of self-report questionnaires is a viable method to measure variables of substance use, for example alcohol consumption in adolescents (Engs & Hanson, 1990). Furthermore, anonymity and the individual format of the questionnaire may reduce the bias of social desirability inherent in the surveys. For the variables bullying and negative mood, although

Table 2. *Prevalence and prevalence ratios for negative mood states in students aged 13 to 16 (Burela, 2015).*

	Prevalence of negative mood states						
	N	**Prevalence (%)**	**IC95%**	**RPno ajusted**	**IC95%**	**RPajusted**	**IC95%**
Sex							
Female	111	13,5	(8,3-21,3)	1			
Male	126	7,9	(4,2-14,2)	0,6	(0,3-1,2)		
Nationality							
Spanish	188	10,6	(6,9-15,9)	1,0	(0,4-2,6)		
Immigrant	49	10,2	(4,2-22,5)	1			
Age							
‹15 years	115	8,0	(4,3-14,3)	0,6	(0,3-1,3)		
›=15 years	97	13,4	(8,2-21,1)	1			
Self-reported educational level							
Low-average	155	11,9	(7,8-17,7)	1,8	(0,6-5,1)		
High	57	6,5	(2,4-16,4)	1			
FAS							
Low	46	8,7	(3,2-21,3)	1			
Medium	94	10,6	(5,8-18,8)				
High	92	11,9	(6,7-20,4)	1,16	(0,7-1,9)		
Alcohol							
Yes	41	12,2	(5,1-26,4)	1,2	(0,5-3,0)		
No	196	10,2	(6,6-15,3)	1			
Smoking							
Yes	25	20	(8,4-40,6)	2,2	(0,9-5,3)		
No	207	9,1	(5,9-13,9)	1			
Cannabis							
Yes	10	30	(9,3-64,2)	3,1	(1,1-8,9)		
No	221	9,5	(6,2-14,2)	1			
Alcohol perceived risk							
Moderately or not risky	186	9,7	(6,2-14,9)	0,9	(0,4-2,0)		
Very risky	51	13,7	(6,6-26,3)	1			
Smoking perceived risk							
Moderately or not risky	154	10,4	(6,4-16,3)	1,1	(0,5-2,3)		
Very risky	82	9,7	(4,9-18,4)	1			
Cannabis perceived risk							
Moderately or not risky	36	22,2	(11,4-38,9)	2,6	(1,2-5,5)	2,3	(1,1-4,9)
Very risky	198	8,6	(5,4-13,4)	1		1	
Bullying							
Yes	29	34,5	(19,3-53,3)	4,8	(2,4-9,6)	4,4	(2,2-9,0)
No	208	7,2	(4,3-11,6)	1		1	

we employed questions previously used in other research (Ahonen et al., 2007; Garcia Continente, Pérez Giménez & Nebot Adell, 2010; Garcia-Continente et al., 2013; Mangot-Sala et al., 2018), the psychometric properties of these questions are not known, so we cannot rule out any classification bias. The small sample size prevented disaggregation by sex, although it should be noted that the survey covered 91% of the school population of Burela's 2nd, 3rd and 4th years high school students. It is important to point out that small populations have been very little studied and that Burela has migratory characteristics that make it a focus of particular interest (Oca, 2013; Pérez, Garcia-Continente & Grup col·laborador enquesta FRESC 2012, 2013).

In our study, 10.5% of students reported suffering negative mood state, a figure in line with the ranges found in our context. Prevalences of 16% have been found, for example, among Catalan students of 14 and 16 years of age (Ahonen et al., 2007) or 19% in 3rd and 4th year high school students (Monteagudo et al., 2013).

In our study, negative mood states were linked in a statistically significant way only to cannabis use and the perceived risk of using it. However, other studies have found statistically significant relationships with smoking or binge drinking (Julià Cano, Escapa Solanas, Marí-Klose & Marí-Klose, 2012; Martínez-Hernáez, Marí-Klose, Julià, Escapa & Marí-Klose, 2012). This may be a result of the sample size of our study as well as of the different methods used in the literature for substance use measurement (Degenhardt et al., 2013; Mangot-Sala et al., 2018; Monteagudo et al., 2013; van Gastel et al., 2013). It should be noted that the causal relationship between negative mood state and substance use is unclear since it can occur in both directions (Merikangas et al., 1998).

The perception of low or no risk involved in the use of an addictive substance is associated with its use (Ojeda et al., 2008; Tortajada Navarro et al., 2008). Our results support this relationship in the case of cannabis, with a low or a lack of perceived risk of using it also linked to negative mood. This should not be underestimated, since it converts the perception of risk into a double risk factor for the health of adolescents: cannabis use together with the negative mood state. This association between the influence on mental health and the use of cannabis in adolescents has also been reported in a study carried out with high school pupils in Barcelona (Mangot-Sala et al., 2018).

Negative mood state is associated with bullying. These results are consistent with other research (Bond, Carlin, Thomas, Rubin & Patton, 2001; Gaete et al., 2017; Garcia-Continente et al., 2013; Mangot-Sala et al., 2018; Mello et al., 2017; Monteagudo et al., 2013; Singham et al., 2017). In addition, there are systematic reviews, meta-analyses (Carta, Fiandra, Rampazzo, Contu & Preti, 2015; Moore et al., 2017) and some longitudinal studies (Bond et al., 2001) which show that being the victim of bullying increases anxiety and depressive symptomatology, or self-destructive behaviors and the risk of suicide in this population. The causality between bullying and negative mood state is again unclear since substance use could function as an intermediate variable between being bullied and negative mood (Livingston et al., 2018), with this particular study, which monitored the daily effect of being a victim of bullying in a sample of North American students, confirming that the use of such substances was a tool to mitigate the negative mood caused by bullying (Livingston et al., 2018).

Conclusions

An association was found in the adolescent population of Burela between negative mood state, cannabis use and being bullied. Our results show the need to implement measures in schools and the social environment of adolescents in order to improve their knowledge of such realities and permit early detection of such risky behaviors. It would thus be advisable to create interventions for the improvement of mental health during adolescence which take into account the use of addictive substances and being a victim of bullying.

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Conflict of interests

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References

Ahonen, E. Q., Nebot, M. & Giménez, E. (2007). Negative mood states and related factors in a sample of adolescent secondary-school students in Barcelona (Spain). *Gaceta Sanitaria*, *21*, 43-52.

Bond, L., Carlin, J. B., Thomas, L., Rubin, K. & Patton, G. (2001). Does bullying cause emotional problems? A prospective study of young teenagers. *BMJ*, *323*, 480-484. doi:10.1136/bmj.323.7311.480.

Carta, M. G., Fiandra, T. D., Rampazzo, L., Contu, P. & Preti, A. (2015). An Overview of International Literature on School Interventions to Promote Mental Health and Well-being in Children and Adolescents. *Clinical Practice and Epidemiology in Mental Health: CP & EMH*, *11*(Suppl 1 M1), 16-20. doi:10.2174/1745017901511010016.

Carvalho, A. F., Stubbs, B., Vancampfort, D., Kloiber, S., Maes, M., Firth, J., … Koyanagi, A. (2018). Cannabis use and suicide attempts among 86,254 adolescents aged 12-15 years from 21 low- and middle-income countries. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *56*, 8-13. doi:10.1016/j.eurpsy.2018.10.006.

Degenhardt, L., Coffey, C., Romaniuk, H., Swift, W., Carlin, J. B., Hall, W. D. & Patton, G. C. (2013). The persistence of the association between adolescent cannabis use and common mental disorders into young

adulthood. *Addiction*, *108*, 124-133. doi:10.1111/j.1360-0443.2012.04015.x.

Díaz Geada, A., Busto Miramontes, A. & Caamaño Isorna, F. (2018). Alcohol, tobacco and cannabis consumption in adolescents from a multicultural population (Burela, Lugo). *Adicciones*, *30*, 264-270. doi:10.20882/adicciones.915.

Engs, R. & Hanson, D. (1990). Gender differences in drinking patterns and problems among college students: A review of the literature. *Journal of Drug and Alcohol Education*, *35*, 36-47.

Espelt, A., Mari-Dell'Olmo, M., Penelo, E. & Bosque-Prous, M. (2017). Applied Prevalence Ratio estimation with different Regression models: An example from a cross-national study on substance use research. *Adicciones*, *29*, *105-112*. doi:10.20882/adicciones.823.

Fonseca-Pedrero, E., Ortuño-Sierra, J., Paino, M. & Muñiz, J. (2016). Psychotic-like Experiences and Substance Use in College Students. *Adicciones*, *28*, 144-153. doi:10.20882/adicciones.781.

Gaete, J., Tornero, B., Valenzuela, D., Rojas-Barahona, C. A., Salmivalli, C., Valenzuela, E. & Araya, R. (2017). Substance Use among Adolescents Involved in Bullying: A Cross-Sectional Multilevel Study. *Frontiers in Psychology*, *8*, 1056. doi:10.3389/fpsyg.2017.01056.

Garcia Continente, X., Pérez Giménez, A. & Nebot Adell, M. (2010). Factores relacionados con el acoso escolar (bullying) en los adolescentes de Barcelona. *Gaceta Sanitaria*, *24*, 103-108. doi:10.1016/j.gaceta.2009.09.017.

Garcia-Continente, X., Pérez-Giménez, A., Espelt, A. & Nebot Adell, M. (2013). Bullying among schoolchildren: Differences between victims and aggressors. *Gaceta Sanitaria*, *27*, 350-354. doi:10.1016/j.gaceta.2012.12.012.

Instituto Nacional de Estadística. (2018). Encuesta Nacional de Salud. 2017. Retrieved at https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176783&menu=resultados&idp=1254735573175.

Julià Cano, A., Escapa Solanas, S., Marí-Klose, M. & Marí-Klose, P. (2012). Psychosocial risk factors in adolescent tobacco use: negative mood-states, peer group and parenting styles. *Adicciones*, *24*, 309-317.

Livingston, J. A., Derrick, J. L., Wang, W., Testa, M., Nickerson, A. B., Espelage, D. L. & Miller, K. E. (2018). Proximal Associations among Bullying, Mood, and Substance Use: A Daily Report Study. *Journal of Child and Family Studies*, 1–14. doi:10.1007/s10826-018-1109-1.

Mangot-Sala, L., Bosque-Prous, M., Bartroli, M., Teixidó-Compañó, E., Brugal, M. T. & Espelt, A. (2018). The Role of Individual and Social Mediators in the Association Between Drug Consumption and Mental Health Among Adolescents in Barcelona. *International Journal of Mental Health and Addiction*. doi:10.1007/s11469-018-9879-7.

Martínez-Hernáez, A., Marí-Klose, M., Julià, A., Escapa, S. & Marí-Klose, P. (2012). Heavy episodic drinking among adolescents: the association with negative mood states and family factors. *Revista Española De Salud Pública*, *86*, 101-114. doi:10.1590/S1135-57272012000100009.

Mello, F. C. M., Silva, J. L. da, Oliveira, W. A. de, Prado, R. R. do, Malta, D. C. & Silva, M. A. I. (2017). The practice of bullying among Brazilian schoolchildren and associated factors, National School Health Survey 2015. *Ciencia e Saude Coletiva*, *22*, 2939-2948. doi:10.1590/1413-81232017229.12762017.

Merikangas, K. R., Mehta, R. L., Molnar, B. E., Walters, E. E., Swendsen, J. D., Aguilar-Gaziola, S., … Kessler, R. C. (1998). Comorbidity of substance use disorders with mood and anxiety disorders: Results of the international consortium in psychiatric epidemiology. *Addictive Behaviors*, *23*, 893-907. doi:10.1016/S0306-4603(98)00076-8.

Monteagudo, M., Rodriguez-Blanco, T., Pueyo, M. J., Zabaleta-del-Olmo, E., Mercader, M., García, J., … Bolíbar, B. (2013). Gender differences in negative mood states in secondary school students: health survey in Catalonia (Spain). *Gaceta Sanitaria*, *27*, 32-39. doi:10.1016/j.gaceta.2012.01.009.

Moore, S. E., Norman, R. E., Suetani, S., Thomas, H. J., Sly, P. D. & Scott, J. G. (2017). Consequences of bullying victimization in childhood and adolescence: A systematic review and meta-analysis. *World Journal of Psychiatry*, *7*, 60-76. doi:10.5498/wjp.v7.i1.60.

Oca, L. (2013). Caboverdianas en Burela (1978/2008): migración, relacións de xénero e intervención social. (Tesis doctoral, Universidade de Santiago de Compostela). Retrieved at http://hdl.handle.net/10347/9804.

Ojeda, V. D., Patterson, T. L. & Strathdee, S. A. (2008). The influence of perceived risk to health and immigration-related characteristics on substance use among Latino and other immigrants. *American Journal of Public Health*, *98*, 862-868. doi:10.2105/AJPH.2006.108142.

Ortuño-Sierra, J., Fonseca-Pedrero, E., Paíno, M. & Aritio-Solana, R. (2014). Prevalence of emotional and behavioral symptomatology in Spanish adolescents. *Revista de Psiquiatría y Salud Mental*, *7*, 121-130. doi:10.1016/j.rpsm.2013.12.003.

Pérez, A., Garcia-Continente, X. & Grup collaborador enquesta FRESC 2012. (2013). *Informe FRESC 2012: 25 anys d'enquestes a adolescents escolaritzats de Barcelona*. Barcelona: Agència de Salut Pública de Barcelona.

Plan Nacional Sobre Drogas. (2016). *Encuesta sobre uso de drogas en enseñanzas secundarias en España (ESTUDES), 1994-2014*. Ministerio de Sanidad Servicios Sociales e Igualdad.

Sánchez-Queija, I., García-Moya, I. & Moreno, C. (2017). Trend analysis of bullying victimization prevalence in Spanish adolescent youth at school. *Journal of School Health*, *87*, 457–464. doi:10.1111/josh.12513.

Singham, T., Viding, E., Schoeler, T., Arseneault, L., Ronald, A., Cecil, C. M., … Pingault, J.-B. (2017). Concurrent and Longitudinal Contribution of Exposure to Bullying in Childhood to Mental Health: The Role of Vulnerability and Resilience. *JAMA Psychiatry*, *74*, 1112-1119. doi:10.1001/jamapsychiatry.2017.2678.

Tortajada Navarro, S., Valderrama Zurián, J. C., Castellano Gómez, M., Llorens Aleixandre, N., Agulló Calatayud, V., Herzog, B. & Aleixandre Benavent, R. (2008). Drug consumption and perception among Latin American immigrants. *Psicothema*, *20*, 403-407.

van Gastel, W. A., Tempelaar, W., Bun, C., Schubart, C. D., Kahn, R. S., Plevier, C. & Boks, M. P. M. (2013). Cannabis use as an indicator of risk for mental health problems in adolescents: a population-based study at secondary schools. *Psychological Medicine*, *43*, 1849-1856. doi:10.1017/S0033291712002723.

DSM-5 in patients seeking their first treatment for alcohol use disorder. Sex differences in the multicenter CohRTA study

DSM-5 en pacientes que solicitan el primer tratamiento del trastorno por uso de alcohol. Diferencias de sexo en el estudio multicéntrico CohRTA

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Abstract

Objective: We aimed to analyze sex differences in the DSM-5 criteria among patients admitted to their first treatment of alcohol use disorder (AUD). *Methods:* Assessment of AUD was carried out using DSM-5 diagnostic criteria in a multicenter study (CohRTA) within the Spanish Network on Addictive Disorders. Further, baseline questionnaires including socio-demographics, family history, lifetime alcohol consumption and other substance use, as well as clinical and laboratory parameters were obtained during admission. *Results:* 313 patients (74.8%M) were eligible; mean age at first AUD treatment was 48.8 years (standard deviation (SD): 9.9 years). Age at onset of alcohol use was 15.9 years (SD: 3.3 years) and age at starting regular alcohol consumption was 25.6 years (SD: 9.6 years). Almost 69.3% of patients were tobacco smokers and 61% had family history of AUD. Regarding other substance use, 7.7% were current cocaine users and 18.2% were cannabis users. Women started regular alcohol consumption later than men (p<.001) and used benzodiazepines more frequently (p=.013). According to DSM-5, 89.5% of cases had severe AUD (≥6 criteria). In the adjusted analysis (logistic regression), men were more likely to neglect major rules (OR=1.92, 95%CI: 1.06-3.48) and to have hazardous alcohol use (OR=3.00, 95%CI: 1.65-5.46). *Discussion:* DSM-5 detects sex differences in patients seeking their first AUD treatment. Social impairment and risky alcohol use are significantly more frequent in men.

