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Post-truth Cannabis use: back to evidence-based medicine

Posverdad del consumo de cannabis: de regreso a la medicina basada en la evidencia

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Though post-truth is a widely disseminated concept in the 21st century, already in 1992 the playwright Steve Tesich used this term to refer to American society during his time as "we, as a free people, have freely decided that we want to live in a post-truth world" (Flood, 2016). In 2016, the Oxford Dictionary granted him the word of the year award, together with a clear and concise definition: "Relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief" (*Oxford English Living Dictionaries*, 2017). It seems that the second half of the 20th century brought us evidence-based medicine and that the new century obligates us to defend it. Nowadays, the point is not to use the scientific method for discovering the truth, but rather to exploit science as an instrument for constructing a story. First we create the story and then we look for the evidence to serve as its supporting foundation. In other words, science, in some cases, has fully immersed itself in post-truth. We have some very clear examples, like the relationship between vaccines and autism (Taylor, Swerdfeger & Eslick, 2014; Tomeny, Vargo & El-Toukhy, 2017) but also some less evident ones, like the social discourse concerning cannabis use. It seems irrelevant that there are still many more uncertainties than answers regarding the consequences, both positive and negative, of cannabis use on individuals and society alike; what is most important is to defend an *anti* or *pro* stance.

Over the last 20 years, cannabis use has experienced a major growth in western societies and in our country in particular, from 4.6% cannabis users in the last month among the general population (1997) to 7.3% (2015). In parallel to the increase of regular cannabis use, the perception of risk of regular use has decreased. Whether this is the cause or the consequence is unknown, but over 1/5 of the population thinks that regular cannabis use does not entail a health risk (Delegación del Gobierno para Plan Nacional sobre Drogas, 2015) and society has become more flexible regarding its use and legalisation (Sánchez Caballero, 2014). Likely, the role of post-modern society has had an impact on these changes, in particular among youth (Blasco-Fontecilla, 2018).

What is known and unknown about harm caused by cannabis?

Its impact on mental health has been clearly established. An excellent review by Robin Murray and his collaborators (2016) establishes the relationship between cannabis use and the onset of psychosis. They disarm theories with scarce scientific evidence, like self-medication or the positive impact of CBD on users and stress the prognostic importance of cannabis use for patients with schizophrenia. Murray does not overlook the importance of differentiating between cannabis types used (synthetic, high-potency, traditional) and their impact on psychopathology. This same review refers to other mental health aspects related

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with regular cannabis use, like dependency -1 out of every 10 users, or 17% if onset is during adolescence- or cognitive harm. However, he is more prudent in relating cannabis use with mood and anxiety disorders (Murray, Quigley, Quattrone, Englund & Di Forti, 2016). Nevertheless, a recent meta-analysis provides that the risk of psychosis is related to the intensity of cannabis use (Marconi, Di Forti, Lewis, Murray & Vassos, 2016). Gaps exist as to the relationship between regular cannabis use and mood and anxiety disorders and risk of suicide. Current evidence is insufficient, yet emerging (Marconi et al., 2016). Cognitive harm as a result of cannabis use exists, is dose-dependent and partially reversible upon discontinuation, and is greater if the onset of use occures. Furthermore, there seems to be confirmation that cannabis serves as a gateway to other substances, even as a so-called "reverse gateway"; in other words, that it also serves as a path toward tobacco use (Hall, 2014).

Physical health can also be affected by regular cannabis use. Evidence is most clear regarding cardiovascular health; however, it is less clear regarding lung damage or carcinogenicity. Carcinogenicity of cannabis is not sufficiently documented, but points out the lungs, upper respiratory tract, oesophagus, testicles (non-seminona) and bladder as target organs. One of the main difficulties inherent to these studies is controlling for confounding factors, like tobacco, and in some cases, the absence of prospective studies (Hall, 2014). The cannabinoid hyperemesis syndrome deserves a chapter itself, given that its description dates merely back to 2004 (Allen, de Moore, Heddle & Twartz, 2004) and currently only a series of cases exist on its clinical description (Simonetto, Oxentenko, Herman & Szostek, 2012), a modest study on its prevalence (Bruguera, López-Pelayo, Miquel & Balcells-Oliveró, 2016) and one or another isolated study on its treatment (Pélissier, Claudet, Gandia-Mailly, Benyamina & Franchitto, 2016; Sorensen, DeSanto, Borgelt, Phillips & Monte, 2017). The impact of foetal exposure to cannabis use during pregnancy is not yet fully clear. However, some studies suggest that it would result in low birth weight and greater risk of premature birth. Other possible effects of cannabis use during pregnancy are worse cognitive functioning in adolescence -including intellectual quotient-, behavioural alterations, delinquency, poorer academic performance and mood disorders (Hall, 2014).

Its psychosocial impact, especially in adolescents and young adults, is also backed by a consolidated bibliography. Nevertheless, scientific evidence is contradictory when referring to the risk of academic failure. Although the association is clear, the causality of the same is questionable, as some studies suggest that cannabis use and academic failure share pre-existing risk factors (Lynskey & Hall, 2000). We must not overlook the clear association between traffic accidents and driving under the effects of cannabis; specifically, the risk of accident is double, or even triple, when driving intoxicated. This association has a neurocognitive base in slower reaction time, information processing capacity, eye-hand coordination, motor skill performance, attention and follow-up behaviour (Hall, 2014).

It is important to point out that lack of evidence does not prove inexistent association. Likewise, when a given object of study presents mixed evidence, it is not possible to establish clear cause-effect relationships. Neither can we do so if scientific criteria of causality namely: internal validity (strength of the correlation, dose-response effect, temporal sequence) and scientific coherence (consistency, biological plausibility, specificity of association and analogy, experimental evidence) are missing (Hill, 1965).

Based on the existing bibliography, the "Lower-Risk Cannabis Use Guidelines" clinical guide proposes, with a certain degree of substantial evidence, the following recommendations: 1) the best way to avoid risks associated with cannabis use is abstinence; 2) preventive messages must stress delaying the age of onset, as adverse risks are fewer with later onset; 3) cannabis users should know the concentration of THC and CBD and try to avoid a high THC concentration (Casajuana, López-Pelayo, Balcells, Colom & Gual, 2018) and prioritise a low THC:CBD ratio, as adverse effects are associated with a high dose of THC -those plants that produce high concentrations of THC generate low concentrations of CBD- (Murray et al., 2016); 4) smoking cannabis, whether alone or mixed with tobacco, should be avoided, and instead other types of consumption (vaporizing or eating) should be chosen; 5) regular or daily use is associated with the majority of the adverse effects; users should strive for occasional consumption (once a week, on weekends, or less frequently); 6) users should try to avoid driving for 6 hours after use -as long as this is not in breach of local legislation in effect- and never drive after drinking alcohol and using cannabis, given the potentiation of acute, negative effects on one's driving capacity. Avoiding driving for a minimum of 6 hours after cannabis use is based on the fact that peak THC plasma concentration occurs at between 5-30 minutes after use, and decreases after 2-4 hours, though intoxication and acute cognitive deterioration may persist for between 3-6 hours. This period could be even longer in the case of high THC levels and/or consumption via oral ingestion. With a lesser degree of supporting evidence, the guide also recommends that: 1) users should avoid synthetic cannabis due to the risk of acute adverse effects. Synthetic cannabis has a high affinity with CB1 receptors, a full agonist, compared with traditional cannabis that is a partial agonist, and diverse complications have been reported, including acute psychosis, kidney failure, myocardial infarction, aggressiveness and brain ischemia. Up to 24 cases of death have been associated with the use of synthetic cannabis (Gurney, Scott, Kacinko, Presley & Logan, 2014; Tournebize, Gibaja

& Kahn, 2017); 2) deep inhalation should be avoided to reduce the risk of lung damage; 3) avoid combining two or more of the abovementioned risk behaviours. Beyond the individual risk associated with one's use pattern, certain demographic groups are at risk for any type of cannabis use: personal or family history of psychosis, pregnant and breastfeeding women, persons with cardiovascular problems. Though without solid supporting evidence but out of prudence, cannabis use should be avoided by those individuals with a personal or family history of other mental disorders (Fischer et al., 2017).

There is evidence that the demand for treatment of cannabis dependence is growing (Mounteney et al., 2016), but despite this, we know that the impact of treatment is limited as low abstinence rates are obtained (Hall, 2017), though reducing cannabis use and improving quality of life are achieved (Gates, Sabioni, Copeland, Le Foll & Gowing, 2016a). All treatments should combine a motivational interview, cognitive-behavioural therapy, and incentives for achieving abstinence (Carney, Myers, Louw & Okwundu, 2016; Denis, Lavie, Fatseas & Auriacombe, 2006; Gates, Sabioni, Copeland, Le Foll & Gowing, 2016b). As regards medication, Gabapentin and N-acetylcysteine are promising, though evidence is still weak (Marshall, Gowing, Ali & Le Foll, 2014).

Finally, legalising cannabis could impact its price (reduction), social perception (normalisation of use), availability (greater accessibility) and potency (increase). This could translate into an increase in long-term use of unknown proportions (Álvarez, Gamella & Parra, 2017; Hall, 2017). In this regard, the experts at ALICERAP (www.alicerap.eu) point out that extreme measures (total prohibition or liberalisation) are not a good strategy, but that regulating cannabis use could be beneficial in terms of public health with the goal of preventing the undesired effects of prohibition, like organised crime and violence, stigma and discrimination against users, substance use in public and users' loss of civil rights, employment, home and personal relationships (Apfel, 2013). However, these hypotheses must be evaluated regularly, especially given that indicators show that the legalisation of cannabis in the USA has resulted in increased use and accidental exposure of minors (Wang et al., 2016) as well as a decreased perception of risk (Schuermeyer et al., 2014; Sobesky & Gorgens, 2016). In this regard, indicators on potency, dose, sales, legal production and harm associated with cannabis (traffic accidents, emergency hospital visits, specialised care for cannabis use disorder, prevalence of use in patients with mental health and justice-related issues) must be considered (Hall, 2017). Finally, public policies based on the *Three Best Buys* (limited access to the substance, limited publicity and price increases through taxation measures or minimum price per consumption unit) (Baccini & Carreras, 2014; Matrai et al., 2014) would make sense for the purpose of implementing a model similar to that of tobacco use prevention and different from the scarcely efficient and heterogeneous model of alcohol use prevention. This entails not leaving preventive measures in the hand of the emerging cannabis industry through the "responsible use" slogan and assuming, instead, evidence-based prevention strategies.

Despite the foregoing, we must not fall prey to alarm. Cannabis is a much less harmful substance that others, like alcohol or nicotine. For example, Lachenmeier & Rhem (2015) used the Margin of Exposure (MOE) concept to make a comparative evaluation of the risk of several substances. The MOE is the ratio between the toxicity threshold and the estimation of human consumption, calculated on the basis of the average lethal dose in test animals and studies on individuals and populations. The estimated MOE for daily use of THC is more favourable than for the remaining substances, like benzodiazepines, stimulants (cocaine, amphetamines and methamphetamines), MDMA, nicotine, heroine and alcohol (Lachenmeier & Rehm, 2015).

What is actually known and unknown about the benefits of cannabis?

The use of cannabis in its natural state or as a pharmaceutical formulation (dronabinol) is used for treating several medical conditions. To date, there is insufficient evidence on its efficacy and safty to consider it a therapeutic option for improving appetite, gaining weight or improving mood in patients with HIV/AIDS given that the studies have been conducted over short period of time and with small-sized demographic groups (Lutge, Gray & Siegfried, 2013). Neither does it apparently play a role in treating fibromyalgia (Walitt, Klose, Fitzcharles, Phillips & Häuser, 2016) nor in behavioural alterations of dementia (Krishnan, Cairns & Howard, 2009). There is scarce evidence for its use as an antiemetic for children and youth with oncologic pathologies, for which better alternatives are available with a preferable profile of side effects (Phillips et al., 2016). However, it may be an option for adults with emesis associated with chemotherapy in the case of refractory symptoms. This conclusion could change in the near future with the appearance of new and safer antiemetics (Smith, Azariah, Lavender, Stoner & Bettiol, 2015). Cannabidiol (CBD) could have a positive impact on refractory epilepsy, but it is still too early for this conclusion (Gloss & Vickrey, 2014) and, in addition, the presence of this composition in natural formulations is minimal (Casajuana Kögel et al., 2017), wherefore we cannot recommend its use in this context. Though it seems that cannabis could be efficient for secondary pain in rheumatoid arthritis, its clinical effectiveness has not been sufficiently verified, and some cases describe psychosis and suicidal ideation (Richards, Whittle & Buchbinder, 2012). Neither is the risk-benefit equilibri-

um clear for chronic pain associated with cancer, though it seems to be sufficiently effective (Blake et al., 2017).

A recent analysis of over 10,000 scientific studies by the "US National Academies of Science, Engineering, and Medicine" considered that evidence for medicinal use is only conclusive as regards chronic pain, some symptoms of multiple sclerosis and as a post-chemotherapy antiemetic for adults (Washington, 2017).

Finally, we must bear in mind that the purpose of medicine is to improve quality of life and that in this regard evidence on medicinal cannabis is inconclusive in the best case, when not negative (for example, in patients with HIV) (Goldenberg, Reid, IsHak & Danovitch, 2017).

In any case, it must comply with all safety and evidence-related requirements imposed on any new drug for medicinal use.

What information is lacking for suitable decision-making?

At a time in which scientific evidence shows that regular cannabis use could have considerable adverse effects, its medicinal use is still limited and legislation ranges from prohibition to liberalisation, we should promote evidence-based regularisation. Tools are lacking for prevention in a regulatory framework that are available, in turn, for alcohol and tobacco. Despite the fact that specific demographic groups under risk have been clearly defined (pregnant women, youth, family or personal history of psychotic disorder, etc.), we lack an operating definition of hazardous consumption based on use patterns (amounts and frequency). However, the conceptual definition posed by the WHO on hazardous use of substances is available as a starting point: "a pattern of substance use that increases the risk of harmful consequences for the user (physical and mental health and social consequences). In contrast to harmful use, hazardous use refers to patterns of use that are of public health significance despite the absence of any current disorder in the individual user" (WHO, 2017). For alcohol use, we can identify hazardous use as that in which a user drinks 28 Standard Drink Units weekly for males, and 17 Standard Drink Units weekly for females. Furthermore, it has resulted in the creation of a fast, reliable and efficient screening tool, the AUDIT-C (Gual, Segura, Contel, Heather & Colom, 2002). For the time being, a definition of this type is not available, given the lack of standardisation in registering cannabis use. Recently, we published a study that standardises use according to the Standard Joint Unit (SJU), for which each SJU is equivalent to 7 mg of THC (Casajuana et al., 2017; Casajuana Kögel et al., 2017). This study should be reproduced in other regions and cultures, and adapted, as has been done with the Standard Drink Unit. The next logical step is to establish a hazardous use pattern, according to amount and frequency, by correlating it with the many dimensions of harm associated with cannabis use. Though this goal is quite ambitious, it is a necessary step for intervention policies to focus on groups of higher risk, even if premature and brief, and as a result, efficient.

Furthermore, we consider it necessary to establish work group networks for purposes of early identification and intervention of hazardous cannabis use, as proposed by Socidrogalcohol through Cannared. The main mission is to train professionals on primary and secondary prevention strategies in cannabis use that have demonstrated sufficient evidence for dissemination.

In conclusion, in our post-truth times, it is more important than ever for professionals (scientists, healthcare workers, teachers, etc.) to count with reliable and updated information on the risks and benefits of regular cannabis use. To this end, it is essential to count with registration tools and operating definitions regarding hazardous cannabis use.

Conflict of interests

Hugo López-Pelayo has been paid fees and awarded travel grants by Lundbeck, Lilly, Janssen, Pfizer, Rovi and Esteve. Laia Miquel and María Mercedes Balcells have been paid fees by Lundbeck. The remaining authors declare the inexistence of any potential conflicts of interest. The aforementioned fees have no impact on this article.

References

Allen, J. H., de Moore, G. M., Heddle, R. & Twartz, J. C. (2004). Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut*, *53*, 1566–1570. doi:10.1136/gut.2003.036350.

Álvarez, A., Gamella, J. F. & Parra, I. (2017). The legalization of cannabis derivatives in Spain: Hypothesis on a potential emerging market. *Adicciones*, *29*, 195-206. doi:10.20882/adicciones.807.

Apfel, F. (2013). *Cannabis - from prohibition to regulation "When the music changes so does the dance."* Retrieved at http://www.alicerap.eu/.

Baccini, M. & Carreras, G. (2014). Analyzing and Comparing the Association Between Control Policy Measures and Alcohol Consumption in Europe. *Substance Use & Misuse*, *49*, 1684–1691. doi:10.3109/10826084.2014.914373.

Blake, A., Wan, B. A., Malek, L., DeAngelis, C., Diaz, P., Lao, N., … O'Hearn, S. (2017). A selective review of medical cannabis in cancer pain management. *Annals of Palliative Medicine*, *6*, 805–805. doi:10.21037/apm.2017.08.05.

Blasco-Fontecilla, H. (2018). Posmodernidad, sociedades adictivas, cannabis y comportamiento suicida: ¿Hacia un mundo feliz? *Adicciones*, *30*, 3-8. doi:10.20882/adicciones.1104.

Bruguera, P., López-Pelayo, H., Miquel, L. & Balcells-Oliveró, M. (2016). High prevalence of cannabinoid hyperemesis syndrome in marijuana users. *Emergencias*, *28*, 249-251.

Carney, T., Myers, B. J., Louw, J. & Okwundu, C. I. (2016). Brief school-based interventions and behavioural outcomes for substance-using adolescents. In T. Carney (Ed.), *Cochrane Database of Systematic Reviews* (p. CD008969). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD008969.pub3.

Casajuana, C., López-Pelayo, H., Balcells, M. M., Colom, J. & Gual, A. (2017). Psychoactive constituents of cannabis and their clinical implications: a systematic review. *Adicciones, 30*, 140-151. doi:10.20882/adicciones.858.

Casajuana, C., López-Pelayo, H., Mercedes Balcells, M., Miquel, L., Teixidó, L., Colom, J. & Gual, A. (2017). Estableciendo la unidad de porro estándar: estudio piloto. *Adicciones*, *29,* 227-232. doi:10.20882/adicciones.721.

Casajuana Kögel, C., Balcells-Olivero, M. M., López-Pelayo, H., Miquel, L., Teixidó, L., Colom, J., … Gual, A. (2017). The Standard Joint Unit. *Drug and Alcohol Dependence*, *176*, 109–116. doi:10.1016/j.drugalcdep.2017.03.010.

Delegación del Gobierno para Plan Nacional sobre Drogas. (2015). *Encuesta sobre alcohol y drogas en población general España EDADES 2015-2016*.

Denis, C., Lavie, E., Fatseas, M. & Auriacombe, M. (2006). Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. In C. Denis (Ed.), *Cochrane Database of Systematic Reviews* (p. CD005336). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD005336.pub2.

Fischer, B., Russell, C., Sabioni, P., van den Brink, W., Le Foll, B., Hall, W., … Room, R. (2017). Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. *American Journal of Public Health*, *107*, 1277–1277. doi:10.2105/AJPH.2017.303818a.

Flood, A. (2016). Post-truth' named word of the year by Oxford Dictionaries. *The Guardian*. Retrieved at https://www.theguardian.com/books/2016/nov/15/post-truth-named-word-of-the-year-by-oxford-dictionaries.

Gates, P. J., Sabioni, P., Copeland, J., Le Foll, B. & Gowing, L. (2016a). Psychosocial interventions for cannabis use disorder. In P. J. Gates (Ed.), *Cochrane Database of Systematic Reviews* (p. CD005336). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD005336.pub4.

Gates, P. J., Sabioni, P., Copeland, J., Le Foll, B. & Gowing, L. (2016b). Psychosocial interventions for cannabis use disorder. *The Cochrane Database of Systematic Reviews*, (5), CD005336. doi:10.1002/14651858.CD005336.pub4.

Gloss, D. & Vickrey, B. (2014). Cannabinoids for epilepsy. In D. Gloss (Ed.), *Cochrane Database of Systematic Reviews* (p. CD009270). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD009270.pub3.

Goldenberg, M., Reid, M. W., IsHak, W. W. & Danovitch, I. (2017). The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, *174*, 80–90. doi:10.1016/j.drugalcdep.2016.12.030.

Gual, A., Segura, L., Contel, M., Heather, N. & Colom, J. (2002). AUDIT-3 and AUDIT-4: effectiveness of two short forms of the Alcohol Use Disoders Identification Test. *Alcohol and Alcoholism*, *37*, 591–596.

Gurney, S. M. R., Scott, K. S., Kacinko, S. L., Presley, B. C. & Logan, B. K. (2014). Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs. *Forensic Science Review*, *26*, 54–76.

Hall, W. (2014). What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction*, *110*, 19-35. doi:10.1111/add.12703.

Hall, W. (2017). Alcohol and cannabis: Comparing their adverse health effects and regulatory regimes. *The International Journal on Drug Policy*, *42*, 57–62. doi:10.1016/j.drugpo.2016.10.021.

Hill, A. B. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*, *58*, 295–300.

Krishnan, S., Cairns, R. & Howard, R. (2009). Cannabinoids for the treatment of dementia. In S. Krishnan (Ed.), *Cochrane Database of Systematic Reviews* (p. CD007204). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD007204.pub2.

Lachenmeier, D. W. & Rehm, J. (2015). Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Scientific Reports*, *5*, 8126. doi:10.1038/srep08126.

Lutge, E. E., Gray, A. & Siegfried, N. (2013). The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. In E. E. Lutge (Ed.), *Cochrane Database of Systematic Reviews* (p. CD005175). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD005175.pub3.

Lynskey, M. & Hall, W. (2000). The effects of adolescent cannabis use on educational attainment: a review. *Addiction (Abingdon, England)*, *95*, 1621–1630.

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M. & Vassos, E. (2016). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin*, *42*, 1262–1269. doi:10.1093/schbul/sbw003.

Marshall, K., Gowing, L., Ali, R. & Le Foll, B. (2014). Pharmacotherapies for cannabis dependence. In L. Gowing (Ed.), *Cochrane Database of Systematic Reviews* (p. CD008940). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD008940.pub2.

Matrai, S., Casajuana, C., Allamani, A., Baccini, M., Pepe, P., Massini, G. & Gual, A. (2014). The relationships between the impact of alcoholic beverage control policies,

selected contextual determinants, and alcohol drinking in Spain. *Substance Use & Misuse*, *49*, 1665–1683. doi:10.3109/10826084.2014.913398.

Mounteney, J., Griffiths, P., Sedefov, R., Noor, A., Vicente, J. & Simon, R. (2016). The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. *Addiction*, *111*, 34–48. doi.org/10.1111/add.13056.

Murray, R. M., Quigley, H., Quattrone, D., Englund, A. & Di Forti, M. (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*, *15*, 195–204. doi:10.1002/wps.20341.

Oxford English Living Dictionaries. (2017). Retrieved at https://en.oxforddictionaries.com/definition/post-truth.

Pélissier, F., Claudet, I., Gandia-Mailly, P., Benyamina, A. & Franchitto, N. (2016). Cannabis Hyperemesis Syndrome in the Emergency Department: How Can a Specialized Addiction Team Be Useful? A Pilot Study. *The Journal of Emergency Medicine*, *51*, 544–551. doi:10.1016/j.jemermed.2016.06.009.

Phillips, R. S., Friend, A. J., Gibson, F., Houghton, E., Gopaul, S., Craig, J. V & Pizer, B. (2016). Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. In R. S. Phillips (Ed.), *Cochrane Database of Systematic Reviews* (Vol. 2, p. CD007786). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD007786.pub3.

Richards, B. L., Whittle, S. L. & Buchbinder, R. (2012). Neuromodulators for pain management in rheumatoid arthritis. In B. L. Richards (Ed.), *Cochrane Database of Systematic Reviews* (Vol. 1, p. CD008921). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD008921.pub2.

Sánchez Caballero, D. (2014). Cada vez más jóvenes españoles apoyan la legalización del cannabis. *Eldiario.es*. Retrieved at http://www.eldiario.es/sociedad/Quemando-etapas-regulacion-cannabis_0_296070879.html.

Schuermeyer, J., Salomonsen-Sautel, S., Price, R. K., Balan, S., Thurstone, C., Min, S.-J. & Sakai, J. T. (2014). Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003–11. *Drug and Alcohol Dependence*, *140*, 145–155. doi:10.1016/j.drugalcdep.2014.04.016.

Simonetto, D. A., Oxentenko, A. S., Herman, M. L. & Szostek, J. H. (2012). Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clinic Proceedings*, *87*, 114–119. doi:10.1016/j.mayocp.2011.10.005.

Smith, L. A., Azariah, F., Lavender, V. T., Stoner, N. S. & Bettiol, S. (2015). Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. In L. A. Smith (Ed.), *Cochrane Database of Systematic Reviews* (p. CD009464). Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD009464.pub2.

Sobesky, M. & Gorgens, K. (2016). Cannabis and adolescents: Exploring the substance misuse treatment provider experience in a climate of legalization. *International Journal of Drug Policy*, *33*, 66–74. doi:10.1016/j.drugpo.2016.02.008.

Sorensen, C. J., DeSanto, K., Borgelt, L., Phillips, K. T. & Monte, A. A. (2017). Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review. *Journal of Medical Toxicology*, *13*, 71–87. doi:10.1007/s13181-016-0595-z.

Taylor, L. E., Swerdfeger, A. L. & Eslick, G. D. (2014). Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. *Vaccine*, *32*, 3623–3629. doi:10.1016/j.vaccine.2014.04.085.

Tomeny, T. S., Vargo, C. J. & El-Toukhy, S. (2017). Geographic and demographic correlates of autism-related anti-vaccine beliefs on Twitter, 2009-15. *Social Science & Medicine*, *191*, 168–175. doi:10.1016/j.socscimed.2017.08.041.

Tournebize, J., Gibaja, V. & Kahn, J.-P. (2017). Acute effects of synthetic cannabinoids: Update 2015. *Substance Abuse*, *38*, 344–366. doi:10.1080/08897077.2016.1219438.

Walitt, B., Klose, P., Fitzcharles, M.-A., Phillips, T. & Häuser, W. (2016). Cannabinoids for fibromyalgia. *The Cochrane Database of Systematic Reviews*, *7*, CD011694. doi:10.1002/14651858.CD011694.pub2.

Wang, G. S., Le Lait, M.-C., Deakyne, S. J., Bronstein, A. C., Bajaj, L. & Roosevelt, G. (2016). Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Pediatrics*, *170*, e160971. doi:10.1001/jamapediatrics.2016.0971.

Washington, D. T. N. A. P. (Ed.). (2017). *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. doi:10.17226/24625.

World Health Organization. (2017). *Management of substance abuse*. Retrieved at http://www.who.int/substance_abuse/terminology/definition3/en/.

Muscle dysmorphia: detection of the use-abuse of anabolic androgenic steroids in a Spanish sample

Dismorfia Muscular: detección del uso-abuso de esteroides anabolizantes androgénicos en una muestra española

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Abstract

People who suffer from muscle dysmorphia due to a distorted body image perceive themselves as less muscular than they actually are. With the aim of increasing their muscular development, they resort to the use of anabolic androgenic steroids (AAS). The purpose of this study is to know the prevalence of the use of AAS in a Spanish sample affected by muscle dysmorphia. The study sample was comprised of 562 male and 172 female bodybuilders and weightlifters who were applied anthropometric measurements, Fat-Free Mass Index equation, Escala de Satisfacción Muscular, and Somatomorphic Matrix software. The results show the creation of decision trees and a regression model was used to create explanatory models for muscle dysmorphia (R = .78 and $R2$ = .62). The main conclusion is that almost 50% of both male and female participants affected by this disorder use this kind of AAS.

Key words: muscle dysmorphia; steroids; bodybuilders.

Resumen

Las personas que padecen Dismorfia Muscular (DM) debido a una distorsión en la imagen corporal, se perciben menos musculosas de lo que son en realidad. Para paliar este problema y con el fin de aumentar su musculatura, algunas de estas personas hacen uso de hormonas ilegales, como son los esteroides anabolizantes androgénicos (EAA), cuya función principal es aumentar la musculatura. El objetivo de este estudio es conocer la prevalencia del uso de EAA en personas afectadas por Dismorfia Muscular. La muestra de este estudio estaba compuesto de 562 hombres y 172 mujeres fisicoculturistas y levantadores de pesas, a los que se le administraron medidas antropométricas, la ecuación Fat-Free Mass Index, el cuestionario Escala de Satisfacción Muscular y el test informatizado Somatomorphic Matrix. Como resultado se crearon diferentes modelos de regresión de la DM, empleando las técnicas estadísticas de árboles de decisión (R = .78 y $R2$ = .62) de minería de datos. La principal conclusión es que el 50% de participantes afectados por este trastorno usa EAA.

Palabras clave: dismorfia muscular; esteroides; fisicoculturistas.

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The people affected by muscle dysmorphia (MD) suffer from a mental disorder in which a distortion of the body image in the form of its underestimation prevails (Pope, Phillips, & Olivardia, 2000), recently this disorder has been introduced as an Obsessive Compulsive Disorder in DSM-V (Rodríguez-Testal, Senín-Calderón, & Perona-Garcelán, 2014). As a consequence, one of the prevalent features in this disorder is obsessive weight training, looking for the improvement of the perception of the physical appearance due to the changes that this kind of practice produces in the physique. That is why bodybuilders and weightlifters are the group of sport people most affected by this disorder, because they find in the sport a solution for boosting their muscular development (Barrientos, Escoto, Bosques, Enríquez, & Juárez, 2014; González-Martí, 2012).

But the increase in the musculature is not only the consequence of exhausting training. There are artificial methods that enhance the size of the muscles in a faster and more effortless way. These artificial methods rely on the use of anabolic androgenic steroids (AAS) (Kanayama, Barry, Hudson, & Pope, 2006). They are "drugs of the body image", as Kanayama et al. (2006) named them, because they are not used for their psychoactive action, but for their effect on the body image (Coomber et al., 2014; Van Hout & Kean, 2015) by the people affected by MD (Rohman, 2009). These exogenous substances are illegal in the sport without a prescription due to their harmful side effects on the sport person´s health. But the wish to be muscular turns into an end in itself, and the sport person feels the temptation of using illegal substances that improve his/her performance and level of muscularity (Rocha, Aguiar, & Ramos, 2014). Workouts can be more intense and frequent because the recovery between them is quicker.

The detection of these substances can be made by means of direct or indirect methods. The most common of the former are urine analysis and/or blood analysis, whereas the indirect ones are the indicators derived from the formula of the Fat-Free Mass Index (FFMI; Kouri, Pope, Katz, & Oliva, 1995), which provide information about the level of a person´s lean muscle mass, and whether this level has been achieved by the use of AAS.

In the case of people affected by MD, the use of performance enhancing drugs such as growth hormone and testosterone is the most requested. Testosterone is a natural steroid which is synthesized by the interstitial cells of the testicles in men, and in the ovary and the adrenal cortex in women (De la Torre, 1995). Its androgenic function stimulates the masculine sexual characteristics such as the appearance of soft hair and the hypertrophy of the larynx, which causes the voice to be deep and virile. The anabolic effect increases muscularity. The daily production of testosterone in a man is between 5 and 10 mg. The testosterone concentrations in an adult and healthy man are between 12 and 28 nmol/l and in a woman is 5% of the one generated by a man (De la Torre, 1995). The hypogonadism is a hormonal disorder in which the person does not produce the amount of testosterone of a healthy individual. A research by Bhasin et al. (1997) demonstrates that if the treatment with testosterone applied to patients with hypogonadism increases in 6% their muscular body weight, being 9% their fat free mass, the use of testosterone in healthy individuals would double these percentages. That is why it is not surprising that people affected by MD resort to this hormone in an exogenous way seeking to increase their muscular development (Pipet, Halpern, Woody, & Szobot, 2014).

Testosterone can be administered orally or injected because it is biodegraded by the organism (De la Torre, 1995). That is why its chemical structure is subjected to changes in the laboratory, producing in this way the AAS. The AAS are the hormones to which bodybuilders and weightlifters resort more often due to the increase of muscularity and reduction of body fat they produce (Jampel, Murray, Griffiths, & Blashill, 2016).

In Spain there are not any studies about the influence of the AAS on individuals affected by MD, and the negative health consequences of AAS use-abuse is associated with psychiatric, hepatic, endocrine, neurologic, cardiovascular, mortality risks (Pope et al., 2014, Thiblin et al., 2015) and smaller brain volume and cortical thickness (Bjørnebekk et al., 2017). In consequence the goal of this research is to establish the prevalence of the use of AAS in Spanish men and women, bodybuilders and weightlifters, affected by MD by means of the indirect method of Fat-Free Mass Index. We depart from the hypothesis that the use of these hormones which increases the musculature in the participants with this disorder will be high since the distortion they have and their wish to be bigger and stronger takes them to the use of these illegal substances.

Method

Participants

The sample was composed by 734 bodybuilders and weightlifters, 562 men and 172 women. The age of the male group was between 16 and 63 years (M = 29.38, SD = 8.45), while in the women was between 16 and 61 (M = 32.07, SD =9.04). The average height in the males was 1.74 m. (SD = 6.63), and in the females 1.61 m. (SD = 5.82). The average weight of the men was 78.06 kg. (SD = 10.46) and of the women 59.58 kg. (SD = 8.34). The reported time of weekly weight and cardio training was 8.22 hours (SD = 3.58) in men and 6.56 hours (SD = 4.15) in women.