Key Words: Alcohol use disorder; DSM-5; Sex differences.

Resumen

Objetivo: Analizar las diferencias de sexo en los criterios diagnósticos del DSM-5 de los pacientes que solicitan un tratamiento para el trastorno por uso de alcohol (TUA) por primera vez. *Métodos:* Pacientes incluidos entre enero 2014 y marzo 2016 en el estudio multicéntrico CohRTA de la Red de Trastornos Adictivos. El diagnóstico del TUA se realizó mediante el DSM-5. Además, se recogieron datos sociodemográficos, sobre el consumo de alcohol y otras sustancias, variables clínicas y una analítica general. *Resultados:* se incluyeron 313 pacientes (74,8% hombres); la edad al inicio del primer tratamiento fue de 48,8 años (desviación estándar (DE): 9,9 años), la edad al inicio del consumo de alcohol de 15,9 años (DE: 3,3 años) y la de inicio del consumo regular de 25,6 años (DE: 9,6 años). Un 69,3% de los pacientes eran fumadores y un 61% tenían antecedentes familiares de TUA. Un 7,7% eran consumidores de cocaína y un 18,2% de cannabis. Las mujeres iniciaron el consumo regular de alcohol más tarde que los hombres (p<,001) y usaban benzodiacepinas con mayor frecuencia (p=,013). Según el DSM-5, el 89,5% de los pacientes presentaban un TUA grave (≥6 criterios). En el análisis ajustado (regresión logística), los hombres tenían mayor probabilidad de presentar el criterio diagnóstico relacionado con el incumplimiento de los deberes fundamentales en el trabajo o en el hogar (OR=1,92, IC95%: 1,06-3,48) y el criterio diagnóstico de consumir alcohol en situaciones de riesgo físico (OR=3,00, IC95%: 1,65-5,46). *Discusión:* El DSM-5 detecta diferencias de sexo en pacientes que solicitan el primer tratamiento del TUA. El deterioro social y el consumo de alcohol de riesgo son significativamente más frecuentes en hombres.

Palabras clave: Trastorno por uso de alcohol; DSM-5; Diferencias de sexo.

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Alcohol use is widespread in Western society, with high levels of alcohol abuse and dependence. In Western Europe, abuse of alcohol and other substances is more prevalent among men than women (European Monitoring Centre for Drugs and Drug Addiction, 2015; Observatorio Español de las Drogas y las Toxicomanías, 2011; Teesson et al., 2010). However, population data indicate that the prevalence of alcohol use among men and women may be similar at ages between 15 and 35 (Observatorio Español de las Drogas y las Adicciones, 2017). This closing of the gender gap suggests that problems related to excessive alcohol use may be increasingly frequent in women.

In the USA, risky alcohol use and alcohol use disorder (AUD) in women increased by 60% and 80%, respectively, between the periods 2001-2002 and 2012-2013 (Grant et al., 2017). In addition, the increase in emergency treatments related to alcohol abuse involving women has been greater than among men (White, Slater, Ng, Hingson & Breslow, 2018). Some studies show that women are less likely to seek AUD treatment than men, develop an alcohol dependence syndrome more quickly, and take longer to receive an AUD diagnosis (Bravo, Gual, Lligoña & Colom, 2013; Johnson, Richter, Kleber, McLellan & Carise, 2005; Rehm, Manthey, Struzzo, Gual & Wojnar, 2015), all of which could contribute to a worse prognosis of the disorder in women.

There is considerable clinical variability in the detrimental effects of alcohol on health, which may be due to multiple biopsychosocial factors. Among the biological factors, the different metabolization of ethanol in men and women stands out (Crabb, Matsumoto, Chang & You, 2004). This is caused by the gastric alcohol dehydrogenase enzyme being less active in women, meaning that for the same amount of alcohol ingested, women will have a higher concentration of ethanol (Lieber, 2000; Mezey, 2000). In fact, it is well known that women are more vulnerable to organic injury caused by alcohol (Lieber, 2000). Drinking alcohol to excess can also impact the plasma levels of sex hormones, which in turn are important mediators of the immune response to different pathogens (Bouman, Heineman & Faas, 2005; Mezey, 2000). Moreover, there are several hypotheses regarding the greater genetic susceptibility of women to alcohol use (Bravo et al., 2013; Wodarz et al., 2003).

In terms of psychosocial and work-related aspects, women have been shown to be more vulnerable and to display greater risks of suffering detrimental health effects (Djindjic, Jovanovic, Djindjic, Jovanovic & Jovanovic, 2012; Hallman, Burell, Setterlind, Odén & Lisspers, 2001). The increasing role of women in society and at work may have made them more likely to drink alcohol. Furthermore, marital status, maternity, and/or partner substance use have been associated with an increased risk of alcohol use among women (Bríñez Horta, 2001). However, other authors do not believe that the social and work-related changes affecting women are sufficient on their own to explain the convergence of alcohol use patterns (White et al., 2015).

DSM-5 is a diagnostic classification of mental disorders established by the American Psychiatric Association (American Psychiatric Association, 2013). Regarding substance use disorder, changes with regard to DSM-IV include combining abuse and dependence in a single diagnostic criterion, adding persistent craving as a new criterion and scaling the severity of the disorder in three categories (Bartoli, Carrà, Crocamo & Clerici, 2015; Hasin et al., 2013). According to DSM-5, an AUD is indicated if in the last 12 months a person reports at least two of the 11 established symptomatic criteria. The severity of the disorder is then determined by the number of criteria involved. It is important to determine the severity of AUD because patients with moderate or severe disorder can benefit from intensive treatment (Edelman & Fiellin, 2016). A multinational study using DSM-5 shows that the prevalence of AUD in adults differs between countries (Slade et al., 2016). In Spain, it is estimated that up to 5% of the general adult population could meet AUD diagnostic criteria according to Alcohol Use Disorder Identification Test (AUDIT) (Observatorio Español de las Drogas y las Adicciones, 2017). However, clinical data when using DSM-5 as a diagnostic tool are still scarce.

The multicentre cohort study within the Spanish Network on Addictive Disorders (Red de Trastornos Adictivos), CohRTA, focuses on patients who seek AUD treatment for the first time. An analysis of cases during first treatment of the disorder provides us with current clinical characteristics and avoids the selection of chronic patients, who have had multiple prior treatments. The principal aim of this study was to use DSM-5 to describe sex differences among those seeking first-time AUD treatment.

Methodology

This is a cross-sectional study of patients seeking first treatment of AUD in public primary or hospital care centers. As of December 2017, nine centers in four autonomous communities (Cataluña, Castilla y León, Islas Baleares and Madrid) participated in the study: Hospital del Mar, Hospital Clínic de Barcelona, Hospital Universitari de Bellvitge, Hospital Universitari Germans Trias i Pujol, Centro Municipal de Atención a las Drogodependencias de Badalona (Centro Delta), Hospital Clínico de Salamanca, Alcohólicos Rehabilitados de Valladolid, Hospital Universitario 12 de Octubre and Hospital Universitari Son Espases.

The study was approved by the Clinical Research Ethics Committee (CREC) of the coordinating center (Hospital Universitari Germans Trias i Pujol) and by the CREC

of each participating center. CohRTA patients signed informed consent, which included the transfer of data and biological samples. The methods used in this study comply with the ethical standards for medical research and the principles of good clinical practice established in the Declaration of Helsinki.

The baseline questionnaire included sociodemographic characteristics, family history of the disorder, variables related to alcohol use (age of onset, age of onset of regular consumption, amount, total cumulative time of abstinence up to the beginning of the first AUD treatment, number of alcohol poisonings requiring emergency department attention) and to the use of other substances (tobacco, cannabis, amphetamine, benzodiazepine, opioid use in the last month, history of parenteral drug use); also included for analysis were general blood parameters including blood count (hemoglobin), coagulation (prothrombin time) and biochemistry (sodium, potassium, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], total cholesterol, albumin, total bilirubin, urea and creatinine). Likewise, blood samples were collected and stored in the Red de Trastornos Adictivos biobank (Universidad Miguel Hernández, Alicante). Further details of the study protocol are available (Sanvisens et al., 2018).

AUD diagnosis using DSM-5 involves 11 criteria and assesses four major areas: 1) Impaired control over substance use (higher than expected amounts, longer than expected duration, unsuccessful attempts to quit drinking, spending a great deal of time on alcohol use activities, persistent desire to drink), 2) Social impairment (neglect of major work or home rules, reduction or giving up of social activities, problems in the social sphere), 3) Risky drinking (in situations involving physical risk, despite having drink-related physical and/or psychological problems) and, 4) Pharmacological criteria (substance tolerance and withdrawal).

The severity of the disorder is measured on a three-point scale: 1) mild (2-3 diagnostic criteria), 2) moderate (4-5 criteria), and 3) severe (≥6 criteria).

Between January 2014 and March 2016, 369 patients met the criteria for inclusion in the CohRTA study. For this study, 56 patients were excluded because they did not meet all the DSM-5 criteria. However, age on first admission for treatment ($p = .60$), sex ($p = .36$) and age of onset of alcohol use ($p = .51$) were similar among the 313 patients who entered the study analysis and the 56 patients excluded.

Statistical analysis

Descriptive data analysis showed the relative frequencies of the categorical variables and the means ± standard deviations (SD) of the continuous variables. Bivariate analyses were performed to establish sex differences using chi-square and Fisher tests for the comparison of categorical variables and Student's t-tests to determine differences in means.

Multivariate analysis was performed using logistic regression models with each DSM-5 diagnostic criterion as a dependent variable. Independent variables included were those with statistically significant differences between men and women in the univariate analysis.

Values of $p < .05$ were considered statistically significant. Statistical analysis was performed with Stata software (version 11.0, College Station, Texas, USA).

Results

A total of 313 patients (74.8% men) were included, with a mean age ± SD at the beginning of the first treatment of 48.8 ± 9.9 years. The mean onset age was 15.9 ± 3.3 years and regular drinking started at 25.6 ± 9.6 years. Smokers made up 69.3% of the sample and 61% had a family history of AUD. Regarding other substances, 7.7% of the patients were cocaine users and 18.2% used cannabis.

In the general blood parameters, mean hemoglobin was 13.9 ± 2.5 g/dL, total cholesterol was 209 ± 49 mg/dL, and mean albumin was 39.8 ± 8.8 g/L. AST was > 40 U/L in 46% of patients, ALT > 40 U/L in 32.8%, and GGT > 50 U/L in 67.2%. Tables 1 and 2 show the socio-demographic characteristics, the results of the general blood parameters and the characteristics of alcohol and other substance use at the beginning of the treatment.

Women started regular alcohol consumption later (6 years on average) ($p < .001$) and had a higher prevalence of benzodiazepine use ($p = .013$) than men (Table 2).

Overall, the most prevalent DSM-5 criteria were: drinking alcohol in higher amounts or for longer periods than expected (97.1%), continuing to drink despite physical or psychological problems caused or exacerbated by alcohol (91.4%) and showing signs of tolerance to the substance (85.9%). In 73.5% of cases, signs or symptoms of alcohol withdrawal were present, and 78.3% showed a persistent craving to drink.

Severe AUD was found in 89.5% of the cases (≥ 6 DSM-5 criteria), with 9.3% presenting moderate (4-5 criteria) and 1.3% mild (2-3 criteria) AUD; no sex differences were observed ($p = .487$).

Table 3 shows the sex differences for the DSM-5 criteria. Men had higher prevalence of withdrawal criteria ($p=.038$), drinking in situations of physical risk ($p<.001$), failing to fulfill major rules at work or at home ($p=.001$) and giving up or reducing social, professional or leisure activities ($p=.064$) than women.

Figure 1 shows the probability of men presenting DSM-5 diagnostic criteria with respect to women, adjusting for the age of onset of regular drinking, benzodiazepine consumption and employment. Logistic regression analysis indicates that men were up to 3 times more likely than women to use alcohol in situations involving physical risk (OR = 3.00, CI

Table 1. *Sociodemographic and analytical characteristics of 313 patients admitted to AUD treatment.*

	Total N=313 n (%)	**Men N=234 n (%)**	**Women N=79 n (%)**	**p value**
Age, mean ± SD	48.8 ± 9.9	48.6 ± 10.1	49.1 ± 9.1	.726
Born in Spain	299 (95.5)	225 (96.1)	74 (93.7)	.356
Educational level (n=303)				
Does not know how to read or write	5 (1.7)	4 (1.8)	1 (1.3)	.710
Primary education	65 (21.4)	51 (22.6)	14 (18.2)	
Secondary education	181 (59.7)	135 (59.7)	46 (59.7)	
University student	52 (17.2)	36 (15.9)	16 (20.8)	
Marital status (n=309)				
Single	77 (25.0)	61 (26.3)	16 (20.7)	.328
Married or domestic partner	132 (42.7)	101 (43.5)	31 (40.3)	
Widowed, separated or divorced	100 (32.3)	70 (30.2)	30 (39.0)	
Employment (n=309)				
Working	144 (46.6)	113 (48.6)	31 (40.3)	**<.001**
Unemployed, permanent disability, pensioner	155 (50.2)	117 (50.5)	38 (49.3)	
Students/Home/Other tasks	10 (3.2)	2 (0.9)	8 (10.4)	
Cohabitation (n=308)				
Living alone	53 (17.2)	40 (17.3)	13 (16.9)	.198
With partner and/or children	169 (54.9)	120 (51.9)	49 (63.6)	
With family of origin	70 (22.7)	59 (25.6)	11 (14.3)	
Other situations	16 (5.2)	12 (5.2)	4 (5.2)	
General analysis at the beginning of AUD treatment		*mean* ± SD		
Hemoglobin (g/dL) (n=298)	13.9 ± 2.5	14.5 ± 2.4	12.7 ± 2.3	**.010**
Prothrombin time (INR) (n=277)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	.436
Total cholesterol (mg/dL) (n=279)	209 ± 49	204 ± 45	219 ± 56	.255
Albumin (g/L) (n=279)	39.8 ± 8.8	41.3 ± 7.4	36.8 ± 10.7	.073
Total bilirubin (mg/dL) (n=279)	0.9 ± 0.7	0.9 ± 0.6	0.8 ± 0.8	.665
Sodium (mEq/L) (n=298)	139 ± 3.2	139 ± 3.4	139 ± 2.6	.607
Potassium (mEq/L) (n=298)	4.4 ± 0.4	4.4 ± 0.5	4.4 ± 0.3	.876
AST (U/L) (n=279)	59.4 ± 50.5	61.2 ± 50.0	55.4 ± 53.0	.710
ALT (U/L) (n=279)	42.6 ± 31.9	46.3 ± 33.5	34.5 ± 27.0	.185
GGT (U/L) (n=279)	245 ± 504	305 ± 594	116 ± 141	.157
Urea (mg/dL) (n=298)	22.6 ± 9.4	24.4 ± 9.3	18.6 ± 8.5	**.028**
Creatinine (mg/dL) (n=298)	0.7 ± 0.2	0.8 ± 0.2	0.6 ± 0.1	**.002**

95%: 1.65-5.46), and also more likely to neglect major rules (OR = 1.92, CI 95%: 1.06-3.48).

Discussion

This study shows that women with AUD start regular drinking later than men. However, the age at which they seek admission for treatment of the disorder for the first time is similar to that of men, which suggests that excessive alcohol use could develop into in AUD more quickly among women. In this multicenter study, first AUD treatment is sought late (at the age of almost 50 for both men and women) and occurs several decades after the start of regular drinking, thus increasing the likelihood of presenting greater morbidity when treatment is first sought. Several studies describe a marked delay between AUD diagnosis and therapy (Chapman, Slade, Hunt & Teesson, 2015; Teesson et al., 2010). However, a recent study in Australia analyzing predictors of delay did not observe sex differences (Chapman et al., 2015). On the other hand, it has been reported that women are less likely to seek treatment for the disorder, although they are more compliant once they have initiated it (Bravo et al., 2013; Rehm et al., 2015). In any case, only a minority of people with AUD seek treatment of the disorder at some stage during their lifetime

Table 2. *Characteristics of alcohol and substance use of 313 patients with AUD.*

	Total N=313 n (%)	**Men N=234 n (%)**	**Women N=79 n (%)**	**p value**
Age of onset of alcohol use, *mean ± SD*	15.9 ± 3.3	15.7 ± 3.1	16.7 ± 3.8	**.016**
Age of onset of regular drinking, *mean ± SD*	25.6 ± 9.6	24.0 ± 8.6	30.5 ± 11.0	**‹.001**
Alcohol use (g/day), *mean ± SD*	134.8 ± 80.6	138.7 ± 86.2	123.1 ± 60.2	.316
Total cumulative time of alcohol abstinence (years), (n = 307), *mean ± SD*	2.1 ± 3.4	2.1 ± 3.4	2.2 ± 3.7	.843
Family history of AUD (n = 307)	188 (61.0)	138 (60.3)	50 (64.1)	.548
Lifetime number of alcohol poisonings (n = 304)				
None	132 (43.4)	98 (43.4)	34 (43.6)	.977
1-5	159 (52.3)	118 (52.2)	41 (52.6)	
›5	13 (4.3)	10 (4.4)	3 (3.8)	
Tobacco smoker				
Yes	217 (69.3)	157 (67.1)	60 (75.9)	.137
No	62 (19.8)	47 (20.1)	15 (19.0)	
Ex-smoker	34 (10.9)	30 (12.8)	4 (5.1)	
Consumption in the last month:				
Cocaine	24 (7.7)	18 (7.7)	6 (7.6)	.978
Cannabis/marijuana (n=312)	57 (18.2)	47 (20.2)	10 (12.7)	.135
Amphetamines	6 (1.9)	5 (2.4)	1 (1.3)	.625
Benzodiazepines	18 (5.7)	9 (3.8)	9 (11.4)	**.013**
Opiates	1 (0.3)	1 (0.4)	0 (0)	.561
History of parenteral drug use (n=311)	9 (2.9)	6 (2.6)	3 (3.8)	.579

Table 3. *Sex differences in the diagnostic criteria and severity of AUD according to DSM-5 in 313 patients admitted to treatment for the first time.*

	Total N=313 n (%)	**Men N=234 n (%)**	**Women N=79 n (%)**	**p value**
DSM-5				
Impaired control				
Greater amounts/extended time	304 (97.1)	229 (97.9)	75 (94.9)	.178
Amounts greater than expected	301 (96.2)	227 (97.1)	74 (93.7)	.182
Longer than expected	281 (89.8)	211 (90.2)	70 (88.6)	.692
Unsuccessful attempts to abandon/control use	262 (83.7)	196 (83.8)	66 (83.5)	.964
Spending a lot of time on alcohol use activity	183 (58.5)	137 (58.6)	46 (58.2)	.960
Craving	245 (78.3)	181 (77.3)	64 (88.0)	.495
Social impairment				
Neglect of major rules	196 (62.6)	129 (55.1)	27 (34.2)	**.001**
Reduction or giving up of social activities	143 (45.7)	114 (48.7)	29 (36.7)	.064
Problems in the social sphere	231 (73.8)	176 (75.2)	55 (69.6)	.328
Risky consumption				
Physical risk	196 (62.6)	165 (70.5)	31 (39.2)	**‹.001**
Physical/psychological problems	286 (91.4)	213 (91.0)	73 (92.4)	.706
Pharmacological criteria				
Withdrawal	230 (73.5)	179 (76.5)	51 (64.6)	**.038**
Two or more symptoms	222 (70.9)	171 (73.1)	51 (64.6)	.149
Drinking to relieve symptoms	166 (53.0)	131 (56.0)	35 (44.3)	.072
Substance tolerance	269 (85.9)	204 (87.2)	65 (82.3)	.279
Need for greater quantities	259 (82.7)	195 (83.3)	64 (81.0)	.637
Reduced effect	236 (75.4)	182 (77.8)	54 (68.3)	.093
Severity				
Number of criteria, *mean ± SD*	10.1 ± 2.4	10.4 ± 2.4	9.3 ± 2.3	**.001**
Mild (2-3 criteria)	4 (1.3)	2 (0.8)	2 (2.5)	.487
Moderate (4-5 criteria)	29 (9.3)	21 (9.0)	8 (10.1)	
Severe (≥6 criteria)	280 (89.4)	211 (90.2)	69 (87.4)	

(Dawson, Goldstein & Grant, 2012; Edlund, Booth & Han, 2012; Rehm et al., 2015).

In the univariate analysis, women show a higher prevalence of benzodiazepine use than men. This finding coincides with data from the Spanish Observatory on Drugs in its 2017 survey on alcohol and drug use in the general population (Observatorio Español de las Drogas y las Adicciones, 2017). The design of this cross-sectional study does not allow us to establish whether the higher prevalence of benzodiazepine use by women is due to psychiatric comorbidity or other concurrent symptoms, such as alcohol withdrawal syndrome which is treated with this family of drugs (Mirijello et al., 2015; Saitz, 2005).

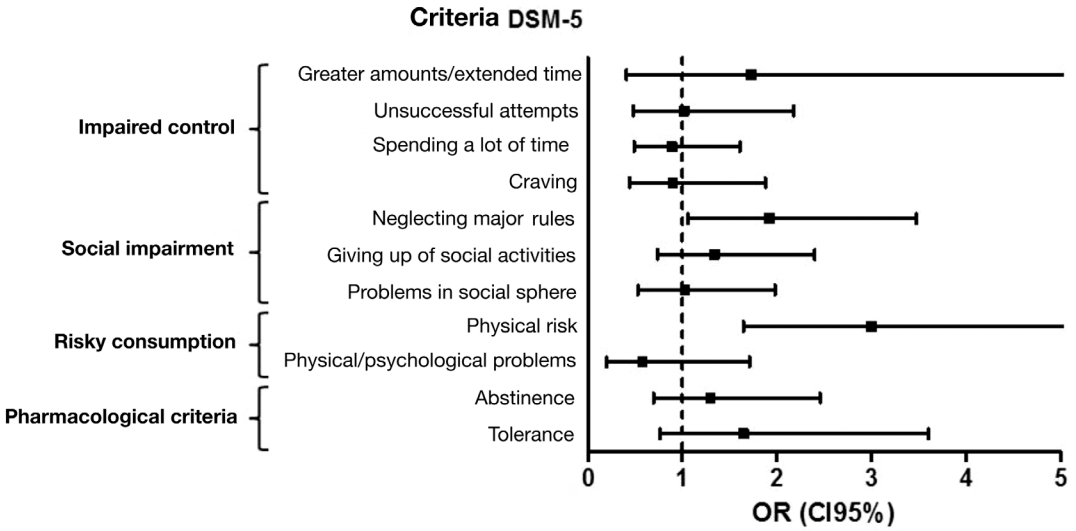

Figure 1. Adjusted probability * (logistic regression) of men admitted to AUD treatment for the first time presenting DSM-5 diagnostic criteria compared to women

Note. * Adjusted for age of onset of regular alcohol consumption, benzodiazepine use and employment status

Another sex difference observed in the univariate analysis is in the employment situation. An analysis of possible causes suggests that these differences are mainly due to the fact that some of the women with an AUD report housework as their employment (data not shown).

With reference to DSM-5, the prevalence of severe AUD was high in this series of cases admitted for treatment of the disorder, with no differences between men and women. However, sex differences in this study are detected by DSM-5 in certain diagnostic areas such as social deterioration and alcohol use in situations of risk, more likely in men. These differences may be due to multiple factors, associated with lifestyle or with other reasons; it is known, for example, that men are exposed to situations of risk more frequently than women in relation to alcohol abuse (Schwartz & Davaran, 2013; White, Hingson, Pan & Yi, 2011). It is interesting to note that when DSM-5 is used to detect AUD in the general population, the same conclusions are drawn: recurrent alcohol use in situations involving physical risk and social impairment are always more prevalent in men (Caetano, Gruenewald, Vaeth & Canino, 2018). In fact, there is a lot of scientific evidence of sex differences in some physiological and psychosocial neural processes in relation to AUD (Kelly, Ostrowski & Wilson, 1999; Nolen-Hoeksema & Hilt, 2006).

On the other hand, some genetic factors may influence the behavioral aspects of AUD and can be divided into two major groups: the genetic neurotransmission modifiers, such as the genes that encode the GABA receptor, and the genetic modifiers of ethanol metabolism, in particular, the polymorphisms of the enzymes involved (Anstee, Daly & Day, 2015). It would thus be interesting to have more studies showing the genetic and environmental interaction in AUD (Salvatore, Cho & Dick, 2017).

This study has several limitations which must be mentioned. First, given the cross-sectional design, we cannot draw conclusions about the causality of the DSM-5 diagnostic criteria. Second, there may be some bias in patient selection towards cases with severe AUD attended in public centers, most of them hospitals, compared to those treated for the first time in primary care centers, who may be younger and with lower comorbidity. Finally, it has been argued that DSM-5 has some limitations as a diagnostic tool, among them its heterogeneous diagnostic criteria and an approach which is excessively strict when analyzing the severity of the disorder as it does not distinguish between alcohol abuse and dependence, nor determine the severity of these conditions (Helzer, van den Brink & Guth, 2006; Lane & Sher, 2015; Muthén, 2006). Neverthe-

less, the strength of this multicenter study lies in the fact that it includes other variables which complement DSM-5 (e.g., polydrug use), allowing us to better characterize the disorder. The results presented here reveal the need to advance the diagnosis of AUD and encourage treatment at the earliest stages of the disease.

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Conflicts of interest

None.

References

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th Ed). Washington, DC: American Psychiatric Association.

Anstee, Q., Daly, A. & Day, C. (2015). Genetics of Alcoholic Liver Disease. *Seminars in Liver Disease*, *35*, 361–374. doi:10.1055/s-0035-1567832.

Bartoli, F., Carrà, G., Crocamo, C. & Clerici, M. (2015). From DSM-IV to DSM-5 alcohol use disorder: An overview of epidemiological data. *Addictive Behaviors*, *41*, 46–50. doi:10.1016/j.addbeh.2014.09.029.

Bouman, A., Heineman, M. J. & Faas, M. M. (2005). Sex hormones and the immune response in humans. *Human Reproduction Update*, *11*, 411–423. doi:10.1093/humupd/dmi008.

Bravo, F., Gual, A., Lligoña, A. & Colom, J. (2013). Gender differences in the long-term outcome of alcohol dependence treatments: An analysis of twenty-year prospective follow up. *Drug and Alcohol Review*, *32*, 381–388. doi:10.1111/dar.12023.

Bríñez Horta, J. A. (2001). Diferencias de género en problemas con el alcohol, según el nivel de consumo. *Adicciones*, *13*, 439-455. doi:10.20882/adicciones.559.

Caetano, R., Gruenewald, P., Vaeth, P. A. C. & Canino, G. (2018). DSM-5 Alcohol Use Disorder Severity in Puerto Rico: Prevalence, Criteria Profile, and Correlates. *Alcoholism, Clinical and Experimental Research*, *42*, 378–386. doi:10.1111/acer.13572.

Chapman, C., Slade, T., Hunt, C. & Teesson, M. (2015). Delay to first treatment contact for alcohol use disorder. *Drug and Alcohol Dependence*, *147*, 116–121. doi:10.1016/j.drugalcdep.2014.11.029.

Crabb, D. W., Matsumoto, M., Chang, D. & You, M. (2004). Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. *The Proceedings of the Nutrition Society*, *63*, 49–63.

Dawson, D. A., Goldstein, R. B. & Grant, B. F. (2012). Factors associated with first utilization of different types of care for alcohol problems. *Journal of Studies on Alcohol and Drugs*, *73*, 647–656.

Djindjic, N., Jovanovic, J., Djindjic, B., Jovanovic, M. & Jovanovic, J. J. (2012). Associations between the Occupational Stress Index and Hypertension, Type 2 Diabetes Mellitus, and Lipid Disorders in Middle-Aged Men and Women. *The Annals of Occupational Hygiene*, *56*, 1051–1062. doi:10.1093/annhyg/mes059.

Edelman, E. J. & Fiellin, D. A. (2016). Alcohol Use. *Annals of Internal Medicine*, *165*, 379–380. doi:10.7326/L16-0107.

Edlund, M. J., Booth, B. M. & Han, X. (2012). Who seeks care where? Utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *Journal of Studies on Alcohol and Drugs*, *73*, 635–646.

European Monitoring Centre for Drugs and Drug Addiction (2015). *European Drug Report 2015: Trends and Development*. Luxembourg: Publications Office of the European Union.

Grant, B. F., Chou, S. P., Saha, T. D., Pickering, R. P., Kerridge, B. T., Ruan, W. J., … Hasin, D. S. (2017). Prevalence of 12-Month Alcohol Use, High-Risk Drinking, and *DSM-IV* Alcohol Use Disorder in the United States, 2001-2002 to 2012-2013. *JAMA Psychiatry*, *74*, 911-923. doi:10.1001/jamapsychiatry.2017.2161.

Hallman, T., Burell, G., Setterlind, S., Odén, A. & Lisspers, J. (2001). Psychosocial risk factors for coronary heart disease, their importance compared with other risk factors and gender differences in sensitivity. *Journal of Cardiovascular Risk*, *8*, 39–49.

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., … Grant, B. F. (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *The American Journal of Psychiatry*, *170*, 834–851. doi:10.1176/appi.ajp.2013.12060782.

Helzer, J. E., van den Brink, W. & Guth, S. E. (2006). Should there be both categorical and dimensional criteria for the substance use disorders in DSM-V? *Addiction*, *101*, 17–22. doi:10.1111/j.1360-0443.2006.01587.x.

Johnson, P. B., Richter, L., Kleber, H. D., McLellan, A. T. & Carise, D. (2005). Telescoping of Drinking-Related Behaviors: Gender, Racial/Ethnic, and Age Comparisons. *Substance Use & Misuse*, *40*, 1139–1151. doi:10.1081/JA-200042281.

Kelly, S. J., Ostrowski, N. L. & Wilson, M. A. (1999). Gender differences in brain and behavior: hormonal and neural bases. *Pharmacology, Biochemistry, and Behavior*, *64*, 655–664.

Lane, S. P. & Sher, K. J. (2015). Limits of Current Approaches to Diagnosis Severity Based on Criterion Counts. *Clinical Psychological Science*, *3*, 819–835. doi:10.1177/2167702614553026.

Lieber, C. S. (2000). Ethnic and gender differences in ethanol metabolism. *Alcoholism, Clinical and Experimental Research*, *24*, 417–418.

Mezey, E. (2000). Influence of sex hormones on alcohol metabolism. *Alcoholism, Clinical and Experimental Research*, *24*, 421.

Mirijello, A., D'Angelo, C., Ferrulli, A., Vassallo, G., Antonelli, M., Caputo, F., … Addolorato, G. (2015). Identification and Management of Alcohol Withdrawal Syndrome. *Drugs*, *75*, 353–365. doi:10.1007/s40265-015-0358-1.

Muthén, B. (2006). Should substance use disorders be considered as categorical or dimensional? *Addiction*, *101*, 6–16. doi:10.1111/j.1360-0443.2006.01583.x.

Nolen-Hoeksema, S. & Hilt, L. (2006). Possible Contributors to the Gender Differences in Alcohol Use and Problems. *The Journal of General Psychology*, *133*, 357–374. doi:10.3200/GENP.133.4.357-374.

Observatorio Español de las Drogas y las Adicciones. (2017). *Informe 2017. Alcohol, tabaco y drogas ilegales en España. Consumo problemático de drogas en España, 2006-2015*. Madrid: Ministerio de Sanidad, Política Social e Igualdad.