Instruments

For detecting muscle dysmorphia. An abridgement of the questionnaires was used and their answers were asses-

Table 1. *Instruments used to detect MD*

Instruments	Variables/factors and coefficient of reliability
Demographic Questionnaire	Sex, Use of supplements and/or hormones, and Sport habits
Escala de Satisfacción Muscular (ESM; González-Martí, Fernández, Contreras, & Mayville, 2012)	Bodybuilding Dependence, Substance Use, Injury, Muscle Dissatisfaction, and Muscle Checking (a = .90)
Somatomorphic Matrix (SM; Gruber, Pope, Borowiecki, & Cohane, 1999)	Perceived and desired FFMI, and perceived and desired Body Fat.

Table 2. *Categorization of FFMI according to sex*

Category	Men (Kg/m²)	Women (Kg/m²)	Muscularity level
1	16.5-19.9	11.5-14.9	Slight
2	20-22.9	15-17.9	Noticeable
3	23-24.9	18-19.9	Notable
4	25-25.9	20-20.9	Muscular (likely use of AAS)
5	≥ 26	≥ 21	Very muscular (product of use-abuse of AAS)

sed by a group of experts to categorize an individual with MD. These instruments are compiled in Table 1.

For detecting the use of AAS. A group of direct questions in relation to the use of these substances was used within the demographic questionnaire. Three kinds of answers were possible: never, sometimes and always. Also, the aim of taking them, their function and an open question about the type of hormones taken by the participant. The equation Fat-Free Mass Index (FFMI) was administered. This formula was conceived by Kouri et al. (1995) in order to know the degree of muscularity of a participant and whether this muscularity had been achieved by the intake of steroids. With this aim and following the standardized protocol of the International Society for the Advancement of Kinanthropometry (ISAK), six skinfolds in men and three in women were anthropometrically measured. These measurements along with the participant´s age were applied to the formula conceived by Jackson & Pollock (1978) in order to know the body fat percentage. The resulting data was introduced in the FFMI equation, which is different for each gender. For the female gender it is: [(weight (100-% body fat) /100) height²] and for the male one: [[(weight (100-% body fat) 100) height²] + 6.1 (1.8 – height)]]. The height is represented in meters and the weight in kilograms. To know whether the muscle mass obtained through the FFMI equation was the result of the use of steroids, a categorization was established. It is based on the categories proposed by Kouri et al. (1995), Pope et al. (2000) and Kyle, Schutz, Dupertuis, & Pichard (2003). In Table 2 the FFMI categorization proposed in this research is shown.

Procedure

For the management of the instruments. After initial contacts, the managers of the gymnasiums were addressed to obtain their authorization to carry out this research in their sport centers. After explaining them the objective of the work, some Spanish gyms decided not participate in this study for the reason of AAS detection, finally thirteen gyms took part in the study, in the provinces of Albacete, Murcia, Valencia and Madrid, in Spain. Once the necessary material was located in a room ready for this aim, the participants with an apparently muscular physique were explained the purpose of the research, the anonymity of the results and the voluntary nature of the participation. If they agreed, they had to sign the document of informed consent. The under-age participants had to come with their father/mother or legal tutor, who authorized them to partake in the research by signing both the document of informed consent. This procedure never exceeded twenty-five minutes. The study was approved by the Ethical Committee of the University of Castilla - La Mancha.

For detecting if the participant suffered from MD. In order to find hidden patterns and research which factors influence most on muscle dysmorphia, decision trees trained with M5P and REPTree algorithms was used. Moreover, different explanatory models of MD were created with regression models analyses (González-Martí, 2012; González-Martí, Fernández, & Contreras, 2012; Sokolova, González-Martí, Contreras, & Fernández, 2013) and the best one explaining this disorder was selected as having the highest values of R = .786 and $R2$ = .62, which means that the explanatory variables described 62% of the target variable.

Bodybuilding Dependence = – 0.016 Age – 0.027 Desired Body Fat + 0.466 Muscle Checking + 0.281 Substance Use + 0.467 Injury – 0.059 Physical Atractiveness + 0.092 Strength– 0.032 General Physical Self-concept + 3.714.

The attributes of the model were selected with the help of the questionnaire Escala de Satisfacción Muscular (ESM: González-Martí et al., 2012) and their categorizations (González-Martí, Fernández, Hernández-Martínez,

Table 3. *Classification of muscle dysmorphia according to the ESM and SM categorizations*

Instrument	Puntuation	Category	Categorization	MD
ESM (González-Martí et al., 2014)	19-38	1	Muscular Satisfaction	No
	39-57	2	Slight Muscular Dissatisfaction	No
	58-76	3	Moderate Muscular Dissatisfaction	Yes
	77	4	Severe Muscular Dissatisfaction	Yes
Instrument	Discrepancy between current, perceived and ideal	Category	Categorization	DM
SM (Pope et al., 2000)	Body fat of 1-15%	1	Not suffering from any distortion in the body image	No
	Body fat over 15%	2	Distortion in the body image like Anorexia or MD	Yes
	FFMI of 0-2.9 kg/m²	1	No suffering from any distortion in the body image	No
	FFMI ≥ 3 kg/m²	2	Distortion in the body image MD	Yes

& Contreras, 2014) as well as with that of the Somatomorphic Matrix (SM; Gruber et al.; 1999; Pope et al., 2000). These categorizations provide us with the necessary information to know whether a participant suffers from this disorder or not, according to the answers obtained in the questionnaire and the classification models. Table 3 shows the likelihood of suffering from MD in relation to these categorizations.

Thus, it was considered that a participant was affected by the disorder of MD if his/her results were classified in the categories 3 or 4 of ESM (González-Martí, 2012; González-Martí et al., 2014) and in the category 2 of body fat and the category 2 of FFMI of SM (Pope et al., 2000).

Results

Categorization of current FFMI based on the statement of having used AAS.

Thirty-two per cent of the male participants who recognize using AAS occasionally for their muscular development belong to the category 5 of FFMI, that is to say, their muscularity is a consequence of the use of these substances, as well as the 21.4% of the men who use AAS on a regular basis. Nevertheless, 3.1% of the male participants said that they never used illegal substances without prescription and their FFMI reveals the opposite. Regarding females, all the women in this research denied using AAS, whereas according to their FFMI (Kouri et al., 1995), 11% of them are using these substances and 4.7% could be using them, by belonging to the categories 5 and 4 of FFMI, respectively (Kouri et al., 1995; Pope et al., 2000).

One hundred percent of the sample who stated being consuming this kind of hormones did it with the aim of enhancing muscularity. The AAS (Hildebrandt et al., 2011) most used by the males who recognized being ingesting them occasionally or usually were Deca-Durabolin, with 78%, and Dianabol (22%), and by the females they were Androgel (47%), Dianabol (33%) and Deca-Durabolin (20%).

Categorization of FFMI according to gender.

We perform an analysis of frequency to notice the distribution of the participants based on the established categories. In this way we learn that 5.9% of the men owned a muscular physique suspicious of the use of AAS (category 4), while 4.8% of the men had a lean muscle mass higher than 26 Kg/m², a consequence of having used AAS. On the females side, 4.7 % of them were very muscular, with a development very difficult to achieve in a natural way (category 4), and 11% had a high FFMI, consequence of the use of AAS (category 5) (Kouri et al., 1995; Pope et al., 2000).

Detection of the use of AAS in participants affected by muscle dysmorphia.

The detection of MD found in this study, according to the classification of Table 3 based on decisions tree of data mining, is 18.3% (N = 734). Out of the total affected by the disorder (N = 134), 70.1% corresponded to the male group (n = 94), whilst 29.9% represented the females group (n = 40). Regarding the participants suffering from MD and using AAS, this group makes up the 44.4 %, while

Table 4. *Detection of the use of AAS in participants affected by muscle dysmorphia*

FFMI categories	MD	Sex	
		Men	Women
		Frequency (%)	Frequency (%)
1	No	76 (90.5)	11 (100)
	Yes	8 (9.5)	-----
2	No	252 (87.5)	91 (84.3)
	Yes	36 (12.5)	17 (15.7)
3	No	102 (78.5)	16 (61.5)
	Yes	28 (21.5)	10 (38.5)
4	No	23 (69.7)	4 (50)
	Yes	10 (30.3)	4 (50)
5	No	15 (55.6)	10 (52.6)
	Yes	12 (44.4)	9 (47.4)

Note. Men FFMI Categories: 1 = 16.5-19.9 Kg/m²; 2 = 20-22.9 Kg/m²; 3 = 23-24.9 Kg/m²; 4 = 25-25.9 Kg/m²; 5 = ≥ 26 Kg/m²; Women FFMI Categories: 1 = 11.5-14.9 Kg/m²; 2 = 15-17.9 Kg/m²; 3 = 18-19.9 Kg/m²; 4 = 20-20.9 Kg/m²; 5 = ≥ 21Kg/m².

30.3 % of the male participants with MD were suspicious of using the substances, as it is shown in Table 4. Regarding the female group who suffers from MD, we can notice in this Table that the detection of the use of AAS is of 47.4 %, and of 50 % in the female participants whose muscularity is suspicious of the use of these illegal substances.

As shown in Table 5, considering only those athletes who had been classified with DM, in the applied of multivariate analysis of the different variables studied (ESM scales and current FFMI-perceived FFMI scales) we can notice how the categories 4 and 5 of FFMI, that is, the sample whose muscle mass index points out having ingested AAS for the increase of the muscles size, and those who obtain a muscularity suspicious of being the result of the use of AAS are the group most affected by MD in comparison with other endowed with a more discreet FFMI (categories 1, 2, and 3) and obtained significantly higher scores ($p < .05$ - $.001$) in all of the variable comparison.

Discussion

The objective of this research is to release the detection of the use of AAS by the side of the Spanish sample affected by MD, because there is not any study for establishing this relationship in this cultural context nowadays. With this aim, we separate the results according to gender, since the instrument FFMI used for the detection of the use-abuse of AAS by this indirect method required it. Furthermore, a direct question was made to the participants in relation to the frequent use or hormones or not. The use of these illegal substances starts with the goal of increasing the muscle mass and quality and losing fat, and this fact is in direct relation to the MD disorder (Hildebrandt, Harty, & Langenbucher, 2012; Kanayama, Pope, Cohane, & Hudson, 2003; Kanayama et al., 2006; Kanayama, Hudson, & Pope, 2009; Olivardia, Pope, & Hudson, 2000; Pope et al., 2005). This is why the relation between the use of AAS and MD is bidirectional, in such a way that the use of steroids has been accepted as indicator of muscular development and MD (Kanayama et al., 2006; Murray, Griffiths, Mond, Kean, & Blashill, in press). And the people who suffer from this disorder are increasingly using these drugs (Pope et al. 2005).

The responses to the question made to the participants about their relation with the use of AAS reported over the prevalence of their use, corroborated by the sample in this research, of 21.4% in males. Although this figure could be higher, since the FFMI of 3.1 percent of the partakers shows that they are using AAS despite they do not confirm this fact. In women, none of them declared their use, however the FFMI of 15.7% disclosed that they did. These results can stem from the fact that using steroids in the sport without prescription is an illicit act. For this reason it is difficult to establish the exact prevalence of their consumption because the people who take do it in a clandestine way in secret most of the times without prescription, and getting them in the black market (Coomber et al., 2014; Pope et al., 2000; Van Hout & Kean, 2015).

According to the results found through the FFMI indirect method to know whether a participant uses steroids, the women in this research offer similar data to the men regarding the percentage of the sample with FFMI suspicious of having used AAS (4.7% and 5.9%, respectively), and higher results in the category 5, that is, in the case of having used AAS (11% in women and 4.8% in men).

Consequently, there is a high correlation between the use of anabolic androgenic steroids and the level of muscularity of a person and, also, the disorder of MD. The answers to the open question show, thus, than the participants who stated consuming AAS on a regular basis and

Table 5. *Descriptive results and MANOVA of ESM and current FFMI – perceived FFMI according to the addition of FFMI categories based on the possibility or not AAS use-abuse*

Variables	Σ FFMI categories 1,2,3 (not possibility of AAS use)	Σ FFMI categories 4,5 (possibility of AAS use)				
	(*N* = 99)	(*N* = 35)	MANOVA			
	M	*SD*	*M*	*SD*	*F*	*p*
Bodybuilding Dependence	11.46	4.43	14.69	6.42	10.64	.001(**)
Muscle Checking	7.95	3.93	10.91	5.54	11.71	.001(**)
Substance Use	6.86	3.70	10.17	5.64	15.43	.000(***)
Injury	6.76	3.03	8.74	3.57	10.07	.002(**)
Muscle Dissatisfaction	10.06	2.68	11.37	2.57	6.28	.013(*)
current FFMI - perceived FFMI	3.01	2.72	7.35	4.17	48.71	.000(***)

Note. * $p < .05$; ** $p < .01$; *** $p < .001$.

those who did occasionally had a current FFMI higher than the clean ones.

In this respect, Hildebrandt, Schlundt, Langenbucher, & Chung (2006) in a male sample suffering from MD, got a means of BMI of 27.46 Kg/m², which correspond to 24.5 Kg/m² of FFMI, which showed the use of AAS to get this superior level of lean muscular development. In a similar way, Kanayama et al. (2006) found in a study performed with weightlifters that the distortion in the body image related to MD was directly linked with the ingestion of anabolic androgenic steroids.

In this sense Kanayama et al., (2009) and Cole, Smith, Halford, & Wagstaff (2003) found a strong correlation between the consumers dependent on AAS and the disorder of MD. This correlation is corroborated again by Pope, Kanayama, & Hudson (2012), in whose study the weightlifters with MD also consumed AAS. Pope et al., (2005) stated that the vast majority of participants with MD used steroids to increase their muscle mass (Pope, Kanayama, Ionescu-Pioggia, & Hudson, 2004; Pope et al., 2005), and a high rate of consumption of other drugs was found as well.

In the present study the detection of the use of anabolic androgenic steroids by the part of the sample affected by MD is 44.4% in the men and 47.4% in the women, since it is within category 5 of FFMI. These results can be augmented if we add the participants whose level of FFMI is suspicious of the use of this sort of drugs and of those who are actually consuming them although their FFMI does not reveal it yet.

As we can notice, the detection of the use of steroids in the partakers in this research is slightly higher in the women´s group that in the males one. This fact can mean a discrepancy with the existing literature, where the percentage of men using AAS is larger (González-Martí, 2012). According to these authors three million sport people are the consumers of these substances, being 90% men bodybuilders and 80 percent of the female bodybuilders.

The superior detection of the use of AAS in the female population can be explained by the fact that this study has one of the wider samples of women, in comparison with previous investigations over MD and the use of steroids (González-Martí, Hernández-Martínez, Fernández, & Contreras, 2016). The only comparable results in relation to the prevalence of the use of steroids in female participants are those established by Pope, Gruber, Choi, Olivardia, & Phillips (1997), in which 38% of female bodybuilders used this kind of drugs, results that are inferior to ours. Regarding the male gender, we obtain similar results to the ones of Olivardia et al., (2000), who found that the prevalence of the use of steroids is of 46% of the sample who suffered MD. They are also close to the prevalence established by Pope et al. (1993), in which 51% of the male sample with MD used AAS.

It is necessary to assume that this study presents a limitation regarding the categorization of FFMI, which is the result of the abridgement of the classifications set up by Kouri et al. (1995), Pope et al. (2000) and Kyle et al. (2003).

As a conclusion, and confirming the initial hypothesis, there is a high detection of the use of AAS among Spanish individuals who suffer from MD, reaching even 47% in women and 44% in men, consequently nearly 50% of the participants with this disorder use these drugs. This means that there is a strong correlation between the use of AAS and the disorder of MD. In both genders there is an overwhelming desire to be bigger and stronger, resorting to the use of steroids, in most of the cases even being aware of the fact they are not healthy. It is necessary, therefore, to deep in future works in the treatment of these people, in order to have a better understanding of the disorder and help them in every way we can in the Spanish cultural context.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

Barrientos, N., Escoto, C., Bosques, L. E., Enríquez, J. & Juárez, C. S. (2014). Interiorización de ideales estéticos y preocupación corporal en hombres y mujeres usuarios de gimnasio. *Revista Mexicana de Trastornos Alimentarios, 5,* 29-38.

Bhasin, S., Storer, T. W., Berman, N., Yarasheski, K. E., Clevenger, B., Phillips, K., … Casaburi, R. (1997). Testosterone replacement increases fat-free mass and muscle size in hypogonodal men. *Journal of Clinical Endocrinology & Metabolism, 82,* 407-413. doi:10.1210/jc.82.2.407.

Bjørnebekk, A., Walhovd, K., Jørstad, M., Due-Tønnessen, P., Hullstein, I. & Fjell, A. (2017). Structural brain imaging of long term anabolic-androgenic steroid users and non-using weightlifters structural brain imaging of long term steroid use. *Biological Psychiatry, 82,* 294-302.

Cole, J. C., Smith, R, Halford, J. C. & Wagstaff, G. F. (2003). A preliminary investigation into the relationship between anabolic androgenic steroids use and the symptoms of reverse anorexia in both current and ex users. *Psychopharmacology, 166,* 424-429.

Coomber, R., Pavlidis, A., Hanley, G., Wilde, M., Schmidt, W. & Redshaw, C. (2014). The supply of steroids and other performance and image enhancing drugs (PIEDs) in one English city: fakes, counterfeits, supplier trust, common beliefs and access. *Performance Enhancement & Health, 3,* 135–144.

De la Torre, R. (1995). Esteroides anabolizantes-androgénicos [Anabolic-androgenic steroids]. In I. D. d. Drogodependencia (Ed.), *Drogas y deporte: farmacología del doping*, pp. 53-63.

González-Martí, I. (2012). *Elementos que integran el perfil de la persona afectada por Dismorfia Muscular (Vigorexia). Prevalencia del trastorno en fisicoculturistas y usuarios de la sala de musculación.* (Unpublished doctoral dissertation). Universidad de Castilla-La Mancha, Cuenca.

González-Martí, I., Fernández, J. G., Contreras, O. R. & Mayville, S. B. (2012). Validation of a Spanish version of the Muscle Appearance Satisfaction Scale: Escala de Satisfacción Muscular. *Body Image, 9*, 517-523. doi:10.1016/j.bodyim.2012.05.002.

González-Martí, I., Fernández, J. G. & Contreras, O. R. (2012). Contribución para el criterio diagnóstico de la Dismorfia Muscular (Vigorexia) [Contribution to the diagnostic criteria for Muscle Dysmorphia (Bigorexia)]. *Revista de Psicología del Deporte, 21*, 351-358.

González-Martí, I., Fernández, J. G., Hernández-Martínez, A. & Contreras, O. R. (2014). Physical perceptions and self-concept in athletes with muscle dysmorphia symptoms. *The Spanish Journal of Psychology, 17* (e43), 1-7. doi:10.1017/sjp.2014.45.

González-Martí, I. Hernández-Martínez, A., Fernández, J. G. & Contreras, O. R. (2016). Prevalence of muscle dysmorphia on female weightlifters and bodybuilders. Article presented for publication.

Gruber, A. J., Pope, H. G., Borowiecki, J. & Cohane, G. (1999). The development of the somatomorphic matrix: a biaxial instrument for measuring body image in men and women. In T. S. Olds, J. Dolloman & K. I. Norton (Eds.), Kinanthropometry VI (pp. 217-232). Sydney: International Society for the Advancement of Kinanthropometry.

Hildebrandt, T., Schlundt, D., Langenbucher, J. & Chung, T. (2006). Presence of muscle dysmorphia symptomology among male weightlifters. *Comprehensive Psychiatry, 47*, 127-135. doi:10.1016/j.comppsych.2005.06.001.

Hildebrandt, T., Lai, J., Langenbucher, J., Schneider, M., Yehuda, R. & Pfaff, D. (2011). The diagnostic dilemma of pathological appearance and performance enhancing drug use. *Drug and Alcohol Dependence, 114*, 1-11. doi:10.1016/j.drugalcdep.2010.09.018.

Hildebrandt, T., Harty, S. & Langenbucher, J. W. (2012). Fitness supplements as a gateway substance for anabolic-androgenic steroid use. *Psychology of Addictive Behaviors, 26*(4), 955-962. doi:10.1016/j.drugalcdep.2010.09.018.

Jackson, A. & Pollock, M. (1978). Generalized equations for predicting body density in man. *British Journal Nutrition, 40*, 497-504.

Jampel, J. D., Murray, S. B., Griffiths, S. & Blashill, A. J. (2016). Self-perceived weight and anabolic steroids misuse among US adolescent boys. *Journal of Adolescent Health, 58*, 397-402. doi:10.1016/j.jadohealth.2015.10.003.

Kanayama, G., Pope, H. G., Cohane, G. & Hudson, J. I. (2003). Risk factors for anabolic androgenic steroid use among weightlifters: a case-control study. *Drug and Alcohol Dependence, 71*, 77-86. doi:10.1016/S0376-8716(03)00069-3.

Kanayama, G., Barry, S., Hudson, J. I. & Pope Jr., H. G. (2006). Body image and attitudes toward male role in anabolic-androgenic steroid users. *American Journal of Psychiatry, 163*, 697-703. doi:10.1176/appi.ajp.163.4.697.

Kanayama, G., Hudson, J. I. & Pope Jr., H. G. (2009). Features of men with anabolic-androgenic steroid dependence: a comparison with nondependent AAS users and with AAS nonusers. *Drug and Alcohol Dependence, 102*, 1030-137. doi:10.1016/j.drugalcdep.2009.02.008.

Kouri, E. M., Pope, H. G., Katz, D. L. & Oliva, P. (1995). Fat-Free Mass Index in users and nonusers of anabolic-androgenic steroids. *Clinical Journal of Sports Medicine, 5*, 223-228. doi:10.1097/00042752-199510000-00003.

Kyle, U. G., Schutz, Y., Dupertuis, Y. M. & Pichard, C. (2003). Body composition interpretation: contributions of the fat-free mass index and the body fat mass index. *Nutrition, 19*, 597-604. doi:10.1016/S0899-9007(03)00061-3.

Murray, S. B., Griffiths, S., Mond, J. M., Kean, J. & Blashill, A. J. (In press). Anabolic steroid use and body image psychopathology in men: delineating between appearance-versus performance-driven motivations. *Drug and Alcohol Dependence.* doi:10.1016/j.drugalcdep.2016.06.008.

Olivardia, R., Pope, H. G. & Hudson, J. (2000). Muscle dysmorphia in male weightlifters: a case-control study. *American Journal of Psychiatry, 157*, 1291-1296. doi:10.1176/appi.ajp.157.8.1291.

Pipet, S., Halpern, R., Woody, G. E. & Szobot, C. (2014). Association between AAS use, muscle dysmorphia and illicit drug use among gym frequenters. *Drug and Alcohol* Dependence, 140, e178. doi:10.1016/j.drugalcdep.2014.02.499.

Pope, H. G., Katz, D. & Hudson, J. (1993). Anorexia nervosa and "reverse anorexia" among 108 male bodybuilders. *Comprehensive Psychiatry, 34*, 406-409.

Pope, H. G., Gruber, A., Choi, P., Olivardia, R. & Phillips, K. (1997). Muscle dysmorphia. An underrecognized form of Body Dysmorphic Disorder. *Psychosomatics, 38*, 548-557. doi:10.1016/S0033-3182(97)71400-2.

Pope, H. G., Phillips, K. & Olivardia, R. (2000). *The Adonis Complex. How to identify, treat and prevent body obsession in men and boys.* New York: A Touchstone Book.

Pope, H. G., Kanayama, G., Ionescu-Pioggia, M. & Hudson, J. I. (2004). Anabolic steroid users´ attitudes towards physicians. *Addiction, 99*, 1189-1194. doi:10.1111/j.1360-0443.2004.00781.x.

Pope, C. G., Pope, H. G., Menard, W., Fay, C., Olivardia, R. & Phillips, K. (2005). Clinical features of muscle dys-

morphia among males with dysmorphic disorder. *Body Image, 2*, 395-399. doi:10.1016/j.bodyim.2005.09.001.

Pope, H. G., Kanayama, G. & Hudson, J. I. (2012). Risk for illicit anabolic-androgenic steroid use in male weightlifters: a cross-sectional cohort study. *Biological Psychiatry, 71*, 254-261. doi:10.1016/j.biopsych.2011.06.024.

Pope, H. G., Kanayama, G., Athey, A., Ryan, E., Hudson, J. I. & Baggish, A. (2014). The lifetime prevalence of anabolic-androgenic steroid use and dependence in Americans: current estimates. *American Journal on Addiction 23*, 371-373. doi:10.1111/j.1521-0391.2013.12118.x.

Rocha, M., Aguiar, F. & Ramos, H. (2014). O uso de esteroides androgénicos anabolizantes e outros suplementos ergogénicos – uma epidemia silenciosa. *Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo, 9*, 98-105. doi:10.1016/j.rpedm.2014.09.002

Rodríguez-Testal, J. F., Senín-Calderon, C. & Perona-Garcelán, S. (2014). From DSM-IV-TR to DSM-5: Analysis of some changes. *International Journal of Clinical and Health Psychology, 14*, 221-231. doi:10.1016/j.ijchp.2014.05.002.

Rohman, L. (2009). The relationship between anabolic androgenic steroids and muscle dysmorphia: a review. *Eating Disorder, 17*, 187-199. doi:10.1080/10640260902848477.

Sokolova, M. V., González-Martí, I., Contreras, O. R. & Fernández, J. G. (2013). A case study of muscle dysmorphia disorder diagnostics. *Expert Systems with Applications, 40*, 4226-4231. doi:10.1016/j.eswa.2013.01.023.

Thiblin, I., Garmo, H., Garle, M., Holmberg, L., Byberg, L., Michaëlsson, K. … Gedeborg, R. (2015). Anabolic steroids and cardiovascular risk: a national population-based cohort study. *Drug and Alcohol Dependence, 152*, 87-92. doi:10.1016/j.drugalcdep.2015.04.013.

Van Hout, M. C. & Kean, J. (2015). An exploratory study of image and performance enhancement drug use in a male British South Asian community. *International Journal of Drug Policy, 26*, 860–867. doi:10.1016/j.drugpo.2015.03.002.

Screening of alcohol use disorders in psychiatric outpatients: influence of gender, age, and psychiatric diagnosis

Cribaje de trastornos por consumo de alcohol en pacientes psiquiátricos ambulatorios: influencia de género, edad, y diagnóstico psiquiátrico

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Abstract

Alcohol use disorders (AUD) are 2 times higher among psychiatric patients than in the general population. The under-recognition of this dual diagnosis can entail several negative outcomes. Early assessment with a screening tool like the CAGE questionnaire could be an opportunity to improve patients' prognoses. The objective of this study is to assess AUD risk in an outpatient psychiatric sample with a modified CAGE, considering the influence of age, gender and clinical psychiatric diagnosis. An observational, multicentric, descriptive study was carried out. The 4-item CAGE scale, camouflaged in a healthy lifestyle questionnaire, was implemented, using a cut-off point of one. 559 outpatients were assessed. 54% were female and the average age was 50.07 years. 182 patients presented a CAGE score ≥1 (45.1% of men and 21.9% of women). Gender was the strongest predictor of a positive result in CAGE, as men were 3.03 times more likely to score ≥1 on the CAGE questionnaire (p < .001, 95% CI: 0.22-0.49). Patients with bipolar and personality disorders had the highest rates of CAGE scores ≥1 (45.2 and 44.9%, respectively), with a significant association between diagnosis and a positive score (p = .002). Patients above 60 years were 2.5 times less likely to score ≥1 on the CAGE (p = .017, 95% CI: 0.19-0.85). Specific screening questionnaires, like the CAGE scale, can be an easy and useful tool in the assessment of AUD risk in psychiatric outpatients. Male patients with a bipolar or personality disorder present a higher risk of AUD.

Keywords: Alcohol use disorder; CAGE; Screening; Dual pathology; Psychiatric outpatients.

Resumen

Los trastornos por uso de alcohol (TUA) son 2 veces más frecuentes en pacientes psiquiátricos que en la población general. El infradiagnóstico de patología dual puede tener diversas consecuencias negativas; una valoración precoz con herramientas de cribaje como la escala CAGE podría mejorar el pronóstico de estos pacientes. El objetivo de este estudio es valorar el riesgo de TUA en pacientes psiquiátricos ambulatorios con una CAGE modificada, considerando la influencia de edad, género, y diagnóstico psiquiátrico. Se realizó un estudio descriptivo observacional, multicéntrico. La escala CAGE de 4 ítems, camuflada en un cuestionario de vida saludable, se aplicó utilizando el punto de corte de 1. Se valoraron 559 pacientes. El 54% eran mujeres, y la edad media fue de 50,07 años. 182 pacientes presentaron una puntuación ≥1 (45,1% de los hombres y 21,9% de las mujeres). El género fue el predictor principal de un resultado positivo en la escala CAGE, siendo 3,03 veces más probable que los hombres obtengan una puntuación ≥1 (p < ,001, 95% IC: 0,22-0,49). El trastorno bipolar y los trastornos de personalidad presentaron las tasas más altas de puntuaciones ≥1 (45,2 y 44,9%, respectivamente) con una asociación significativa entre diagnóstico y un resultado positivo (p = ,002). Los pacientes de más de 60 años mostraron 2,5 veces menos probabilidades de obtener una puntuación positiva (p = ,017, 95% IC: 0,19-0,85). Cuestionarios específicos, como CAGE, pueden ser herramientas sencillas y útiles para valorar el riesgo de TUA en pacientes psiquiátricos ambulatorios. Los pacientes hombres con trastorno bipolar o de personalidad presentan un riesgo más elevado de TUA.

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

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According to a recent study (Rehm et al., 2015), the prevalence of alcohol dependence (AD) in the general population in Europe has been estimated to be around 3.4%. In the Spanish general population, although low rates of AD have been published (1.4% of men and 0.3% of women), rates of at risk alcohol consumption have been considered to be around 4-6% (Pulido et al., 2014). In primary care, higher rates of alcohol use disorder (AUD) and AD have been established (11.7 and 8.9%, respectively) (Miquel et al., 2016). AUD prevalence could probably have been underestimated in Spain due to cultural factors (Rehm, Rehm, Shield, Gmel, & Gual, 2013). Alcohol use disorders (AUD) are more frequent in psychiatric patients than in the general population, with a risk approximately 2 times higher among psychiatric patients (Mansell, Spiro, Lee, & Kazis, 2006; Regier et al., 1990). Dual diagnosis (DD) patients are described as those patients suffering from the co-existence of a psychiatric illness and a substance use disorder, such as AUD (Luoto, Koivukangas, Lassila, & Kampman, 2016; Morojele, Saban, & Seedat, 2012; San et al., 2016; Torrens, Mestre-Pintó, Montanari, Vicente, & Domingo-Salvany, 2017). Several negative outcomes associated with AUD have been described in psychiatric populations. AUD might exacerbate positive symptoms, interfere with treatment adherence, tolerance and response, and worsen the prognosis of psychiatric disorders (Dixon, Weiden, Haas, Sweeney, & Frances, 1992; Duke, Pantelis, & Barnes, 1994; Fowler, Carr, Carter, & Lewin, 1998; Lejoyeux et al., 2013; Noordsy et al., 1991; Sullivan, Fiellin, & O'Connor, 2005; Vorspan, Mehtelli, Dupuy, Bloch, & Lépine, 2015; Worthington et al., 1996). A lower quality of life, social complications, higher rates of violence and suicide, higher frequency and longer hospital admissions have also been described (Cantor-Graae, Nordström, & McNeil, 2001; Dervaux et al., 2006; Drake, Osher, & Wallach, 1989; Gerding, Labbate, Measom, Santos, & Arana, 1999; Hulse & Tait, 2002; Mueser et al., 2000; Mukamal, Kawachi, Miller, & Rimm, 2007; Soyka, 2000; Soyka, Albus, Immler, Kathmann, & Hippius, 2001; Suominen, Isometsä, Haukka, & Lönnqvist, 2004; Urbanoski, Cairney, Adlaf, & Rush, 2007). AUD are also associated with multiple medical conditions and psychiatric comorbidities, and imply negative consequences across physical and psychological outcomes (Bowman & Gerber, 2006; Mathalon, Pfefferbaum, Lim, Rosenbloom, & Sullivan, 2003). Therefore, an early identification of AUD can be useful to prevent several complications, as well as an intervention opportunity to propose an integrated treatment to DD patients.

Under-recognition of AUD in the general population, in clinical settings (Barrio et al., 2016; Ratta-Apha et al., 2014; Shaner et al., 1993; Weisner & Matzger, 2003), and in psychiatric populations (Pristach, Smith, & Perkins, 1993; Smith & Pristach, 1990) has been systematically reported. The literature supports the use of screening instruments to increase early recognition of AUD (Barnaby, Drummond, McCloud, Burns, & Omu, 2003; Fiellin, Reid, & O'Connor, 2000). The CAGE questionnaire is a brief, easily applied, and widely used screening questionnaire in the detection of AUD in the general population (Baltieri & Andrade, 2008; Curran, Gawley, Casey, Gill, & Crumlish, 2009) as well as in clinical (Berks & McCormick, 2008; Fiellin et al., 2000; Lejoyeux et al., 2012; Mitchell, Bird, Rizzo, Hussain, & Meader, 2014) and psychiatric samples (Castells & Furlanetto, 2005; Derks, Vink, Willemsen, van den Brink, & Boomsma, 2014; Etter & Etter, 2004; Kim, Shin, Kim, & Lee, 2016; Lejoyeux et al., 2014; Malet, Schwan, Boussiron, Aublet-Cuvelier, & Llorca, 2005; Oe at al., 2016; Tang et al., 2016). It has also been used to assess geriatric patients (Draper et al., 2015; León-Muñoz et al., 2015), and in gender studies (de Oliveira, Kerr-Correa, Lima, Bertolote, & Santos, 2014).

The CAGE scale consists of four questions on the use of alcohol (Ewing, 1984; Mayfield, McLeod, & Hall, 1974). The name derives from the first letter from the keywords included in each question:

1. Have you ever felt you should cut down on your drinking?
2. Have people annoyed you by criticizing your drinking?
3. Have you ever felt bad or guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

This questionnaire seems to detect alcohol abuse and dependence more accurately than other screening tools (Fiellin et al., 2000; Hearne, Connolly, & Sheehan, 2002). An average sensitivity of 71% and specificity of 90% for clinical populations has been estimated (Dhalla & Kopec, 2007; Mitchell et al., 2014). It has been validated in several languages, including Spanish (Rodríguez-Martos, 1986). In order to make the interview less intimidating for the patient, modified or "camouflaged" questionnaires derived from the original CAGE have been also designed (Castells & Furlanetto, 2005) and used in general and clinical Spanish populations (Córdoba et al., 1998; Escobar, Espí, & Canteras, 1995; González García et al., 1997; Rodríguez-Martos, 1986; Rodríguez Fernández, Gómez Moraga, & García Rodríguez, 1997), but to date there is a lack of studies in psychiatric Spanish populations. The reliability of the CAGE scale to assess AUD has been validated in psychiatric outpatients, schizophrenic patients and anxiety or depressive disorders (Corradi-Webster, Laprega, & Furtado, 2005; Dervaux et al., 2006; Encrenaz, Kovess-Masféty, Sapinho, Chee, & Messiah, 2007; Rosenberg et al., 1998; Teitelbaum & Mullen, 2000). However, these few studies in mental health population have been focused on a single diagnostic category (Agabio, Marras, Gessa, & Carpiniello, 2007; Dervaux et al., 2006; Etter & Etter, 2004), have not performed comparative analyses between diagnostic

categories (Corradi-Webster et al., 2005; Ratta-Apha et al., 2014; Teitelbaum & Mullen, 2000) or have only included inpatients (Dervaux et al., 2006, Masur & Monteiro, 1983; Rosenberg et al., 1998).

Several authors have described differences in AUD prevalence according to gender in general and psychiatric populations (Cantor-Graae et al., 2001; Dervaux et al., 2006; Eberhard, Nordström, Höglund, & Ojehagen, 2009; Goldstein, Smith, Dawson, & Grant, 2015; Gual et al., 2016; Hasin, Stinson, Ogburn, & Grant, 2007; Keyes, Grant, & Hasin, 2008; Khan et al., 2013; McCreadie, 2002; Pulido et al., 2014; Rehm et al., 2015; Satre, Wolfe, Eisendrath, & Weisner, 2008). The frequency of AUD has also been related to age (Hasin et al., 2007), especially in psychiatric patients (Sheidow, McCart, Zajac, & Davis, 2012). However, the influence of age and gender on the prevalence of AUD, in relation to different psychiatric disorders, has not been thoroughly described.

The primary objective of the present study is to describe the prevalence of AUD in a large Spanish sample of psychiatric outpatients using the "camouflaged" CAGE questionnaire. As secondary objectives, the authors aim to investigate age and gender differences, as well as differences related to the psychiatric clinical diagnosis, according to the CAGE screening results.

Methods

Design and study population

An observational, multicentric, descriptive and transversal study was carried out. The sample was recruited in four different outpatient psychiatric clinics (Centre de Salut Mental Terrassa Rambla, Hospital Universitari Mutua Terrassa, Barcelona; Equipo de Salud Mental de Zafra, Servicio Extremeño de Salud, Badajoz; Equipo de Salud Mental de Llerena, Servicio Extremeño de Salud, Badajoz; Centre de Salut Mental Cornellà, Parc Sanitari Sant Joan de Deu, Barcelona). Patients were recruited using convenience sampling. Due to urban-rural clinical differences in psychiatry (Peen, Schoevers, Beekman, & Dekker, 2010), patients from both settings were included. Even though their exact role varies by region, psychiatric outpatient clinics are essential to mental health care access in Spain.

Inclusion criteria were: older than 18 years, being able to understand the study and provide reliable information, and agree to participate in the study. Patients who did not agree to participate or presented an intellectual disability were excluded. Participants provided written informed consent. This study was approved by the local ethic committees.

Data collection and study procedures

The inclusion period was from May 2015 to August 2015. A total of 559 patients were recruited and interviewed by trained interviewers. After providing informed consent, patients performed an in-person interview and written questionnaires. Sociodemographic data (age and gender) and the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, World Health Organization, 1992) diagnosis were obtained from medical records. Patients completed the 4-item CAGE questionnaire camouflaged in a healthy lifestyle questionnaire. This modified "camouflaged" CAGE includes 8 extra questions about exercise, diet, sleeping habits, smoking and use of other drugs (Annex). Each affirmative response in the original 4-item CAGE was scored as 1. A cut-off score ≥1 was used in the statistical analysis of the present study. Patients were classified according to the main psychiatric diagnostic categories: schizophrenia and other related psychotic disorders, bipolar disorders, depressive disorders, anxiety disorders, and personality disorders. In order to analyze the CAGE scores according to age, patients were also divided in four age subgroups (18-30 years, 31-45 years, 46-60 years, and above 60 years).

Data analysis

The prevalence of a comorbid AUD with another mental disorder in Spanish population has been found to be 23.43% (Autonell et al., 2007). Using this report to estimate the initial sample size at the 0.05 level of significance with a confidence level of 99% for testing the hypothesis, the power analysis showed that 466 individuals would be the minimum required sample.

For descriptive statistics, numbers and frequencies were used for qualitative variables, and means and standard deviations for the quantitative variables analysis. Chi square statistic was used to compare categorical and t Student test for quantitative variables. As the influence of gender could change across different age groups due to cultural differences and generation gap, a combined analysis of gender*age was performed, as well as a gender*psychiatric diagnoses, to assess influence on CAGE scores. A two-way between groups analysis of variance (ANOVA) was used to investigate the influence of gender and age, and gender and psychiatric diagnoses, on CAGE scores. The multivariate analysis was based on direct logistic regression. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software for Windows (version 19).

Results

Description of the sample

The final sample consisted of 559 patients, 257 (46%) patients were male and 302 (54%) were female. The average age was 50.07±13.56 years, ranging between 18 and 85 years old. No significant association was found between age and gender (χ^2=0.30, p=0.96).

The most frequent diagnostic category was depressive disorders (42.8%), followed by psychotic disorders (23.8%) and anxiety disorders (17%). Personality disorders (8.8%) and bipolar disorders (7.6%) were the other diagnoses included in the sample. Statistically significant differences were found in the diagnostic distribution according to gender (χ^2=22.32, p<0.001, phi=–0.20) with depressive disorders being more common in women and psychotic disorders more common in men.

Mean CAGE scores

The mean CAGE score in the whole sample was 0.7±1.17, with men showing a statistically significant higher mean CAGE score (M=1.04, SD=1.34) than women (M=0.42, SD=0.91) (t=6.33, p<0.01, two-tailed). The magnitude of the mean difference (MD=0.63, 95% CI: 0.431-0.820) was moderate (eta squared=0.071). When each single item of the CAGE questionnaire was analyzed independently, men also showed a statistically higher percentage of positive responses than women in all of them. The size of the effect of gender was small to moderate according to the Cohen's criteria (Cohen, 1988) (Table 1).

Figure 1 illustrates the mean CAGE scores according to gender and age group. Mean scores in men were highest between 30 to 60 years, and decreased thereafter, while in women mean scores were highest in the group between 18-30 years and progressively decreased with age. A two-way between-groups analysis of variance (ANOVA) was conducted to explore the impact of sex and age on CAGE scores. Patients were divided in four age groups, as described previously. The interaction effect between sex and age group effect was not statistically significant, F(2,559)=0.59, p=0.62. There was a statistically significant main effect for age, F(2,559)=2.72, p=0.044, and for gender F(2, 559)=24.87, p<0.001. The effect size for age was small (partial eta squared=0.015), while the effect size for gender was small to moderate (partial eta squared=0.043). *Post-hoc* comparisons (Tukey HSD test) indicated that the mean score for the >60 year age group (M=0.47, SD=0.94) was significantly different from the 30-45 group (M=0.82, SD=1.3) (p=0.045). The 18-30 year age group (M=0.78, SD=1.01) and the 45-60 year age group (M=0.75, SD=1.2) did not differ significantly from either of the other groups.

An analysis of the influence of sex and diagnostic categories on the mean CAGE scores was performed using a two-way between-groups analysis of variance (ANOVA). Highest mean CAGE scores were found in the subgroup of patients with personality disorders in both genders. Thereafter, in women, bipolar and depressive disorders showed highest scores as compared with other diagnostic subgroups, while men with psychotic and bipolar disorders had highest scores (Figure 2). The interaction effect between sex and diagnostic group was not statistically significant, F(2,554)=2.13, p=0.75. There was a statistically significant main effect for diagnostic group, F(2,554)=5.29, p<0.001, and for gender F(2, 554)=33.82, p<0.001. The effect size for diagnosis was small to moderate (partial eta squared=0.037), while the effect size for gender was moderate (partial eta squared=0.059). *Post-hoc* comparisons using the Tukey HSD test indicated several differences between diagnostic groups (table 2).

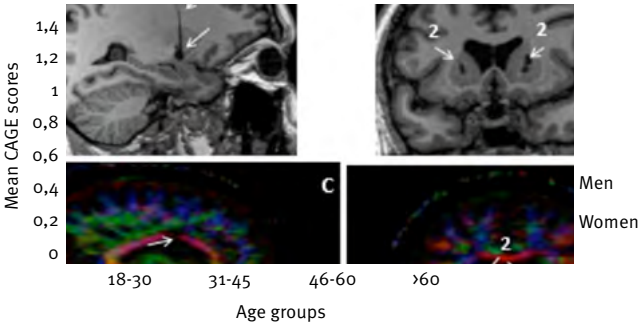

Figure 1. Mean CAGE scores in each age group according to gender

Table 1. *CAGE items results by gender*

	Men (n=257)	**Women** (n=302)	**Total** (n=559)	**Test**	***p***	**Size effect *phi***
CAGE 1: Have you ever felt you should **Cut down** on your drinking? (n, % "yes")	92 (35.8%)	32 (10.6%)	124 (22.2%)	χ^2 =49.64	‹0.001	0.30
CAGE 2: Have people **Annoyed** you by criticizing your drinking? (n, % "yes")	69 (26.8%)	47 (15.6%)	116 (20.8%)	χ^2 =10.08	0.002	0.14
CAGE 3: Have you ever felt bad or **Guilty** about your drinking? (n, % "yes")	73 (28.4%)	35 (11.6%)	108 (19.3%)	χ^2 =24.12	‹0.001	0.21
CAGE 4: Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**Eye-opener**)? (n, % "yes")	42 (16.3%)	11 (3.6%)	53 (9.5%)	χ^2 =24.63	‹0.001	0.22

Note. χ2: chi square test, t: T Student test for independent variables.

Table 2. *Influence of sex and diagnostic categories on the mean CAGE scores: Post-hoc comparisons (Tukey HSD test)*

Diagnostic group	Diagnostic group	Mean difference	p
Psychotic disorders	Bipolar disorders	0.01	1
	Depressive disorders	0.39*	0.011
	Anxiety disorders	0.51**	0.006
	Personality disorders	-0.16	0.904
Bipolar disorders	Psychotic disorders	-0.01	1
	Depressive disorders	0.38	0.24
	Anxiety disorders	0.50	0.10
	Personality disorders	-0.17	0.94
Depressive disorders	Psychotic disorders	-0.39*	0.011
	Bipolar disorders	-0.38	0.24
	Anxiety disorders	0.12	0.89
	Personality disorders	-0.55*	0.013
Anxiety disorders	Psychotic disorders	-0.51**	0.006
	Bipolar disorders	-0.50	0.10
	Depressive disorders	-0.12	0.89
	Personality disorders	-0.68**	0.005
Personality disorders	Psychotic disorders	0.16	0.90
	Bipolar disorders	0.17	0.94
	Depressive disorders	0.55*	0.013
	Anxiety disorders	0.68**	0.005

Note. *p<0.05, **p<0.01.

Positive results in CAGE screening

A CAGE score ≥1 was found in 182 patients (32.6% of the sample, 45.1% of men and 21.9% of women). A significant association between gender and a CAGE score ≥1 was noted (χ^2=33.22, p<0.01, phi=–0.248). The phi coefficient, using Cohen's criteria (Cohen, 1988), indicates a small to medium effect of gender on a positive result in the CAGE scale.

A significant association between diagnosis and a score ≥1 on the CAGE questionnaire was found (χ2=16.6, p=0.002). The effect size was moderate (Cramer´s V=0.17). The diagnostic groups where more patients scored ≥1 in the CAGE questionnaire were bipolar (45.2%) and personality disorders (44.9%), followed by psychotic disorders (39.4%). The anxiety disorder group had the lower percentage of patients with a positive CAGE score (Table 3).

Regarding the influence of age in a positive result in the CAGE scale, a Chi-square test for independence was conducted. As noted in Table 2, the group under 30 years showed the highest percentage of patients scoring ≥1 (44.9%), while the group over 60 showed the lowest percentage (24.8%). These results did not reach statistical significance (p=0.068).

A logistic regression was performed to assess the likelihood of a positive result (cut-off ≥1) in the CAGE questionnaire. The model contained three independent variables (sex, age group, and diagnostic category). The full model containing all predictors was statistically significant (χ2=53.34, p<0.001), and hence was able to identify patients presenting an AUD. The model explained between 9.2% (Cox and Snell R square) and 12.8% (Nagelkerke R squared) of the variance in a positive CAGE score and correctly classified 68.8% of cases. All the independent variables made a statistically significant contribution to the model. The strongest predictor of a positive screening was gender, with an odds ratio of 0.33. Women were 3.03 times less likely to have a CAGE score above one as compared to men (p<0.001, 95% CI: 0.22-0.49). The second strongest predictor was related to age, as the group over 60 years presented

Table 3. *CAGE scores according to diagnostic categories and age groups (n, %)*

Diagnoses	CAGE<1	CAGE≥1	*Test*	*p*
Psychotic disorders	80 (60.6%)	52 (39.4%)		
Bipolar disorders	23 (54.8%)	19 (45.2%)		
Depressive disorders	172 (72.6%)	65 (27.4%)		
Anxiety disorders	73 (77.7%)	21 (22.3%)		
Personality disorders	27 (55.1%)	22 (44.9%)		
Total*	375 (67.7%)	179 (32.3%)	χ^2 =16.64	0.002
Age				
18-30	27 (55.1%)	22 (44.9%)		
31-45	101 (66.0 %)	52 (34.0%)		
46-60	152 (66.7%)	76 (33.3%)		
>60	97 (75.2%)	32 (24.8%)		
Total	377 (67.4%)	182 (32.6%)	χ^2 =7.13	0.068

Note. χ^2: chi square test. *Diagnostic data was missing for 5 patients.

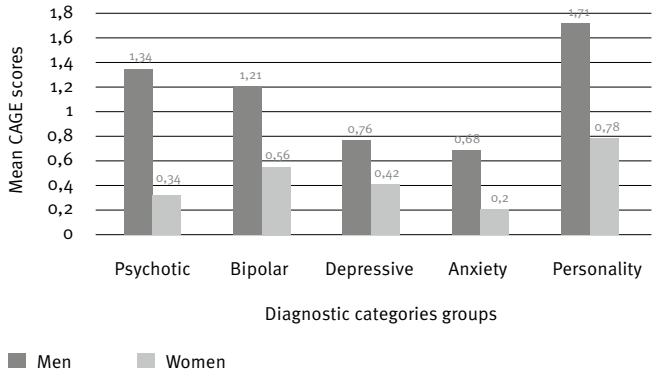

Figure 2. Mean CAGE scores in each diagnostic group according to gender

an odds ratio of 0.4. Therefore, older patients were 2.5 times less likely to have a CAGE score above one (p=0.017, 95% CI: 0.19-0.85). The last predictor was the diagnostic category, with an odds ratio of 0.48 for the anxiety disorder group (p=0.021, 95% CI: 0.26-0.89), a result indicating that patients suffering from anxiety disorders were 2.08 times less likely to have a positive score on the CAGE scale, after controlling for all the other factors in the model. The other diagnostic categories, separately assessed, had no significant association with a positive score in the CAGE scale.

Discussion

This is the first study to evaluate the prevalence of AUD using the CAGE questionnaire in a Spanish psychiatric population. In addition, to our knowledge, this study also provides the first data about the influence of age, gender and psychiatric diagnostic categories in this assessment.

The aim of this study was to assess the prevalence of AUD in a sample of Spanish psychiatric outpatients using the CAGE scale. In any diagnostic test, cut-off value is an important issue as it affects test sensitivity and specificity. The overall sensitivity and specificity of the CAGE questionnaire has been estimated to be 71% and 90% respectively for clinical populations (Dhalla & Kopec, 2007; Mitchell et al., 2014). In schizophrenic patients, a cut-off score of 1 or more shows a 91% sensitivity and an 83% specificity (Dervaux et al., 2006), varying to 82% and 94% respectively, when using a cut-off point of 2. In another sample of psychiatric outpatients (Corradi-Webster et al., 2005), a cut-off point of 1 rendered a 100% sensitivity and a 73% specificity, while a cut-off point of 2 showed a 53% sensitivity and 87% specificity. Hence, in psychiatric samples, a cut-off point of 1 seems to provide high sensitivity while maintaining sufficient specificity. Furthermore, although a CAGE cut-off value of 2 (two or more affirmative answers) has been used in several studies (Berks & McCormick, 2008; Castells & Furlanetto, 2005; Fiellin et al., 2000; Hearne et al., 2002; Mayfield et al., 1974; Paz Filho et al., 2001), several published results suggest that the best cut-off value for the CAGE questionnaire among psychiatric outpatients is 1 (Agabio et al., 2007; Bradley, Bush, McDonell, Malone, & Fihn, 1998; McGarry & Cyr, 2005; Ogborne, 2000). In relation to age and gender, it has also been established that the cut-off point for case definition should be one positive response, as this value may improve sensitivity for women or elderly people (Bradley et al., 1998; Cherpitel, 1995; Jones, Lindsey, Yount, Soltys, & Farani-Enayat, 1993). Therefore, in this study, a cut-off of 1 was used.

Our finding of positive screening of AUD in 32.6% in psychiatric outpatients, as defined by a CAGE score ≥1, is similar to that found in other studies, albeit with smaller samples. Sample sizes of 56 patients (Agabio et al., 2007), 71 (Teitelbaum & Mullen, 2000), 114 (Masur & Monteiro, 1983; Dervaux et al., 2006), 127 (Corradi-Webster et al., 2005), 151 (Etter & Etter 2004), 165 (Ratta-Apha et al., 2014), 247 (Rosenberg et al., 1998), and 366 patients (Mayfield et al., 1974) have so far been published.

Regarding gender differences, our results were consistent with several published reports and epidemiologic surveys describing higher rates of AUD in men than in women both in the general population (Goldstein et al., 2015; Hasin et al., 2007; Keyes et al., 2008; Khan et al., 2013; Rehm et al., 2015) and in psychiatric samples (Cantor-Graae et al., 2001; Dervaux et al., 2006; Eberhard et al., 2009; McCreadie, 2002; Satre et al., 2008). Gender differences were also noted in the pattern of positive answers obtained in the CAGE test (Table 1). Men more frequently provided a positive answer to CAGE1 and CAGE3 questions (35.8% and 28.4%, respectively), while positive answers in women were more related to guilt and self-reproach feelings (CAGE2 and CAGE3) (15.6% and 11.6%, respectively). In both genders, the question with lower percentages of positive answers was CAGE4 (16.3% in men and 3.6% in women). These results could point out to a different sensitivity of the CAGE questions to detect AUD in men and women.

In the general population, the frequency of AUD has been inversely related to age (Hasin et al., 2007), as patients over 65 years seem to have lower rates of alcohol consumption and AUD, as compared to those aged 50-64 (Gum, King-Kallimanis, & Kohn, 2009; Moore et al., 2005; Moos, Schutte, Brennan, & Moos, 2009; Wu & Blazer, 2014). In agreement with these results a negative association between a positive screening in the CAGE and being older than 60 years was found in the present study. AUD have also been reported to be higher in younger subjects from the general population (Glass, Grant, Yoon, & Bucholz, 2015; Grant et al., 2015; Rehm et al., 2015). There are very few studies assessing the influence of age in AUD screening in psychiatric samples. Younger age has been associated with substance use disorders, but not with AUD in a sample of psychiatric severely ill inpatients (Mueser et al., 2000). Rates of AUD and drug use disorder could be even higher in the emerging adulthood with mental health disorders, as evidenced

in a study performed in patients aged from 18 to 25 years (Sheidow et al., 2012). In our sample, younger patients did not present higher rates of positive CAGE screening as compared to the other age groups in the whole sample. When our sample was divided by gender (Figure 1), women did present a higher positive screening in the age group between 18-30 years, while men presented higher positive rates in the middle age groups (31-60 years). These results could suggest a different risk of alcohol consumption according to gender in psychiatric populations.

As to our knowledge, this is the first study to assess AUD screening in different diagnostic categories from a large sample of psychiatric outpatients using the CAGE questionnaire. So far, most of the studies performed in psychiatric facilities have focused on a single disorder or diagnostic category, i.e., outpatients with schizophrenia or schizoaffective disorder (Dervaux et al., 2006; Etter & Etter, 2004), or mood disorders (Agabio et al., 2007), while other studies have not informed about the psychiatric diagnoses (Corradi-Webster et al., 2005; Masur & Monteiro, 1983; Ratta-Apha et al., 2014; Rosenberg et al., 1998; Teitelbaum & Mullen, 2000). Regarding the clinical setting, patients have been recruited at hospitalization facilities (Masur & Monteiro, 1983; Mayfield et al., 1974; Rosenberg et al., 1998), both inpatient and outpatient units (Dervaux et al., 2006; Teitelbaum & Mullen, 2000) or from community services (Agabio et al., 2007; Etter & Etter, 2004; Ratta-Apha et al., 2014). A selection bias, especially in inpatient settings, can overestimate AUD due to Berkson's fallacy, because of the higher probability of receiving specialized treatment (Soyka, 2000; Etter & Etter, 2004). None of the studies developed in general psychiatric community facilities have performed a comparison between diagnostic categories.

AUD seems to coexist with several psychiatric diseases, mainly affective disorders, anxiety disorders, and personality disorders (Anthenelli, 2012; Grant et al., 2004a, 2004b, 2015; Hasin & Grant, 2015; Kessler et al., 1997; Klimkiewicz, Klimkiewicz, Jakubczyk, Kieres-Salomoński, & Wojnar, 2015; Mellos, Liappas, & Paparrigopoulos, 2010; Rosenberg et al., 1998). Different hypothesis have been proposed to explain the comorbidity between psychiatric conditions and AUD: self-medication, alleviation of dysphoria, psychosocial risk factors, genetic predisposition, or shared neurobiological vulnerability (Buckley, 2006; Mueser, Drake, & Wallach, 1998). Patients suffering from severe mental illnesses, as bipolar disorders, schizophrenia, or some personality disorders, could be especially prone to present dysphoria and negative affects, as well as to exhibit multiple risk factors (Mueser et al., 1998). In our study, patients with bipolar disorders (45.2%) or personality disorders (44.9%) showed the highest rates of a CAGE score ≥1, followed by psychotic disorders (39.4%). These prevalence rates are in line with those reported in the literature. The presence of AUD in patients with a bipolar disorder has been estimated to be around 45% in several studies (Cardoso et al., 2008; Farren, Hill, & Weiss, 2012; Kessler et al., 1997), which is similar to our reported rate. In the study from Agabio et al. (2007), 30.4% of the outpatients with an affective disorder showed a CAGE score ≥1. In their study, no differences were found in the frequency of AUD between unipolar and bipolar spectrum, although this analysis was performed using the diagnostic criteria from the Structured Clinical Interview for DSM-IV, Axis I Disorders, not the CAGE questionnaire. Other authors have reported prevalence rates from 10 to 60% of lifetime AUD in unipolar depressed patients (Klimkiewicz et al., 2015; Satre et al., 2008; Sullivan et al., 2005; Worthington et al., 1996). In agreement with our results, a prevalence of AUD between 16.4 to 30% has been reported in patients with a diagnosis of personality disorder (Echeburúa, de Medina, & Aizpiri, 2005; Grant et al., 2004a; Klimkiewicz et al., 2015; Mellos et al., 2010).

Regarding AUD in patients with schizophrenia and related disorders, a prevalence rate between 29 to 60% has been consistently reported (Dervaux et al., 2006; Cantor-Graae et al., 2001; McCreadie, 2002; Soyka, 2000). Similar CAGE scores as the presented in our study have been published in a sample of outpatients with schizophrenia and schizoaffective disorders, with CAGE score ≥1 in 37.7% of the patients (Etter & Etter, 2004). In our sample, patients with an anxiety disorder had a lower percentage of a positive CAGE score (22.3%) than other diagnostic groups. AUD has been described in 7 to 18% of patients with anxiety disorders (Klimkiewicz et al., 2015; Vorspan et al., 2015). A recent metaanalysis has confirmed the association between AUD and anxiety disorders, with an OR of 1.636 for any anxiety disorder and alcohol abuse, and an OR of 2.53 for alcohol dependence (Lai, Cleary, Sitharthan, & Hunt, 2015). Other authors have found non-significant or no associations between AUD and specific anxiety disorders (Grant et al., 2004b; Hasin & Kilcoyne, 2012; Goldstein et al., 2015; Grant et al., 2015). These discrepant results could be explained by the high clinical heterogeneity in this subgroup of patients, possibly leading to distinct comorbidity with AUD.

Gender differences in positive AUD screening were also observed when our sample was split by diagnosis (Figure 2). Personality disorders had the highest positive rates for both genders. Afterwards, men showed high positive rates in the subgroup with psychotic disorders followed by bipolar disorder, while in women, the second diagnostic group with more prevalent positive results for the CAGE screening was the bipolar disorder, followed by psychotic disorders. This gender difference, according to psychiatric diagnosis, strengthens the need of gender specific approaches when screening and treating AUD in psychiatric patients.

In the present study, the strongest predictor of a positive screening for AUD using the CAGE scale was gender, followed by age, and psychiatric diagnoses. Therefore, presenting a male gender and being younger than 60 years

were predictors of a positive result. Patients diagnosed with an anxiety disorder were more likely to obtain a negative score in the CAGE scale as compared to the other diagnostic groups. Other authors also described male gender, younger age, and antisocial personality disorder, among others, as predictive of substance use disorders in psychiatric patients (Mueser et al., 2000).

This study has several limitations. Firstly, AUD were not assessed with structured interviews to confirm the results provided by the CAGE questionnaire. The cross-sectional design prevents analysis of causal relationships between AUD, psychiatric conditions, and other risk factors. Sociodemographic data, as well as substance use disorders and medical conditions, which could act as confounding factors, were not registered. The use of a cut-off point of 1 in the CAGE questionnaire provides a higher sensitivity but a lower specificity, therefore some patients classified by our screening as presenting a high risk for an AUD could be false positives, overestimating the frequency of AUD risk in our sample. As for the strengths of our study, a large sample of outpatients, from a broad age range and different diagnostic categories, was included. Moreover, 54% of our patients were female, often under-represented in studies. For all these reasons, our sample might provide a more realistic perspective of AUD in this population.

In summary, the high rates of AUD seen in psychiatric outpatients, and the difficulty to accurately assess these patients, supports the use of specific screening instruments, like the CAGE questionnaire. Special attention should be provided to patients presenting risk factors for an AUD, as male gender, age under 60 years old, as well as the presence of bipolar, personality, and psychotic disorders. Further research may examine the relationship between AUD and comorbid psychiatric disorders, together with the influence of other medical, social, and demographic factors.

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Disclosures

The authors do not report any conflict of interest associated with the present study.

References

Agabio, R., Marras, P., Gessa, G. L. & Carpiniello, B. (2007). Alcohol use disorders, and at-risk drinking in patients affected by a mood disorder, in Cagliari, Italy: sensitivity and specificity of different questionnaires. *Alcohol and Alcoholism, 42*, 575–581. doi:10.1093/alcalc/agm072.

Anthenelli, R. M. (2012). Overview: stress and alcohol use disorders revisited. *Alcohol Research: Current Reviews*, *34*, 386–390.

Autonell, J., Vila, F., Pinto-Meza, A., Vilagut, G., Codony, M., Almansa, J., … Haro, J. M. (2007). One year prevalence of mental disorders comorbidity and associated socio-demographic risk factors in the general population of Spain. Results of the ESEMeD-Spain study. *Actas Españolas de Psiquiatría*, *35*, 4–11.

Baltieri, D. A. & de Andrade, A. G. (2008). Comparing serial and nonserial sexual offenders: alcohol and street drug consumption, impulsiveness and history of sexual abuse. *Revista Brasileira de Psiquiatria, 30*, 25–31.

Barnaby, B., Drummond, C., McCloud, A., Burns, T. & Omu, N. (2003). Substance misuse in psychiatric inpatients: comparison of a screening questionnaire survey with case notes. *British Medical Journal, 327*, 783–784. doi:10.1136/bmj.327.7418.783.

Barrio, P., Miquel, L., Moreno-España, J., Martínez, A., Ortega, L., Teixidor, L., ... Gual, A. (2016). Alcohol in Primary Care. Differential characteristics between alcohol-dependent patients who are receiving or not receiving treatment. *Adicciones*, 28, 116-122. doi:10.20882/adicciones.779.

Berks, J. & McCormick, R. (2008). Screening for alcohol misuse in elderly primary care patients: a systematic literature review. *International Psychogeriatrics*, *20*, 1090–1103. doi:10.1017/S1041610208007497.

Bowman, P. T. & Gerber, S. (2006). Alcohol in the older population, Part 2: MAST you speak the truth in an AUDIT or are you too CAGE-y? *The Case Manager*, *17*, 48–53, 59.

Bradley, K. A., Bush, K. R., McDonell, M. B., Malone, T. & Fihn, S. D. (1998). Screening for problem drinking : Comparison of CAGE and AUDIT. *Journal of General Internal Medicine*, *13*, 379–388. doi:10.1046/j.1525-1497.1998.00118.x.

Buckley P. (2006). Prevalence and consequences of the dual diagnosis of substance abuse and severe mental illness. *The Journal of Clinical Psychiatry, 67*, 5-9.

Cantor-Graae, E., Nordström, L. G. & McNeil, T. F. (2001). Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophrenia Research, 48*, 69–82.

Cardoso, B. M., Kauer Sant'Anna, M., Dias, V. V., Andreazza, A. C., Ceresér, K. M. & Kapczinski, F. (2008). The impact of co-morbid alcohol use disorder in bipolar patients. *Alcohol*, *42*, 451–457. doi:10.1016/j.alcohol.2008.05.003.

Castells, M. A. & Furlanetto, L. M. (2005). Validity of the CAGE questionnaire for screening alcohol-dependent inpatients on hospital wards. *Revista Brasileira de Psiquiatria*, *27*, 54–57.

Cherpitel, C. J. (1995). Analysis of cut points for screening instruments for alcohol problems in the emergency room. *Journal of Studies on Alcohol*, *56*, 695–700.

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

Córdoba, R., Delgado, M. T., Pico, V., Altisent, R., Fores, D., Monreal, A., … López del Val, A. (1998). Effectiveness of brief intervention on non-dependent alcohol drinkers (EBIAL): a Spanish multi-centre study. *Family Practice*, *15*, 562–568.

Corradi-Webster, C. M., Laprega, M. R. & Furtado, E. F. (2005) Performance assessment of CAGE screening test among psychiatric outpatients. *Revista Latino-Americana de Enfermagem*, *13*, 1213–1218. doi: S0104-11692005000800017.

Curran, T. A., Gawley, E., Casey, P., Gill, M. & Crumlish, N. (2009). Depression, suicidality and alcohol abuse among medical and business students. *Irish Medical Journal*, *102*, 249–252.

de Oliveira, J., Kerr-Correa, F., Lima, M., Bertolote, J. & Santos, J. (2014). Validity of Alcohol Screening Instruments in General Population Gender Studies: An Analytical Review. *Current Drug Abuse Reviews*, *7*, 59–65. doi:10.2174/1874473707666141015214708.

Derks, E. M., Vink, J. M., Willemsen, G., van den Brink, W. & Boomsma, D. I. (2014). Genetic and environmental influences on the relationship between adult ADHD symptoms and self-reported problem drinking in 6024 Dutch twins. *Psychological Medicine*, *44*, 2673–83. doi:10.1017/S0033291714000361.