Observatorio Español de las Drogas y las Toxicomanías. (2011). *Informe 2011. Situación y tendencias de los problemas de drogas en España*. Madrid: Ministerio de Sanidad, Política Social e Igualdad.

Rehm, J., Manthey, J., Struzzo, P., Gual, A. & Wojnar, M. (2015). Who receives treatment for alcohol use disorders in the European Union? A cross-sectional representative study in primary and specialized health care. *European Psychiatry*, *30*, 885–893. doi:10.1016/j.eurpsy.2015.07.012.

Saitz, R. (2005). Clinical practice. Unhealthy alcohol use. *The New England Journal of Medicine*, *352*, 596–607. doi:10.1056/NEJMcp042262.

Salvatore, J. E., Cho, S. Bin, & Dick D. M. (2017). Genes, Environments, and Sex Differences in Alcohol Research. *Journal of Studies on Alcohol and Drugs*, *78*, 494–501.

Sanvisens, A., Zuluaga, P., Rivas, I., Rubio, G., Gual, A., Torrens, M., … Muga, R. (2018). Patients with alcohol use disorder: initial results from a prospective multicenter registry in the Spanish Network on Addiction Disorders. CohRTA Study. *Adicciones*, *30,* 292-300. doi: 10.20882/adicciones.931

Schwartz, J. & Davaran, A. (2013). Enforcement following 0.08% BAC law change: Sex-specific consequences of changing arrest practices? *Addictive Behaviors*, *38*, 2506–2512. doi:10.1016/J.ADDBEH.2013.04.004.

Slade, T., Chiu, W.T., Glantz, M., Kessler, R. C., Lago, L., Sampson, N., … Degenhardt, L. (2016). A Cross-National Examination of Differences in Classification of Lifetime Alcohol Use Disorder Between DSM-IV and DSM-5: Findings from the World Mental Health Survey. *Alcoholism: Clinical and Experimental Research*, *40*, 1728–1736. doi:10.1111/acer.13134.

Teesson, M., Hall, W., Slade, T., Mills, K., Grove, R., Mewton, L., … Haber, P. (2010). Prevalence and correlates

of DSM-IV alcohol abuse and dependence in Australia: findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction*, *105*, 2085–2094. doi:10.1111/j.1360-0443.2010.03096.x.

White, A., Castle, I. J. P., Chen, C. M., Shirley, M., Roach, D. & Hingson, R. (2015). Converging Patterns of Alcohol Use and Related Outcomes Among Females and Males in the United States, 2002 to 2012. *Alcoholism, Clinical and Experimental Research*, *39*, 1712–1726. doi:10.1111/acer.12815.

White, A. M., Hingson, R. W., Pan, I.J. & Yi, H.Y. (2011). Hospitalizations for alcohol and drug overdoses in young adults ages 18-24 in the United States, 1999-2008: results from the Nationwide Inpatient Sample. *Journal of Studies on Alcohol and Drugs*, *72*, 774–786. doi:10.15288/JSAD.2011.72.774.

White, A. M., Slater, M. E., Ng, G., Hingson, R. & Breslow, R. (2018). Trends in Alcohol-Related Emergency Department Visits in the United States: Results from the Nationwide Emergency Department Sample, 2006 to 2014. *Alcoholism, Clinical and Experimental Research*, *42*, 352–359. doi:10.1111/acer.13559.

Wodarz, N., Bobbe, G., Eichhammer, P., Weijers, H. G., Wiesbeck, G. A. & Johann, M. (2003). The candidate gene approach in alcoholism: are there gender-specific differences? *Archives of Women's Mental Health*, *6*, 225–230. doi:10.1007/s00737-003-0011-y.

The relationship between Gender Norms and Alcohol Consumption: A Systematic Review

Relación entre las normas de género y el consumo de alcohol: una revisión sistemática

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Abstract

There are different profiles of alcohol consumption for men and women, and different courses and prognoses associated with problems caused by alcohol abuse. There is evidence of these differences by sex, but research on their links to differences associated with gender dimensions is scarcer. In order to know what has been researched on the subject, this article reviews the literature regarding the relationship between conformity with gender norms and alcohol use and/or abuse in adults. A systematic review was conducted using the electronic databases of PubMed, PsycINFO and ScienceDirect. Twenty-four articles published in English or Spanish were included and analysed. The main findings were: 1) conformity to norms associated with traditional masculine role (dominance, womanising, aggressiveness, risk behaviours) is related to greater alcohol use; 2) conformity to norms associated with traditional feminine role (interest in home life and family care) is related with lower alcohol use. These findings provide evidence of the relationship between dimensions associated with gender and drinking. It is considered that the possibilities of modifying beliefs and gender patterns linked to risk behaviours is an aspect to be taken into account in the field of prevention, with the development of gender measures a necessary task to further deepen the study of these relationships.

Key Words: Gender norms; Masculinity; Femininity; Alcohol; Health.

Resumen

El consumo de alcohol presenta perfiles diferenciales entre hombres y mujeres, existiendo diferencias igualmente respecto al curso y pronóstico de los problemas derivados del abuso de alcohol. Existe evidencia acerca de estas diferencias en función del sexo, pero la investigación acerca de su relación con diferencias en función de dimensiones asociadas al género es más escasa. Con el objetivo de conocer qué es lo que se ha investigado sobre el tema, se revisa la literatura acerca de la relación entre la conformidad con las normas de género y consumo de alcohol en adultos. Se llevó a cabo una revisión sistemática de la literatura sobre el tema en las bases de datos PubMed, PsycINFO y ScienceDirect. Se incluyeron y analizaron 24 estudios publicados en inglés o español. Los resultados más importantes fueron: 1) la conformidad con normas asociadas al rol tradicional masculino (dominancia, donjuanismo, agresividad, conductas de riesgo) está relacionada, en general, con un mayor consumo de alcohol; 2) la conformidad con normas asociadas al rol tradicional femenino (interés en vida hogareña y cuidado de la familia) se asocia con menor consumo de alcohol. Estos hallazgos proporcionan evidencia acerca de la relación entre dimensiones asociadas al género y el consumo de alcohol. Se considera que las posibilidades de modificación de las creencias y patrones de género vinculados con comportamientos de riesgo es un aspecto a considerar en el ámbito de la prevención, siendo el desarrollo de medidas de género una tarea necesaria para continuar profundizando en el estudio de estas relaciones.

Palabras clave: Normas de género; Masculinidad; Feminidad; Alcohol; Salud.

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According to the Spanish Observatory on Drugs and Addictions (2017), alcohol use is more widespread among men than among women, although this difference seems to be on the decrease in recent years. The National Survey on Alcohol and Other Drugs in Spain states that in 2015, the prevalence of alcohol use was 82.9% among men and 72.1% for women, a difference of 10.8 points. This difference between the sexes was larger in the surveys prior to 2013, standing at 14.8 points in 2005 (84% vs. 69.2%) and at 21.3 points in 1995 (79.3% vs. 58%).

Different studies have highlighted important variation between the sexes in the prevalence of alcohol use and problematic drinking. The prevalence of problems with alcohol increases with the level of alcohol use, and women are more likely than men to have drinking problems with the same pattern of consumption and especially with severe use (Bríñez-Horta, 2001; Ely, Hardy, Longford & Wadsworth, 1999). While women have a later age of onset and drink less, abuse develops more rapidly than among men (the so-called telescoping effect), and they have greater difficulty in controlling alcohol use, more problems associated with drinking and higher incidence of depressive and anxiety pathologies (Alvanzo et al, 2011; Ávila & González, 2007; Ehlers et al., 2010; Díaz-Mesa et al., 2016; Míguez & Permuy, 2017; Sánchez-Autet et al., 2018). These differences are of great interest in clinical practice, since men and women have different forms of illnesses, different profiles, courses and prognoses with respect to problems caused by alcohol use; this implies the need to deepen the study of the factors determining such differences, with the aim of improving the development of prevention strategies and programs regarding alcohol use.

In the field of health, the study of the differences between men and women can be related to the well-known morbidity-mortality paradox (Nathanson, 1975; Verbrugge, 1982). According to the World Health Organization (2016), although men have a lower life expectancy than women, women suffer from worse health and more chronic diseases. Among the factors noted to account for these differences between men and women are: 1) biological risks; 2) risks acquired through work and lifestyle; 3) the behaviours that people adopt to improve or maintain health; 4) the forms used to communicate the symptoms and health issues; and 5) the use of the health care system (Verbrugge, 1989).

Human behaviour is partially influenced both by biological and environmental factors. Meta-analytic studies based on research of twins suggest that genetic factors account for 47%, 46% and 50% of the variance observed in cognitive aspects, psychiatric disorders and neurological disorders, respectively (Polderman et al., 2015), as well as 49% of the differences observed in disorders due to alcohol use (Verhulst, Neale & Kendler, 2015). Although the factors associated with biological risks are important determinants of health, other factors, such as risks associated with lifestyle and health behaviours (for example, exposure to toxic agents, microbial agents, accidents, incidents with fire, illicit use of drugs, smoking, alcohol, inadequate diet or lack of exercise), can be equally important, accounting for, for example, 50% of mortality (Mokdad, Marks, Stroup & Gerberding, 2004). Therefore, taking into account the biological differences associated with sex as the only explanatory variable of health can prove reductionist. The literature argues that maleness is associated with an increase in the probability of adopting health-risk behaviours (drinking alcohol, smoking, not seeking medical help, etc.), which increases the likelihood of getting sick, being injured or dying (Courtenay, 2000), and has led to growing research interest in studying such determinants of health.

Given that human behaviour is strongly governed by social norms, some authors have argued that if men's lifestyle leads to worse health, it is very important to find out why these risky behaviours are more frequent in men and how to promote healthy behaviours, focusing on the study of behavioural differences between men and women and, in particular, regarding compliance with gender norms (Mahalik, Burns & Syzdek, 2007a).

According to Sánchez-López (2013), although the concepts of sex and gender are sometimes used interchangeably in health research, both terms involve different aspects. The former focuses on differences of a more biological nature, highlighting hormonal, chromosomal, gonadal or brain aspects and genital dimorphism in relation to being male or female, while the second highlights social and cultural differences with respect to roles, relationships, behaviours, values or attitudes that society attributes differentially to each sex with reference to masculinity and femininity. Some of the characteristics associated with the traditional male role have to do with a protective function and being the family provider, and with features reflected in adjectives such as active, determined, competitive, persistent and self-confident, while the traditional female role is seen in terms of functions of reproduction, child-raising and emotional support for the family, and with traits such as dedication to others, emotionality, kindness, understanding and warmth, among others (Sánchez-López, 2013; Sánchez-López & Limiñana-Gras, 2017). After a person understands what society expects from them, they may or may not conform to these norms based on a series of contextual and individual variables, with a greater or lesser degree of conformity or acceptance (Sánchez-López, Saavedra, Dresch & Limiñana-Gras, 2014). Gender norms are acquired through socialisation processes and may reflect some differences based on the values of each culture or society; for example, differences have been found in the degree of conformity to certain masculine gender norms between American and Spanish samples, with Spanish

people showing less acceptance than Americans of norms related to contempt towards homosexuality, the importance of winning, the importance of status, attraction to violence and risk, and greater conformity with values related to womanising (Cuellar-Flores, Sánchez-López & Dresch, 2011). Based on this differentiation between the concepts of sex and gender, recent reviews of health research from a gender perspective point to the need to take sex and gender factors into account in order to deepen understanding of health determinants in both sexes, how they are interrelated and involved in differential exposure to risk-protection factors and in different health and illness outcomes (Sánchez-López & Limiñana-Gras, 2017).

The purpose of this review is to provide evidence regarding current research in the study of gender norms and their relationship to alcohol use. The objectives of this review are to explore and identify studies on gender and drinking, as well as to describe and analyse the results of each instrument used. It is hoped that this will contribute to answering the question of whether gender (and its dimensions) is related to the consumption of alcoholic drinks in men and women, and in what way.

Method

The review was carried out following the steps and stages of identification, screening, eligibility and inclusion of the PRISMA guidelines (*preferred reporting items for systematic reviews and meta-analyses*) (Liberati et al., 2009).

To identify the studies, three bibliographic databases were searched: PubMed, PsycINFO and ScienceDirect. Due to the exploratory nature of the proposed review, the search was not temporally restricted and involved all articles in the databases up to February 2017. The following search terms were used: "gender conformity", "conformity to masculine norms" "conformity to feminine norms" "masculinity", "femininity" in combination with the term "alcohol" and the Boolean operators OR and AND. Complementarily, a search was made using the Researchgate portal and a review of references used in the articles that were finally selected.

After an initial analysis of the articles obtained in the screening phase, the following inclusion criteria were applied: a) any matching search terms in the title, summary or key words, b) studies published in English or Spanish, c) articles with access to the full text and d) empirical studies, or those of which it was not possible to determine with accuracy, based on the information contained in the abstract, whether they were empirical studies or not. Within the eligibility phase, after reading the content of the included articles in depth, the following exclusion criteria were applied: a) non-empirical studies; b) studies not dealing with the relationship between gender and alcohol use or abuse; c) "gender" used in the sense of "sex" (male/female) rather than "gender" or "social norms" (masculine/feminine); d) alcohol not assessed in terms of use or abuse; e) results not linking alcohol use or abuse to gender and its factors; and f) qualitative assessment. After application of the ex-

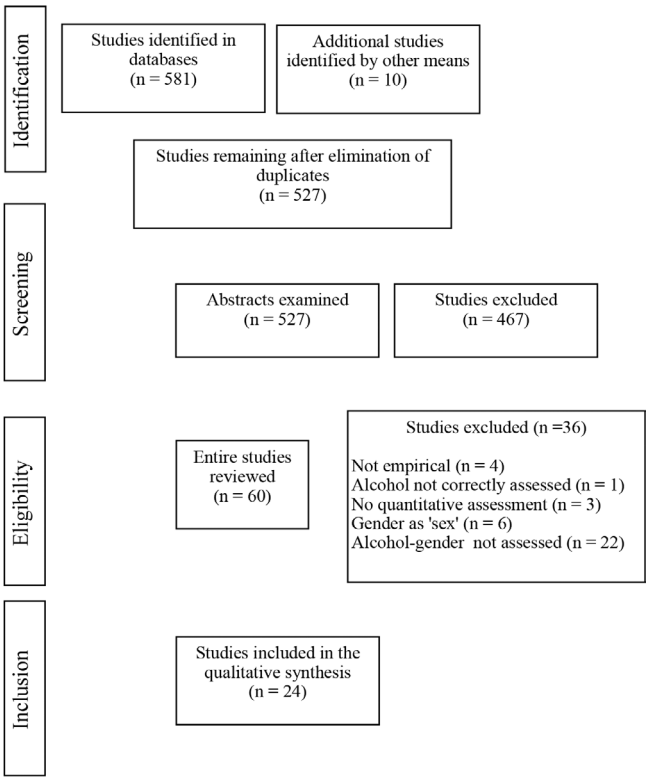

Figure 1. Flow diagram of the study search and selection process

clusion criteria, the number of articles included for the qualitative synthesis was reduced to 24. Figure 1 summarises the number of studies included in each stage of the search and selection process.

Results

Apart from two studies written in Spanish (Brabete & Sánchez-López, 2012; Brabete, Sánchez-López, Cuéllar-Flores & Rivas-Diez, 2013), the rest of those reviewed were in English. Two other studies were found which were researched in Spain (Sánchez-López, Cuéllar-Flores & Dresch, 2012; Sánchez-López, Rivas-Diez & Cuéllar-Flores, 2013), two in Sweden (Hensing & Spak, 2009; Hensing, Spak, Thundal & Östlund, 2003), four in Australia (Mahalik, Levi-Minzi & Walker, 2007b; Ricciardelli, Williams & Kieman, 1998; Williams & Ricciardelli, 1999; Williams & Ricciardelli, 2001), one in Germany (Möller-Leimkühler, Schwarz, Burtscheidt & Gaebel, 2002) and the other thirteen in the United States.