Dervaux, A., Bayle, F. J., Laqueille, X., Bourdel, M. C., Leborgne, M., Olie, J. P. & Krebs, M. O. (2006). Validity of the CAGE questionnaire in schizophrenic patients with alcohol abuse and dependence. *Schizophrenia Research*, *81*, 151–155. doi:10.1016/j.schres.2005.09.012.

Dhalla, S. & Kopec, J. A. (2007). The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clinical and Investigative Medicine. Médecine Clinique et Experimentale*, *30*, 33–41.

Dixon, L., Weiden, P. J., Haas, G., Sweeney, J. & Frances, A. J. (1992). Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. *Comprehensive Psychiatry*, *33*, 121–122.

Drake, R. E., Osher, F. C. & Wallach, M. A. (1989). Alcohol use and abuse in schizophrenia. A prospective community study. *The Journal of Nervous and Mental Disease*, *177*, 408–414.

Draper, B., Ridley, N., Johnco, C., Withall, A., Sim, W., Freeman, M., … Lintzeris, N. (2015). Screening for alcohol and substance use for older people in geriatric hospital and community health settings. *International Psychogeriatrics / IPA*, *27*, 157–66. doi:10.1017/S1041610214002014.

Duke, P. J., Pantelis, C. & Barnes, T. R. (1994). South Westminster schizophrenia survey. Alcohol use and its relationship to symptoms, tardive dyskinesia and illness onset. *The British Journal of Psychiatry*, *164*, 630–636.

Eberhard, S., Nordström, G., Höglund, P. & Ojehagen, A. (2009). Secondary prevention of hazardous alcohol consumption in psychiatric out-patients: a randomised controlled study. *Social Psychiatry and Psychiatric Epidemiology*, *44*, 1013–1021. doi:10.1007/s00127-009-0023-7.

Echeburúa, E., de Medina, R. B. & Aizpiri, J. (2005). Alcoholism and personality disorders: an exploratory study. *Alcohol and Alcoholism*, *40*, 323–326. doi:10.1093/alcalc/agh158.

Encrenaz, G., Kovess-Masféty, V., Sapinho, D., Chee, C. C. & Messiah, A. (2007). Utilization of mental health services and risk of 12-month problematic alcohol use. *American Journal of Health Behavior*, *31*, 392–401. doi:10.5555/ajhb.2007.31.4.392.

Escobar, F., Espí, F. & Canteras, M. (1995). Diagnostic tests for alcoholism in primary health care: compared efficacy of different instruments. *Drug and Alcohol Dependence*, *40*, 151–158. doi:10.1016/0376-8716(95)01200-1.

Etter, M. & Etter, J.-F. (2004). Alcohol consumption and the CAGE test in outpatients with schizophrenia or schizoaffective disorder and in the general population. *Schizophrenia Bulletin*, *30*, 947–956.

Ewing, J. A. (1984). Detecting alcoholism. The CAGE questionnaire. *JAMA*, *252*, 1905–1907.

Farren, C. K., Hill, K. P. & Weiss, R. D. (2012). Bipolar disorder and alcohol use disorder: a review. *Current Psychiatry Reports*, *14*, 659–66. doi:10.1007/s11920-012-0320-9.

Fiellin, D. A., Reid, M. C. & O'Connor, P. G. (2000). Screening for alcohol problems in primary care: a systematic review. *Archives of Internal Medicine*, *160*, 1977–1989.

Fowler, I. L., Carr, V. J., Carter, N. T. & Lewin, T. J. (1998). Patterns of current and lifetime substance use in schizophrenia. *Schizophrenia Bulletin*, *24*, 443–455.

Gerding, L. B., Labbate, L. A., Measom, M. O., Santos, A. B. & Arana, G. W. (1999). Alcohol dependence and hospitalization in schizophrenia. *Schizophrenia Research*, *38*, 71–75.

Glass, J. E., Grant, J. D., Yoon, H. Y. & Bucholz, K. K. (2015). Alcohol problem recognition and help seeking in adolescents and young adults at varying genetic and environmental risk. *Drug and Alcohol Dependence*, *153*, 250–257. doi:10.1016/j.drugalcdep.2015.05.006.

Goldstein, R. B., Smith, S. M., Dawson, D. A. & Grant, B. F. (2015). Sociodemographic and psychiatric diagnostic predictors of 3-year incidence of DSM-IV substance use disorders among men and women in the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychology of Addictive Behaviors*, *29*, 924–932. doi:10.1037/adb0000080.

González García, Y., López Sampedro, P., Saavedra Rielo, M. C., González Arce, D., García Lavandera, L. J. & Cuesta Castro, B. (1997). The early detection of young people with alcohol-related disorders in primary care. *Atención Primaria, 20*, 133–136.

Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J. & Pickering, R. P. (2004). Prevalence correlates, and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *The Journal of Clinical Psychiatry, 65*, 948–958.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., … Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry, 61*, 807–816. doi:10.1001/archpsyc.61.8.807.

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., … Hasin, D. S. (2015). Epidemiology of DSM-5 Alcohol Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry, 72*, 757–766. doi:10.1001/jamapsychiatry.2015.0584.

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.

Gum, A. M., King-Kallimanis, B. & Kohn, R. (2009). Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. *American Journal of Geriatric Psychiatry, 17*, 769–781. doi:10.1097/JGP.0b013e3181ad4f5a.

Hasin, D. S., Stinson, F. S., Ogburn, E. & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry, 64*, 830–842. doi:10.1001/archpsyc.64.7.830.

Hasin, D. & Kilcoyne, B. (2012). Comorbidity of psychiatric and substance use disorders in the United States: current issues and findings from the NESARC. *Current Opinion in Psychiatry, 25*, 165–171. doi: 10.1097/YCO.0b013e3283523dcc.

Hasin, D. S. & Grant, B. F. (2015). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: review and summary of findings. *Social Psychiatry and Psychiatric Epidemiology, 50*, 1609–1640. doi:10.1007/s00127-015-1088-0.

Hearne, R., Connolly, A. & Sheehan, J. (2002). Alcohol abuse: prevalence and detection in a general hospital. *Journal of the Royal Society of Medicine, 95*, 84–87.

Hulse, G. K. & Tait, R. J. (2002). Six-month outcomes associated with a brief alcohol intervention for adult in-patients with psychiatric disorders. *Drug and Alcohol Review, 21*, 105–112. doi:10.1080/09595230220138993.

Jones, T. V, Lindsey, B. A., Yount, P., Soltys, R. & Farani-Enayat, B. (1993). Alcoholism screening questionnaires: are they valid in elderly medical outpatients? *Journal of General Internal Medicine, 8*, 674–678.

Kessler, R. C., Crum, R. M., Warner, L. A., Nelson, C. B., Schulenberg, J. & Anthony, J. C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry, 54*, 313–321.

Keyes, K. M., Grant, B. F. & Hasin, D. S. (2008). Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug and Alcohol Dependence, 93*, 21–29. doi:10.1016/j.drugalcdep.2007.08.017.

Khan, S., Okuda, M., Hasin, D. S., Secades-Villa, R., Keyes, K., Lin, K.-H., … Blanco, C. (2013). Gender differences in lifetime alcohol dependence: results from the national epidemiologic survey on alcohol and related conditions. *Alcoholism, Clinical and Experimental Research, 37*, 1696–1705. doi: 10.1111/acer.12158.

Kim, B., Shin, W.S., Kim, M.K. & Lee, S.H. (2016). White matter microstructural changes are associated with alcohol use in patients with panic disorder. *Journal of Affective Disorders, 199*, 65–72. doi:10.1016/j.jad.2016.03.055.

Klimkiewicz, A., Klimkiewicz, J., Jakubczyk, A., Kieres-Salomoński, I. & Wojnar, M. (2015). Comorbidity of alcohol dependence with other psychiatric disorders. Part I. Epidemiology of dual diagnosis. *Psychiatria Polska, 49*, 265–275. doi:10.12740/PP/25704.

Lai, H. M. X., Cleary, M., Sitharthan, T. & Hunt, G. E. (2015). Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. *Drug and Alcohol Dependence, 154*, 1–13. doi:10.1016/j.drugalcdep.2015.05.031.

Lejoyeux, M., Gastal, D., Bergeret, A., Casalino, E., Lequen, V. & Guillermet, S. (2012). Alcohol use disorders among patients examined in emergency departments after a suicide attempt. *European Addiction Research, 18*, 26–33. doi:10.1159/000332233.

Lejoyeux, M., Nivoli, F., Basquin, A., Petit, A., Chalvin, F. & Embouazza, H. (2013). An Investigation of factors increasing the risk of aggressive behavior among schizophrenic inpatients. *Frontiers in Psychiatry, 4*, 97. doi:10.3389/fpsyt.2013.00097.

Lejoyeux, M., Basquin, A., Koch, M., Embouazza, H., Chalvin, F. & Ilongo, M. (2014). Cannabis Use and Dependence among French Schizophrenic Inpatients. *Frontiers in Psychiatry, 5*, 82. doi:10.3389/fpsyt.2014.00082.

León-Muñoz, L. M., Galán, I., Donado-Campos, J., Sánchez-Alonso, F., López-García, E., Valencia-Martín, J. L., … Rodríguez-Artalejo, F. (2015). Patterns of Alcohol Consumption in the Older Population of Spain, 2008-2010. *Journal of the Academy of Nutrition and Dietetics, 115*, 213–224. doi:10.1016/j.jand.2014.08.017.

Luoto, K. E., Koivukangas, A., Lassila, A. & Kampman, O. (2016). Outcome of patients with dual diagnosis in secondary psychiatric care. *Nordic Journal of Psychiatry, 70*, 470–476. doi:10.3109/08039488.2016.1160149.

Malet, L., Schwan, R., Boussiron, D., Aublet-Cuvelier, B. & Llorca, P.-M. (2005). Validity of the CAGE questionnaire in hospital. *European Psychiatry, 20*, 484–489. doi:10.1016/j.eurpsy.2004.06.027.

Mansell, D., Spiro, A., Lee, A. & Kazis, L. (2006). Validation of the primary care alcohol severity measure. *The Journal of Ambulatory Care Management, 29*, 87–97.

Masur, J. & Monteiro, M. G. (1983). Validation of the "CAGE" alcoholism screening test in a Brazilian psychiatric inpatient hospital setting. *Brazilian Journal of Medical and Biological Research, Revista Brasileira de Pesquisas Médicas e Biológicas, 16*, 215–218.

Mathalon, D. H., Pfefferbaum, A., Lim, K. O., Rosenbloom, M. J. & Sullivan, E. V. (2003). Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. *Archives of General Psychiatry, 60*, 245–252.

Mayfield, D., McLeod, G. & Hall, P. (1974). The CAGE questionnaire: validation of a new alcoholism screening instrument. *The American Journal of Psychiatry, 131*, 1121–1123. doi:10.1176/ajp.131.10.1121.

Miquel L., Barrio P., Moreno-España J., Ortega L., Manthey J. Rehm J. & Gual A. (2016). Detection and prevalence of alcohol use disorders in primary health care in Catalonia. *Atención Primaria, 48,* 175-182. doi:10.1016/j.aprim.2015.04.006.

McCreadie, R. G. (2002). Use of drugs, alcohol and tobacco by people with schizophrenia: case-control study. *The British Journal of Psychiatry, 181*, 321–325.

McGarry, K. A. & Cyr, M. G. (2005). Women and alcohol. *Comprehensive Therapy, 31*, 83–93.

Mellos, E., Liappas, I. & Paparrigopoulos, T. (2010). Comorbidity of personality disorders with alcohol abuse. *In Vivo, 24*, 761–769.

Mitchell, A. J., Bird, V., Rizzo, M., Hussain, S. & Meader, N. (2014). Accuracy of one or two simple questions to identify alcohol-use disorder in primary care: a meta-analysis. *The British Journal of General Practice, 64*, 408-418. doi:10.3399/bjgp14X680497.

Moore, A. A., Gould, R., Reuben, D. B., Greendale, G. A., Carter, M. K., Zhou, K. & Karlamangla, A. (2005). Longitudinal patterns and predictors of alcohol consumption in the United States. *American Journal of Public Health, 95*, 458–465. doi:10.2105/AJPH.2003.019471.

Moos, R. H., Schutte, K. K., Brennan, P. L. & Moos, B. S. (2009). Older adults' alcohol consumption and late-life drinking problems: a 20-year perspective. *Addiction, 104*, 1293–1302. doi:10.1111/j.1360-0443.2009.02604.x.

Morojele, N. K., Saban, A. & Seedat, S. (2012). Clinical presentations and diagnostic issues in dual diagnosis disorders. *Current Opinion in Psychiatry, 25*, 181–186. doi:10.1097/YCO.0b013e328351a429.

Mueser K. T., Drake R. & Wallach M. (1998). Dual diagnosis: a review of etiological theories. *Addictive Behaviors, 23,* 717-734.

Mueser, K. T., Yarnold, P. R., Rosenberg, S. D., Swett, C., Miles, K. M. & Hill, D. (2000). Substance use disorder in hospitalized severely mentally ill psychiatric patients: prevalence, correlates, and subgroups. *Schizophrenia Bulletin, 26*, 179–192.

Mukamal, K. J., Kawachi, I., Miller, M. & Rimm, E. B. (2007). Drinking frequency and quantity and risk of suicide among men. *Social Psychiatry and Psychiatric Epidemiology, 42*, 153–160. doi:10.1007/s00127-006-0144-1.

Noordsy, D. L., Drake, R. E., Teague, G. B., Osher, F. C., Hurlbut, S. C., Beaudett, M. S. & Paskus, T. S. (1991). Subjective experiences related to alcohol use among schizophrenics. *The Journal of Nervous and Mental Disease, 179*, 410–414.

Oe, M., Fujii, S., Maeda, M., Nagai, M., Harigane, M., Miura, I., … Abe, M. (2016). Three-year trend survey of psychological distress, post-traumatic stress, and problem drinking among residents in the evacuation zone after the Fukushima Daiichi Nuclear Power Plant accident [The Fukushima Health Management Survey]. *Psychiatry and Clinical Neurosciences, 70*, 245–252. doi:10.1111/pcn.12387.

Ogborne, A. C. (2000). Identifying and treating patients with alcohol-related problems. *Canadian Medical Association Journal, 162*, 1705–1708.

Paz Filho, G. J., Sato, L. J., Tuleski, M. J., Takata, S. Y., Ranzi, C. C., Saruhashi, S. Y. & Spadoni, B. (2001). Use of the CAGE questionnaire for detecting alcohol use disorders in the emergency room. *Revista Da Associação Médica Brasileira, 47*, 65–69.

Peen, J., Schoevers, R. A., Beekman, A. T. & Dekker, J. (2010). The current status of urban-rural differences in psychiatric disorders. *Acta Psychiatrica Scandinavica, 121*, 84–93. doi:10.1111/j.1600-0447.2009.01438.x.

Pristach, C. A., Smith, C. M. & Perkins, C. (1993). Reliability of the Self-Administered Alcoholism Screening Test (SAAST) in psychiatric inpatients. *Journal of Addictive Diseases, 12*, 77–88. doi:10.1300/J069v12n04_06.

Pulido, J., Indave-Ruiz, B. I., Colell-Ortega, E., Ruiz-García, M., Bartroli, M. & Barrio, G. (2014). Population-based studies on alcohol-related harm in Spain. *Revista Española de Salud Pública, 88*, 493–513. doi:10.4321/S1135-57272014000400005.

Ratta-Apha, W., Sitdhiraksa, N., Pariwatcharakul, P., Saisavoey, N., Limsricharoen, K., Thongchot, L., … N., Ketumarn, P. (2014). Under-recognized alcohol-related disorders in psychiatric outpatient unit. *Journal of the Medical Association of Thailand, 97*, 439–446.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L. & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA, 264*, 2511–2518.

Rehm J., Rehm M.X. Shield K.D., 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. doi:10.20882/adicciones.67.

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

Rodríguez-Martos, A. (1986). Validación de los cuestionarios KFA (CBA) y CAGE para el diagnóstico del alcoholismo. *Drogalcohol, 11*, 132-139.

Rodríguez Fernández, E., Gómez Moraga, A. & García Rodríguez, A. (1997). Relationship between family perception and alcohol consumption. *Atención Primaria, 19*, 117–121.

Rosenberg, S. D., Drake, R. E., Wolford, G. L., Mueser, K. T., Oxman, T. E., Vidaver, R. M., … Luckoor, R. (1998). Dartmouth Assessment of Lifestyle Instrument (DALI): a substance use disorder screen for people with severe mental illness. *The American Journal of Psychiatry, 155*, 232–238. doi:10.1176/ajp.155.2.232.

San L., Arranz B., Arrojo M., Becoña E., Bernardo M., Caballero L., … Zorrilla I. (2016). Clinical guideline for the treatment of dual pathology in the adult population. *Adicciones*, 28, 3-5. doi:10.20882/adicciones.784.

Satre, D., Wolfe, W., Eisendrath, S. & Weisner, C. (2008). Computerized screening for alcohol and drug use among adults seeking outpatient psychiatric services. *Psychiatric Services, 59*, 441–444. doi:10.1176/ps.2008.59.4.441.

Shaner, A., Khalsa, M. E., Roberts, L., Wilkins, J., Anglin, D. & Hsieh, S. C. (1993). Unrecognized cocaine use among schizophrenic patients. *The American Journal of Psychiatry, 150*, 758–762. doi:10.1176/ajp.150.5.758.

Sheidow, A. J., McCart, M., Zajac, K. & Davis, M. (2012). Prevalence and impact of substance use among emerging adults with serious mental health conditions. *Psychiatric Rehabilitation Journal, 35*, 235–243. doi:10.2975/35.3.2012.235.243.

Smith, C. M. & Pristach, C. A. (1990). Utility of the Self-Administered Alcoholism Screening Test (SAAST) in schizophrenic patients. *Alcoholism, Clinical and Experimental Research, 14*, 690–694.

Soyka, M. (2000). Substance misuse, psychiatric disorder and violent and disturbed behaviour. *The British Journal of Psychiatry, 176*, 345–350.

Soyka, M., Albus, M., Immler, B., Kathmann, N. & Hippius, H. (2001). Psychopathology in dual diagnosis and non-addicted schizophrenics–are there differences? *European Archives of Psychiatry and Clinical Neuroscience, 251*, 232–238.

Sullivan, L. E., Fiellin, D. A. & O'Connor, P. G. (2005). The prevalence and impact of alcohol problems in major depression: a systematic review. *The American Journal of Medicine, 118*, 330–341. doi:10.1016/j.amjmed.2005.01.007.

Suominen, K., Isometsä, E., Haukka, J. & Lönnqvist, J. (2004). Substance use and male gender as risk factors for deaths and suicide -a 5-year follow-up study after deliberate self-harm. *Social Psychiatry and Psychiatric Epidemiology, 39*, 720–724. doi:10.1007/s00127-004-0796-7.

Tang, V. K., Pato, M. T., Sobell, J. L., Hammond, T. C., Valdez, M. M., Lane, C. J. & Pato, C. N. (2016). Substance use associated with short sleep duration in patients with schizophrenia or schizoaffective disorder. *American Journal of Medical Genetics, 171*, 525–533. doi:10.1002/ajmg.b.32374.

Teitelbaum, L. & Mullen, B. (2000). The validity of the MAST in psychiatric settings: a meta-analytic integration. Michigan Alcoholism Screening Test. *Journal of Studies on Alcohol, 61*, 254–261.

Torrens M., Mestre-Pintó J.I., Montanari L., Vicente J. & Domingo-Salvany A. (2017). Dual diagnosis: a European perspective, *Adicciones, 29,* 3-5. doi:10.20882/adicciones.933.

Urbanoski, K. A., Cairney, J., Adlaf, E. & Rush, B. (2007). Substance abuse and quality of life among severely mentally ill consumers: a longitudinal modelling analysis. *Social Psychiatry and Psychiatric Epidemiology, 42*, 810–818. doi:10.1007/s00127-007-0236-6.

Vorspan, F., Mehtelli, W., Dupuy, G., Bloch, V. & Lépine, J.-P. (2015). Anxiety and substance use disorders: co-occurrence and clinical issues. *Current Psychiatry Reports, 17*, 4. doi:10.1007/s11920-014-0544-y.

Weisner, C. & Matzger, H. (2003). Missed opportunities in addressing drinking behavior in medical and mental health services. *Alcoholism, Clinical and Experimental Research, 27*, 1132–1141. doi:10.1097/01.ALC.0000075546.38349.69.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines*. Geneva.

Worthington, J., Fava, M., Agustin, C., Alpert, J., Nierenberg, A. A., Pava, J. A. & Rosenbaum, J. F. (1996). Consumption of alcohol, nicotine, and caffeine among depressed outpatients. Relationship with response to treatment. *Psychosomatics, 37*, 518–522. doi:10.1016/S0033-3182(96)71515-3.

Wu, L. T. & Blazer, D. G. (2014). Substance use disorders and psychiatric comorbidity in mid and later life: a review. *International Journal of Epidemiology, 43*, 304–317. doi:10.1093/ije/dyt173.

Annex

CAGE questionnaire camouflaged adapted for Spanish patients (translated to English)

1. Do you think you eat too many sweets?
2. Have you ever been offered a joint or a cocaine dose?
3. Have people annoyed you by criticizing your drinking?
4. Have you ever thought about doing some exercise weekly?
5. Do you consider you sleep enough hours to feel fit during the day?
6. Have you ever felt you should cut down on your drinking?
7. Have you ever considered seriously quitting smoking?
8. Have you ever been told you should eat more fruits and vegetables?
9. Have you ever felt bad or guilty about your drinking?
10. Have you ever been told you should smoke less?
11. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?
12. Have you ever thought about switching your habit of taking sleeping pills to relaxation techniques?

Alcohol, tobacco and cannabis consumption in adolescents from a multicultural population (Burela, Lugo)

Consumo de alcohol, tabaco y cannabis en adolescentes de una población multicultural (Burela, Lugo)

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Abstract

Social inequalities have been associated with morbidity and mortality. Gender, ethnic group and inequalities were studied in an adolescent population to analyze alcohol, tobacco and cannabis consumption. We carried out a cross-sectional study of pupils from high schools in Burela (northern Spain) (n=238). We used the "Factors de Risc en Estudiants de Secundária" questionnaire designed by Agència de Salut Pública de Barcelona. Independent variables: nationality and weekly pocket money. Dependent variables: expectations and consumption of alcohol, tobacco and marihuana. Logistic regression was used.

Participation in the study reached 91%. The proportion of pupils that have tried alcohol on occasion increases with age (27.3%, 47.7%, 75.9%), as with tobacco (1.8%, 7.6%, 17.0%), and cannabis (0%, 3.1%, 7.0%). Higher levels of spending money constitute a risk factor for tasting alcohol (OR=3.01), for high-risk consumption (OR=3.35), for getting drunk (OR=6.45) and for trying marijuana (OR=15.30). Sex and nationality were not shown to be associated with the use of any of these three drugs. The results of our study show that consumption of alcohol, tobacco and cannabis increases with age and with increased spending money. The data do not support the argument that foreign pupils are a risk group for alcohol consumption, so they should not be stigmatized.

Keywords: Adolescents; immigrants; social inequalities; substance use.

Resumen

Las desigualdades en salud en la adolescencia se han asociado a la morbimortalidad de los sujetos. Este estudio pretende evaluar el efecto de género, nacionalidad e inequidades sociales sobre el consumo de alcohol, tabaco y cannabis en adolescentes en un contexto multicultural. Se ha realizado un estudio transversal entre los estudiantes de Educación Secundaria Obligatoria (ESO) de los institutos de Burela (Lugo) (n=238). Se utilizó el cuestionario "Factors de Risc en Estudiants de Secundária" diseñado por la Agència de Salut Pública de Barcelona. Variables independientes: nacionalidad y el dinero disponible semanal. Variables dependientes: expectativas y consumo de alcohol, con consumo de tabaco y marihuana. Se generaron modelos de regresión logística multivariante.

La participación en el estudio alcanzó el 91%. La proporción de alumnos que ha probado el alcohol aumenta con la edad (27,3%, 47,7% y el 75,9%), como ocurre con el tabaco (1,8%, 7,6% y 17%) y el cannabis (0%, 3,1%, 7%). La mayor disponibilidad económica constituye un factor de riesgo para haber probado el alcohol (OR=3,01), para su consumo de riesgo (OR=3,35), para haberse emborrachado (OR=6,45) y para haber probado la marihuana (OR=15,30). Sexo y nacionalidad no han mostrado relación con el consumo de ninguna de estas drogas. Los resultados de nuestro estudio muestran que el consumo de alcohol, tabaco y cannabis aumenta con la edad así como con la mayor disponibilidad económica. Los resultados constatan que los alumnos inmigrantes no constituyen un grupo de riesgoy por ello no deben ser estigmatizados.

Palabras clave: Adolescentes; inmigrantes; desigualdades sociales; consumo de sustancias.

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Adolescence is a stage of learning, education and experimentation which greatly determines behavior in adult life. It has been observed that when this crucial period is set in a context of intercultural interaction, health behaviors can change in noticeable ways and become a potential source of negative repercussions on the well-being and future health of our youth (Bousoño et al., 2017; García-Sánchez et al., 2016; Gonzálvez, Espada, Guillén-Riquelme, Secades, & Orgilés, 2016; Meneses et al., 2009).

Within such a context, ethnicity or belonging to an ethnic group is a key element of social and cultural identification (Meneses et al., 2013), which, alongside the social influence of peers or friends, different role models, family and school can have repercussions on substance use (Giró, 2011; Luengo, Villar, Sobral, Romero & Gómez-Fraguela, 2009; Marsiglia, Kulis, Luengo, Nieri & Villar, 2008; Whal & Eitle, 2010). In addition, the influence of the process of acculturation, defined as the exchange of cultural attitudes and behaviors that takes place when people from different socio-cultural environments come into contact (Luengo et al., 2009), should also be noted.

This concept, although traditionally understood as the adoption of the dominant culture, currently tends to be seen in terms of different possible strategies: integration or biculturalism, assimilation, separation or withdrawal, and marginalization or alienation (Luengo et al., 2009). Several publications highlight the influence of this process of identity formation, which could be linked to drug use given that one of the factors associated with such behaviors is that it is reproduced by the peer group (Giró, 2011). It is important to take a global approach to the concept and to advance in the development of scales that address it as the multidimensional and complex process that it is (Fosados et al., 2007).

It is therefore essential to look beyond the strictly personal variables involved in substance use among adolescents. Although the consumption of all drugs seems to have decreased, according to the national survey of drug use in secondary schools the percentage of Spanish youths between 14 and 18 years of age who have tried alcohol currently stands at 78.9%, with tobacco at 38.4% and marijuana at 29. 1% (Encuesta sobre Uso de Drogas en Estudiantes de Secundaria [ESTUDES], 2016), levels that remain disturbing. These data make it a priority to address the consumption of these substances in order to find early solutions to problems that may arise from their use.

Social inequalities in the early stages of development are contributing factors to inequalities in adult life, a fact that highlights the importance of systematically recording social determinants in child health studies and during adolescence (Font Ribera et al., 2014). Furthermore, the migration dimension cannot be understood independently of social class and gender (Borrell & Artazcoz, 2008; Malmusi, Borrell & Benach, 2010), and this reality reflects the need to understand risk behaviors among immigrant adolescents.

The number of studies conducted in Spain aimed at investigating health inequalities among adolescents and taking into account different ethnic groups or cultural differences is scarce (Charro Baena, 2015; Font-Ribera et al., 2014; Giró, 2011; Luengo et al., 2009; Marsiglia et al., 2008; Meneses et al., 2009; Meneses et al., 2013), despite the importance of knowing about and understanding these diversities in order to increase our capacity to develop preventive strategies involving these subgroups (Meneses, 2009).

Given the current economic context, changes in family and social structure or migration flows, the relevance of an interrelated study of inequalities, emigration and adolescent development in this new reality should be clear, since these are elements that have an important impact on the health of our youth (Bachman, O´Malley, Johnston, Schulenberg & Wallace, 2011; Blum, Beuhring, Shew, Bearinger & Sieving, 2000; Vega, Aramendi & Garín, 2012). The analysis of consumption patterns among adolescents allows us to identify the most vulnerable individuals (Caravaca Sánchez, Navarro-Zaragoza, Luna Ruiz-Cabello, Falcón Romero, & Luna Maldonado, 2017; Luengo et al., 2009) so that we can put in place effective prevention plans.

Burela is a municipality in the north of Lugo province, Galicia. In recent years it has been subject to truly rapid and profound economic and demographic developments (Oca, 2013). It is a multicultural urban centre where around 50 nationalities coexist among its 9,580 inhabitants, of which 8,497 are Spanish nationals and 1,083 are foreigners (INE 2015). The largest immigrant community is made up of Cape Verdeans, and more recently colonies of, for example, Peruvians, Ecuadorians or Senegalese have joined them. This locality is thus a lively example of multicultural coexistence that raises new challenges in the search for a better social integration.

The objective of the present study is to determine the effect of nationality and social inequities on the use of alcohol, tobacco and cannabis among adolescents in a multicultural context.

Methods

Study design and population

A cross-sectional or prevalence study was carried out among students of the 2nd, 3rd and 4th grades of compulsory secondary education (ESO), aged 14 to 18 in the secondary schools of Burela (Lugo). The entire ESO student population was recruited for the study (n = 262).

Data Collection

Data collection was carried out using FRESC questionnaires (Factors de Risc en Estudiants de SeCundária) (Pérez et al., 2013), designed by the Public Health Agency of

Barcelona for the purpose of determining emerging risk behaviors among secondary school pupils. The main indicators included are, for example, sociodemographic variables, consumption of addictive substances, health and mood, free time and sexuality. Two models of the questionnaire were employed: one for the 2nd grade of compulsory secondary education (13-14 years), and one for 4th grade (15-16), differing in some questions on the consumption of addictive substances, mobility or questions related to sexuality. In order to access our population, apart from getting the relevant parental authorization we were also in contact with the school principals and counselors. The data were collected in the classrooms during school hours and in the presence of a teacher and a member of the research team during December 2015. Data confidentiality was guaranteed at all times. In addition to the FRESC questionnaire, the KIDMED questionnaire (Serra-Majem et al., 2004), specifically created for the evaluation of the dietary habits of children and adolescents, was also employed.

Variables

Independent variables

Nationality. The nationality of the father and mother was used to determine whether the student was a Spanish national or an immigrant. Those students whose parents were both born outside Spain were considered immigrants.

Weekly spending money. Students were asked about the money they had available on a weekly basis via the question: "How many Euros do you have per week to spend on yourself?" The amounts were recoded into three categories: less than €10; between €10 and €20; and more than €20.

Sex and age were considered independent variables

Dependent Variables

Expectations regarding alcohol. This variable was measured using the question: "Do you think alcohol makes parties more fun? Totally agree / Quite agree / Quite disagree / Totally disagree". The variable was recoded into two categories: totally or quite agree and totally or strongly disagree.

Trying alcohol. This variable was measured by the question: "Have you ever drunk half a glass of an alcoholic beverage? No, never / Yes, on occasion / Yes, in the last 12 months / Yes, in the last 6 months / Yes, in the last 30 days. "The variable was recoded into two categories (No vs. Yes).

Risky alcohol consumption. The variable was measured with the question: "Have you ever drunk more than 4 alcoholic beverages on a single occasion? (An occasion was considered to be approximately 4 hours.) No, never / Yes, on occasion / Yes, in the last 12 months / Yes, in the last 6 months / Yes, in the last month. The variable was recoded into two categories (No vs. Yes).

Getting drunk. This variable was measured by the question: "Have you ever got drunk? No, never / Yes, on occasion / Yes, in the last 12 months / Yes, in the last 6 months / Yes, in the last month." The variable was recoded into two categories (No vs. Yes).

Buying some alcoholic beverage. A dichotomous variable, measured by the question: "Have you ever bought an alcoholic beverage for yourself? Yes/No". The variable was recoded into two categories (No vs. Yes).

Smoked tobacco. A dichotomous variable, measured by the question: "Have you ever smoked? Yes/No".

Used marijuana. This variable was measured using the question: "Have you ever tried marijuana? No, never / Yes, at some point / Yes, in the last 12 months / Yes, in the last 30 days ". The variable was dichotomized (No vs. Yes).

Statistical analysis

Proportions and means were calculated for the descriptive analysis. Associations were established using logistic regression. Initial theoretical models were generated that included all the independent variables. From these, the final models were calculated in which all the significant variables were included, as well as those that were not significant but whose exclusion altered the coefficients of the remaining variables by more than 10% (confounding variables). The analyses were performed using the statistical package SPSS v22. The calculation of proportions was carried out using the EPIDAT 3.1 statistical program together with the statistical analysis package R.

Results

Participation in the study was 91% (n = 238), of whom 51 were immigrants and 187 were Spanish nationals. In terms of sex, the sample was made up of 111 girls and 127 boys. Table 1 presents the main characteristics of the subjects. Table 2 shows the expectations and use of alcohol, tobacco and cannabis of the subjects by nationality and Table 3 does the same by sex.

Regarding expectations of alcohol use, the multivariate analysis indicates that being a boy [OR = 1.83; 95% CI: 1.04-3.22] and in the highest age group [OR = 2.54; 95% CI: 1.23-5.26] are associated with an increased risk of considering that alcohol makes parties more fun (Table 4). The age variable has also been shown to be associated with the proportion of pupils aged 13, 14 and 15 or older who have tried alcohol on occasion, which was 27.3%, 47.7% and 75.9%, respectively.

It should be noted that a total of 33.7% of Spanish students purchased alcoholic beverages versus 14.7% of immigrant students (p = 0.035) (Table 2), so that being local increases the possibility of buying alcohol [OR = 2.95; 95% CI: 1.04-8.31] (Table 4).

The amount of spending money was shown to be associated with all variables studied. Thus having more than €10 a week increases the risk of consuming more than 4

alcoholic beverages on a single occasion [OR = 3.35; 95% CI: 1.34-8.38] as well as getting drunk [OR = 6.45; 95% CI: 2.31-18.07]. In addition, students with weekly pocket money above €20 are most likely to have tried alcohol [OR = 3.01; 95% CI: 1.16-7.79] as are those aged 15 or older [OR = 8.61; 95% CI: 3.96-18.71].

The proportion of subjects who have tried tobacco was 1.8%, 7.6% and 17% among students aged 13, 14 and 15 or older respectively, with the risk for the latter being 11 times higher [OR = 11.03; 95% CI: 1.43-84.73] (Table 4).

Finally, as regards marijuana, the proportion of subjects who have tried this substance rises from 0% at 13 to 7% at 15. As with the other dependent variables considered, the greater availability of money significantly increases the risk of having tried cannabis [OR = 15.3; 95% CI: 1.80-130.43] (Table 4). The variables of sex and immigrant status were not shown to be linked to the use of any of the three drugs considered.

Table 1. *Description of the student sample. Burela, 2015.*

	Total (n=238)
Variables	Percentage [CI95%]+
Nationality	
Immigrant	21.4 [16.4 – 26.6]
Sex	
Female	46.6 [40.3 – 53.3]
Age	
≤ 13	23.5 [16.8 – 30.3]
14	27.7 [21.0 – 34.5]
≥ 15	48.7 [42.0 – 55.5]
Mean	14.9 [14.8 – 15.1]
Weekly spending money	
≤ 10 euros	55.0 [48.7 – 61.6]
10-20 euros	23.1 [16.8 – 29.7]
≥ 20 euros	16.8 [10.5 – 23.4]
Mean	16.3 [13.8 – 18.9]

Note. +CI: confidence interval.

Table 2. *Expectations and use of alcohol, tobacco and cannabis of subjects by nationality. Burela, 2015.*

Dependent variables	Total (n=238)	Spanish nationals (n=187)	Immigrants (n=51)	p-valor
	Percentage / Mean			
Believe that alcohol makes parties more fun	34.5	32.6	43.1	0.163
Have bought an alcoholic drink for a party on occasion	28.8	33.7	14.7	0.035
Have drunk half a glass of an alcoholic drink on occasion	56.3	53.5	68.6	0.054
Have drunk more than 4 alcoholic drinks on a single occasion	32.0	32.3	31.4	0.929
Have got drunk on occasion	24.1	21.4	31.4	0.235
Have smoked tobacco on occasion	10.5	9.7	14.6	0.333
Have tried marijuana on occasion	4.3	4.9	2.0	0.364

Table 3. *Opinions and habits by sex.*

	Porcentage		
	Female n=46,6	Male n=53,4	p-value
Believe that alcohol makes parties more fun	39.0	61.0	0.080
Have bought an alcoholic drink for a party on occasion	52.6	47.4	0.701
Have drunk half a glass of an alcoholic drink on occasion	49.3	50.7	0.080
Have drunk more than 4 alcoholic drinks on a single occasion	28.1	35.9	0.344
Have got drunk on occasion	46.9	53.1	0.795
Have smoked tobacco on occasion	48.0	52.0	0.933
Have tried marijuana on occasion	3.6	4.9	0.631

Table 4. *Influence of subjects' characteristics on their expectations and habits regarding use of alcohol, tobacco and cannabis. Burela, 2015.*

	Odds Ratio (95% confidence interval)						
Explanatory variables	Believe alcohol makes parties more fun	Have bought alcohol	Have drunk half a glass	Have got drunk	More than 4 drinks on a single occasion	Have smoked tobacco	Have tried marijuana
Sex							
Female	1						
Male	1.83 (1.04 - 3.22)						
Nationality							
Immigrants		1					
Spanish		2.95 (1.04 - 8.31)					
Age							
13 años	1		1			1	
14 años	1.21 (0.53 - 2.77)		2.27 (1.31 - 5.01)			4.43 (0.50 - 39.08)	
15 años	2.54 (1.23 - 5.26)		8.61 (3.96 - 18.71)			11.03 (1.43 -84.73)	
Weekly pocket money							
‹10 euro			1	1	1		1
10-20 euros			0.84 (0.41 - 1.70)	6.45 (2.31 - 18.07)	3.35 (1.34 - 8.38)		15.30 (1.80 - 130.43)
20›			3.01 (1.16 - 7.79)	3.07 (1.08 - 8.73)	1.10 (0.42 - 2.86)		10.42 (1.05 - 103.21)

Note. a Adjusted for all variables included in the column.

Discussion

The results of the present study show that the consumption of alcohol, tobacco and cannabis increases with age as well as with the greater availability of spending money. These data do not show an association between immigrant status and the consumption of any of the substances in question.

The results of the study are consistent with the data yielded by the survey of drug use in secondary schools (ESTUDES, 2016). Thus, our results confirm the trend that as age increases, so does the risk of consuming substances of some sort. However, our data do not agree with other studies that show a higher rate of consumption and a younger starting age in immigrants compared to local people (Luengo et al., 2009, Meneses et al., 2013). This inconsistency may well be due to two reasons: firstly, to the different criteria used in classifying subjects as immigrants or locals - our study has considered nationality and not ethnicity; and secondly, to the fact that these studies analyzed populations of predominantly Latin American origin (Luengo et al., 2009; Marsiglia et al., 2008; Meneses et al., 2013; Tortajada et al., 2008), while our immigrant population is mostly Cape Verdean.

The hypothesis of a possible protective effect of ethnicity has been suggested in the literature (Best et al., 2001; Fosados et al., 2007, Marsiglia, Kulis, Hednt & Sills, 2004), although this seems to be true only in certain groups, such as those in which the importance of religion, paternal control (permissiveness regarding going out at night, where gender inequality should be highlighted), and abstinence within the family could act as protective factors (Giró, 2011).

It should be pointed out that, regarding ethnicity, the literature tends to favor self-classification of the subjects of a study, despite some evident limitations, such as in the qualitative study of Charro Baena (2015) in which student doubts regarding their own ethnicity can be observed. In addition, it is necessary to consider the process of creation of hybrid identities, constructed from contact in earliest childhood with both cultures, as opposed to assimilation, with its subsequent blurring of ethnic differences (Fosados et al., 2007; Luengo et al., 2009; Marsiglia et al., 2008; Tortajada et al., 2008).

It is known that the acculturation process is stronger in adolescents than in children, who live in the community from the earliest stages of their development. Second-generation immigrants tend to imitate the values of the locals by assimilating their values and customs (Marsiglia et al., 2004). Some authors have pointed to the so-called "white male" effect (Bachman et al., 2011), referring to the higher risk of substance use they present. Thus, it is worth reflecting on the fact that by focusing on the search for differences, we may be running the risk of constructing our interventions on variables that are not susceptible to modification (Blum et al., 2000; Vega et al., 2012).

Nevertheless, having said that, numerous studies tend to support the hypothesis that inequalities are not born of nationality or ethnicity, but are more likely to be dependent on the economic resources of our populations. Thus, linking nationality to inequality or inequity regarding health will go hand in hand with socioeconomic status (Floyd, Alexandre, Hedden, Lawson & Latimer, 2010; Malmusi et al., 2010).

With regard to expectations concerning alcohol consumption, our results have shown that being male as well as older increases positive expectations. These results are

consistent with the study by Meneses et al. (2013) and conform to traditional gender roles (Borrell & Artazcoz, 2008). However recent studies have shown similar levels of consumption between men and women (ESTUDES, 2016; Moure-Rodríguez et al., 2016). This effect may be the result of the way in which society itself persists in understanding the equality and empowerment of women as the assimilation of patriarchal roles. That is, a clear link between "being a man" and an unhealthy lifestyle is evident (Borrell & Artazcoz, 2008; Malmusi et al., 2010).

In terms of availability of economic resources, the data obtained support the hypothesis that having more spending money at one's disposal is a decisive factor in greater consumption. Thus, with more money available, it is the pupils who are Spanish nationals who will present the highest rates of alcohol, tobacco and cannabis use. In addition, taking into account the ease of access to or acquisition of alcoholic beverages, it is again the locals who buy more alcohol. These results are consistent with the results obtained in the ESTUDES study (2016), as well as the study by Moure-Rodríguez et al., (2016), carried out among university students in our area, which found a link between higher family socioeconomic level and greater student alcohol consumption.

There are four main limitations of our study: 1) The fact that the questionnaire used to collect the data was self-completed in the classrooms may have caused pupils to give responses which they felt to be more socially acceptable, despite attempts to ensure the greatest confidentiality during the process; 2) The definition of 'immigrant' did not consider the length of stay in Spain, which may have led to a poor classification of the subjects, thereby limiting the identification of immigrant status as a risk factor (Monge et al., 2015); 3) The non-inclusion of vocational training students may have devalued the results, although this limitation will mainly affect the descriptive rather than the analytical results since there is no theoretical basis to consider that the independent variables in question may present different effect in this population group; and 4) It is likely that the external validity of our study is conditioned by the considerable variability in the composition and demography of the different multicultural communities in our country. Even if it is not possible to imagine a reference universe, we believe our results may help to interpret the consumption of alcohol, tobacco and cannabis in other multicultural populations.

In conclusion, the results of our study show that the use of alcohol, tobacco and cannabis increases with age as well as with greater spending money. These data show that immigrant pupils do not constitute a risk group for the consumption of these substances and hence should not be stigmatized. We consider, therefore, that drawing up new proposals for monitoring these inequalities will be fundamental for the improvement of integration programs.

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Conflict of interests

The authors of the article declare that there is no conflict of interest.

Referencias

Bachman, J. G., O'Malley, P. M., Johnston, L. D., Schulenberg, J. E. & Wallace J. M. (2011). Racial/ethnic differences in the relationship between parental education and substance use among U.S. 8th-, 10th-, and 12th-grade students: findings from the Monitoring the Future project. *Journal of Studies on Alcohol and Drugs, 72*, 279-285.

Best, D., Rawaf, S., Rowley, J., Floyd, K., Manning, V. & Strang J. (2001). Ethnic and gender differences in drinking and smoking among London adolescents. *Ethnicity & Health, 6*, 51-57. doi:10.1080/13557850123660.

Blum, R. W., Beuhring, T., Shew, M. L., Bearinger, L. H. & Sieving, R. E. (2000).The effects of race/ethnicity, income, and family structure on adolescent risk behaviors. *American Journal of Public Health, 90*, 1879-1884.

Borrell, C. & Artazcoz, L. (2008). Las desigualdades de género en salud: retos para el futuro. *Revista Española de Salud Pública, 82*, 241-249.

Bousoño, M., Al-Halabí, S., Burón, P., Garrido, M., Díaz-Mesa, E.M., Galván, G.,… Bobes, J. (2017). Substance use or abuse, internet use, psychopathology and suicidal ideation in adolescents. *Adicciones, 29*, 97-104. doi:10.20882/adicciones.811.

Caravaca Sánchez, F., Navarro-Zaragoza, J., Luna Ruiz-Cabello, A., Falcón Romero, M. & Luna Maldonado, A. (2017). Asociación entre victimización por bullying y consumo de sustancias entre la población universitaria en España. *Adicciones, 29*, 22-32. doi:10.20882/adicciones.827.

Charro Baena, B. (2015). Adolescentes inmigrantes y consumo de alcohol. Miscelánea Comillas. *Revista de Ciencias Humanas y Sociales, 72*, 140-141.

Estadística del Padrón Continuo. Varios años (Internet). Madrid: Instituto Nacional de Estadística. Retrieved at http://www.ine.es/nomen2/index.do?accion=busquedaRapida&subaccion=&numPag=0&ordenAnios=ASC&nombrePoblacion=Burela&botonBusquedaRapida=Consultar+selecci%C3%B3n

Floyd, L. J., Alexandre, P. K., Hedden, S. L., Lawson, A. L. & Latimer, W. W. (2010). Adolescent drug dealing and race/ethnicity: a population-based study of the diffe-

rential impact of substance use on involvement in drug trade. *The American Journal of Drug and Alcohol Abuse, 36,* 87-91. doi:10.3109/00952991003587469.

Font-Ribera, L., García-Continente, X., Davó-Blanes, Mª. C., Ariza, C., Díez, E., García Calvente, Mª. M., …Rajmil L. (2014). El estudio de las desigualdades sociales en la salud infantil y adolescente en España. *Gaceta Sanitaria, 28*, 316-325. doi:10.1016/j.gaceta.2013.12.009.

Fosados, R., McClain, A., Ritt-Olson, A., Sussman, S., Soto, D., Baezconde-Garbanati, L. & Unger, J. B. (2007). The influence of acculturation on drug and alcohol use in a sample of adolescents. *Addictive Behaviors, 32*, 2990-3004. doi:10.1016/j.addbeh.2007.06.015.

García-Sánchez, S., Matalí, J.L., Martín-Fernández, M., Pardo, M., Lleras, M., Castellano-Tejedor, C. & Haro, J.M. (2016). Personalidad internalizante y externalizante y efectos subjetivos en una muestra de adolescentes consumidores de cánnabis. *Adicciones, 28*, 231-241. doi:10.20882/adicciones.887.

Giró, J. (2011). Las amistades y el ocio de los adolescentes, hijos de la inmigración. Papers. *Revista de Sociología, 96*, 77-91.

Gonzálvez, M.T., Espada, J.P., Guillén-Riquelme, A., Secades, R. & Orgilés, M (2016). Asociación entre rasgos de personalidad y consumo de sustancias en adolescentes españoles. *Adicciones, 28*, 108-115. doi:10.20882/adicciones.777.

Luengo, M. A., Villar, P., Sobral, J., Romero, E. & Gómez-Fraguela, J. A. (2009). El consumo de drogas en los adolescentes inmigrantes: implicaciones para la prevención. *Revista Española de Drogodependencias, 34*, 448-479.

Malmusi, D., Borrell, C. & Benach, J. (2010). Migration-related health inequalities: showing the complex interactions between gender, social class and place of origin. *Social Science & Medicine 7*, 1610-1619. doi:10.1016/j.socscimed.2010.07.043.

Marsiglia, F. F., Kulis, S., Hecht, M. L. & Sills S. (2004). Ethnicity and ethnic identity as predictors of drug norms and drug use among preadolescents in the US Southwest. *Substance Use & Misuse, 39*, 1061-1094.

Marsiglia, F. F., Kulis, S., Luengo, M. A., Nieri, T. & Villar, P. (2008). Immigrant advantage? Substance use among Latin American immigrant and native-born youth in Spain. *Ethnicity & Health, 13*, 149-170. doi:10.1080/13557850701830356.

Meneses, C., Romo, N., Uroz J., Gil, E., Markez, I., Giménez, S. & Vega, A. (2009). Adolescencia, consumo de drogas y comportamientos de riesgo: diferencias por sexo, etnicidad y áreas geográficas en España. *Trastornos Adictivos, 11*, 51-63.

Meneses, C., Markez, I., Romo, N., Uroz, J., Rua, A. & Laespada, T. (2013). Diferencias de género en el consumo diario de tabaco e intensivo de alcohol en adolescentes latinoamericanos en tres áreas españolas (Andalucía, Madrid y País Vasco). *Revista de la Asociación Española de Neuropsiquiatría, 33*, 525-535. doi:10.4321/S0211-57352013000300005.

Monge, S., Ronda, E., Pons-Vigués, M., Vives, C., Malmusi, D. & Gil-González, D. (2015). Limitaciones y recomendaciones metodológicas en las publicaciones sobre salud de la población inmigrante en España. *Gaceta Sanitaria, 29*, 461-463. doi:10.1016/j.gaceta.2015.07.012.

Moure-Rodríguez, L., Piñeiro, M., Corral Varela, M., Rodríguez Holguín, S., Cadaveira, F. & Caamaño-Isorna, F. (2016). Identifying Predictors and Prevalence of Alcohol Consumption among University Students: Nine Years of Follow-Up. *PLoSOne, 11.* doi:10.1371/journal.pone.0165514. eCollection 2016.

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.

Plan Nacional sobre Drogas. Encuesta estatal sobre uso de drogas en estudiantes de secundaria (ESTUDES). Madrid: Ministerio de Sanidad y Políticas Sociales; 2016. Retrieved at http://www.pnsd.msssi.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2016_ESTUDES_2014-2015.pdf

Pérez, A., García-Continente, X. & Grupo colaborador encuesta FRESC 2012. (2013). Informe FRESC 2012: 25 anysd'enquestes a adolescentsescolaritzats de Barcelona. Barcelona: Agència de Salut Pública de Barcelona.

Serra-Majem, L., Ribas, L., Ngo, J., Ortega, R. M., García, A., Pérez-Rodrigo, C. & Aranceta, J. (2004). Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. *Public Health Nutrition, 7*, 931-935. doi:10.1079/PHN2004556.

Tortajada, S., Valderrama, J., Castellano, M. l., Llorens, N., Agulló, V., Herzog, B. & Aleixandre, R. (2008). Consumo de drogas y su percepción por parte de inmigrantes latinoamericanos. *Psicothema, 20*, 403-407.

Vega, A., Aramendi, P. & Garín, S. (2012). Adolescentes y jóvenes: desde las conductas de riesgo a la inclusión social. *Zerbitzuan*, *52*, 167-178.

Wahl, A. M. & Eitle, T. M. (2010). Gender, acculturation and alcohol use among Latina/o adolescents: a multi-ethnic comparison. *Journal Inmigrant Minor Health, 12*, 153-165. doi:10.1007/s10903-008-9179-6.

Development and validation of the alcohol Expectancy Questionnaire Short Form (EQ-SF)

Desarrollo y validación de la versión corta del cuestionario sobre expectativas de los efectos del alcohol (EQ-SF)

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Abstract

Alcohol expectancies are proximal variables to alcohol use and misuse. In recent decades, different measures have been developed to assess this construct. One of the most frequently used and recommended instruments is the Expectancy Questionnaire (EQ; Leigh y Stacy, 1993). Our aim is to develop a short version of the EQ (EQ-SF) for suitable use in time-limited administrations. Two samples, adolescents (N = 514, 57.20% females) and adults (N = 548, 61.50% females), completed the EQ together with alcohol-use measures. Different item selection strategies were applied to select the 24 items. The EQ-SF structure was explored using confirmatory factor analysis, and measurement invariance was tested running a multi-group analysis comparing groups by sex and age. Reliability was tested using Cronbach's alpha and omega coefficients. Concurrent validity was investigated with regression analyses. The EQ-SF showed acceptable between-groups measurement invariance. Alphas and omegas ranged from .77 to .93. Positive expectancies predicted both alcohol use and alcohol-related problems. Negative expectancies predicted alcohol-related problems. Sex and age moderated these associations. Males with high positive alcohol expectancies showed higher alcohol consumption than females, while adults with high negative alcohol expectancies showed greater alcohol-related problems than adolescents. Different evidence on the validity and reliability of the EQ-SF suggest that it is a suitable instrument to assess alcohol expectancies in the Spanish population.

Keywords: expectancies; alcohol; EQ-SF; assessment; psychometric properties.

Resumen

Las expectativas sobre los efectos del alcohol son una variable proximal al consumo de alcohol. Uno de los instrumentos más usados y recomendados para evaluar este constructo es el Expectancy Questionnaire (EQ; Leigh y Stacy, 1993). El objetivo es desarrollar una versión corta del EQ (EQ-SF) útil para administraciones en las que el tiempo de evaluación es reducido. Dos muestras, una de adolescentes (N = 514, 57,20% mujeres) y una de adultos (N = 548, 61,50% mujeres), completaron el EQ y diversas medidas sobre consumo de alcohol. Se utilizaron diversas estrategias para seleccionar los 24 ítems. Se exploró la estructura del EQ-SF mediante análisis factoriales confirmatorios y la invarianza de medida entre sexos y grupos de edad realizando análisis multigrupo. Se calculó la fiabilidad de las escalas mediante el alfa de Cronbach y el coeficiente omega, y la validez concurrente a través de análisis de regresión. La invariancia entre grupos fue aceptable. Los coeficientes alfa y omega iban de ,77 a ,93. Las expectativas positivas predijeron la cantidad de alcohol consumida y los problemas derivados del consumo, mientras que las negativas predijeron los problemas derivados. Sexo y edad moderaron estas asociaciones. Los hombres con elevadas expectativas positivas bebían más que las mujeres, mientras que los adultos con elevadas expectativas negativas mostraron mayores problemas derivados del consumo que los adolescentes. Las diferentes fuentes de evidencia sobre la validez y fiabilidad del EQ-SF sugieren que es un instrumento adecuado para evaluar las expectativas sobre los efectos del alcohol en población española.

Palabras clave: expectativas; alcohol; EQ-SF; evaluación; propiedades psicométricas.

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Alcohol is one of the most frequently consumed psychoactive drugs worldwide, and one of the most serious global public health problems (World Health Organization, 2014). In fact alcohol is one of the five main causes of illness, disability and death for all age groups (Lim et al., 2012; Rehm et al., 2009), and is the first risk factor that contributes to disability-adjusted life years (DALYs) in young individuals aged 10-24 (Gore et al., 2011). In this scenario, accurate and efficient assessments of the risk and protective factors for alcohol use have become an essential practice to improve current prevention and intervention programs (Hawkins, Catalano, & Miller, 1992; Hawkins, Catalano, & Arthur, 2002).

Alcohol expectancies (AEs) have repeatedly predicted current and future alcohol use (Jones, Corbin, & Fromme, 2001). AEs are defined as positive and negative beliefs about cognitive, affective and behavioral effects of alcohol (Jones et al., 2001; Reich, Below, & Goldman, 2010). Specifically, positive AEs have been related to alcohol use in adolescents (Camacho et al., 2013; Ibáñez et al., 2015; Morean, Zellers, Tamler, & Krishnan-Sarin, 2016) and adults (Harnett, Lynch, Gullo, Dawe, & Loxton, 2013; Mezquita et al., 2015; Wardell, Read, Colder, & Merrill, 2012). Positive AEs have been linked to alcohol-related problems (i.e., abuse and dependence symptoms and other behavioral problems associated with excessive drinking) in younger (Grigsby, Forster, Unger, & Sussman, 2016; Ibáñez et al., 2015; Morean et al., 2016) and older individuals (Corbin, Iwamoto, & Fromme, 2011; Dunne, Freedlander, Coleman, & Katz, 2013; Mezquita et al., 2015).

As negative AEs have been less frequently examined, their role in alcohol use and abuse is not that clear. Different studies have shown a slightly protective role for alcohol use (Camacho et al., 2013; Ibáñez et al., 2015; Leigh & Stacy, 2004), whereas other authors have failed to replicate these associations (Mezquita et al., 2015; Nicolai, Moshagen, & Demmel, 2012; Pabst, Kraus, Piontek, Mueller, & Demmel, 2014).

Regarding alcohol-related problems (APs), there is evidence for positive associations between negative AEs and APs in younger (Ibáñez et al., 2015) and older participants (Dunne et al., 2013; Mezquita et al., 2015; Pabst et al., 2014). These positive associations between negative AEs and APs suggest that negative AEs might be the result of bad alcohol consumption experiences rather than their cause (Spillane, Cyders, & Maurelli, 2012). In line with this idea, differences between AEs when comparing clinical and non clinical samples are bigger for negative AEs than for positive AEs (Li & Dingle, 2012). Despite previous findings, more research is needed to clarify the role of negative AEs in different alcohol-related outcomes.

As a result of existing research into AEs, the assessment of alcohol expectancies has been recommended in prevention and treatment programs of alcohol use and abuse (Cox & Klinger, 2004). Several measures of AEs exist (see Camacho et al., 2013 for a discussion on existing measures). Of these, the Expectancy Questionnaire (Leigh & Stacy, 1993) is frequently recommended because it includes both positive and negative expectancies, and presents good reliability and predictive validity indices (Mezquita et al., 2015; Monk & Heim, 2016). The EQ is composed of 34 items. Exploratory and confirmatory factor analyses have consistently replicated a hierarchical model with eight first-order factors (i.e. four positive and four negative AEs) and two second-order factors, namely positive and negative AEs (Camacho et al., 2013; Leigh & Stacy, 1993). Positive expectancies of alcohol use include social positive (i.e., social facilitation), fun (i.e., positive affect potentiation), sex (i.e., sexual disinhibition) and tension reduction (i.e., stress relief). Negative expectancies are social negative (i.e., antisocial effects of alcohol use), emotional negative (i.e., negative emotional states due to alcohol consumption), physical negative (i.e., undesirable physical effects), and cognitive negative (i.e., cognitive impairment).

Although the EQ is a psychometrically robust measure, as far as we know no other research has tested whether the EQ can be reduced to a more manageable set of items. Item reduction is a highly recommended practice in both clinical and research settings, especially when several questionnaires are to be administered together, and particularly in samples of youngsters for whom long scales could be a problem due to tiredness. As AEs are only one of the psychological factors involved in alcohol use, reducing the number of items in the EQ might facilitate the inclusion of a measure of AEs in future studies or treatment programs for which administration time is limited. Therefore, the aim of the present study was to create a reduced version of the Expectancy Questionnaire (EQ-SF) with adequate psychometric properties. Like the EQ, we expected the EQ-SF to receive evidence from different sources about its validity and reliability in the assessment of alcohol expectancies. Specifically, we hypothesized that the EQ-SF: a) will present a similar hierarchical structure to the original EQ; b) the measure will be invariant between males and females and between adolescents and adults; c) its scales will present between good and excellent reliability indices; and d) associations with alcohol-related outcomes will be in line with previous studies (see the Introduction) (Camacho et al., 2013; Leigh & Stacy, 1993). Finally, as some differences in the association of alcohol expectancies and alcohol-related outcomes have been found among sex and age groups (Monk & Heim, 2016; Nicolai et al., 2012), we explored whether sex and age would moderate associations.

Method

Procedures

The development and evaluation of the EQ-SF was carried out with two different Spanish samples: adolescents and adults.

Adolescents sample. Seven high schools from rural and urban areas of the provinces of Valencia and Castellon participated in this study. Research assistants asked students to answer questionnaires in class during three different sessions, and helped them whenever necessary. All the participants returned an informed consent form signed by their parents. Adolescents voluntarily completed the questionnaires and did not receive any compensation for participating in the research.

Adult sample. Adults were recruited via advertisements placed at the Universitat Jaume I. Participants were offered to respond to the most of the battery of questionnaires (i.e., demographics, alcohol expectancies, alcohol-related problems among others) either in a paper-and-pencil format (academic year 2011) or online (academic year 2012). To ensure that participants understood the SDUs concept and completed the alcohol use measure correctly, they all responded to the AIS-UJI in the lab. All the participants signed an informed consent form and were paid 30 euros for their collaboration.

Participants

Adolescents sample. The sample that completed the EQ was composed of 514 secondary education students, aged 14-17 years (57.20% females; mean age = 15.21, *SD* = .63). Of these, 428 (83.3%) completed a measure of alcohol use (57.24% females; mean age = 15.18; SD = .61). This subsample showed differences in age ($t = 2.63$; $p = .01$) and sex ($\chi^2 = 10.65$; $p = .001$) compared to the total sample. However, they did not show any significant differences in the EQ. Once again, only a subsample of 393 students (76.5% of the initial sample) completed a measure of alcohol-related problems (57.25% females; mean age = 15.16; *SD* = .60). As in previous analyses, differences in age ($t = 3.09$; $p = .002$) and sex ($\chi^2 = 10.65$; $p = .001$) were found, but not in alcohol expectancies. The reasons for not completing the second and third administrations could not be changed (i.e., not wanting to continue or to participate, or missing school). Most participants were born in Spain (81.1%). The remaining countries of origin obtained very low rates and are not presented herein for the sake of simplicity.

Adults sample. The adults sample comprised 548 participants aged 18-53 years (61.50% females, mean age = 24.19, *SD* = 3.92). Of these, 202 (36.9%) completed the survey online (except for the AIS-UJI, which was completed in the lab), while 326 (59.5%) completed it as a paper-and-pencil format in the lab. Of the total sample, 64.00% were students, 23.30% were active workers, 8.30% were unemployed, and the remaining 4.40% presented other job situations. Regarding level of educational, almost all participants had either completed university (77.1%) or secondary (22.3%) education studies. Only a few participants (0.6%) indicated lower levels of educational. The vast majority of participants were Spanish (91.8%).

Measures

Alcohol Expectancies. The Spanish version (Camacho et al., 2013) of the Expectancy Questionnaire (EQ; Leigh & Stacy, 1993) consists of 34 items and uses a 6-point Likert format to measure positive and negative AEs. Positive AEs (19 items) comprise expectancies about social facilitation, positive affect potentiation, sexual disinhibition and tension reduction; negative AEs (15 items) include expectancies about antisocial effects of alcohol, negative emotional states, as well as undesirable physical and cognitive effects. Items are short phrases prefaced by "When I drink alcohol..." Respondents have to indicate the likelihood of the indicated consequences happening to them when they drink. Non drinkers were asked to answer according to what they thought would have happened if they had drunk. The Spanish version of the EQ showed reliability indices that ranged from good to excellent in previous studies ($.76 \leq \alpha \leq .93$) (Camacho et al., 2013).

Alcohol use. The Alcohol Intake Scale-UJI (AIS-UJI; Grau & Ortet, 1999) is a 21-item self-report questionnaire of alcohol use-related variables. In this research we used questions that asked about the participants' alcohol consumption during the week (Monday–Thursday) and at weekends (Friday–Sunday) in Standard Drink Units (SDUs; Rodríguez-Martos, Gual, & Llopis, 1999). In Spain, one SDU is the equivalent to 10 g of alcohol (Rodríguez-Martos et al., 1999).

Alcohol misuse. The Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001) includes 10 items on 3- and 5-point Likert scales. They are grouped into three subscales, namely "alcohol consumption," "alcohol dependence", and "harmful alcohol use". We used the last two scales (seven items) to assess alcohol-related problems, which presented an alpha coefficient of .76.

Missing data imputation

In the item analysis and structure analysis, of the possible values of the EQ (1062 participants x 34 items), missing values only amounted to 0.31%. Consequently, we followed a person mean imputation approach on each EQ scale (Bentler, 2006). In the regression analyses we used the pair-wise deletion of the missing values because missing completely at random (MCAR) could not be guaranteed.

Data analyses

Item selection strategies. The aim of this study was to reduce the number of the original scale items without losing conceptual breadth, while maintaining psychometric robustness. For this reason, we reduced only the length of the scales with more than three items; i.e., social positive, fun positive, sex positive, physical negative, and cognitive negative.

We used different item-selection strategies. Following Meyers' recommendations (2014), we combined classical item analysis and Rasch measurement procedures to identify the best items for each scale. First, we performed item-total correlations (i.e., classical item discrimination). By considering the number of points on the Likert scales, the discrimination index should be .58, or higher. Second, we evaluated person-item outfit and infit using the unweighted mean square (UMS) and the weighted mean square (WMS) fit statistics, respectively. Values between .80 and 1.20 are recommended in both cases, where more attention should be paid to high values rather than low ones (Meyer, 2014). In order to illustrate the probability of a response, as well as the item's contribution to measurement given different values of the theta scores, the characteristic curve and the item information function were also performed. Before running the item analysis, the dimensionality and local independence assumptions were confirmed.

As the EQ has been previously used in adolescents and adults samples, and in males and females, we decided to create a short version that would be useful for all these populations. In order to test this, we carried out a differential item functioning (DIF) analysis. We calculated the magnitude of the differences in performance in each item between groups (males/females; adolescents/adults) using the standardized P-DIF (sP-DIF). A standardized P-DIF value below .05 indicates no differences in performance between groups; values between .05 and .09 indicate a moderate difference; values of .10 or above indicate a large amount of DIF, and are a matter of concern (Meyer, 2014).

In addition to these statistical considerations, when items showed good fit indices, we preferred items that pointed out the different aspects of an expectancy factor; i.e., when the content of two items was similar, only one was included in the short form. We also made some theoretical considerations; i.e., we did not remove any items that were a crucial component of an expectancy scale (see Kuntsche & Kuntsche, 2009 for a similar procedure). All the item analyses were performed with the jMetrik software (Meyer, 2014).

Testing the questionnaire structure. Following previous research conducted with the EQ (Camacho et al., 2013; Leigh & Stacy, 1993), and after selecting the final 24 items, a hierarchical confirmatory factor analysis (CFA) was performed. In the CFA, we followed the Satorra-Bentler's robust method as our data were non normally distributed. In order to consider that a model has an *excellent* fit, the $_{S\text{-}B}$ χ^2 must be non significant. However as this is infrequent in a CFA, using other fit indices to compare competing models is a common practice. Our study included the non normed fit index (NNFI), the comparative fit index (CFI), the incremental fit index (IFI), the root mean square error of approximation (RMSEA), the 90% CI of RMSEA, and Akaike's information criterion (AIC). The models with NNFI, CFI, and IFI values above .90, a RMSEA value below.10, and low AIC scores, are argued to have an *acceptable* fit. The models with CFI, IFI and NNFI ≥ .95 and RMSEA ≤ .06 are considered to present an *adequate* fit (Byrne, 2006).