As regards samples, in some studies these comprised only men (Good et al., 2008; Gordon et al., 2013; Iwamoto, Corbin, Lejuez & MacPherson, 2014; Iwamoto, Cheng, Lee, Takamatsu & Gordon, 2011), others only women (Kaya, Iwamoto, Grivel, Clinton & Brady, 2016), and the rest used mixed samples.

Table 1 presents the different instruments used to assess conformity with gender norms, developed over four decades, from 1974 to 2014. The proportion of studies per instrument is rather modest: the instrument most widely used is the CMNI (Mahalik et al., 2003), in 37.5% of studies, followed by CFNI (Mahalik et al., 2005), in 16.6%. The use of questionnaires with reliability indices below 0.80 in all or some of their scales is relatively frequent, but only two of the 16 instruments report reliability indices below 0.60 (see Kulis, Marsiglia, Lingard, Nieri & Nagoshi, 2008; and Van Gundy, Schieman, Kelley & Rebellon, 2005). Some instruments were found which were difficult to access or not well known, such as the GEPAQ (Runge, Frey, Gollwitzer, Helmreich & Spence, 1981) or MRNI-R (Levant et al., 2007). In terms of alcohol use assessment, it should be noted that most studies tend to include this in a series of items as part of a battery of questions regarding general health, while others use specific questionnaires, as in the case of *Daily Drinking Questionnaire* (DDQ) by Collins, Parks and Marlatt (1985), the *Brief Young Adult Alcohol Consequences Questionnaire* (B-YAACQ) by Kahler, Strong and Read (2005), or the *Rutgers Alcohol Problem Index* (RAPI) by White and Labouvie (1989).

Table 2 shows the main characteristics of the studies included in the review and their principal results, which vary according to the different instruments used and the different scales included in each. First, three studies do not use a standardised instrument to assess conformity with gender norms, but select items to evaluate gender identity from other studies, research and/or instruments validated and standardised in the framework of other research. The first of these, by Kulis et al. (2008), concludes that there is a significant relationship between aggressive masculinity (aggressiveness, domination, disobedience) and substance use, including alcohol, as well as between affective femininity (empathy, expression of emotions) with lower alcohol use and more protective behaviours, all with small to moderate effect size. In a later study (Kulis, Marsiglia & Nagoshi, 2010), a significant relationship was found between assertive masculinity (assertiveness, personal value, self-confidence) and lower alcohol use in men, while in women aggressive masculinity and submissive femininity (submission, dependence) was positively related to higher levels of drinking, with a moderate effect size in all. Finally, the study by Lye and Waldron (1998), found that attitudes towards non-traditional gender roles were associated with lower alcohol use in men, with moderate to large effect size, and that non-traditional attitudes towards cohabitation and marriage were associated with less drinking in both men and women, particularly in the case of attitudes towards cohabitation, where the effect size was large.

The remaining studies reviewed used a total of 14 standardised instruments, including the short versions. The following were not used very frequently in the study of alcoholism. First, the *Personal Attributes Questionnaire* (PAQ), used by Van Gundy et al. (2005) on a sample of men and women from Toronto, obtained positive relationships between femininity and alcohol use in women, with a moderate effect size. Second, the *German Extended Personal Attributes Questionnaire* (GEPAQ) was used in a single study with a clinical sample (Möller-Leimkühler et al., 2002), which found a predominance of female identity, undifferentiated in alcoholic women and men, while a predominance of masculine or androgynous identity was found in non-alcoholic men, and of androgynous identity in non-alcoholic women. Third, the use of the *Gender Role Conflict Scale* (GRCS) highlighted a direct relationship of moderate effect size between the success, power and competition dimensions of this questionnaire and the number of alcoholic drinks per episode (Good et al., 2008). This scale was applied in another study together with the *Male Role Norms Inventory Revised instrument* (MRNI-R), obtaining results with a large effect size which linked alcohol use in men with traditional masculine ideology (Uy, Massoth & Gottdiener, 2014). Similarly, but with a small effect size and using the *Masculine Role Norms Scale* (MRNS) instrument, the study also revealed that certain aspects of traditional masculinity, such as "toughness", were linked to alcohol use (Gordon et al., 2013).

Other instruments have been used more assiduously by researchers in the study of alcohol and other substance use. One such case is the *Bem Sex Role Inventory* (BSRI)

Table 1. *Gender measurement instruments used in the studies included in the review*

	Instrument	Author(s) & Year	Psychometric properties	Studies in which it was used
1	Sex-Role Inventory (BSRI)	Bem (1974)	60 items. 3 scales: Masculinity, Femininity and Social desirability. Internal consistency between α=.70 and α=.86.	Van Gundy, Schieman, Kelley & Rebellon (2005)
2	Personal Attributes Questionnaire (PAQ)	Spence & Helmreich (1978)	24 items. 2 scales: Instrumentality-Masculinity and Expressivity-Femininity. Internal consistency of α=.69 and α=.52 respectively.	Van Gundy, Schieman, Kelley & Rebellon (2005)
3	Bem Sex-Role Inventory – Short Form (BSRI-S)	Bem (1981)	18 items. 3 scales: Personal masculinity, Social masculinity and Femininity. Internal consistency between α=.66 and α=.92.	Vaughan, Wong & Middendorf (2014)
4	Australian Sex-Role Scale (ASRS)	Antill, Cunningham Russell & Thompson (1981)	40 items. 4 scales: Positive masculinity, Negative masculinity, Positive femininity, Negative femininity. Internal consistency between α=.62 and α=.81.	Ricciardelli, Williams & Kieman (1998) Williams & Ricciardelli (1999) Williams & Ricciardelli (2001)
5	German Extended Personal Attributes Questionnaire (GEPAQ)	Runge, Frey, Gollwitzer, Helmreich & Spence (1981)	40 items. 2 scales: Masculinity and Femininity. Internal consistency of α=.82 and α=.85 respectively.	Möller-Leimkühler, Schwarz, Burtscheidt & Gaebel (2002)
6	Gender Role Conflict Scale (GRCS)	O'Neil, Helms, Gable, David & Wrightsman (1986)	37 items. 4 factors: Success, Power, Competition; Restricted emotionality; Restricted affectionate behaviour among men; Conflict between work and family relationships. Internal consistency between α=.80 and α=.87.	Good et al. (2008) Uy, Massoth & Gottdiener (2014)
7	Masculine Role Norms Scale (MRNS)	Thompson & Pleck (1986)	26 items. 3 scales: Status, Tenacity and Antifemininity. Internal consistency between α=.74 and α=.81.	Gordon et al. (2013)
8	Masculinity and Femininity Questionnaire (M/F-Q)	Bergman et al. (1988)	31 items. 4 scales: Leadership, Concern for others, Self-affirmation and Emotivity. Internal consistency between α=.63 and α=.76.	Hensing, Spak, Thundal & Ostlund (2003) Hensing & Spak (2009)
9	Cuestionario sobre roles de género y cohabitación	Lye & Waldron (1998)	Not standardised. 15 items selected from four different questionnaires about traditional attitudes towards gender roles. Internal consistency of α›.60.	Lye & Waldron (1998)
10	Conformity to Masculine Norms Instrument (CMNI)	Mahalik et al. (2003)	94 items. 11 scales: Winning, Emotional control, Risk taking, Violence, Power over women, Dominance, Womanising, Self-reliance, Primacy of work, Disdain of homosexuality and Pursuit of status. Internal consistency: Total α=.94; Scales between α=.72 and α=.91. Spanish adaptation (Cuéllar-Flores, Sánchez-López & Dresch, 2011). Total α=.89; Subscales between α=.64 and α=.81.	Liu & Iwamoto (2007); Mahalik, Levi-Minzi & Walkier (2007); Good, Schopp, Thomson, Hathaway, Mazurek & Sanford-Martens (2008); Iwamoto et al. (2011); Iwamoto & Smiler (2013); Brabete & Sánchez-López (2012); Sánchez-López, Cuéllar-Flores & Dresch (2012); Brabete, Sánchez-López, Cuéllar-Flores & Rivas-Diez (2013); Sánchez-López, Rivas, Diez, & Cuéllar-Flores (2013)
11	Conformity to Feminine Norms Inventory (CFNI)	Mahalik et al. (2005)	84 items. 8 scales: Nice in relationships, Caring for children, Thinness, Sexual fidelity, Modesty, Romantic relationship, Domestic and Invest in appearance. Internal consistency: Total α=.88; Subscales between α=.77 and α=.92. Spanish adaptation (Sánchez-López, Cuéllar-Flores, Dresch & Aparicio-García, 2009).Total α=.87; Subscales between α=.64 and α=.86.	Brabete & Sánchez-López (2012). Sánchez-López, Cuéllar-Flores & Dresch (2012). Brabete, Sánchez-López, Cuéllar-Flores & Rivas-Diez (2013). Sánchez-López, Rivas, Diez & Cuéllar-Flores (2013).
12	Male Role Norms Inventory-Revised (MRNI-R)	Levant et al. (2007)	53 items. 7 scales: Avoidance of femininity, Negativity towards sexual minorities, Self-reliance, Aggression, Dominance, Non-relational attitudes towards sexuality, Restrictive emotionality. Internal consistency: Total α=.97. Subscales between α=.73 and α=.96.	Uy, Massoth & Gottdiener (2014)
13	Gender Identity Questionnaire	Kulis, Marsiglia, Lingard, Nieri & Nagoshi (2008)	Not standardised. 13 items derived from Bem Sex-Role Inventory (BSRI) and Australian Sex-Role Scale (ASRS). 4 scales: Assertive masculinity Negative masculinity, Affective femininity and Negative femininity. Internal consistency between α=.50 and α=.66.	Kulis, Marsiglia, Lingard, Nieri & Nagoshi (2008) Kulis, Marsiglia & Nagoshi (2010)
14	14. Conformity to Masculine Norms Inventory-46 (CMNI-46)	Parent & Moradi (2009)	Short version of CMNI. 46 items. Internal consistency of subscales between α=.77 and α=.91.	Iwamoto et al. (2011) Iwamoto, Corbin, Lejuez & MacPherson (2014)
15	15. Conformity to Feminine Norms Inventory-45 (CFNI-45)	Parent & Moradi (2010)	Short version of CFNI. 45 items. The Sweet and nice scale was added. Internal consistency of subscales between α=.67 and α=.90.	Kaya, Iwamoto, Grivel, Clinton & Brady (2016)
16	16. Conformity to Masculine Norms Inventory-29 (CMNI-29)	Hsu & Iwamoto (2014)	Short version of CMNI. 29 items. 8 scales: Winning, Womanising, Independence, Violence, Heterosexual presentation, Risk taking, Emotional control and Power. Internal consistency of subscales between α=.70 and α=.85.	Kaya, Iwamoto, Grivel, Clinton & Brady (2016)

and its short form (BSRI-S). In the study by Van Gundy et al. (2005), the BSRI yields a negative association between masculinity and drinking levels in men; Vaughan, Wong and Middendorf (2014) on the other hand, using the BSRI-S, which distinguishes between personal and social facets of masculinity, found that social masculinity is related to excessive alcohol use, both in men and women. Both studies had large effect sizes. In the studies that used the *Australian Sex Role Scale* (ASRS) (Ricciardelli et al., 1998; Williams & Ricciardelli, 1999; Williams & Ricciardelli, 2001), it is clear that high scores in the scales of negative masculinity (aggressiveness, boasting) were linked in both sexes to problems with alcohol (dependence) and risk taking caused by drinking (disinhibition), while low scores in positive masculinity and femininity (characteristics positively associated with masculinity, such as assertiveness and self-confidence, and with femininity, such as love of children) were associated with people with a high probability of developing alcohol problems; these relationships were reported to have moderate to large effect sizes. Two of the studies reviewed (Hensing et al., 2003; Hensing & Spak, 2009) used the *Masculinity and Femininity Questionnaire* (M/F-Q) with an exclusively female sample. The results showed low scores on leadership and self-affirmation to be significantly related, albeit with a small effect size, with an increased likelihood of alcohol problems and abuse. Moreover, significant relationships of moderate effect size were found between the increase in this probability and high scores in emotivity.

Finally, a total of ten studies were found which used the *Conformity to Masculine Norms Inventory* (CMNI) and *Conformity to Feminine Norms Inventory* (CFNI) and its different versions. Four of the studies reviewed were carried out with the Spanish adaptation of the instrument. Among its results are positive relationships of moderate effect size between male drinking and the total score for conformity with masculine norms, as well as with the scales for playboy (or womanising) and pursuit of status (Brabete & Sánchez-López, 2012). Also positive, but with a small effect size were the relationships with dominance, violence and risk taking (Brabete et al., 2013; Sánchez-López et al., 2012). Negative relationships were found between male alcohol use and the scales for emotional control and heterosexual presentation (Brabete & Sánchez-López, 2012; Sánchez-López et al., 2012; Sánchez-López et al., 2013). Among women, drinking was inversely linked to total agreement with traditional feminine norms (Brabete & Sánchez-López, 2012) and with the scales for childcare (Brabete & Sánchez-López, 2012; Brabete et al., 2013), sexual fidelity (Brabete & Sánchez-López, 2012; Brabete et al., 2013; Sánchez-López et al., 2012; Sánchez-López et al., 2013), domestic and modesty (Brabete et al., 2013), and romantic relationship (Brabete et al., 2013; Sánchez-López et al., 2012); conformity with the invest in appearance norm was the only one directly linked to greater alcohol use. Effect sizes in most of these relationships were moderate.

Kaya et al. (2016) used only female samples when applying the short versions of questionnaires regarding agreement with male and female gender roles (CMNI-29 and CFNI-45). The results obtained indicated direct associations between alcohol use and the scales for risk taking, emotional control and nice in relationships, and negative or inverse associations with the scales for power over women, modesty and sexual fidelity. Regarding problems caused by drinking, positive relationships were found for risk taking, thinness and invest in appearance, and a negative one with the sexual fidelity.

Finally, it is worth highlighting six studies which used only the CMNI exclusively with samples of men, together with the study by Iwamoto and Smiler (2013), which did so with samples of men and women. Good et al. (2008), in the same study mentioned above, found direct associations, also of moderate effect size, between excessive drinking or drunkenness and the masculinity norm of dominance of the CMNI. In the study by Iwamoto et al. (2011), alcohol poisoning and alcohol-related problems were directly linked to the winning, risk taking, playboy, power over women, self-reliance and primacy of work scales, all with small to moderate effect sizes. Likewise, the results showed that the masculine norms which increase the risk of alcohol-related problems are the playboy role, with a moderate effect size, and, with a small effect, risk taking and self-reliance, (Iwamoto et al., 2011). In the study by Iwamoto & Smiler (2013), the highest level of conformity with the risk taking and heterosexual presentation norms predicted the consumption of alcohol in men, as did conformity with risk taking in women. In general, the results of the Iwamoto et al. studies with men's samples showed a positive correlation between drinking and the CMMI playboy, winning and risk taking scales, with small to moderate effect sizes, as well as a direct relationship between the increased risk of alcohol problems and the scales for risk taking, self-reliance and playboy (Iwamoto & Smiler, 2013; Iwamoto et al., 2014; Liu & Iwamoto, 2007). Finally, the study by Mahalik et al. (2007b) found a direct relationship between the highest number of health-risk behaviours (including high alcohol use) and the self-reliance, playboy and violence scales, with moderate effect sizes.

Discussion

The aim of this study was to provide evidence, through a systematic review of the research that has been carried out in the field of study, regarding conformity with gender norms in terms of the possible relationship with alcohol use among men and women, as well as how to synthesise the main conclusions obtained in the research on the subject.