Reliability of scores. To test the reliability of the eight subscales and the two second-order factors, we calculated the Cronbach's alphas and omegas (Dunn, Baguley, & Brunsden, 2014) with 95% CI using the jMetriK (Meyer, 2014) and the R 3.4.0 (R Core Team, 2013) software, respectively.

Measurement invariance across sex and age groups. Structural Equation Models (SEM) were performed to determine the measurement invariance of the questionnaire across males and females, and also across different age groups. In the first step, we tested the model separately for each sex and age group. Second, we explored configural invariance across groups by performing a multi-group analysis between the sex and age groups. Then we tested metric, scalar, and error invariances (Milfont & Fischer, 2010). Differences in CFI and RMSEA were not allowed to exceed .01 and .015, respectively, to be able to consider that there were no differences between groups when adding constraints (Chen, 2007; Cheung & Rensvold, 2002). All the CFAs were performed with version 6.1 of the EQS software (Bentler & Wu, 2002).

Relation between alcohol expectancies and alcohol outcomes. We conducted descriptive analyses with version 22 of the SPSS statistic package (IBM Corp, 2013). The same software was used to carry out the regression analyses to investigate the associations between alcohol expectancies and alcohol-related outcomes. We also calculated the moderation effect of the age and sex groups in these associations. In the regression we entered the standardized scores of the following variables: sex, age group, and positive and negative AEs; and the interactions of sex x positive AEs, age x positive AEs, sex x negative AEs, and age x negative AEs. We performed graphical representations as a *post hoc* test whenever any significant interactions appeared (Dawson, 2014).

Results

Item selection

The results of the Item and Rash analyses are presented in Table 1, while the item response category characteristic curves and the item information curves are graphically represented in Figure 1.

Similar plots emerged in the items of the same subscale (Figure 1) and all of them showed positive discrimination indices (Table 1). However item 24, which corresponded to the physical negative scale, and item 30, which corresponded to the fun positive scale, showed low discrimination indices (Table 1). Based on the UMS and WMS statistics, we ruled out items 1 and 9, which both corresponded to the social positive scale, and item 8, which corresponded to the cognitive negative scale. When taking the remaining

Table 1. *Item and Rasch Analyses.*

Subscale	Item	Discrimination	Difficulty	UMS	WMS	sP-DIFF Sex	sP-DIFF Age
Social positive	1. I am more accepted socially	.59	1.30	1.84	1.37	.04	.02
	9. I am more outgoing	.73	-.74	1.22	1.28	-.01	.03
	16. It is easier for me to socialize	.81	-.17	.85	.86	.00	-.00
	23. I am able to talk more freely	.74	-.17	1.03	1.11	.01	-.06
	28. I am friendlier	.83	-.20	.67	.71	.00	-.01
	32. I feel more social	.82	-.02	.77	.78	.01	.02
Fun positive	**3. I enjoy the buzz**	.74	-.33	1.11	1.19	-.01	.05
	10. I feel happy	.75	-.27	1.00	1.03	-.02	-.03
	18. I have a good time	.80	-.93	.85	.88	.00	-.03
	25. It is fun	.80	-.06	.80	.82	.01	.01
	30. I feel pleasant physical effects	.51	1.61	1.90	1.50	.02	.00
	33. I feel good	.82	-.02	.68	.70	.00	-.00
Sex positive	5. I have more desire for sex	.83	-.39	.96	.99	-.01	.03
	12. I become more sexually active	.79	.61	1.21	1.14	-.01	-.02
	19. I am more sexually responsive	.87	.11	.76	.77	-.00	.00
	27. I am more sexually assertive	.82	-.32	1.06	1.10	.02	-.01
Physical negative	**6. I feel sick**	.61	.23	.96	.94	-.02	-.02
	15. I get a hangover	.59	-1.00	1.13	1.18	.01	.04
	24. I experience unpleasant physical effects	.53	.81	1.08	1.01	.01	-.01
	29. I get a headache	.66	-.04	.86	.85	-.00	-.01
Cognitive negative	8. I am less alert	.61	-.59	1.35	1.41	.02	.05
	17. I become clumsy or uncoordinated	.73	.04	.83	.83	.01	.02
	26. I have problems driving	.67	.33	.99	.97	-.01	-.06
	31. I can't concentrate	.73	-.04	.86	.89	-.00	-.01
	34. I have problems with memory and concentration	.69	.25	.97	.95	-.01	.01

Note. In bold, items that were retained in the EQ-SF. The positive sP-DIF values favor the female and adolescent participants.

items, items 23 and 26 showed the lowest discrimination indices on their scales, as well as medium-sized differences in performance between adolescent and adult participants. Accordingly, they were excluded from the short version of the EQ. For the final selection of items, we preferred those with better indices and less content overlap. The item composition of the EQ-SF is marked in bold in Table 1 and Figure 1.

Sources of validity evidence of the EQ-SF structure

As seen in Table 2, the fit indices of the hierarchical CFA using EQ-SF were between acceptable (i.e., NNFI, CFI, and IFI) and adequate (RMSEA). The item-to-subscale factor loadings were between .67 and .89 (Figure 2).

Measurement invariance of the scale across sex and age groups

Measurement invariance of the EQ-SF across sex and age was tested using the hierarchical cumulative steps recommended by Milfont and Fischer (2010). When the hierarchical model was tested separately for each sex and age group, the fit indices were acceptable (Table 2). Next configural invariance was calculated. The results from the multigroup CFA for the sex and age groups also showed acceptable fit indices (Table 2). Adding constraints between the factor loadings (metric invariance), intercepts (scalar invariance) and error variances of both groups resulted in going below ΔCFI and ΔRMSEA than .01 and .015, respectively. This suggests a full measurement invariance of the EQ-SF between males and females and between adolescents and adults.

Reliability of scores

The Cronbach's alphas and omega coefficients of the scales with 95% CI are presented in Table 3. The reliability of all the scales went from good to excellent (all the alpha and omega coefficients between .77 and .93).

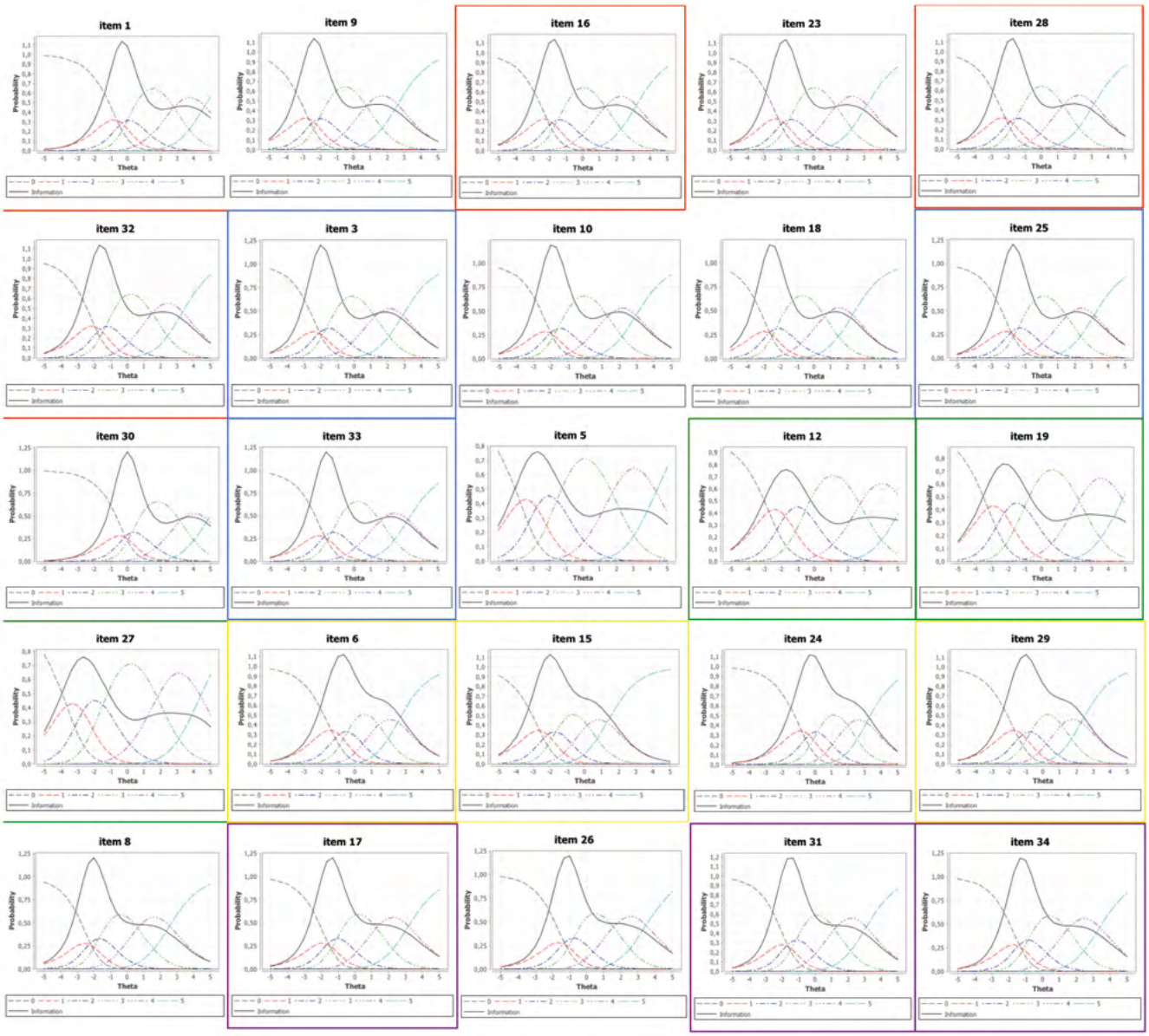

Figure 1. Item response category characteristic curves and item information curves of the EQ scales with more than three items. The final 3-item solution for the social positive, fun positive, sex positive, physical negative and cognitive negative scales of the EQ-SF is marked in red, blue, green, yellow and purple, respectively.

Sources of validity evidence in relation with other variables

The descriptive analyses gave higher scores in sex positive, social negative expectancies, and alcohol use in males than females, but effect size was small (Table 3). Adults scored significantly higher than adolescents for all the expectancies scales, except for emotional negative expectancies, and also for all the alcohol-related outcomes. The magnitude of the effect was: low for the fun positive, tension-reduction positive, social negative, physical negative, cognitive negative, negative expectancies, and alcohol-related problems; medium for the social positive, sex positive, positive expectancies and weekdays SDUs; large for the weekend SDUs (Table 3).

The regression analyses showed that positive expectancies predicted alcohol use (SDUs) during the week and at weekends, while positive and negative expectancies predicted alcohol-related problems (Table 4). Five significant interactions were also found. Given the number of independent variables, we set a more restrictive p value of .005 (Bonferroni correction). The interactions that remained significant after this correction were the sex x positive expectancies in the prediction of weekday and weekend SDUs, and the age x negative expectancies in the prediction of alcohol-related problems (see Figure 3 for a graphical representation). The effect of positive alcohol expectancies on alcohol use during the week and at weekends was much stronger for males than for females. Being an

Table 2. *Analysis of the Model Fit of the EQ-SF.*

		$_{S\text{-}B}\chi^2$	df	NNFI	CFI	IFI	RMSEA (90% CI)	AIC
Hierarchical CFA	Whole sample	948.79	243	.938	.945	.945	.052 (.049/.056)	462.79
	Males	570.05	243	.925	.934	.934	.056 (.050/.062)	84.05
	Females	620.59	243	.947	.953	.953	.050 (.045/.054)	134.59
	Adolescents	601.29	243	.942	.949	.949	.054 (.048/.059)	115.29
	Adults	617.54	243	.922	.932	.932	.053 (.048/.058)	131.54
Sex invariance	Configural invariance	1189.02	486	.938	.945	.946	.052 (.048/.056)	217.14
	Metric invariance	1213.76	502	.939	.945	.945	.052 (.048/.055)	209.76
	Scalar invariance	1356.91	526	.936	.944	.944	.053 (.049/.056)	304.91
	Error variance invariance	1367.55	550	.937	.945	.945	.051 (.048/.055)	267.55
Age invariance	Configural invariance	1217.78	486	.933	.941	.941	.053 (.050/.057)	245.78
	Metric invariance	1266.42	502	.932	.938	.938	.054 (.050/.057)	262.42
	Scalar invariance	1605.36	526	.932	.940	.941	.056 (.052/.059)	553.36
	Error variance invariance	1729.11	550	.926	.935	.936	.058 (.054/.061)	629.11

Note. All $_{S\text{-}B}\chi^2$ values were significant at p < .001.

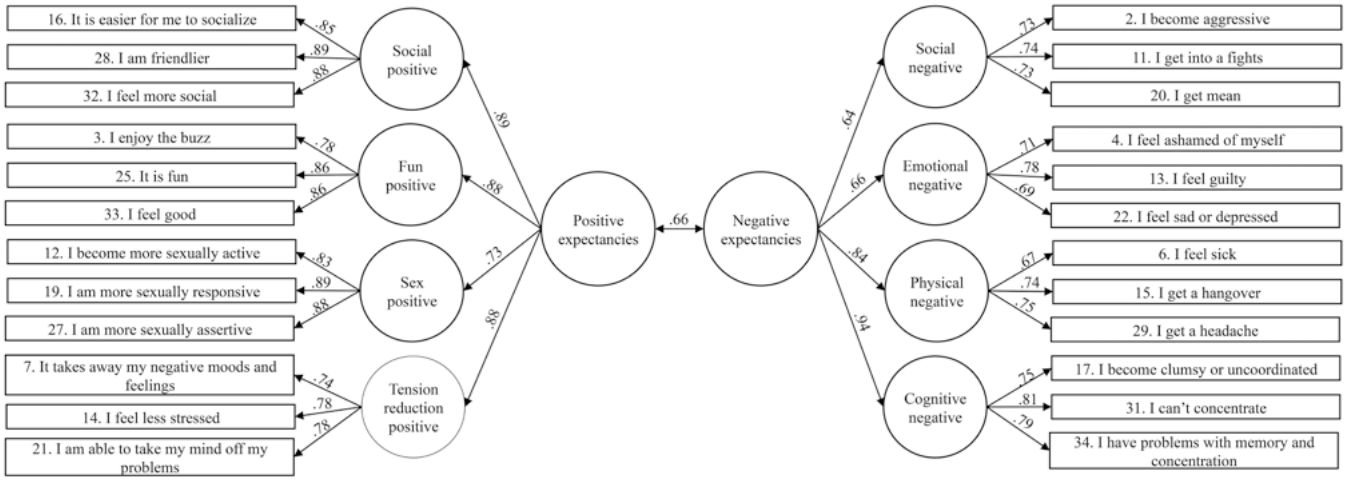

Figure 2. The CFA of the EQ-SF. Factor loadings are on the unidirectional lines, correlations are on the bidirectional lines. They were all significant at p< .001.

Table 3. *Descriptive Analysis and Reliability Indices for the EQ-SF, t-Test Values, and Cohen's d Associated with Sex and Age.*

	Whole sample				Males		Females				Adolescents		Adults			
	X	SD	α	Ω	X	SD	X	SD	*t*	*d*	X	SD	X	SD	*t*	*d*
Social positive	7.81	3.89	.91 (.90/.92)	.91 (.89/.92)	7.58	3.82	7.97	3.93	-1.63	-.10	6.72	4.10	8.84	3.37	-9.23***	-.56
Fun positive	8.40	3.59	.87 (.85/.88)	.87 (.85/.89)	8.33	3.68	8.45	3.52	-0.55	-.03	7.60	4.05	9.16	2.90	-7.25***	-.44
Sex positive	6.00	4.10	.90 (.89/.91)	.90 (.89/.92)	6.53	3.97	5.65	4.15	3.47**	.22	4.82	4.00	7.12	3.87	-9.52***	-.58
Tension positive	6.57	3.62	.81 (.79/.83)	.81 (.78/.83)	6.56	3.65	6.58	3.60	-.05	-.01	6.19	3.69	6.93	3.51	-3.36**	-.21
Social negative	2.66	2.84	.77 (.75/.80)	.78 (.75/.81)	3.35	3.02	2.19	2.61	6.67***	.41	2.90	3.14	2.44	2.51	2.66**	.16
Emotional negative	3.40	2.92	.77 (.74/.79)	.78 (.75/.80)	3.45	2.93	3.36	2.92	.48	.03	3.41	3.02	3.39	2.83	.15	.01
Physical negative	6.45	3.62	.77 (.74/.79)	.77 (.74/.80)	6.17	3.50	6.64	3.69	-2.07*	-.13	5.83	3.81	7.03	3.33	-5.49***	-.34
Cognitive negative	6.55	3.65	.82 (.81/.84)	.83 (.81/.85)	6.70	3.63	6.45	3.65	1.06	.07	5.91	3.82	7.15	3.37	-5.62***	-.34
Positive expectancies	28.79	12.81	.93 (.92/.94)	.93 (.92/.93)	29.00	12.92	28.65	12.75	.44	.03	25.32	13.55	32.04	11.15	-8.85***	-.54
Negative expectancies	19.07	10.29	.88 (.87/.89)	.88 (.87/.89)	19.68	10.50	18.65	10.14	1.59	.10	18.06	11.08	20.01	9.41	-3.10**	-.19
Weekdays SDU	1.17	2.59	-	-	1.74	3.32	.79	1.85	5.72***	.35	.45	1.57	1.74	3.05	-7.95***	-.53
Weekend SDUs	6.32	6.51	-	-	7.63	8.02	5.44	5.06	5.24***	.33	3.21	4.54	8.76	6.77	-14.58***	-.96
Alcohol-related problems	1.67	2.86	-	-	2.00	3.53	1.45	2.28	2.89**	.19	1.37	2.87	1.89	2.84	-2.79**	-.18

Note. Cronbach's alphas and omega coefficients with 95% CI. The Cohen's d values of .20, .50, and .80 correspond to the small, medium and large effect sizes, respectively (Cohen, 1992). *p< .05, **p< .01, ***p< .001.

Table 4. *Regression Analyses between Expectancies and Alcohol Outcomes, Including Moderation of Sex and Age.*

	Weekdays SDUs			Weekends SDUs			Alcohol-related problems		
	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2
Sex	-.19	.000	.12*	-.18	.000	.31**	-.08	.007	.15*
Age	-.22	.000		-.36	.000		-.02	.612	
Positive expectancies	.13	.000		.31	.000		.26	.000	
Negative expectancies	.01	.895		-.03	.377		.13	.000	
Sex x positive expectancies	-.11	.002		-.12	.000		-.09	.015	
Sex x negative expectancies	.06	.089		.01	.783		-.04	.251	
Age x positive expectancies	-.07	.059		-.07	.022		-.01	.758	
Age x negative expectancies	-.01	.820		-.04	.187		-.12	.001	

*p ‹ ,05,**p ‹ ,001.

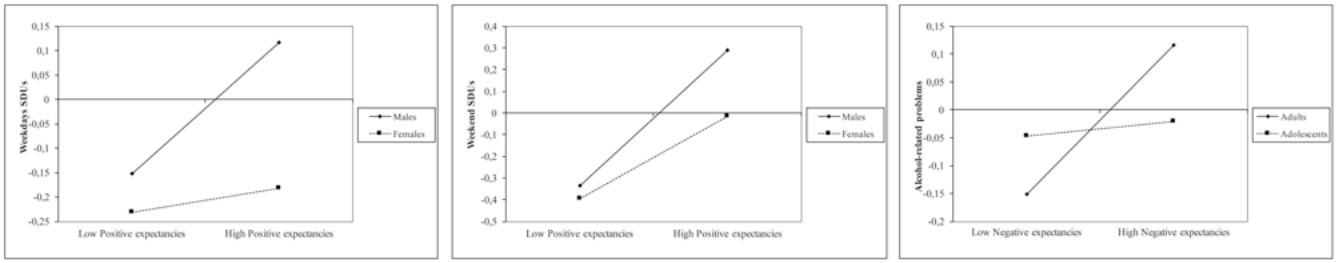

Figure 3. Graphical representation of the moderation effect of sex and age on the relationship between alcohol expectancies and alcohol-related outcomes.

adult and presenting high negative expectancies were also associated with higher alcohol-related problems.

Discussion

The present study aimed to develop a short version of the EQ (Camacho et al., 2013; Leigh & Stacy, 1993) by Item and Rasch analyses. We also hypothesized that evidence for validity and reliability of the EQ-SF to assess alcohol expectancies would emerge from difference sources: the study of the questionnaire structure, the measurement of invariance between the age and gender groups, the reliability indices of the scales, and the ability of the questionnaire scales to predict alcohol outcomes. The moderating role of sex and age in these last associations was also explored.

The results of the Item and Rasch analyses provided a 24-item solution in which all the items showed adequate discrimination, as well as good UMS and WMS indices (Meyer, 2014). When item functioning was compared between the sex and age groups, the magnitude of the differences in the performance in the 24-item solution indicated no differences in performance between groups, except for item 3 when comparing adolescents and adults. As this difference was only moderate, the item was kept because it is a crucial component of the fun expectancy scale.

The CFA results showed that the hierarchical model with the 24-item solution presented not only similar fit indices to the original questionnaire (Leigh & Stacy, 1993), but also better indices than the previous Spanish adaptation of the long measure (Camacho et al., 2013). It is also noteworthy that all the factor loadings were adequate and much higher than the recommended cut-off of .30 (Brown, 2006). These findings, together with the fact that the questionnaire showed measurement invariance among males, females, adolescents and adults, suggested that the EQ-SF offers satisfactory construct validity. It is also worth noting that, even though a drop in internal consistency is frequently seen when the number of items lowers (Field, 2009), the expectancy subscales in the EQ-SF displayed good to excellent internal consistency (all the values were higher than .70), and values were similar to those found in the original long version of the EQ. These results, together with those of the omega coefficients, suggest that the EQ-SF is a reliable measure to assess alcohol expectancies in the Spanish population.

When we looked at the criterion validity of the EQ-SF, i.e., the ability of alcohol expectancies to predict alcohol use, our results were consistent with previous findings. Specifically, positive expectancies predicted alcohol-related outcomes (Corbin et al., 2011; Harnett et al., 2013; Morean et al., 2016). However, the effect of positive expectancies on alcohol use was much stronger on weekend SDUs than on weekday SDUs. It is noteworthy that previous results on expectancies and different alcohol use patterns during the week and at weekends were obtained, in part with the present sample (Camacho et al., 2013; Ibáñez et al., 2015;

Mezquita et al., 2015). Nonetheless, other studies on related variables, such as reasons for drinking, have also shown greater associations of drinking motives with weekend SDUs than with weekdays SDUs in adolescents (Mezquita et al., 2018) and adult samples (Mezquita, Ibáñez, Moya, Villa, & Ortet, 2014; Studer et al., 2014). Taken together, these findings suggest that when a large quantity of alcohol is consumed at weekends, expectancies about the positive effects of alcohol use, as well as the motivation to experience these effects, might play a salient role in the decision to drink.

Apart from the aforementioned findings, our interaction analyses showed that the enhancing effect of positive expectancies in alcohol use was much stronger for males than for females. This is important because, even when no differences between the mean levels of positive expectancies between sex groups were found, presenting a higher level of positive expectancies was a higher risk factor of alcohol consumption for males than for females.

Regarding the association between negative alcohol expectancies and alcohol-related outcomes, once the effect of positive expectancies was controlled for, negative expectancies were positively related only to alcohol-related problems. This finding is consistent with previous studies conducted with young adults (Pabst et al., 2014). No moderation effect of sex and age was found in the relationship between negative alcohol expectancies and alcohol use. However, being an adult exacerbated the risk of showing alcohol-related problems when high negative expectancies were present. These results are in line with the hypothesis that negative expectancies are the result of having bad experiences with alcohol, as opposed to the cause (Spillane et al., 2012).

The present study is not without its limitations. First, the study design was cross-sectional and, consequently, causal inferences should be taken cautiously; e.g., while expectancies may be a risk factor for alcohol use and misuse, they might also be a consequence of experimenting with the drug. Second, as the adolescent sample was assessed during different sessions due to time restrictions, part of the sample did not complete all the questionnaires, which compromises the generalizability of the results. These findings support the need for shorter measures, as in the EQ-SF. Third, the procedure followed to assess each sample was different (i.e., with *vs.* without economic compensation, online *vs.* on paper responses). This, together with the fact that all the used measures were based on self-reports, could affect the validity of the findings. Finally, we did not include important measures of alcohol use other than SDUs and alcohol problems, such as binge drinking or heavy drinking, which could be highly informative.

In light of the aforementioned limitations, implications for further research are proposed. First, prospective and experimental studies are necessary to disentangle the direction of the associations between alcohol expectancies and alcohol use. Second, the psychometric properties of the EQ-SF (i.e., sources of validity) would be strengthened by exploring their associations with important alcohol research outcomes not included in the present research. It is also essential to replicate previous findings with the EQ using the EQ-SF and to test if the measure is useful for assessing alcohol expectancies in different languages and cultures (Mezquita, Stewart, Kuntsche, & Grant, 2016).

To conclude, the present research shows the utility of the EQ-SF to assess alcohol expectancies among Spanish adolescents and adults in a shortened form. The sound psychometric properties and the similarity of the results, compared to those reported in previous studies using the EQ (Camacho et al., 2013; Leigh & Stacy, 1993), suggest that the short 24-item version of the EQ is a good alternative to the long questionnaire in time-limited assessments; e.g., with adolescents or clinical samples. Attention should be paid to positive expectancies at all ages, but especially in males because they might be an underlying factor to explain increased alcohol use. Moreover, clinicians might wish to explore negative expectancies as they seem to be a consequence of a longer experience with alcohol effects and could be an indicator of alcohol-related problems.

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Conflicts of interest

The authors declare no conflict of interest.

References

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B. & Monteiro, M. G. (2001). *AUDIT - The Alcohol Use Disorders Identification Test: Guidelines for use in primary care* (2nd ed.). Geneva: World Health Organization.

Bentler, P. M. (2006). *EQS 6 structural equations program manual*. Encino, CA: Multivariate Software Inc.

Bentler, P. M. & Wu, E. J. C. (2002). EQS 6 for Windows User's Guide [Computer software]. Software, Inc.

Brown, T. A. (2006). *Confirmatory factor analysis for applied research*. New York: Guildord Press.

Byrne, B. M. (2006). *Structural equation modeling with EQS: Basic concepts, applications, and programming* (2nd ed.). Mahwah, NJ: Erlbaum.

Camacho, L., Mezquita, L., Ibáñez, M. I., Moya, J., Villa, H., Viruela, A. & Ortet, G. (2013). Spanish adaptation of the Expectancy Questionnaire (EQ) about alcohol effects in

adolescents. *Psicothema, 25*, 529–535. doi:10.7334/psicothema2012.354.

Chen, F. F. (2007). Sensitivity of goodness of fit indexes to lack of measurement invariance. *Structural Equation Modeling: A Multidisciplinary Journal, 14,* 464–504. doi:10.1080/10705510701301834.

Cheung, G. & Rensvold, R. (2002). Evaluating goodness-of-fit indexes for testing measurement invariance. *Structural Equation Modeling, 9,* 233–255. doi:10.1207/S15328007SEM0902_5.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 110,* 155–159. doi:10.1037/0033-2909.112.1.155.

Corbin, W. R., Iwamoto, D. K. & Fromme, K. (2011). A comprehensive longitudinal test of the acquired preparedness model for alcohol use and related problems. *Journal of Studies on Alcohol and Drugs, 72,* 602–10. doi:10.15288/jsad.2011.72.602.

Cox, W. M. & Klinger, E. (2004). A Motivational Model of Alcohol Use (MMAU): Determinants of use and change. InW. M. Cox & E. Klinger (Eds.), *Handbook of motivational counseling: Concepts, approaches, and assessment.* (pp. 121–138). New York: John Wiley & Sons Ltd.

Dawson, J. F. (2014). Moderation in management research: What, why, when, and how. *Journal of Business and Psychology, 29,* 1–19. doi:10.1007/s10869-013-9308-7.

Dunn, T. J., Baguley, T. & Brunsden, V. (2014). From alpha to omega: A practical solution to the pervasive problem of internal consistency estimation. *British Journal of Psychology, 105,* 399–412. doi:10.1111/bjop.12046.

Dunne, E. M., Freedlander, J., Coleman, K. & Katz, E. C. (2013). Impulsivity, expectancies, and evaluations of expected outcomes as predictors of alcohol use and related problems. *The American Journal of Drug and Alcohol Abuse, 39,* 204–10. doi:10.3109/00952990.2013.765005.

Field, A. (2009). *Discovering statistics using SPSS.* (3rd ed.). London: Sage publications.

Gore, F. M., Bloem, P. J. N., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., … Mathers, C. D. (2011). Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet, 377,* 2093–102. doi:10.1016/S0140-6736(11)60512-6.

Grau, E. & Ortet, G. (1999). Personality traits and alcohol consumption in a sample of non-alcoholic women. *Personality and Individual Differences, 27,* 1057–1066. doi:10.1016/S0191-8869(99)00047-1.

Grigsby, T. J., Forster, M., Unger, J. B. & Sussman, S. (2016). Predictors of alcohol-related negative consequences in adolescents: A systematic review of the literature and implications for future research. *Journal of Adolescence, 48,* 18–35. doi:10.1016/j.adolescence.2016.01.006.

Harnett, P. H., Lynch, S. J., Gullo, M. J., Dawe, S. & Loxton, N. (2013). Personality, cognition and hazardous drinking: Support for the 2-Component Approach to Reinforcing Substances Model. *Addictive Behaviors, 38,* 2945–8. doi:10.1016/j.addbeh.2013.08.017.

Hawkins, J. D., Catalano, R. F. & Arthur, M. W. (2002). Promoting science-based prevention in communities, *27,* 951–976. doi:10.1016/S0306-4603(02)00298-8.

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.

Ibáñez, M. I., Camacho, L., Mezquita, L., Villa, H., Moya-Higueras, J. & Ortet, G. (2015). Alcohol expectancies mediate and moderate the associations between Big Five personality traits and adolescent alcohol consumption and alcohol-related problems. *Frontiers in Psychology, 6.* doi:10.3389/fpsyg.2015.01838.

IBM Corp. (2013). IBM SPSS Statistics for Windows, Version 22.0 [Computer software]. Armonk, NY: IBM Corp.

Jones, B. T., Corbin, W. & Fromme, K. (2001). A review of expectancy theory and alcohol consumption. *Addiction, 96,* 57–72. doi:10.1080/09652140020016969.

Kuntsche, E. & Kuntsche, S. (2009). Development and validation of the Drinking Motive Questionnaire Revised Short Form (DMQ-R SF). *Journal of Clinical Child and Adolescent Psychology, 38,* 899–908. doi:10.1080/15374410903258967.

Leigh, B. C. & Stacy, A. W. (1993). Alcohol outcome expectancies: Scale construction and predictive utility in higher order confirmatory models. *Psychological Assessment, 5,* 216–229. doi:10.1037/1040-3590.5.2.216

Leigh, B. C. & Stacy, A. W. (2004). Alcohol expectancies and drinking in different age groups. *Addiction, 99,* 215–227. doi:10.1111/j.1360-0443.2003.00641.x.

Li, H. K. & Dingle, G. A. (2012). Using the Drinking Expectancy Questionnaire (revised scoring method) in clinical practice. *Addictive Behaviors, 37,* 198–204. doi:10.1016/j.addbeh.2011.10.002.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., … Ezzati, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380,* 2224–2260. doi:10.1016/S0140-6736(12)61766-8.

Meyer, J. P. (2014). *Applied Measurement with JMetrik.* New York: Taylor & Francis.

Mezquita, L., Camacho, L., Ibáñez, M. I., Villa, H., Moya-Higueras, J. & Ortet, G. (2015). Five-Factor Model and alcohol outcomes: Mediating and moderating role of alcohol expectancies. *Personality and Individual Differences, 74,* 29–34. doi:10.1016/j.paid.2014.10.002

Mezquita, L., Ibáñez, M. I., Moya-Higueras, J., Villa, H., Arias, B., Fañanás, L. & Ortet, G. (2018). Psychometric Properties of Drinking Motives Questionnaire-Revised

(DMQ-R) in Spanish Adolescents. *European Journal of Psychological Assessment, 34*, 145-153. doi:10.1027/1015-5759/a000319.

Mezquita, L., Ibáñez, M. I., Moya, J., Villa, H. & Ortet, G. (2014). A longitudinal examination of different etiological pathways to alcohol use and misuse. *Alcoholism, Clinical and Experimental Research, 38,* 1770–9. doi:10.1111/acer.12419.

Mezquita, L., Stewart, S.H., Kuntsche, E. & Grant, V.V. (2016). Cross-cultural examination of the five-factor model of drinking motives in Spanish and Canadian undergraduates. *Adicciones, 28,* 215-220. doi:10.20882/adicciones.822.

Milfont, T. L. & Fischer, R. (2010). Testing measurement invariance across groups: Applications in cross-cultural research. *International Journal of Psychological Research, 3,* 111–121. doi:10.21500/20112084.857.