Table 2. *Characteristics and main results of the studies included in the review*

Authors and date of publication	Country	Objective	Sample and instruments	Main results
Brabete & Sánchez-López (2012)	Spain	Determine if gender norms are related to health variables in a sample of Romanians living in Spain.	188 Rumanians in Spain (70 women / 48 men) Gender: aCMNI and CFNI. Alcohol: 1 question about use in a health test.	Women: total conformity in CFNI, and conformity with the norms "Childcarer" and "Sexual fidelity", linked to lower use (rbp= -0.30, p‹.01; rbp= -0.35, p‹.01; and rbp= -0.48, p‹.01); conformity with norm "Invest in appearance" linked to higher use (rbp= 0.25, p‹.05). Men: total conformity en CMNI, conformity with "Playboy" and with "Pursuit of status", linked to greater use (rbp= 0.27; p‹.05; rbp= 0.43, p‹.01; and rbp= 0.27, p‹.05); and conformity with the norm "heterosexual presentation" linked to lower use (rbp= -0.30; p‹.05).
Brabete et al. (2013)	Spain	Determine if gender norms are related to smoking and alcohol use in a sample of Romanians living in Spain.	750 Rumanians in Spain (489 women / 261 men) Gender: CMNI and CFNI. Alcohol: two questions to confirm smoking and alcohol use	Women: total conformity in CFNI, and conformity with the norms "Childcarer", "Sexual fidelity", "Modesty", "Romantic relationship" and "Domestic", linked to lower use (rbp= 0-.20, p‹0.5; rbp= -0.19, p‹0.5; rbp= -0.22, p‹0.5; rbp= -0.20, p‹0.5; and rbp= -0.11, p‹0.5). Men: conformity with norms "Risk taking", "Violence" and "Playboy", linked to higher use (rbp= 0.11, p‹0.1; rbp= 0.11, p‹0.1; and rbp= 0.10, p‹0.1).
Good et al. (2008)	USA	Improve the understanding of male roles and conflicts associated with alcohol use in men with serious injuries.	52 men with spinal cord injuries and brain trauma. Gender: bGRCS and CMNI. Alcohol: drinks consumed in a session and the current frequency of binge drinking.	Masculine roles associated with "Success, Powere, or Competing" are linked to greater use (rs= 0.46, p‹.05). Greater conformity with the norm "Dominance", linked to higher consumption of drinks per sitting (rs= 0.43, p‹.05) and with excessive use or binge drinking (rs= 0.47, p‹.05).
Gordon et al. (2013)	USA	Examine the relationship between traditional male norms of an ethnically and racially diverse group of young men who have become parents and the substance use (tobacco, alcohol, marijuana, drugs) and their health habits (diet, exercise).	296 men. Gender: cMRNS. Alcohol: question about alcohol use and *Recreational Drug Use Scale*.	Greater acceptance of "Toughness" is linked to higher alcohol use [OR (95% CI)= 1.725; p‹ .01]. The norm "Status" is linked to lower use, although only weakly [OR (95% CI)= 0.78; p=.063].
Hensing & Spak (2009)	Sweden	Analyse in women the association between four dimensions of gender identity and the variables of alcohol use (1AUD and 1HED)	930 women. Gender: dM/F-Q. Alcohol: AUD and HED (at least 60 g in a single day at least once a month).	Women with low "Leadership", greater likelihood of alcohol abuse and dependence [OR (95% CI)=1.95 (1.17- 3.26)].
Hensing et al. (2003)	Sweden	Analyse the dimensions of gender identity and its association with psychiatric disorders and alcohol use (1HED and 3HAC).	836 women. Gender: *M/F-Q.* Alcohol: Dependence and abuse (DSM-III-R), HED (at least 60 g of ethanol in a single day at least once a month) and HAC (at least ≥600 g ethanol per month during the last 12 months).	Women with low "Leadership", greater likelihood of alcohol abuse and dependence [OR (95% CI)= 1.93 (1.23–3.01)]. Women with low "Self-affirmation", greater likelihood of abuse and dependence" [OR (95% CI)= 1.98 (1.25–3.07)]. Women with high "Emotivity", greater likelihood of abuse and dependence [OR (95%)= 3.22 (1.96–5.30)]
Iwamoto & Smiler (2013)	USA	Analyse the relationship between gender conformity, group pressure and alcohol use in the young population.	124 women and 138 men. Gender: 5 of the CMNI subscales. Alcohol: frequency with which "beer, soft drinks mixed with wine or cider" are consumed.	Greater conformity with "Heterosexual presentation" *(.16, p‹.05),* Playboy *(.25, p‹.01),* and "risk taking" *(.17, p‹01)* predicts drinking among men. Greater conformity with "Risk taking" *(.20, p‹.01)* predicts drinking among women.
Iwamoto et al. (2011)	USA	Analyse the relationship between gender and risk factors of intoxication and other alcohol-related problems, specifically in men.	776 men. Gender: eCMNI-46. Alcohol: Drinking to intoxication and Alcohol Related Problems (4 RAPI).	Masculine norms of "Winning" (r = 0.14, p‹.01), "Risk taking" (r = 0.20, p ‹.01), and "Playboy" (r = 0.25, p ‹.01), were positively associated with drinking to intoxication. Masculine norms of "Risk taking" (r = 0.19, p ‹.01), "Power over women" (r = 0.20, p ‹.01), Playboy (r = 0.28, p ‹.01), "Self-reliance" (r = 0.10, p ‹.01), and "Primacy of work" (r = 0.09, p ‹.05) are linked to increased alcohol-related problems. The three masculine norms which increase the risk of alcohol-related problems are "Playboy" (IRR = 5.01, p ‹0.001), "Risk taking" (IRR = 2.66, p‹0.001), e "Self-reliance" (IRR =3.12, p ‹0.001).
Iwamoto et al. (2014)	USA	Investigate the role of positive expectations of alcohol use as a mediator between male gender norms and drinking among university men.	806 men. Gender: CMNI-46. Alcohol: 5DDQ (Estimated alcohol consumption in the last three months) and one item on binge drinking.	The masculine norms directly linked to higher consumption are "Playboy" (r= 0.26, p‹0.1), "Risk taking" (r= 0.1, p‹0.1) and "Winning" (r= 0.23 (p‹0.1) . The masculine norm "Heterosexual presentation" is inversely related to frequency of alcohol use (r= -0.13, p‹0.1).
Kaya et al. (2016)	USA	Examine the conformity of women to masculine and feminine norms and their relation with drinking and alcohol-related problems in a sample of female university students.	645 women. Gender: fCMNI-29, gCFNI-45. Alcohol: HED and alcohol-related problems (6B-YAACQ).	Three masculine norms were significantly linked to HED: "Risk taking" and "Emotional control" with greater use (IRR = 1.11, p ‹.05, and IRR= 1.07, p ‹ .05); and "Power over women" with lower use (IRR =.89, p ‹.01) Three feminine norms were significantly linked to HED: "Modesty" (IRR=.93, p ‹.05) and "Sexual fidelity" (IRR=.86, p ‹.001) with lower HED, "Relationships" (IRR=1.06, p ‹.05) with higher HED.

				The masculine norm "Risk taking" (IRR=1.65, p ‹ .001), and the feminine norms "Thinness" (IRR =1.20, p ‹.01) and "Invest in appearance" (IRR=1.16, p ‹.01), were positively linked to alcohol-related problems. The feminine norm "Sexual fidelity" was negatively linked to alcohol-related problems (IRR=.70, p ‹.001).
Kulis et al. (2010)	USA	Analyse the relationship between positive and negative gender roles, externalizing and internalizing behaviour problems and substance use.	151 Latino students. 91 women, 60 men. Gender: 12-item scale for four gender role orientations. Alcohol: 6 items about drinking.	"Assertive masculinity" linked to lower drinking in men (r= -0.27, p‹.05). "Aggressive masculinity" and "Submissive femininity", linked to higher drinking in men (r= 0.31, p‹.01; r= 0.25, p‹.05)
Kulis et al. (2008)	USA	Analyse if measures of gender identity predict substance use, intentions of use, expectations, among others.	327 Latino students. Gender: 12-item scale for four gender role orientations. Alcohol: 6 items about drinking.	"Aggressive masculinity" was associated with higher substance use, including alcohol (scores from r = 0.12 to 0.29). "Affective femininity" linked to lower recent alcohol use (*r* = -0. 21) and less excessive drinking (*r* = -0. 17), and with more protective behaviours, such as lower intention of drinking (*r*=-0.12), and less approval (*r* = -0. 28).
Liu & Iwamoto (2007)	USA	Explore the relationship between Asian values, gender roles, coping styles and substance use.	154 Asian-American students. Gender: CMNI. Alcohol: alcohol use and binge drinking behaviour.	Higher alcohol consumption was positively related to total conformity with male norms (r=0.17, p‹.05), Winning (r=0.20, p‹.05), Pursuit of status (r=29, p‹.01), Playboy (r=20, p‹.05), Risk taking (r=17, p‹.05) and violence (r=17, p‹.05); and negatively to emotional control (r=-0.20, p‹.05). Binge drinking was positively linked to total conformity with masculine norms (r=0.18, p‹.05), and with the norms of "Winning" (r=19, p‹0.5), "Pursuit of status" (r=23, p‹.01), and "Playboy" (r=29, p‹.01); and negatively to emotional control (r=-0.18, p‹.05). The norm "Power over women" significantly predicts alcohol abuse (OR= 1.31, p‹.01).
Lye & Waldron (1998)	USA	Analyse the relationship between alcohol consumption, marijuana and other illicit drugs and attitudes regarding gender roles, family and cohabitation.	Range: 756-963 women, 821-1095 men. Gender: 36 items on four different questionnaires about non-traditional attitudes towards gender roles, and towards cohabitation and marriage. Alcohol: items about past drinking habits and consumption in the last 30 days.	Attitudes towards non-traditional gender roles in men were associated with lower alcohol use (p‹.001). Among women, there were only a few and weaker and inconsistent relationships between the measures of traditional gender roles and alcohol use. Non-traditional attitudes towards cohabitation and marriage were strongly associated with lower alcohol consumption in both men and women, particularly for attitudes towards cohabitation (p‹.001).
Mahalik, Levi-Minzi & Walker (2007b)	Australia	Confirm whether the health of Australian men and their health behaviours have a significant relationship with the conformity to traditional male norms.	253 Australian men. Gender: CMNI. Alcohol: item included in *Health Behavior Inventory* (HBI).	The frequency of health-risk behaviour (including alcohol use) was associated with the norms "Self-reliance" (r=0.24, p‹.001), "Womanising" (r=0.29, p‹.001) and "Violence" (r=0.26, p‹.001).
Möller-Leimkühler et al. (2002)	Germany	Explore if the understanding gender orientation would be a useful contribution to the hypothesis that the increase of women with alcoholism is due to the change in traditional feminine roles.	112 persons currently detoxed (36 women, 76 men). Gender: gender role orientation (hGEPAQ). Alcohol: results of assessment before detoxification.	Significant differences for each of the four identities in gender roles in both samples, alcoholics and non-alcoholics (p ‹.05): - predominance of undifferentiated feminine identity in alcoholic women and men; - predominance in non-alcoholic men of masculine or androgynous identity; - predominance in non-alcoholic women of androgynous identity.
Ricciardelli et al. (1998)	Australia	Investigate the relationship between desirable and undesirable aspects of masculinity and femininity and aspects derived from eating (restriction) and drinking alcohol.	114 women students. Gender: iASRS. Alcohol: two items on consumption per week and the *Alcohol Dependence Scale*.	"Negative Masculinity" was linked to high scores on "Alcohol dependence" and "Disinhibition" (p‹.05).
Sánchez-López et al. (2012)	Spain	Evaluate if gender is related to substance use and chronic diseases.	Spanish university students. 234 women and 226 men. Gender: CMNI and CFNI. Alcohol: item about frequency of alcohol use.	Drinking in men was directly linked to conformity with norms of "Dominance" (r= 0.138, p‹.05) and "Playboy" (r= 0.199, p‹.05). Drinking in women was inversely linked to total conformity (r= -0.244, p‹.001), "Sexual fidelity" (r= -0.277, p‹.001) and "Being romantic" (r= -0.331, p‹.001). Positive conformity with the norms "Playboy" and "Dominance", and negative or inverse conformity with "Winning", accounting for 7% of the variance in male alcohol use (p ‹.001). Conformity with feminine norms "Being romantic" and "Sexual fidelity "were associated with lower alcohol use, accounting for 13% of the variance in women (F=19.61; p ‹.001)
Sánchez-López et al. (2013)	Spain	Analyse the impact of conformity to gender norms in conformity and alcohol use.	Spanish university students. 435 women and 419 men. Gender: CMNI and CFNI. Alcohol: items on frequency of consumption in the last two weeks taken from the National Health Survey (INE, 2006).	Men with higher scores on the "emotional control" scale were less likely to drink alcohol (R2=7.6%, p ‹.001). Men with higher scores on the scale of "Playboy" and "Violence" were more likely to drink (R2= 10.2% and 7.4%, p‹.01 and p‹.05 respectively) Women with higher scores on the "Sexual fidelity" scale were less likely to drink (R2=10.4%, p‹.01).

Uy et al. (2014)	USA	Analyse the link between traditional masculine ideology, the conflict of gender roles, reasons for drinking and alcohol use.	109 men. Gender: jMRNI-R and kGRCS. Alcohol: *Drinking Motives Questionnaire-Revised and Daily Drinking Questionnaire-Revised*.	A significant total indirect effect of traditional male ideologies on alcohol problems was observed (.19, p<.05) 25.9% of the variance associated with alcohol use was due to traditional male ideologies and reasons for drinking.
Van Gundy et al. (2005)	USA	Examine the effects of sex, masculinity and femininity on alcohol use.	Moscow: 1996 sample of 804 personas. // Toronto: 1995 sample of 1361 personas. Gender: lBSRI (Moscow) and mPAQ (Toronto). Alcohol: frequency of use in last 30 days and quantity (Moscow) and frequency last 12 months and quantity (Toronto).	Significant interaction between sex and masculinity in the Moscow sample: masculinity is negatively associated with level of alcohol use in men, and weakly and *positively* among women (*b* =.808; p<.01) Significant interaction and femininity in the Toronto sample: femininity increases women's alcohol use (b =.366; p<.05)
Vaughan et al. (2014)	USA	Test the relationship between gender roles and binge drinking in a sample of adult Latinos.	660 people. Gender: nBSRI-S (femininity, social masculinity and personal masculinity) Alcohol: binge drinking and alcohol problems.	Social masculinity is associated with excessive alcohol use in men and women (OR= >100, p<.05).
Williams & Ricciardelli (1999)	Australia	Examine the relationship between stereotyped gender characteristics and alcohol use.	422 university students (243 women and 179 men). Gender: ASRS. Alcohol: *Short Form Michigan Alcoholism Screening Test* (SMAST), average drinks per episode and average number of drink days per week.	Two consumption patterns were identified: One linked to Negative masculinity (.69) and Positive femininity (-.86). Another linked to Positive masculinity and femininity (-.96 and -.41) The importance of including gender attributes, both positive and negative, in the study of gender stereotypes and alcohol use behaviours is highlighted.
Williams & Ricciardelli (2001)	Australia	Study the relationship between symptoms of alcohol problems and eating disorders with gender characteristics and with evidence of comorbidity in students.	217 university women. Gender: ASRS. Alcohol: SMAST, average drinks per sitting, average number of drink days per week and *The Alcohol Dependence Scale* (ADS).	Two consumption patterns were identified: One linked to Positive masculinity (.89) and Negative femininity (-.61). Another to Negative masculinity (.85).

Note. Gender instruments: a = Conformity to Masculine/Feminine Norms Inventory, b = Gender Role Conflict Scale, c = Masculine Role Norms Scale, d = Masculinity and Femininity Questionnaire, e = Conformity to Masculine Norms Inventory-46, f = Conformity to Masculine Norms Inventory-29, g = Conformity to Feminine Norms Inventory-45 , h = German Extended Personal Attributes Questionnaire, i = Australian Sex-Role Scale, j = Male Role Norms Inventory-Revised, k = Gender-Role Conflict Scale, l = Bem Sex Role Inventory, m = Personal Attributes Questionnaire, n = Bem Sex Role Inventory-Short Form.
Notes:1AUD= Alcohol use disorder; 2HED= Heavy episodic drinking, 3HAC= High alcohol consumption, 4RAPI= Rutgers Alcohol-Related Problems, 5DDQ= Daily Drinking Questionnaire, 6B-YAACQ= Brief Young Adult Alcohol Consequences Questionnaire.

One of the main aspects observed in this review has been the diversity of conclusions reached by the different authors. This could be explained by the variability of the questionnaires used and the different characteristics and provenance of the samples under study, with few results which permit generalisation. In general, and despite this diversity, three aspects can be highlighted on which consistent evidence has been obtained in the studies reviewed regarding the relationship between gender and alcohol consumption.

First, heavier drinking seems to be related to masculinity. Different studies have found that traditional masculine ideology is linked with a large effect size to higher levels of drinking in men (Uy et al., 2014), and the social facet or dimension associated with masculinity is related to excessive use or drunkenness (Vaughan, Wong & Middendorf, 2014). Equally noteworthy are some specific dimensions associated with gender norms, linked with moderate effect sizes to alcohol use in men, such as aggression (Kulis et al., 2008; Mahalik et al., 2007b; Sánchez-López et al., 2013), dominance (Brabete & Sánchez-López, 2012; Good et al.,2008), risk taking (Iwamoto et al., 2011; Iwamoto et al., 2014; Iwamoto & Smiler, 2013; Kaya et al., 2016), womanising (Brabete & Sánchez-López, 2012; Iwamoto et al., 2011; Iwamoto et al., 2014; Iwamoto & Smiler, 2013; Liu & Iwamoto, 2007; Mahalik et al., 2007b; Sánchez-López et al., 2012; Sánchez-López et al., 2013), independence (Mahalik et al., 2007b), success (Good et al.,2008; Iwamoto & Smiler, 2013; Liu & Iwamoto, 2007) or the pursuit of admiration or social status (Brabete & Sánchez-López, 2012; Liu & Iwamoto, 2007).

Second, there seems to be some consensus on the relationship between drinking and female gender norms. In general, the characteristics that define traditional femininity appear as protective variables in connection with alcohol consumption. Both general conformity with traditional feminine norms, as well as some specific dimensions such as interest in raising children (Brabete & Sánchez-López, 2012; Brabete et al., 2013), sexual fidelity (Brabete & Sánchez-López, 2012; Brabete et al., 2013; Kaya et al., 2016; Sánchez-López et al., 2013), domestic (Brabete & Sánchez-López, 2012; Brabete et al., 2013) or romantic relationship (Brabete et al., 2013; Sánchez-López et al., 2012), appear as variables linked to lower alcohol use in women, with moderate to large effect sizes.

Third, despite some evidence of the relationship between traditionally male behaviour and drinking, and also of the protective profile of aspects linked to traditional femininity in terms of alcohol use, the reverse is not the case; that is,

there is not as much evidence regarding protective variables in men, or of variables related to higher levels of drinking in women. Some studies confirm the hypothesis that men who agree more with positive or assertive aspects of masculinity (Gordon et al., 2013; Kulis et al., 2010) drink less alcohol, and also that women who identify more with negative aspects of traditional femininity, such as submission, and masculinity, such as aggression, drink more (Kulis et al., 2010; Van Gundy et al., 2005). However, such data are not common and should be studied in greater depth; similarly, instead of questionnaires designed for men being used to evaluate women, measurement instruments are being developed which are adapted to both sexes for the assessment of identification with both male and female norms.Furthermore, the present review raises the issue of how relevant changes in social norms and roles are. Some authors point out that the traditional role of women is being transformed and with it the reasons to drink. For example, it has been suggested that one of the reasons for drinking in women may be based on the need to feel equal to men by adopting health-risk behaviours such as alcohol use, as has been seen in the case of women identifying or conforming more strongly with the negative aspects associated with traditional masculinity-related gender norms (Kaya et al., 2016; Williams & Ricciardelli, 1999). There is thus a clear need to consider new research hypotheses for the study of how conformity with both masculine and feminine gender norms can influence women's health behaviours, given the changes in the social roles of men and women, and the evidence of rising alcohol use in women (Möller-Leimkühler et al., 2002).

Although the existing data on alcohol use substantiate higher rates of drinking among men than women, this difference appears to be progressively diminishing in many countries. Such changes in drinking patterns have been linked to changes in social roles involving greater equality of opportunity between men and women and greater incorporation of women into public life, which has been associated, for example, with the incorporation of women into employment outside the home, with the adoption of typically masculine values and behaviour, or with the greater economic and consumer freedom of women (Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018; Holmila & Raitasalo, 2005). Other studies indicate that there seems to be a generational change regarding the development of female gender identity and its relationship to the social perception of drinking among women. Traditionally, alcohol use has been associated with masculinity, the construction of masculine ties, aggression and transgressive behaviour (Graham & Wells, 2003), being perceived socially as less reprehensible than female drinking, which has been considered more as a threat to traditional femininity and to the management of domestic chores and family care (de Visser & McDonnell, 2012). Some authors argue that this development, more than exclusively an effect of women imitating the values associated with masculinity, could be explained by the growth of new models of femininity in which drinking is not perceived as negatively as in the traditional model. Thus, for example, it has been pointed out that younger generations of women perceive alcohol to have less of a negative influence on female identity than older women, socialised as they were in a more traditional gender identity model (Simonen, Törrönen & Tigerstedt, 2013). However, this perception seems to be linked to drinking in certain places or situations, such as social or leisure spaces (Törrönen, Rolando & Beccaria, 2017). From this perspective, recent research has pointed out the importance of studying the combined role of age and gender roles in the onset and maintenance of alcohol use (Fernández Rodríguez, Dema Moreno & Fontanil Gómez, 2019).

In light of the data reviewed, research seems to confirm that there are significant relationships between drinking and conformity with certain gender norms, aspects which have to do with learning processes and differential socialisation with regard to what is considered masculine and feminine within each society, thereby highlighting its relevance to the development of strategies and programs for prevention and intervention. The morbidity or mortality profiles of any given country are linked to patterns of health behaviours, and the possibility that these may be modified by promoting healthy practices depends on identifying social beliefs, such as those around traditional male and female roles. However, one of the greatest challenges facing research on this subject is the difficulty of obtaining generalisable results for the study of gender norms due to the influence on them of the specific culture and society in which they are assessed. The development and standardisation of gender measures and their adaptation to different cultural and geographical contexts, as is the case of some of the questionnaires used in the studies reviewed (CMNI or CFNI), is a necessary task to continue deepening the understanding of these relationships and to enable generalisations and valid conclusions to be drawn from research on conformity with gender norms and their relationship to variables linked to health, such as alcohol consumption.

Among the limitations of this review, it should be noted that the results observed are limited to the selection criteria and databases which were used. Thus, publications indexed in other electronic databases, studies written in languages other than English and Spanish, or the review of other types of research not published in specialised journals have not been included in the present analysis. However, and despite the paucity of research on the subject in question, the present review allows us to draw a series of conclusions which are consistent across the studies analysed, and which highlight limitations and future research challenges.

Finally, and by way of conclusion, we can confirm that certain negative aspects traditionally related to masculinity seem to act as risk factors for alcohol use. Conversely, cer-

tain characteristics associated with femininity and a positive or assertive masculinity appear to have a protective effect against drinking. The possibility of modifying certain belief patterns associated with identity and gender norms can be an important aspect in the change and modification of certain health-risk behaviours. This possibility raises a series of future research challenges through which the study of these relationships can be deepened, gender-appropriate measurement instruments developed, and new hypotheses regarding the development of new models of femininity and masculinity explored.

Conflict of interest

The authors declare no conflicts of interest.

References

Alvanzo, A. A., Storr, C. L., La Flair, L., Green, K. M., Wagner, F. A. & Crum, R. M. (2011). Race/ethnicity and sex differences in progression from drinking initiation to the development of alcohol dependence. *Drug and Alcohol Dependence, 118*, 375-382. doi:10.1016/j.drugalcdep.2011.04.024.

Antill, J. K., Cunningham, J. D., Russell, G. & Thompson, N. L. (1981). An Australian Sex-Role Scale. *Australian Journal of Psychology, 33*, 169-183.

Ávila, J. & González, D. (2007). Diferencias de género en la enfermedad alcohólica. *Adicciones, 19*, 383-392. doi:10.20882/adicciones.297.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology, 42*, 155–162. doi:10.1037/h0036215.

Bem, S. L. (1981). *Bem Sex Role Inventory professional manual*. Palo Alto, CA: Consulting Psychologists Press.

Bergman, H., Bergman, I., Engelbrektsson, K., Holm, L., Johannesson, K. & Lindberg, S. (1988). *Psykologhandbok del 1 (Manual for Psychologists: Part 1)*. Stockholm: The Magnus Huss Clinic, Karolinska Hospital.

Brabete, A. C. & Sánchez-López, M. P. (2012). How does the gender influence people's health? Data of a sample of Romanian people living in Spain. *Procedia-Social and Behavioral Sciences, 33*, 148-152. doi:10.1016/j.sbspro.2012.01.101.

Brabete, A. C., Sánchez-López, M. P., Cuéllar-Flores, I. & Rivas-Díez, R. (2013). The impact of gender norms on alcohol and tobacco use at Romanians. *Procedia-Social and Behavioral Sciences, 78*, 230-234. doi:10.1016/j.sbspro.2013.04.285.

Bríñez-Horta, J. A. (2001). Diferencias de género en problemas con el alcohol, según el nivel de consumo. *Adicciones, 13*, 439-455. doi:10.20882/adicciones.559.

Collins, R. L., Parks, G. A. & Marlatt, G. A. (1985). Social determinants of alcohol consumption: The effects of social interaction and model status on the self-administration of alcohol. *Journal of Consulting and Clinical Psychology, 53*, 189–200. doi:10.1037/0022-006x.53.2.189.

Courtenay, W. H. (2000). Behavioral factors associated with disease, injury, and death among men: Evidence and implications for prevention. *The Journal of Men's Studies, 9*, 81-142. doi:10.3149/jmh.0103.281.

Cuéllar-Flores, I., Sánchez-López, M.P. & Dresch, V. (2011). El Inventario de Conformidad con las Normas de Género Masculinas (CMNI) en la población española. *Anales de Psicología, 27*, 170-178.

de Visser, R. & McDonnell, E. J. (2012). "That's OK. He's a guy": A mixed-methods study of gender double-standards for alcohol use. *Psychology & Health*, 27, 618-639. doi:10.1080/08870446.2011.61744.

Díaz Geada, A., Busto Miramontes, A. & Caamaño Isorna, F. (2018). Alcohol, tobacco and cannabis consumption in adolescents from a multicultural population (Burela, Lugo). *Adicciones, 30*, 264-270. doi:10.20882/adicciones.915.

Díaz-Mesa, E. M., García-Portilla, P., Fernández-Artamendi, S., Sáiz, P. A., Bobes, T., Casares, M. J., … Bobes, J. (2016). Diferencias de género en la gravedad de la adicción. *Adicciones, 28*, 221-230. doi:10.20882/adicciones.829.

Ehlers, C. L., Gizer, I. R., Vieten, C., Gilder, A., Gilder, D. A., Stouffer, G. M., … Wilhelmsen, K. C. (2010). Age at Regular Drinking, Clinical Course, and Heritability of Alcohol Dependence in the San Francisco Family Study: A Gender Analysis. *The American Journal on Addictions, 19,* 101–110. doi:10.1111/j.1521-0391.2009.00021.x.

Ely, M., Hardy, R., Longford, N. & Wadsworth, M. (1999). Gender differences in the relationship between alcohol consumption and drink problems are largely accounted for body water. *Alcohol and Alcoholism*, *34*, 894–902. doi:10.1093/alcalc/34.6.894.

Fernández Rodríguez, M.A., Dema Moreno, S. & Fontanil Gómez, Y. (2019). The influence of gender roles in alcohol consumption: a qualitative study of adolescents and young adults in Asturias. *Adicciones, 31*, 260-273. doi:10.20882/adicciones.1003.

Good, G. E., Schopp, L. H., Thomson, D., Hathaway, S. L., Mazurek, M. O. & Sanford-Martens, T. C. (2008). Men with serious injuries: Relations among masculinity, age, and alcohol use. *Rehabilitation Psychology, 53*, 39-45. doi:10.1037/0090-5550.53.1.39.

Gordon, D. M., Hawes, S. W., Reid, A. E., Callands, T. A., Magriples, U., Divney, A., ... Kershaw, T. (2013). The many faces of manhood: Examining masculine norms and health behaviors of young fathers across race. *American Journal of Men's Health, 7*, 394-401. doi:10.1177/1557988313476540.

Graham, K. & Wells, S. (2003). Somebody's Gonna Get Their Head Kicked in Tonight Aggression among Young Males in Bars: A Question of Values? *British Journal of Criminology, 43,* 546-566. doi:10.1093/bjc/43.3.546.

Hensing, G. & Spak, F. (2009). Lack of leadership confidence relates to problem drinking in women: gender identity, heavy episodic drinking and alcohol use disorders in Swedish women. *Alcohol and Alcoholism, 44*, 626-633. doi:10.1093/alcalc/agp072.

Hensing, G., Spak, F., Thundal, K. L. & Östlund, A. (2003). Decreased risk of alcohol dependence and/or misuse in women with high self-assertiveness and leadership abilities. *Alcohol and Alcoholism, 38*, 232-238. doi:10.1093/al-calc/agg058.

Holmila, M. & Raitasalo, K. (2005). Gender differences in drinking: why do they still exist? *Addiction*, *100*, 1763-1769. doi:10.1111/j.1360-0443.2005.01249.x.

Hsu, K. & Iwamoto, D. K. (2014). Testing for measurement invariance in the Conformity to Masculine Norms-46 across White and Asian American college men: Development and validity of the CMNI-29. *Psychology of Men & Masculinity*, *15*, 397-406. doi:10.1037/a0034548.

Iwamoto, D. K., Corbin, W., Lejuez, C. & MacPherson, L. (2014). College men and alcohol use: Positive alcohol expectancies as a mediator between distinct masculine norms and alcohol use. *Psychology of Men & Masculinity, 15*, 29-39. doi:10.1037/a0031594.

Iwamoto, D. K., Cheng, A., Lee, C. S., Takamatsu, S. & Gordon, D. (2011). "Maning" up and getting drunk: The role of masculine norms, alcohol intoxication and alcohol-related problems among college men. *Addictive Behaviors, 36*, 906-911. doi:10.1016/j.addbeh.2011.04.005.

Iwamoto, D. K. & Smiler, A. P. (2013). Alcohol makes you macho and helps you make friends: The role of masculine norms and peer pressure in adolescent boys' and girls' alcohol use. *Substance Use & Misuse, 48*, 371-378. doi:10.3109/10826084.2013.765479.

Kahler, C. W., Strong, D. R. & Read, J. P. (2005). Toward Efficient and Comprehensive Measurement of the Alcohol Problems Continuum in College Students: The Brief Young Adult Alcohol Consequences Questionnaire. *Alcoholism: Clinical & Experimental Research, 29*, 1180–1189. doi:10.1097/01.alc.0000171940.95813.a5.

Kaya, A., Iwamoto, D. K., Grivel, M., Clinton, L. & Brady, J. (2016). The role of feminine and masculine norms in college women's alcohol use. *Psychology of Men & Masculinity, 17*, 206-214. doi:10.1037/men0000017.

Kulis, S., Marsiglia, F. F., Lingard, E. C., Nieri, T. & Nagoshi, J. (2008). Gender identity and substance use among students in two high schools in Monterrey, Mexico. *Drug and Alcohol Dependence, 95*, 258-268. doi:10.1016/j.dru-galcdep.2008.01.019.

Kulis, S., Marsiglia, F. F. & Nagoshi, J. L. (2010). Gender roles, externalizing behaviors, and substance use among Mexican-American adolescents. *Journal of Social Work Practice in the Addictions, 10*, 283-307. doi:10.1080/1533256X.2010.497033.

Levant, R. F., Smalley, K. B., Aupont, M., House, A. T., Richmond, K. & Noronha, D. (2007). Initial validation of the Male Role Norms Inventory-Revised (MRNI-R). *The Journal of Men's Studies, 15*, 83-100. doi:10.3149/jms.1501.83.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., ... Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine*, *6*, e1000100. doi:10.1371/journal.pmed.1000100.