Monk, R.L. & Heim, D. (2016). Expectativas relacionadas con el alcohol en adultos y adolescentes: semejanzas y diferencias. *Adicciones, 28,* 35-40. doi:10.20882/adicciones.788.

Morean, M. E., Zellers, S., Tamler, M. & Krishnan-Sarin, S. (2016). Psychometric validation of measures of alcohol expectancies, retrospective subjective response, and positive drinking consequences for use with adolescents. *Addictive Behaviors, 58,* 182–187. doi:10.1016/j.addbeh.2016.02.036.

Nicolai, J., Moshagen, M. & Demmel, R. (2012). Patterns of alcohol expectancies and alcohol use across age and gender. *Drug and Alcohol Dependence, 126,* 347–53. doi:10.1016/j.drugalcdep.2012.05.040.

Pabst, A., Kraus, L., Piontek, D., Mueller, S. & Demmel, R. (2014). Direct and indirect effects of alcohol expectancies on alcohol-related problems. *Psychology of Addictive Behaviors, 28,* 20–30. doi:10.1037/a0031984.

R Core Team (2013). R: A language and environment for statistical computing [Computer software]. R Foundation for Statistical Computing, Vienna, Austria.

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.

Reich, R. R., Below, M. C. & Goldman, M. S. (2010). Explicit and implicit measures of expectancy and related alcohol cognitions: A meta-analytic comparison. *Psychology of Addictive Behaviors, 24,* 13–25. doi:10.1037/a0016556.

Rodríguez-Martos, A., Gual, A. & Llopis, J. J. (1999). The "standard drink unit" as a simplified recording system of alcohol consumption and its measurement in Spain. *Medicina Clínica, 112,* 446–450.

Spillane, N. S., Cyders, M. A. & Maurelli, K. (2012). Negative urgency, problem drinking and negative alcohol expectancies among members from one First Nation: a moderated-mediation model. *Addictive Behaviors, 37,* 1285–8. doi:10.1016/j.addbeh.2012.06.007.

Studer, J., Baggio, S., Mohler-Kuo, M., Dermota, P., Daeppen, J.B. & Gmel, G. (2014). Differential association of drinking motives with alcohol use on weekdays and weekends. *Psychology of Addictive Behaviors, 28,* 651–658. doi:10.1037/a0035668.

Wardell, J. D., Read, J. P., Colder, C. R. & Merrill, J. E. (2012). Positive alcohol expectancies mediate the influence of the behavioral activation system on alcohol use: a prospective path analysis. *Addictive Behaviors, 37,* 435–43. doi:10.1016/j.addbeh.2011.12.004.

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

Spanish version validation of the Marihuana Motives Measure in a drug-consuming adolescent sample

Propiedades psicométricas de la versión española del Marihuana Motives Measure en población adolescente consumidora

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Abstract

Introduction: Cannabis is the illicit drug mostly widely consumed by adolescents in Spain. The understanding of consumption motives is an important factor for intervention. In Spain, there are no available instruments for their evaluation, hence, the goal of this paper is to study the psychometric properties of the Marihuana Motives Measure (MMM) in a sample of adolescent consumers.

Material and Method: Firstly, translation and back-translation was performed. A total of 228 adolescent consumers of cannabis were evaluated. Factorial analysis was conducted, and the reliability of the total scores and of each scale of the questionnaire was studied through Cronbach's alpha. Test-retest reliability was analyzed through interclass correlations. Validity evidence of the MMM was examined through correlations between current cannabis use, subjective consumption effects measured with the Addiction Research Center Inventory (ARCI), and personality measured with the Millon Adolescent Clinical Inventory (MACI).

Results: High reliability was observed in total score of the MMM (Cronbach α = .86), and high and moderate reliability for each of the five factors obtained in the factorial analysis of the MMM, Social = .82, Enhancement = .72, Coping = .83, Expansion = .74, and Conformity = .64. Significant correlations were also observed between cannabis consumption motives and subjective effects, and between consumption motives and personality.

Conclusion: The Spanish version of the MMM shows a similar factorial structure as the one obtained by the original author, and its measures are reliable and valid for the study of cannabis consumption motives in adolescent consumer population.

Keywords: Adolescents; addiction; cannabis; motives; Marihuana Motives Measure.

Resumen

Introducción: El cannabis es la sustancia ilegal que más consumen los adolescentes españoles. Entender los motivos de consumo es un factor importante para la intervención. Actualmente no existe en España un instrumento para su evaluación. El objetivo del presente trabajo es estudiar las propiedades psicométricas de la versión española del cuestionario *Marihuana Motives Measure* (MMM) en una población de adolescentes consumidores.

Material y Métodos: Se llevó a cabo una traducción y retrotraducción del MMM. Un total de 228 adolescentes consumidores de cánnabis fueron evaluados. Se realizó un análisis factorial y se estudió la fiabilidad de la puntuación total y de cada una de las escalas del cuestionario a partir del Alfa de Cronbach. El estudio de la evidencia de validez del MMM se realizó mediante el examen de las correlaciones entre el uso actual de cánnabis, los efectos subjetivos del consumo través del cuestionario ARCI (*Addiction Research Center Inventory*) y la personalidad, mediante el cuestionario MACI (*Millon Adolescent Clinical Inventory*).

Resultados: Se observó una alta fiabilidad de la puntuación total del MMM (Alfa de Cronbach= 0,86) y entre alta y moderada para cada uno de los cinco factores obtenidos al realizar el análisis factorial del MMM, *Social* = 0,82; *Enhancement* = 0,72; *Coping* = 0,83; *Expansion* = 0,74; *Conformity* = 0,64. Además, se observaron correlaciones significativas tanto entre motivos de consumo de cannabis y efectos subjetivos, así como entre motivos de consumo y personalidad.

Conclusiones: La versión española del MMM muestra una estructura factorial similar a la obtenida por el autor original y sus medidas resultan fiables y válidas para el estudio de los motivos de consumo de cánnabis en población adolescente consumidora.

Palabras clave: Adolescentes; adicción; cannabis; motivos; Marihuana Motives Measure.

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Introduction

Cannabis is the illicit drug most frequently consumed by Spanish adolescents (ESTUDES, 2014). In addition, cannabis use is currently one of the causes that generates a greater demand for psychiatric treatment in this age group in Spain (ESTUDES, 2014), and the most highly present in patients who visit child-juvenile psychiatric emergency units (Arias Constantí et al., 2010). This situation is particularly concerning when considering the verified evidence of the multiple negative consequences associated with cannabis consumption (Degenhardt et al., 2010; Fox, Towe, Stephens, Walker, & Roffman, 2011), with school impact being one of the main ones (Horwood et al., 2010).

Possibly as a result of this increase in adolescent consumers of cannabis and the serious repercussions of its consumption, in recent years, studies on the effectiveness of treatments have increased (Fox, Towe, Stephens, Walker, & Roffman, 2011). The studied modalities include interventions based on motivational strategies that have proven to be effective in adolescent consumers (Fox, Towe, Stephens, Walker, & Roffman, 2011). Motivational models of substance use suggest that there are different motives for consumption and they consider these reasons to be essential in order to understand the context and the circumstances of addictive behavior, such as *when* or *where* people consume or with what *frequency* or which *amounts* (Cooper, 1994).

Taking as reference point the motivational model, Simons, Correia, Carey, and Borsari (1998) developed the *Marihuana Motives Measure* (MMM) to quantify the motives for cannabis consumption. The study of the psychometric properties of the MMM indicated that the instrument could be grouped into 5 subscales or factors with an internal consistency between .93 and .85. The original scales were called: 1) *Enhancement* or consumption to improve positive feelings, 2) *Social* or consumption to improve reinforcement and social cohesion, 3) *Coping* or consumption to cope with negative emotions, 4) *Conformity* or consumption to avoid social rejection, and 5) *Expansion* or consumption to expand consciousness. The different scales or motives included in the MMM have been proven to be predictors of cannabis-related problems (Simons, Correia, & Carey, 2000). Specifically, studies show the importance of the Social and Conformity motives for consumption as predictors of the consequences of consumption (Simons, Gaher, Correia, Hansen, & Christopher, 2005), as well as a positive correlation between the number of acknowledged reasons for consumption and greater severity (Zvolensky et al., 2007). Moreover, the psychometric properties of the MMM have been studied in non-Anglo-Saxon samples (Chabrol, Ducongé, Casas, Roura, & Carey, 2005), confirming the 5-factor structure and high internal validity of the questionnaire.

The motives for consumption have been studied mainly following two lines of research. The first line, focused on consumption and the perception of discomfort reduction, shows a consistent association between the subjective effects reported by cannabis users and their motives for using it, for example, the motivation to consume to deal with a worrisome situation and the reported relaxation effect (Dekker, Linszen, & De Haan, 2009; Scherrer et al., 2009; Zeiger et al., 2012). The second line of study aims to analyze the relationship between consumption motives and personality (Tragesser, Trull, Sher, & Park, 2008; Littlefield, Sher, & Wood 2010a; Littlefield, Sher, & Wood 2010b). These studies show that consumption motives are a clear mediator between personality and consumption (Adams, Kaiser, Lynam, Charnigo, & Milich, 2012). Specifically, personality factors related to negative affect are mainly associated with the consumption of cannabis and other substances due to Coping motives (Mezquita et al., 2011). Conversely, personality factors related to extraversion, sensation seeking, and impulsivity are primarily associated with the use of cannabis and other substances due to Enhancement motives (Mezquita et al., 2011).

The above-mentioned evidence emphasizes the need to identify and improve our understanding of the motives for consumption in adolescents. In addition, it emphasizes the importance of taking these motives into account as a key aspect for the development of pharmacological, psychotherapeutic, and preventive interventions (Hartwell, Back, McRae-Clark, Shaftman, & Brady, 2012). Given that experiences related to substance use during adolescence can affect and produce changes in the expectations of consumption at later stages (Monk, & Heim, 2016), understanding the motives for cannabis use at this stage can be an important factor for the development of interventions (Fox, Towe, Stephens, Walker, & Roffman, 2011). In addition, such assessment must be specific to each substance, as different reasons for consumption for different substances have been observed (Hartwell, Back, McRae-Clark, Shaftman, & Brady, 2012), as well as different motives for consumption according to the comorbid mental disorders presented by patients (Thornton et al., 2012). Therefore, the existence of measurement instruments, specific to the adolescent cannabis-consumer population, which evaluate the intention to consume (Lloret Irles, Morell-Gomis, Laguía, & Moriano, 2018), the motivation to change (Kaminer, Ohannessian, McKay, & Burke, 2016), or the reasons for consumption are very relevant for the planning and monitoring of clinical interventions. However, research on the motives for cannabis use in adolescent population that presents a mental disorder is scarce, and there are no studies in our environment. One of the reasons for the lack of studies is the non-existence of instruments validated in Spanish to measure consumption motives.

The goal of the present paper is to study the psychometric properties of the MMM in a sample of adolescents with cannabis use disorder. We will thus try to offset the lack of measuring instruments with good psychometric properties, specific to each substance. The specific objectives of the paper are to translate and adapt the MMM questionnaire of Simons, Correia, Carey, and Borsari (1998) and to analyze the structure, reliability, and validity of the Spanish version of the MMM scores. We expected that the Spanish version of the MMM would show a factorial structure similar to the original version (Simons, Correia, Carey, & Borsari, 1998), good reliability of the instrument's total score and of the scores of each of its subscales. We also expected that the indices found would not be very different from the validation carried out in French adolescent population (Chabrol, Ducongé, Casas, Roura, & Carey, 2005).

Method

Participants

The participants were selected during the years 2011-2014 through consecutive sampling among the users of the Adolescents' Unit of Addictive Behaviors of the Psychiatry Service of the Sant Joan de Déu Hospital, Barcelona. The sample was made up of 228 participants, 64.9% (n = 148) boys and 35.1% (n = 80) girls, with an average age of 15.7 years (SD = 1.3).

Instruments

Consumption Record: cannabis use was assessed with the administration of an ad hoc clinical interview, recording, among other data, the following: age of consumption onset (first consumption), regular consumption age (1 monthly consumption), and current consumption (last 6 months and last month)

Psychopathology: we used the semi-structured interview *Kiddie-Sads-Present and Lifetime* (K-SADS-PL), Spanish version (Mattos & Rohde, 2007), which follows DSM-IV criteria. The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents, according to DSM-IV criteria. This scale is administered to the parents and the patient separately, obtaining a final score that collects all the information sources used.

Motives for consumption: we used the Spanish translation of the *Marihuana Motive Measure* (MMM; Simons, Correia, Carey, & Borsari, 1998). This is a 25-item questionnaire with a Likert-type response format. In adult population, the study of the factorial structure has yielded 5 factors (Expansion, Social, Conformity, Enhancement and Coping) and it has been shown to be reliable and valid (see Introduction).

Subjective effects of cannabis use: we administered the *Addiction Research Center Inventory* (ARCI; Martin, Sloan, Sapira, & Jasinski, 1971), validated in Spanish population by Lamas, Farré, Llorente, and Camí (1994). This questionnaire consists of 49 items and 5 scales: the *Pentobarbital-Chlorpromazine-Alcohol Group* (PCAG) scale, which measures the intensity of the sedative effect on a range from 0 to 15; the *Morphine-Benzedrine Group* (MBG) scale, which measures euphoria on a range from 0 to 16; the *Lysergic-acid-Dyethyl-amide* (LSD) scale, which measures dysphoria and somatic symptoms, ranging from 0 to 14; the *Benzedrine Group* (BG) scale, which measures stimulation and ranges from 0 to 13; and the *Amphetamine* (A) scale measures empirical phenomena and ranges from 0 to 11 (Busquets, Torrens, Soler, Farré, & Bulbena, 2005). In the validated version in Spanish population, the reliability coefficients of the scales are: PCAG .87; MBG .81; LSD .55; BG .79; and A .49.

Personality: We administered the *Millon Adolescent Clinical Inventroy* (MACI; Millon, 1993). It consists of 160 items with a true/false format and is organized into 31 scales, 27 with clinical significance, 12 personality patterns, 8 of expressed concerns, and 7 of clinical symptoms. In the validated version in Spanish population, the alpha coefficients of the basic personality scales range from (submissive) .74 to .90 (self-demeaning) (Millon, 2004).

Procedure

The translation of the questionnaire was carried out following the guidelines for the translation and adaptation of tests of the International Test Commission (Muñiz, Elosua, & Hambleton, 2015). After assessing the relevance of the construct and the questionnaire, we contacted the author (Dr. Simons), who gave his authorization for the study of the MMM. Subsequently, two independent translations were made. On one hand, the authors of the study jointly conducted a translation, paying special interest to the linguistic, cultural, and psychological characteristics of the adapted text. On the other hand, the questionnaire was translated separately by three professional Spanish-speaking experts in child-adolescent mental health and with a high level of English. The two translations were subsequently compared, differences were discussed, and the final text was agreed on at a meeting in which the different translators participated. At this stage, consensus was sought, taking into account the linguistic, conceptual, and cultural aspects. Then, an official translator made the back-translation, which was sent to Dr. Simons. Once the modifications proposed by the original author of the questionnaire were considered by the authors, appropriate changes were made, and the translation was approved. This translation was administered to 15 patients of the Adolescent Unit of Addictive Behaviors independent interviews, in which comprehension of the questionnaire's content was assessed. The results of these interviews were then discussed by the authors, and changes were made

by consensus. The final version was again reviewed by the official translator and approved by all the professionals who had participated in the translation.

After obtaining the approval of the Ethics Committee of the Sant Joan de Déu Hospital, the study began. Participants were informed about the study and, if they agreed to participate, they signed their consent before being included. Inclusion criteria were being younger than 18 years of age and presenting abuse or dependence criteria (DSM-IV-TR) at the time of the evaluation. The only exclusion criterion was presenting acute mental pathology that would hinder comprehension of the questionnaires. No participant was excluded by this criterion.

The assessment is part of the routine diagnostic Protocol of the Adolescent Unit of Addictive Behaviors, where we performed three 45-minute visits. In the first visit, the psychiatric and toxicological anamnesis was performed, consumption was recorded, and urine analysis was carried out. In the second visit, the *Kiddie-Sads* interview was administered to the parents or guardians and the questionnaires were handed to the adolescent. On the third visit, the questionnaires were collected, and we supervised that they were duly completed, thus avoiding missing values. Twenty-four patients did not correctly complete all the questionnaires, so they were not included in the study.

Statistical analysis

The study of the psychometric properties of the MMM was carried out following these steps: study of the factor structure, reliability of the measures, and evidence of validity. The statistical software used was SPSS 21 (IBM Corp, 2010). The factor structure of the MMM was studied using principal component factor analysis. As we expected that the different subscales would correlate with each other (Simons, Correia, Carey, & Borsari, 1998), we performed a principal components procedure with promax rotation. The name of retained factors was determined based on the analysis of two criteria. The first was the eigenvalues of the extracted factors, and the second was based on the study of the change of slope in the scree plot of the different factors. After determining the number of factors, we studied the reliability of the different measures of the questionnaire via Cronbach's alpha. We also analyzed test-retest reliability of the measure in a subsample (n = 24) of the total sample, using intraclass correlations. The study of the evidence of validity of the measures of the MMM was carried out with Pearson correlations between the measures of the subscales of the MMM and the MACI and ARCI questionnaires.

Results

Participants

The mean age of onset of consumption was 12.9 years (*SD* = 1.7) and the mean age of regular consumption was 13.8 years (*SD* = 1.5). No significant differences were observed in the distribution by sex of the onset age of consumption (boys: M = 13.07, SD = 1.69 vs. girls: M = 12.81, SD = 1.6, $t_{(226)}$ = 1.14, p = .25), or in the age of regular consumption (boys: M = 13.86, SD = 1.44 vs. girls: M = 13.59, SD = 1.59, $t_{(226)}$ = 1.34, p = .19).

Regarding preferences, 83.8% of the adolescents reported preferring marijuana (n = 191) to hashish, with no sex differences (boys: 81.8 % (n = 121) vs. girls: 87.5 % (n = 70); $\chi^2_{(1)}$ = 1.26, p = .26). The participants were diagnosed according to the DSM IV-TR criteria, 32.9% (n = 75) with cannabis abuse and 67.1% (n = 153) with cannabis dependency, with no significant sex differences ($\chi^2_{(1)}$ = 0.009; p = .93).

Regarding comorbid psychopathology, we observed that 62.7% (n = 143) presented a conduct disorder (a syndrome that includes disruptive behavior disorder not otherwise specified, oppositional defiant disorder, and dysocial disorder), 11.8% (n = 27) presented attention-deficit and hyperactivity disorder, 11.8% (n = 27) presented a psychotic disorder, 11.0% (n = 25) presented an affective disorder (grouping major depressive disorder and bipolar disorder), 3.1% (n = 7) presented an adaptive disorder, 3.9% (n = 9) presented an eating disorder, and 4.4% (n = 10) had an anxiety disorder.

Factor structure of the MMM

Principal components factor analysis yielded a five-factor structure with eigenvalues equal to or greater than 1.00. The resulting structure explained 53.8% of the variance. The factor analysis showed a Kaiser-Meyer-Olkin index of 0.82 and a significant Bartlett's sphericity test ($C^2(300)$ = 1917.02, p < .001), indicating that the procedure selected to reduce the scale was appropriate. The five-factor solution was the same as that of the original scale with the exception of items 15 and 5 (see Table 1). Regarding these items, our results showed that Item 15 ("Because I feel safer and more confident") loaded on the Coping factor instead of on the Social factor, and Item 5 ("to be sociable") had a similar loading on all factors (see Table 1).

Reliability of the measures of the MMM

The reliability study showed a high reliability of the total MMM score (Cronbach α = .86) and values between moderate and high in the scores of each of the subscales (Social = .82, Enhancement = .72, Coping = .83, Expansion = .74, and Conformity = .64), as shown in Table 1. Pearson correlations of the subscale scores ranged between .21 in the scores of Conformity and Expansion and .57 in the scores of Enhancement and Social (in all cases, ps = .01).

The intraclass correlation between the test-retest of the different MMM scores revealed correlations equal to or less than .42 . The correlations were significant for all scores (Coping = .40, Enhancement = .35, Expansion = .30,

Table 1. *Exploratory factor analysis of the Marihuana Motives Measure*

Items	Coping	Expansion	Social	Enhancement	Conformity
(1) To forget my worries	.89		-.21		
(17) To forget problems	.89		-.11		
(4) Because it helps me feel better when I am depressed or nervous	.79		.13		
(6) To encourage me when I'm in a bad mood	.65		.22		
(15) Because I feel safer and more confident	.43	.35			
(23) To understand things differently		.81			-.13
(24) To expand the boundaries of my conscience		.76			-.23
(21) To get to know me better		.68		-.13	
(22) Because it helps me to be more creative and original		.67	-.17	.21	
(25) To be more open to new experiences		.57			
(16) To celebrate special occasions with friends			.86		
(14) Because it makes celebrations more fun			.84		
(3) Because it helps me to have fun			.77		
(11) Because it makes social events more fun			.70	.15	
(7) Because I like the feeling				.79	-.19
(13) Because it gives me pleasure				.70	.16
(10) To get high	.15			.65	
(18) Because it's fun			.23	.54	.10
(9) Because it's exciting				.45	
(20) So as not to feel isolated from others		-.12	-.15		.80
(12) To feel that I am part of the group of people who like me					.79
(19) So others will like me			-.12	.13	.73
(2) Because my friends insist	-.14	.34		-.21	.43
(8) Because the others would laugh at me for not doing so		-.22	.20	-.13	.35
(5) To be sociable	.23	.23	.21	-.12	-.28
Eigenvalue	6.09	2.38	1.97	1.84	1.17
% variance	24.34	9.51	7.89	7.36	4.68
Cronbach's alpha	.83	.74	.82	.72	.65

Note. Values below 0.10 were not included in the table. Rotated promax matrix.

and MMM total = .42; all ps £ . 05), with the exception of Social (.22, p = .12) and Conformity (.001).

Evidence of the validity of the MMM measures

Evidence of the validity of the MMM was studied through the correlations between the current use of cannabis, the questionnaire of subjective effects of consumption (ARCI), and the personality questionnaire (MACI). Consumption of cannabis in the last 6 months was significantly and positively associated with the motives of Coping (r = .22, p = .001) and Enhancement (r = .21, p = .002). However, cannabis use was not significantly associated with the motives of Expansion (r = .11, p = .09), Social (r = .08, p = .220), or Conformity (r = -.06, p = .359). As seen in Table 2, the subjective effects of cannabis showed significant correlations with the consumption motives.

Table 2. *Validity of the MMM using Pearson's correlations with the ARCI and MACI questionnaires*

	MMM Factors				
	Coping	Expansion	Social	Enhancement	Conformity
ARCI					
Sedation	.26**	.12	.11	.07	.17*
Euphoria	.35**	.39**	.24**	.22**	.16*
Dysphoria	.24**	.09	.15*	.12	.11
Stimulation	.08	.18**	-.03	.01	-.007
Empirical phenomena	.28**	.29**	.08	.007	.22**
MACI					
Introversive	.21**	.08	-.01	-.06	.23**
Inhibited	.21**	.01	.02	-.05	.29**
Doleful	.38**	.15	-.07	-.07	.21**
Submissive	.12	-.09	.03	-.08	.21**
Dramatizing	-.27**	.01	.03	.04	-.27**
Egocentric	-.26**	.04	.004	.07	-.24**
Unruly	-.004	.14	.02	.14	-.15
Forceful	.06	.07	-.001	.13	-.05
Conforming	-.27**	-.22**	-.004	-.10	-.06
Oppositional	.29**	.21**	-.01	-.01	.04
Self-demeaning	.33**	.12	-.05	-.002	.24**
Borderline Tendency	.29**	.008	.002	.003	.11

Note. MMM = Marihuana Motives Measure; ARCI = Addiction Research Center Inventory; MACI = Millon Adolescent Clinical Inventory. *p = .05. **p = .01.

The Coping scale of the MMM correlated significantly with all the scales of the ARCI (r = .24 to .35; $p \leq .01$), with the exception of the Stimulation scale. The Expansion scale correlated significantly with the Euphoria (p <.001) and Stimulation (p = .006) scales of the ARCI. The Social scale correlated significantly with the Euphoria (p = .002) and Dysphoria/Somatic Symptoms scales of the ARCI (p = .03). The Enhancement scale only correlated significantly with the Euphoria scale of the ARCI (p = .001). Finally, the Conformity scale correlated significantly with the Empirical symptoms (p = .001), Euphoria (p = .02) and Sedation scales (p = .01). Lastly, the 5 MMM scales showed significant correlations with the personality scales of the MACI, mainly the Coping and Conformity scales of the MMM (see Table 2), which showed positive correlations with almost all the MACI scales, with the exception of Histrionic (-.29, p = .01), Egocentric (-.26, p = .01) and Conforming scales (-.27, p = .01), which correlated negatively with Coping; and Histrionic (-.27, p = .01) and Egocentric scales (-.24, p = .01) which showed negative correlations with Conformity (see Table 2).

Discussion

This study was conducted to analyze the psychometric properties of the Spanish version of the *Marihuana Motive Measure* (MMM) in a sample of adolescents with cannabis use disorder. As expected, the factorial analysis of the questionnaire shows a five-factor structure similar to the one proposed by the original author. Furthermore, the results of reliability and evidence of validity of the different measures of the Spanish version of the MMM indicate that it is a good tool to use with Spanish adolescent consumers of cannabis.

The Spanish version of the MMM showed the same structure factor as the original version (Simons, Correia, Carey, & Borsari, 1998). The solution of five factors (Social, Coping, Conformity, Enhancement and Expansion) obtained is the same as the structure of the original scale with the exception of Items 15 and 5. Item 15 ("because I feel safer and more confident) loaded on the Coping factor instead of on the Social factor. The loading of this item on the Coping factor can be explained by the patients' perception that consumption helps them to deal with complex situations or emotions with more assuredness and self-confidence. On the other hand, the loading of Item 5 ("to be sociable") was similar on all factors, mainly on Coping, Expansion and Social. This could be interpreted as patients' perception that consumption provoked greater social disinhibition and therefore, it would help some of them to better cope with social situations that caused more anxiety or inhibition. This would also explain the negative loading of these items on the Conformity factor.

Internal consistency is good for the total scale and for each of the subscales, except for Conformity, which shows moderate internal consistency. A possible explanation is adolescents' difficulty to acknowledge the fear of being rejected. That is, when an adolescent is in a context of consumer friends and does not have sufficient skills to cope with it, these friends exert direct or social pressure to consume. On the other hand, this moderate consistency may be due to the fact that the Conformity factor includes items both related to the desire or need to feel acknowledged or approved by the group and items related to fear of rejection. The desire or need for approval and the fear of rejection may not be present in all patients, or they may not be aware of the relationship between these two motives and their own gregarious behavior. Finally, another explanation of this moderate consistency could be that the tools designed for adults do not necessarily behave the same way when applied to adolescents. The difference in development, consumption patterns, the relationship with family and friends may affect the factor structure of the instruments (Martin, Copeland, Gilmour, Gates, Swift, 2006). However, it can be considered that the factor structure of the Spanish translation shows good content validity for the different scales of the questionnaire.

Regarding the test-retest reliability of the scores, we expected low correlations between the two measurements with the MMM. This hypothesis was developed because the MMM assesses motives for consumption at a certain moment and, according to the motivational model, these motives are susceptible to change depending on the process of change experienced by the patient. In this sense, the results observed in this study show a low intraclass correlation (Fleiss, 1986), which, as mentioned, indicates that the motives for consumption are modified by the psychotherapeutic intervention. The only exception was the intraclass correlation of the Coping scale. This could indicate the patients' need to consume to ease their discomfort, which has been called the "spiral of discomfort", that is, the maintenance of consumption not in order to have fun but to avoid suffering, which is an indicator of the severity of consumption. This statement gains consistency when considering that the study sample was of patients presenting cannabis use disorder with a high prevalence of comorbid mental disorders. The results raise the possibility that the MMM is an adequate tool to monitor change in the therapeutic process.

The association observed between the motives and the subjective effects of the consumption is significant and points in the same direction, as observed in other studies (Deker, Linszen, & De Haan, 2009). In this regard, the results of this study shows that the Coping motives are related to the scales of Sedation and Dysphoria, a relationship that can be understood as the patient's need to seek emotion regulation and relaxation. Likewise, the

positive relationship between Coping and the subjective effect of Euphoria may indicate the energy gain secondary to decreasing discomfort. The Conformity factor is related to the Sedation scale, indicating that those who consume due to Conformity motives may be seeking to decrease the discomfort or concern they feel when they are exposed to interpersonal contexts. Finally, the relationship observed between Expansion motives for consumption and the Empirical phenomena scale is direct, as the two questionnaires evaluate the same construct, although the relationship is not perfect. This moderate relationship of the two phenomena can be explained because the Expansion factor measures motivation and the scale of Empirical phenomena, symptoms.

The intensity of the relationship between the MMM motives and scales of the ARCI is consistent with the study of Dekker, Linszen, and De Haan (2009), in which cannabis users reported many more positive than negative effects in the modulation of affect and the increase of relaxation when consuming, and moderately more positive than negative effects in the increase of energy and socialization. In fact, these authors state that the self-reported effects of consumption could be grouped into 4 main groups: to improve positive feelings, to relieve dysphoria, social reasons, and reasons related to disease and the sedative effects of the medication.

These results are important because they show the importance of the need to open future lines of research that will help clarify the relationship between the subjective response to drug consumption as a significant predictor of subsequent use and abuse of this substance, as noted in previous studies (Littlefield, Sher, & Wood, 2010a; Adams, Kaiser, Lynam, Charnigo, & Milich, 2012). In this sense, these investigations indicate that positive consumer experiences are associated with more prolonged use and an increased risk of abuse and dependency, whereas negative experiences are associated with less duration and frequency of consumption (Scherrer et al., 2009; Zeiger et al., 2012).

The study of the relationship between motives to consume and personality is based on the mediating role of the motives between personality and consumption (Littlefield, Sher, & Wood, 2010a; Adams, Kaiser, Lynam, Charnigo, & Milich, 2012), and also on the conceptualization that personality traits contribute to the motivation of behavior in general and to the motivation to consume substances, in particular (Littlefield, Sher, & Wood, 2010b). Our results revealed a relationship between Coping motives and personality traits associated with insecurity and the presence of interpersonal difficulties. Also, as expected, the Conformity motives are related to submissive personalities and assertiveness difficulties. These results are consistent with other studies that have found a clear and direct association between neuroticism and Coping motives (Kuntsche, Knibbe, Gmel, & Engels, 2006). On the other hand, previous research had linked impulsiveness to the Enhancement motive (Littlefiel, Sher, & Wood, 2010), arguing that the latter acts as a mediator between extroversion and alcohol consumption (Adams, Kaiser, Lynam, Charnigo, & Milich, 2012). However, we could not confirm these findings in our study because the basic personality scales were not significantly related to the Enhancement motive. This contradictory result could be explained by the type of questionnaire used in this study, designed to assess pathological personality traits, and by the fact that it was applied to a sample of patients who were being treated for the use of cannabis-related problems.

Despite the interest of the study results, there are some limitations that must be taken into account when generalizing the results, which underscore the need for studies that confirm the psychometric properties of the MMM in other samples. First, the sample was made up of adolescents who sought treatment for cannabis use disorder; therefore, the generalization of the results to community samples of adolescents with more normative consumption patterns should be carried out with caution. However, as discussed in the introduction, this study is the first one conducted with patients presenting cannabis use disorder. In this regard, the results of this study show that the measures of the MMM of the motives for consumption, when used in adolescents with cannabis consumption disorder, shows psychometric properties similar to those obtained by the original author (Simon et al., 1998) and in French adolescent population (Chabrol, Ducongé, Casas, Roura, & Carey, 2005), revealing the usefulness of the MMM in this population and the need for future studies of adolescents with more normative consumption. Secondly, the procedure used for the study of reliability was not the most appropriate (Zumbo et al., 2007). Although the Cronbach alpha coefficient of consistency has been widely used and is still used as a internal consistency index in questionnaires with a Likert-type response scale, this index may be an attenuated estimate of the lower limit of reliability, especially when the items have few response options and their asymmetry is high. In these cases, the ordinal alpha coefficient is more appropriate (Gadermann, Guhn, & Zumbo, 2012). Although the MMM has five responses, and the response asymmetry of the items approaches 0 in most of the items, this does not allow us to infer a low attenuation of Cronbach's alpha (Gadermann, Guhn, & Zumbo 2012), and although the estimate performed in this paper allows us to compare it with previous studies (Simon et al., 1998, Chabrol, Ducongé, Casas, Roura, & Carey, 2005), future studies should confirm the reliability of the measurements using the ordinal alpha coefficient. Thirdly, the lack of tools validated in our context to assess the evidence of the instrument's validity more consistently forced us to study the validity based on the use of measures

of indirectly related constructs. Despite these limitations, we believe that the results of this work are of great importance, as it focuses on the validation of a tool that will allow us to develop future research in a field as important as adolescent substance abuse.