Liu, W. M. & Iwamoto, D. K. (2007). Conformity to masculine norms, Asian values, coping strategies, peer group influences and substance use among Asian American men. *Psychology of Men & Masculinity, 8*, 25-39. doi:10.1037/1524-9220.8.1.25.

Lye, D. N. & Waldron, I. (1998). Relationships of substance use to attitudes toward gender roles, family and cohabitation. *Journal of Substance Abuse, 10*, 185–198. doi:10.1016/s0899-3289(99)80133-3.

Mahalik, J. R., Locke, B. D., Ludlow, L. H., Diemer, M. A., Scott, R. P., Gottfried, M. & Freitas, G. (2003). Development of the Conformity to Masculine Norms Inventory. *Psychology of Men & Masculinity*, *4*, 3-25. doi:10.1037/1524-9220.4.1.3.

Mahalik, J. R., Morray, E. B., Coonerty-Femiano, A., Ludlow, L. H., Slattery, S. M. & Smiler, A. (2005). Development of the Conformity to Feminine Norms Inventory. *Sex Roles*, *52*, 417-435. doi:10.1007/s11199-005-3709-7.

Mahalik, J. R., Burns, S. M. & Syzdek, M. (2007a). Masculinity and perceived normative health behaviors as predictors of men's health behaviors. *Social Science & Medicine*, *64*, 2201-2209. doi:10.1016/j.socscimed.2007.02.035.

Mahalik, J. R., Levi-Minzi, M. & Walker, G. (2007b). Masculinity and health behaviors in Australian men. *Psychology of Men & Masculinity, 8*, 240-249. doi:10.1037/1524-9220.8.4.240.

Míguez, M. C. & Permuy, B. (2017). Características del alcoholismo en mujeres. *Revista de la Facultad de Medicina, 65*, 15–22. doi:10.15446/revfacmed.v65n1.57482.

Mokdad, A. H., Marks, J. S., Stroup, D. F. & Gerberding, J. L. (2004). Actual causes of death in the United States, 2000. *JAMA, 291*, 1238-1245. doi:10.1001/jama.291.10.1238.

Möller-Leimkühler, A. M., Schwarz, R., Burtscheidt, W. & Gaebel, W. (2002). Alcohol dependence and gender-role orientation. *European Psychiatry, 17*, 1-8. doi:10.1016/S0924-9338(02)00624-7.

Nathanson, C. A. (1975). Illness and the feminine role: a theoretical review. *Social Science & Medicine*, *9*, 57-62. doi:10.1016/0037-7856(75)90094-3.

Observatorio Español de las Drogas & las Adicciones (2017). Alcohol, tabaco y drogas ilegales en España: Informe 2017. Encuesta sobre alcohol y drogas en España (EDADES) 1995-2015. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved at htttp://www.

pnsd.mscbs.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2017_Informe_EDADES.pdf.

O'Neil, J. M., Helms, B. J., Gable, R. K., David, L. & Wrightsman, L. S. (1986). Gender-Role Conflict Scale: College men's fear of femininity. *Sex Roles, 14*, 335-350. doi:10.1007/BF00287583.

Organización Mundial de la Salud (2016). Life expectancy and healthy life expectancy. Retrieved at http://apps.who.int/gho/data/view.main.SDG2016LEXREGv?lang=en.

Parent, M. C. & Moradi, B. (2009). Confirmatory factor analysis of the Conformity to Masculine Norms Inventory and development of the Conformity to Masculine Norms Inventory-46. *Psychology of Men & Masculinity, 10*, 175-189. doi:10.1037/a0015481.

Parent, M. C. & Moradi, B. (2010). Confirmatory factor analysis of the conformity to feminine norms inventory and development of an abbreviated version: the CFNI-45. *Psychology of Women Quarterly, 34*, 97-109. doi:10.1111/j.1471-6402.2009.01545.x.

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M. & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics, 47*, 702–709. doi:10.1038/ng.3285.

Ricciardelli, L. A., Williams, R. J. & Kiernan, M. J. (1998). Relation of drinking and eating to masculinity and femininity. *The Journal of Social Psychology, 138*, 744-752. doi:10.1080/00224549809603259.

Runge, T. E., Frey, D., Gollwitzer, P. M., Helmreich, R. L. & Spence, J. T. (1981). Masculine (instrumental) and feminine (expressive) traits. A comparison between students in the United States and West Germany. *Journal of Cross-Cultural Psychology, 12*, 142-162. doi:10.1177/0022022181122002.

Sánchez-Autet, M., Garriga, M., Zamora, F. J., González, I., Usall, J., Tolosa. L., … Arranz, B. (2018). Screening of alcohol use disorders in psychiatric outpatients: influence of gender, age, and psychiatric diagnosis. *Adicciones, 30*, 251-263. doi:10.20882/adicciones.885.

Sánchez-López, M. P. (2013). La salud desde la perspectiva de género: el estado de la cuestión. En M. P. Sánchez-López (Eds.), *La salud de las mujeres* (pp.17-40). Madrid, España: Síntesis.

Sánchez-López, M. P., Cuéllar-Flores, I. & Dresch, V. (2012). The impact of gender roles on health. *Women & Health, 52*, 182-196. doi:10.1080/03630242.2011.652352.

Sánchez-López, M. P. & Limiñana-Gras, R. M. (2017). Health from a gender perspective. En M. P. Sánchez-López & R. M. Limiñana-Gras (Eds.), *The Psychology of Gender and Health* (pp.1-52). London: Elsevier. doi:10.1016/b978-0-12-803864-2.00001-8.

Sánchez-López, M. P., Rivas-Díez, R. & Cuéllar-Flores, I. (2013). Masculinity and Femininity as predictors of tobacco and alcohol consumption in Spanish university students. *Health and Addictions, 13*, 15-22. doi:10.21134/haaj.v13i1.189.

Sánchez-López, M. P., Saavedra, A. I., Dresch, V. & Limiñana-Gras, R. M. (2014). Conformity to Traditional Gender Norms in a Feminized Occupation: The Influence on Health Behaviors. *Health, 6*, 2775-2789. doi:10.4236/health.2014.620317.

Simonen, J., Törrönen, J. & Tigerstedt, C. (2013). Femininities of drinking among Finnish and Swedish women of different ages. *Addiction: Research & Theory, 22,* 98–108. doi:10.3109/16066359.2013.779676.

Spence, J. T. & Helmreich, R. L. (1978). *Masculinity and femininity: their psychological dimensions, correlates, and antecedents*. Austin, TX: University of Texas Press.

Thompson, E. H. & Pleck, J. H. (1986). The structure of Male Role Norms. *American Behavioral Scientist, 29*, 531-543. doi:10.1177/000276486029005003.

Törrönen, J., Rolando, S. & Beccaria, F. (2017). Masculinities and femininities of drinking in Finland, Italy and Sweden: Doing, modifying and unlinking gender in relation to different drinking places. *Geoforum, 82,* 131–140. doi:10.1016/j.geoforum.2017.04.005.

Uy, P. J., Massoth, N. A. & Gottdiener, W. H. (2014). Rethinking male drinking: Traditional masculine ideologies, gender-role conflict, and drinking motives. *Psychology of Men & Masculinity, 15*, 121-128. doi: 10.1037/a0032239.

Van Gundy, K., Schieman, S., Kelley, M. S. & Rebellon, C. J. (2005). Gender role orientations and alcohol use among Moscow and Toronto adults. *Social Science & Medicine, 61*, 2317-2330. doi:10.1016/j.socscimed.2005.07.033.

Vaughan, E. L., Wong, Y. J. & Middendorf, K. G. (2014). Gender roles and binge drinking among Latino emerging adults: a latent class regression analysis. *Psychology of Addictive Behaviors, 28*, 719-726. doi:10.1037/a0037406.

Verbrugge, L. M. (1982). Sex differentials in health. *Public Health Reports, 97*, 417-437.

Verbrugge, L. M. (1989). The twain meet: empirical explanations of sex differences in health and mortality. *Journal of Health and Social Behavior, 30*, 282-304. doi:10.2307/2136961.

Verhulst, B., Neale, M. C. & Kendler, K. S. (2014). The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychological Medicine, 45*, 1061–1072. doi:10.1017/s0033291714002165.

White, H. R. & Labouvie, E. W. (1989). Rutgers Alcohol Problem Index. PsycTESTS Dataset. doi:10.1037/t00517-000.

Williams, R. J. & Ricciardelli, L. A. (1999). Gender congruence in confirmatory and compensatory drinking. *The Journal of Psychology, 133,* 323-331. doi:10.1080/00223989909599745.

Williams, R. J. & Ricciardelli, L. A. (2001). Sex-role traits and the comorbidity of symptoms of disordered eating and problem drinking. *Eating Behaviors, 2*, 67-77. doi:10.1016/s1471-0153(00)00024-6.

Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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

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

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

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

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

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

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

PRESENTACIÓN DE LOS TRABAJOS

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

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

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

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

1. NOMBRE DEL MEDICAMENTO. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de paliperidona equivalentes a 175 mg de paliperidona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de paliperidona equivalentes a 263 mg de paliperidona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de paliperidona equivalentes a 350 mg de paliperidona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de paliperidona equivalentes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA 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. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a la inyección trimestral de palmitato de paliperidona. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

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

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

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

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

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

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

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

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

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

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

Dosis omitidas

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

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

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

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

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en Insuficiencia renal las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥ 50 a < 80 ml/min), se debe ajustar la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada 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 < 1×10^9/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 diabética 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 o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepino. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepino 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 cuando hay cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia**. Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. No se debe utilizar TREVICTA durante el embarazo a menos que sea claramente necesario. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas**. La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas**. Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en ≥ 5% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimada en los ensayos clínicos realizados con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1.000 a <1/100), *raras* (≥1/10.000 a <1/1.000), *muy raras* (<1/10.000) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

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

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

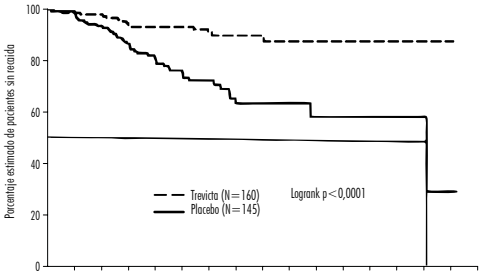


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

En el estudio de no inferioridad, 1.429 pacientes con enfermedad aguda (puntuación PANSS total media en el momento inicial: 85,7) que cumplían los criterios DSM-IV de esquizofrenia se incorporaron a la fase abierta y recibieron tratamiento con palmitato de paliperidona inyectable mensual durante 17 semanas. Se permitía ajustar la dosis (esto es, 50 mg, 75 mg, 100 mg o 150 mg) después de 5 semanas y 9 inyecciones y el lugar de inyección podía ser el deltoides o el glúteo. De los pacientes que cumplían los criterios de aleatorización en las semanas 14 y 17, 1.016 fueron aleatorizados en proporción 1:1 para seguir recibiendo una vez al mes la inyección de palmitato de paliperidona mensual o bien cambiar a TREVICTA, multiplicando por 3,5 la dosis de las semanas 9 y 13 de palmitato de paliperidona inyectable mensual, durante un 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.

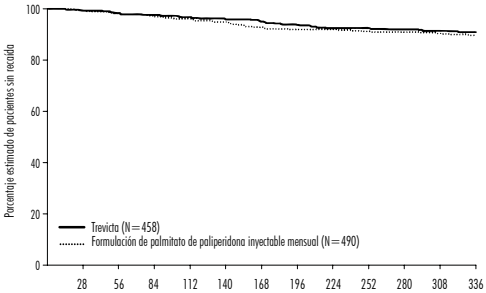


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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 $T_{máx}$ 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 $C_{máx}$ 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 $C_{máx}$. 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 (ClCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (ClCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (ClCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{inf}) 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 $C_{máx}$ 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 FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.**

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

1. NOMBRE DEL MEDICAMENTO. Xeplion 25 mg suspensión inyectable de liberación prolongada. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 25 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 39 mg de palmitato de paliperidona equivalentes a 25 mg de paliperidona. 50 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. 75 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. 100 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. 150 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLINICOS. 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 o 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes <18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). *Administración en el músculo deltoides.* El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinada por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. *Administración en el músculo glúteo.* El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos <1x10^9/l) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma diabética y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con Xeplion se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia cardiaca, infarto de miocardio o isquemia, trastornos de la conducción), enfermedad cerebrovascular o afecciones que predispongan al paciente a la hipotensión (p. ej. deshidratación e hipovolemia). Convulsiones. Xeplion debe utilizarse con precaución en pacientes con antecedentes de convulsiones u otros trastornos que potencialmente puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona aumentan en pacientes con insuficiencia renal y por tanto, se recomienda un ajuste de la dosis en pacientes con insuficiencia renal leve. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos en pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. Pacientes de edad avanzada con demencia. No se ha estudiado Xeplion en pacientes de edad avanzada con demencia. Xeplion se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de padecer ictus. La experiencia con risperidona citada más adelante se considera válida también para paliperidona. *Mortalidad global.* En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapina y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. *Reacciones adversas cerebrovasculares.* Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y los beneficios de prescribir Xeplion a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DCL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, obnubilación, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en el transcurso de 4 horas. Regulación de la temperatura del organismo. Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescriba Xeplion a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p.ej., ejercicio físico intenso, exposición a calor extremo, que reciban medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xeplion y adoptar medidas preventivas. Efecto antiemético. Se observó un efecto antiemético en los estudios preclínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de Xeplion en un vaso sanguíneo. Síndrome del Iris Flácido Intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como Xeplion (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. 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 puedan 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 raros* (<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	neumonia, 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	catatonia, estado confusional, somnambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación/somnolencia, distonia[a], mareos, discinesia[a], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, convulsión[a], trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		

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

*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. †Referido a "Hiperprolactinemia" a continuación. ‡Referido a "Síntomas extrapiramidales" a continuación. §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. **¶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 miodonía), distonía (incluye distonia, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, 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 las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. ***Tratamiento agudo de la esquizofrenia.*** La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de Xeplion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xeplion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xeplion fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xeplion en el día 8. 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).

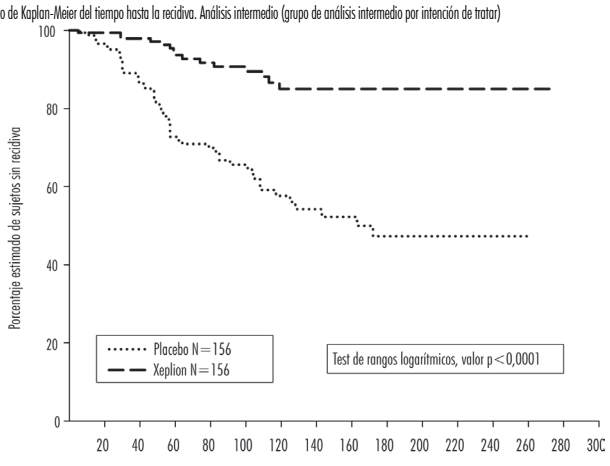
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 las primeras 12 semanas del período de mantenimiento. Se realizó la asignación aleatoria de un total de 410 pacientes estabilizados a Xeplion (mediana de la duración de 171 días [intervalo de 1 día a 407 días]) o a placebo (mediana de la duración de 105 días [intervalo de 8 días a 441 días]) hasta que experimentaran una recidiva de los síntomas de la esquizofrenia en la fase doble ciego de duración variable. El ensayo se suspendió antes de tiempo por motivos de eficacia, dado que se observó un tiempo significativamente más largo hasta la recidiva (p<0,0001, Figura 1) en los pacientes tratados con Xeplion en comparación con el placebo (cociente de riesgos=4,32; IC 95%: 2,4-7,7).

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CrCl=10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{∞}) de 1,5; 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. 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 30ºC. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada PVL: 168,18 €; PVP: 214,09 €; PVP (IVA): 222,65 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 218,62 €; PVP: 269,53 €; PVP (IVA): 280,31 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 269,10 €; PVP: 320,01 €; PVP (IVA): 332,81 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 403,64 €; PVP: 454,55 €; PVP (IVA): 472,73 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

MIRANDO *al* FUTURO

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