In conclusion, from a therapeutic point of view, acting at an early stage in adolescent cannabis consumers is a key element to prevent long-term negative consequences (Castro-Fornieles, 2013) associated with consumption. Our understanding of the motives to initiate and maintain consumption can be useful to identify adolescents who are at risk and to establish prevention and intervention programs (Lee, Neighbors, Hendershot, Greossbars, 2009). The results of this study, conducted in a clinical sample, show that the measurements of the motives for consumption obtained with the MMM make this instrument a useful tool for clinical practice and the study of these patients. Measuring instruments applicable in our environment, like the MMM, facilitate individual assessment to address the complexity of adolescents' reasons for using drugs and offer the opportunity for future studies, given the importance of the motivational aspects to improve our understanding and management of these adolescents (Miller, & Rollnick, 1991).

Conflict of interest

The authors declare they have no conflict of interest.

References

Adams, Z.W., Kaiser, A.J., Lynam, D.R., Charnigo, R.J. & Milich, R. (2012). Drinking motives as mediators of the impulsivity-substance use relation: pathways for negative urgency, lack of premeditation, and sensation seeking. *Addictive Behaviors, 37,* 848–55. doi:10.1016/j.addbeh.2012.03.016.

Arias Constantí, V., Sanz Marcos, N., Trenchs Sainz de La Maza, V., Curcoy Barcenilla, A.I., Matalí Costa, J. & Luaces Cubells, C. (2010). Psychoactive drugs use and related visits of adolescents to the emergency department. *Medicina Clínica (Barcelona), 134,* 583–586. doi:10.1016/j.medcli.2010.01.019.

Busquets, E., Torrens, M., Soler, A., Farré, M. & Bulbena, A. (2005). Differences in the subjective effects of drugs in patients with a first psychotic episode. Preliminary results. *Actas Españolas de Psiquiatría, 33,* 19-25.

Castro-Fornieles, J. (2013). Child and adolescent psychiatry: the need for training and development. *Revista de Psiquiatría y Salud Mental, 6,* 57-59. doi:10.1016/j.rpsm.2012.10.001.

Chabrol, H., Ducongé, E., Casas, C., Roura, C. & Carey, K.B. (2005). Relations between cannabis use and dependence, motives for cannabis use and anxious, depressive and borderline symptomatology. *Addictive Behaviors, 30,* 829–840. doi:10.1016/j.addbeh.2004.08.027.

Cooper, L. (1994). Motivations for alcohol use among adolescents: Development and validation of a four-factor model. *Psychological Assessment, 6,* 117–128. doi:10.1037/1040-3590.6.2.117.

Degenhardt, L., Coffey, C., Carlin, J.B., Swift, W., Moore, E. & Patton, G.C. (2010). Outcomes of occasional cannabis use in adolescence: 10-year follow-up study in Victoria, Australia. *The British Journal of Psychiatry, 196,* 290–295. doi:10.1192/bjp.bp.108.056952.

Dekker, N., Linszen, D.H. & De Haan, L. (2009). Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders. *Psychopathology, 42,* 350–360. doi:10.1159/000236906.

Fleiss, J.L. (1986). *The design and analysis of clinical experiments*. Nueva York: John Wiley, & Sons, Inc.

Fox, C.L., Towe, S.L., Stephens, R.S., Walker, D.D. & Roffman, R. (2011). Motives for cannabis use in high-risk adolescent users. *Psychology of Addictive Behaviors, 25,* 492–500. doi:10.1037/a0024331.

Gadermann, A.M., Guhn, M. & Zumbo, B.D. (2012). Estimating ordinal reliability for Likert-type and ordinal item response data: A conceptual, empirical, and practical guide. Practical Assessment, *Research, & Evaluation, 17,* 1–13. Retrieved at http://pareonline.net/pdf/v17n2.pdf.

Hartwell, K.J., Back, S.E., McRae-Clark, A.L., Shaftman, S.R. & Brady, K. T. (2012). Motives for using: a comparison of prescription opioid, marijuana and cocaine dependent individuals. *Addictive Behaviors, 37,* 373–378. doi:10.1016/j.addbeh.2011.11.014.

Horwood, L.J., Fergusson, D.M., Hayatbakhsh, M.R., Najman, J.M., Coffey, C., Patton, G.C.,… Hutchinson, D.M. (2010). Cannabis use and educational achievement: findings from three Australasian cohort studies. *Drug and Alcohol Dependence, 110,* 247–253. doi:10.1016/j.drugalcdep.2010.03.008.

IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.

Kuntsche, E., Knibbe, R., Gmel, G. & Engels, R. (2006) Who drinks and why? A review of socio-demographic, personality and contextual issues behind the drinking motives in young people. *Addictive Behaviors, 31,* 1844–1857. doi:10.1016/j.addbeh.2005.12.028.

Kaminer, Y., Ohannessian, C.M., McKay, J.R. & Burke, R.H. (2016). The Adolescent Substance Abuse Goal Commitment (ASAGC) Questionnaire: An Examination of Clinical Utility and Psychometric Properties. *Journal of Substance Abuse Treatment, 61,* 42–46. doi:10.1016/j.jsat.2015.09.007.

Lamas, X., Farré, M., Llorente, M. & Camí, J. (1994). Spanish version of the 49-item short form of the Addiction Research Center Inventory (ARCI). *Drug*

and Alcohol Dependence, 35, 203–209. doi:10.1016/0376-8716(94)90075-2.

Littlefield, A.K., Sher, K.J. & Wood, P.K. (2010a). Do changes in drinking motives mediate the relation between personality change and "maturing out" of problem drinking? *Journal of Abnormal Psychology, 119,* 93–105. doi:10.1037/a0017512.

Littlefield, A., Sher, K. & Wood, P. (2010b). A Personality-Based Description of Maturing Out of Alcohol Problems: Extension with a Five-Factor Model and Robustness to Modeling Challenges. *Addictive Behaviors, 35,* 948–954. doi:10.1016/j.addbeh.2010.06.008.

Lee, C.M., Neighbors, C., Hendershot, C.S. & Grossbard, J.R. (2009). Development and preliminary validation of a comprehensive marijuana motives questionnaire. *Journal of Studies on Alcohol and Drugs, 70,* 279–287. doi:10.15288/jsad.2009.70.279.

Lloret Irles. D., Morell-Gomis, R. Laguía, A. & Moriano, J.A. (2018). Design and validation of a Cannabis Use Intention Questionnaire (CUIQ) for adolescents. *Adicciones, 30*, 54-65. doi:10.20882/adicciones.865.

Mattos, P. & Rohde, L.A. (2007). The Kiddie-Sads Present and Lifetime Version. *Journal of Attention Disorders, 11,* 100. doi:10.1177/1087054707305152.

Martin, G., Copeland, J., Gilmour, S., Gates, P. & Swift, W. (2006). The Adolescent Cannabis Problems Questionnaire (CPQ-A): psychometric properties. *Addictive Behaviors, 31,* 2238–2248. doi:10.1016/j.addbeh.2006.03.001.

Martin, W.R., Sloan, J.W., Sapira, J.D. & Jasinski, D.R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology and Therapeutics, 12,* 245–258. doi:10.1002/cpt1971122part1245.

Mezquita, L., Stewart, S.H., Ibáñez, M.I., Ruipérez, M.A., Villa, H., Moya, J. & Ortet, G. (2011). Drinking motives in clinical and general populations. *European Addiction Research, 17,* 250–261. doi:10.1159/000328510.

Miller, W.R. & Rollnick, S. (1991). *Motivational interviewing: Preparing people to change addictive behavior.* New York: Guilford Press.

Millon, T. (1993). *Manual of Millon Adolescent Clinical Inventory.* Systems NC, editor. Minneapolis.

Millon, T. (2004). *MACI: inventario clínico para adolescentes de millón*. Ediciones TEA, editor. Madrid.

Monk, R.L. & Heim, D. (2016). Expectativas relacionadas con el alcohol en adultos y adolescentes: semejanzas y diferencias. *Adicciones, 28,* 35-40. doi:10.20882/adicciones.788.

Muñiz, J., Elosua, P. & Hambleton, R.K. (2013). Directrices para la traducción y adaptación de los tests: segunda edición. *Psicothema, 25,* 151-157. doi:10.7334/psicothema2013.24.

Observatorio Español sobre Drogas. Encuesta estatal sobre el consumo de drogas en enseñanzas secundarias (ESTUDES) (2014). *Observatorio Español de las Drogas y las Adicciones,* Madrid.

Scherrer, J.F., Grant, J.D., Duncan, A.E., Sartor, C.E., Haber, J.R., Jacob, T. & Bucholz, K. K. (2009). Subjective effects to cannabis are associated with use, abuse and dependence after adjusting for genetic and environmental influences. *Drug and Alcohol Dependence, 105,* 76–82. doi:10.1016/j.drugalcdep.2009.06.014.

Simons, J., Correia, C.J., Carey, K.B. & Borsari, B.E. (1998). Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology, 45,* 265–273. doi:10.1037/0022-0167.45.3.265.

Simons, J., Correia, C.J. & Carey, K.B. (2000). A comparison of motives for marijuana and alcohol use among experienced users. *Addictive Behaviors, 25,* 153–160. D: doi:10.1016/S0306-4603(98)00104-X.

Simons, J.S., Gaher, R.M., Correia, C.J., Hansen, C.L. & Christopher, M.S. (2005). An affective-motivational model of marijuana and alcohol problems among college students. *Psychology of Addictive Behaviors, 19,* 326–334. doi:10.1037/0893-164X.19.3.326.

Tragesser, S.L., Trull, T.J., Sher, K.J. & Park, A. (2008). Drinking motives as mediators in the relation between personality disorder symptoms and alcohol use disorder. *Journal of Personality Disorders, 22,* 525–537. doi:10.1521/pedi.2008.22.5.525.

Thornton, L.K., Baker, A.L., Lewin, T.J., Kay-Lambkin, F.J., Kavanagh, D., Richmond, R.,… Johnson, M.P. (2012). Reasons for substance use among people with mental disorders. *Addictive Behaviors, 37,* 427–434. doi:10.1016/j.addbeh.2011.11.039.

Zvolensky, M.J., Vujanovic, A., Bernstein, A., Bonn-Miller, M.O., Marshall, E.C. & Leyro, T.M. (2007). Marijuana use motives: A confirmatory test and evaluation among young adult marijuana users. *Addictive Behaviors, 32,* 3122–3330. doi:10.1016/j.addbeh.2007.06.010.

Zeiger, J.S., Haberstick, B.C., Corley, R.P., Ehringer, M.A., Crowley, T.J., Hewitt, J. K. & Rhee, S. (2012) Subjective effects to marijuana associated with marijuana use in community and clinical subjects. *Drug and Alcohol Dependence, 123,* S52–S58. doi:10.1016/j.drugalcdep.2012.02.014.

Zumbo, B.D., Gadermann, A.M. & Zeisser, C. (2007). Ordinal versions of coefficients alpha and theta for Likert rating scales. *Journal of Modern Applied Statistical Methods, 6,* 21-29. doi:10.1016/j.drugalcdep.2009.12.026.

Patients with alcohol use disorder: initial results from a prospective multicenter registry in the Spanish Network on Addiction Disorders. CohRTA Study

Pacientes con trastorno por uso de alcohol: resultados iniciales de un registro multicéntrico en la Red de Trastornos Adictivos-RTA. Estudio CohRTA

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Abstract

The Alcohol Program of the Spanish Network on Addictive Disorders-RTA requires a longitudinal study to address different research questions related to alcoholism. The cohort study (CohRTA) focuses on patients seeking treatment for alcohol use disorder, as a multicentre, collaborative research project aimed to improve secondary prevention and early diagnosis of pathological processes associated with the disorder.

Methods: multicentre cohort study in adults (>18 years) seeking their first treatment of the disorder. Patients sign an informed consent and data is collected in an online platform specifically designed for the study; patients are also requested to provide biological samples that are stored in a biobank. Baseline and prospective, socio-demographic, epidemiological, clinical and treatment data are collected. Currently there are 10 participating centres that expect to recruit more than 1,000 patients.

Results: As of December 2015, 344 patients (77% men) were included. Median age at admission was 50 years (IQR: 43-55 years). Median age at the start of alcohol consumption was 15 years (IQR: 14-18 years) and 61% of cases reported antecedents of alcohol use disorder in the family. During the 30 days prior to admission, alcohol consumption amounted to 12.5 SDU/day (IQR: 7.1-20 SDU/day), 72% of the patients were tobacco smokers and 30% currently used cocaine. Organising an open cohort of patients with alcohol use disorder may be crucial to better understand the clinical consequences of alcoholism in Spain. This cohort may potentiate quantitative and qualitative research within the Spanish Network on Addictive Disorders-RTA/RETICS. Having a well-established, representative cohort of patients will increase translational research on consequences of alcoholism in our country.

Keywords: Alcohol use disorder; Cohort study; Research.

Resumen

El Programa Alcohol de la Red de Trastornos Adictivos (RTA) requiere de un estudio clínico longitudinal para dar respuesta a preguntas de investigación en el trastorno por uso de alcohol. El proyecto CohRTA es un estudio multicéntrico de investigación cooperativa que se pone en marcha para mejorar la prevención secundaria y el diagnóstico precoz de los procesos patológicos asociados al trastorno por uso de alcohol.

Método: estudio observacional en cohorte multicéntrica de pacientes mayores de 18 años que solicitan tratamiento del trastorno por primera vez y autorizan su participación. La información clínica se recoge en una plataforma online diseñada para el estudio y puede ir acompañada de una muestra biológica que se deposita en un biobanco. Se recogen datos basales y prospectivos, sociodemográficos, epidemiológicos, clínicos y de tratamiento. A diciembre de 2015 son 10 los centros proveedores de pacientes y se espera reclutar más de 1.000 pacientes en los próximos años.

Resultados: se dispone de 344 pacientes (77% hombres) que cumplen los criterios de inclusión en el estudio y con una edad de 50 años (RIQ: 43-55 años). La edad de inicio de consumo de alcohol fue de 15 años (RIQ: 14-18 años) y un 61% tenían antecedente familiar de trastorno por uso de alcohol. Durante los 30 días previos al inicio del tratamiento los pacientes bebían 12.5 UBE/día (RIQ: 7.1-20 UBE/día), el 72% fumaba tabaco y el 30% consumía cocaína.

Conclusiones: Disponer de una cohorte abierta y multicéntrica de pacientes con trastorno por uso de alcohol será útil para analizar las consecuencias del abuso de alcohol, potenciar la investigación traslacional y añadir valor a la investigación clínica y básica del Programa Alcohol dentro de RTA/RETICS. Con una cohorte bien establecida y representativa se espera aumentar la cantidad y calidad científica en relación a las complicaciones del trastorno por uso de alcohol y sus consecuencias clínicas y sociales en España.

Palabras clave: Trastorno por uso de alcohol; Estudio de cohorte; Investigación.

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The World Health Organization estimates that 76 million people worldwide abuse alcohol or are alcohol-dependent (World Health Organization, 2010). In Spain, the prevalence of alcohol use is high, given that 79% of the general population between the ages of 15-64 years has consumed alcohol over the last year (84% of men, 73% of women) and 11% drink alcohol daily, according to a 2009-2010 home-based interview (Observatorio Español sobre Drogas, 2011). This same survey considers that 4.4% of the general population are hazardous drinkers (alcohol ingestion of over 50 grams/day for men and 30 grams/day for women). In the age group between 15-24 years, the prevalence of hazardous alcohol use in women is 6% and in men is 5% (Observatorio Español sobre Drogas, 2011) .

Health-related problems associated with alcohol abuse are relatively common among the Spanish population and, as a result, in the public health system. Furthermore, each year close to 30,000 people seek treatment for the disorder and up to 61% of these have also used cocaine (Observatorio Español sobre Drogas, 2011).

Alcohol use disorder is a chronic illness that may be accompanied by numerous alterations of the body. The harm alcohol causes to organs and tissues basically depends on the total amount of ethanol ingested over one's lifetime and the usage pattern, though genetic, biological and environmental variables also intervene; among the main alterations of the body resulting of alcoholism, now defined as alcohol use disorder per the DSM-5 (American Psychiatric Association, 2013), are worth highlighting: hepatitis, neuropsychiatric disorders, cardiovascular disease, infectious diseases and cancer; furthermore, the risk of suffering an illness associated with alcohol abuse starts with relatively low levels of daily alcohol ingestion (30g/day) (Thomas et al., 2000).

The prognosis of many physical disorders derived of alcohol abuse also depends on diverse factors. Alcohol may cause lesions to organs and systems after prolonged consumption, but also in the short term, after binge drinking, or in the context of alcohol poisoning. Marked differences also exist by gender: women are at a greater risk of developing hepatitis than men, and in recent years the higher risk of breast cancer in frequent drinkers has also been emphasised (Bagnardi, Blangiardo, La Vecchia, & Corrao, 2001). On another hand, exaggerated alcohol use would also explain a significant part of mortality resulting of non-intentional lesions (accidents, drowning, hypothermia, burns), intentional lesions (suicide) or other serious illnesses with high mortality during an acute episode (Naimi et al., 2003). In any case, the mortality of patients with alcohol use disorder is high, even up to 20 times greater than that of the general population of the same age (Fuster et al., 2015; Rivas et al., 2013; Roerecke & Rehm, 2013).

Another aspect to be considered in the current epidemiology of alcohol use disorder is concurrence of the use of other substances, especially cocaine, cannabis and tobacco (Fuster et al., 2015; Observatorio Español sobre Drogas, 2011; Rivas et al., 2013). The use of cocaine in combination with alcohol increases the plasma levels of cocaine by up to 30%, thereby entailing the risk of developing a cardiovascular disease, in addition to generating cocaethylene, a metabolic intermediary that is highly psychotropic and with cardiotoxic effects (Pennings, Leccese, & de Wolff, 2002). From a behavioural perspective, the use of cocaine facilitates the use of alcohol in that the ingestion of cocaine allows for drinking alcohol for a longer time period which, in turn, may increase the amount of cocaine used (Gossop, Manning, & Ridge, 2006).

It is well known that clinical information contributed by case series are essential for improving the quality of attention and for updating the prognosis of any illness. In this regard, having a cohort of patients with alcohol use disorder may be key for improving treatment of this illness and for promoting patient-focused research. In fact, revitalising clinical research is a main objective of Spanish and European research bodies; furthermore, the treatment of patients should be the bridge between basic science and clinical effectiveness (Pons, Rodés, Andreu, & Arenas, 2013).

The Network on Addiction Disorders (RTA) is one of the Thematic Networks for Cooperative Research in Health (RETICS) of the Carlos III Health Institute. Since its founding in 2003, the scientific objectives of the RTA focus on substance abuse-related research and, since the phase launched in 2013, on the two substances of greatest societal impact: alcohol and cocaine.

The RTA Alcohol Program has driven the creation of a multicentre cohort study of patients seeking treatment for the disorder for the first time (CohRTA project). In cohort studies, patients are selected in accordance with a specific characteristic or exposure factors, and after the initial visit are monitored by the recruitment centre to analyse long-term changes and the development of clinical impacts, depending on the various exposure factors. This RTA study's objectives and action plan have been presented in scientific congresses of the Spanish Society of Internal Medicine (SEMI) and the Spanish Scientific Society for Research on Alcohol, Alcoholism and Other Drug Addictions (Socidrogalcohol). In addition to financial support provided by ISCIII, the CohRTA project received additional financial assistance from the 2014 research grants of the National Drug Plan (PNSD); additional support by the PNSD has allowed for extending the project to clinics beyond the RTA, increasing the number of cases, as well as the external validity, of the cohort study.

The ultimate aim of the study is to establish a stable platform of treatment centres to promote clinical and basic knowledge on alcohol use disorder.

Method

Study design

CohRTA is an open, prospective and multicentre cohort study of adults seeking treatment for alcohol use disorder for the first time. This study is linked to treatment centres of the National Public Health System belonging to the RETICS Network of Addiction Disorders as well as others interested in participating after receiving a proposal.

In its initial phases, the project had 10 participating centres and 1 biobank for collecting biological samples from cohort study patients. Table 1 displays the centres participating in the study and their characteristics.

Patient recruitment began in June 2013, upon official project approval by the Clinical Research Ethics Committee (CEIC) of the centre coordinating the study, though each centre launched its recruitment as of the approval of its own CEIC (Table 1). Patients must meet the following criteria for inclusion in the multicentre cohort study: be over the age of 18, have a diagnosis of alcohol use disorder in accordance with the criteria of the DSM-5 (American Psychiatric Association, 2013) and sign an informed consent form for disclosing personal data and submitting biological samples.

Ethical issues

Each participating centre coordinated with its own CEIC the approval of the study protocol and the informed consent form to be given to the patients during their first visit. The informed consent form for the use of clinical data and biological samples was designed jointly with members of the RTA Biobank at the Miguel Hernández University in San Juan de Alicante, and was approved by each participating centre's CEIC.

Furthermore, the project is also recognised by the Spanish Agency of Medicines and Medical Devices as a non post-authorization Observational Study (No-EPA).

Patients signing the informed consent form do so under the premise that the data provided is anonymous and that consent is revocable at any time, as per the Spanish Organic Law on Data Protection. The informed consent also offers patients the option of providing only clinical data.

Registered information

Two structured questionnaires were designed: one for use upon the patient's inclusion in the cohort study and another for use during follow-up visits.

The baseline questionnaire includes variables concerning sociodemographic data, family history, alcohol use and substance abuse, and variables related to clinical symptoms, results of analyses and treatment of the disorder.

The Cumulative Illness Rating Scale-Substance Abuse (CIRS-SA) index is used to evaluate clinical comorbidity of patients participating in the study (Castillo et al., 2004). This tool analyses the presence or absence of illness in 13 organs or systems: 1) Cardio, 2) Vascular, 3) Respiratory, 4) Eyes, ears, nose, throat and larynx, 5) Upper gastrointestinal, 6) Lower gastrointestinal, 7) Liver, 8) Renal, 9) Genital-urinary, 10) Muscular-skeletal, 11) Neurological, 12) Infections, endocrinological, metabolical, and 13) HIV infection.

Table 1. *Centres participating in the CohRTA study, Alcohol Program, Network on Addiction Disorders (RTA), up to December 2015.*

Centre	City	Treatment type	Profile	Association	CEIC Code
Hospital Univ. Germans Trias i Pujol*	Badalona	Addiction Unit	Internal Medicine	RETICS / PNSD	PI-13-031
Hospital del Mar	Barcelona	Addiction Unit	Psychiatry	RETICS	2013/5313/I
Hospital Clínic de Barcelona	Barcelona	Alcoholism Unit	Psychiatry	RETICS	2013/8738
Hospital Universitari de Bellvitge	L'Hospitalet de Llobregat	Addiction Unit	Internal Medicine	PNSD	PR049/14
Hospital Clínico Universitario	Salamanca	Department of Internal Medicine	Internal Medicine	RETICS	E.O. 13/337
Hospital 12 de Octubre	Madrid	Psychiatry Department	Psychiatry	RETICS	15/065
Universidad de Valladolid	Valladolid	Recovered Alcoholics of Valladolid (ARVA)	Primary Care	RETICS	PI13-120
Hospital Universitari Son Espases	Palma de Mallorca	Alcohol-related Problems Unit (UPRA)	Internal Medicine	PNSD	IB 2357/14 PI
Hospital Lucus Augusti	Lugo	Department of Internal Medicine	Internal Medicine	PNSD	2015/010
Delta Centre	Badalona	Municipal Drug Addiction Treatment Centre	Primary Care	PNSD	PI-13-031
Miguel Hernández University	San Juan de Alicante	Biobank		RETICS	

Note. *Coordination centre.

In addition, each organ or system is scored between 0 and 4 depending on the severity of the impact: 0, no impact; 1, mild impact (current mild problem or background of significant problem); 2, moderate impact (moderate disability or morbidity requiring first-line treatment); 3, severe impact (severe/continuous disability or uncontrollable chronic problems); 4, highly severe impact (extremely serious/requires immediate treatment/organic insufficiency/severe functional deterioration).

To evaluate psychiatric comorbidity, the CohRTA study screens for depression, psychosis, attention deficit hyperactivity, posttraumatic stress, generalized anxiety, panic, social phobia and mania disorders.

Table 2 displays a detailed summary of these variables.

The patients' follow-up questionnaire includes data on alcohol use after the first treatment, in addition to the developed of clinical symptoms and death.

Also, the option of adding a series of specific modules to the study's initial protocol for further study has been foreseen; among these, some centres have already begun using the PRISM (Psychiatric Research Interview for Substance and Mental Disorder). Others are being considered, such as suicidal ideation, use of public health services and quality of life. For now, a model that includes the SF-12 general health survey has been used.

The SF-12 survey is comprised of 12 questions that offer a subjective assessment of health status. Eight aspects are evaluated: physical conditions, limitations caused by physical health problems, social functioning, bodily pain, mental health, limitations caused by personal or emotional problems, vitality and overall health. It is a brief version of the SF-36 survey, validated in different populations and countries, and sensitive to therapeutic changes (Gandek et al., 1998; Salyers, Bosworth, Swanson, Lamb-Pagone, & Osher, 2000).

Table 2. *Study variables of patients participating in the CohRTA study, Alcohol Program, Network on Addiction Disorders (RTA).*

Association	Patient identifiers Birthdate Gender Inclusion date Biological sample collection and date
Sociodemographics	Marital status Socioeconomic and employment status Level of education
Diagnosis	Severity of alcohol use disorder as per DSM-5
Alcohol use	History of use Current use pattern* (amount and frequency) Abstinence period Alcohol poisonings Family history
Use of other substances	Tobacco (history of use, current use pattern) Cocaine (history of use, current use pattern) Cannabis (current use pattern) Amphetamines (current use pattern) Hallucinogens (current use pattern) Opioids (current use pattern) Inhalants (current use pattern) Emerging drugs (current use pattern) Intravenous drugs (history of use, current use pattern)
General blood test	Hemogram (10 parameters) Biochemical (28 parameters) Anaemia diagnosis (8 parameters) Serology test to identify viruses (10 parameters) Drugs in urine (opioids, cocaine, cannabis, amphetamines)
Comorbidity	Organic as per CIRS-SA** Psychiatric as per screening for different pathologies
Treatment	Pharmacological (drugs, start/end dates, prescribed dose) Non-pharmacological, therapeutic interventions (type and date)

Note. *Current use is defined as use over the last 30 days; **Cumulative Illness Rating Scale-Substance Abuse.

Data collection process

Each participating centre has a designated person in charge of collecting data from patients in the study. Storage and periodical update of this information are performed using a platform designed for this purpose (Coresoft Clínico, www.coresoft.es) for professionals dedicated to the development, maintenance and support of online clinical records, in compliance with the Organic Law on Data Protection, as well as current legislation on security and confidentiality. The use of this application for data entry was scheduled in two phases: an initial phase (September 2014), when the information modules were available with regards to sociodemographic variables and drug use, accessible only by RTA groups, and a second phase (September 2015), when the clinical modules were implemented and access to the platform was open to all clinical groups included thanks to the additional financial assistance granted by the PNSD.

Biobank

The centres participating in the CohRTA study have a biobank as reference for reception and storage of biological samples. Each sample is linked with the clinical database by a patient code identification number. The biological sample collected is the extraction of 10 mL of blood for processing to obtain DNA.

The CohRTA project's biobank is located at the Neuroscience Institute of the Miguel Hernández University in San Juan de Alicante. The biobank has a scientific committee comprised of the RTA Coordinator, a local Manager and Researchers belonging to the network. The biobank management system complies with the UNE-EN-ISO 9001:2008 international standard (Registration Number ER-0614/2010).

Current legislation permits ceding biological samples to research projects of the RTA on alcohol use disorder, upon prior authorization granted by an Ethics Committee.

Authorship criteria

The CohRTA project has a document on criteria applicable for scientific authorship of the project's results. These criteria define an order for the authors in the heading of scientific articles and presentations made at congresses, and determine the content of the Annex reflecting the different participants and research centres. Different authorship criteria are set forth, depending on the level of participation, use of samples and/or clinical data, and whether the projects have been implemented by members of the CohRTA project or by other preclinical researchers of the RTA who may use biological samples of CohRTA project patients.

Data analysis

Variables for sociodemographic data, use of alcohol and consumption of other drugs for all patients registered between June 2013 and November 2015 were extracted from the application. Descriptive analysis of the data was performed: continuous variables were described using the median and the interquartile range (IQR) and categorical variables were expressed as relative frequencies. The SPSS Statistics 15.0 package was used for data analysis (SPSS, Chicago, IL, USA).

Results

Between June 2013 and November 2015, 344 patients; 264 (76,7%) were men; median age at inclusion was 50 (IQR: 43-55). Age at onset of alcohol use was 15 years (IQR: 14-18 years) and 61% had a family history of alcohol use disorder. During the 30 days preceding the start of the treatment, the patients ingested a median of 12.5 SDU/day (IQR: 7.1-20 SDU/day), 72% were tobacco smokers and 29,7% used cocaine. Table 3 displays sociodemographic data and the history of use of alcohol and other substances.

Of those patients included in the CohRTA project, there are currently 76 blood samples ready for a DNA analysis. The fact that this study is associated with a repository of biological samples will enable a series of projects in which preclinical groups with experience in animal-based models may transfer their hypotheses to research with humans.

Given the potential of clinical and biological data collectable through this study, it may serve as a platform for training new clinical researchers in Spain and for publishing doctoral theses. The integration of different centres and the participation of clinical treatment groups in scientific settings may foster research by making available suitable methods for addressing the challenges of diagnosis, prognosis and treatment of the illness. Furthermore, the public health system and RETICS scientific policy support these types of projects, patient-oriented and based on national research structures. ISCIII research training programs, like Rio Hortega and Juan Rodés, focus on improving the research skills of young physicians.

In summary, with a consolidated cohort of patients, we expect to increase the volume and quality of scientific studies on complications arising of alcohol use disorder and its clinical and social consequences in Spain.

Discussion

The demand for treatment of alcohol use disorder in Spain has grown. The profile of patients seeking treatment for the disorder is: middle-aged adults, predominantly men, and who might use cocaine and cannabis. This profile is similar to the description of patients with alcohol use disorder or hazardous alcohol use receiving brief interventions in emergency services, primary care and during hospitalization for other reasons (Heather, 2014; Mdege et al., 2013; Nilsen et al., 2008). This study's results reveal the severity of the disorder in those seeking treatment for the first time, and confirm that this occurs, on the average, 30 years after the onset of alcohol use. A recent, systematic review of the disorder shows that the first treatment episode is late and occurs when the disorder is clinically established (Connor, Haber & Hall, 2016). Moreover, two-thirds of the patients had a family history of alcohol use disorder; in fact, this is one of the previously mentioned risk factors for this illness (Connor et al., 2016).

Given the scarcity of multicentre studies in Spain on this pathology, the research project presented herein will allow for knowing the clinical dimension of the problem, its treatment and, in summary, will update the illness' prognosis. In addition, the study will generate knowledge on alcohol use by women and its long-term consequences, which to date have not been clearly defined; women with alcohol use disorder represent merely 20% of the total, and requires a broad recruitment of cases to obtain a representative sample. Furthermore, the results obtained through this project may be useful for proposing new diagnosis strategies for the disorder.

The capacity for research and transfer of knowledge is key for multicentre projects. Working as a network provides the opportunity for disseminating patient-oriented research. Bringing clinical and basic groups with similar interests together poses countless advantages and the CohRTA project may act as a suitable platform for adapting to future research.

Cohort studies have entailed a radical change in our knowledge of certain illnesses. As just one example, a significant part of current knowledge on the risk of developing cardiovascular diseases is due to the Framingham study (USA), a prospective cohort study that began its recruitment in 1948 to establish today's most well-known risk factors of cardiovascular disease (McKee, Castelli, McNamara, & Kannel, 1971). Years later, the longitudinal research

Table 3. *Sociodemographic data, use of alcohol and consumption of other substances in 344 patients with alcohol use disorder seeking treatment for the first time. Alcohol Program, Network on Addiction Disorders-RTA.*

	N = 344 n (%)
Sociodemographics	
Men	264 (76.7)
Age, *median [IQR]*	50 [43-55]
Spanish	324 (94.2)
Marital status (n = 335)	
Unmarried	89 (26.6)
Married – Cohabitation	138 (41.2)
Widowed	11 (3.3)
Separated – Divorced	97 (28.9)
Employment (n = 337)	
Employed	152 (45.1)
Unemployed	104 (30.9)
Permanent disability / pensioner	69 (20.5)
Other situations	12 (3.6)
Use of alcohol and other drugs	
Severity of alcohol use disorder as per DSM-5 (n = 340)	
2-5	62 (18.2)
6-8	169 (49.7)
9-11	109 (32.1)
Age at onset of alcohol use, *median [IQR]*	15 [14-18]
Age at onset of regular alcohol use, *median [IQR]*	22 [18-30]
SDU/day, last 30 days, *median [IQR]*	12,5 [7.1-20]
Period of total abstinence from alcohol (years), *median [IQR]*	1 [0-3]
Family history of alcohol use disorder (n = 334)	203 (60.8)
Number of alcohol poisonings requiring medical attention over the lifetime (n = 321)	
None	147 (45.8)
1-5	162 (50.5)
>5	12 (3.7)
Tobacco (n = 341)	
Yes	245 (71.8)
No	62 (18.2)
Ex-smoker	34 (10.0)
Use in the last 30 days of:	
Cocaine	33 (29.7)
Cannabis/marihuana	78 (22.9)
Amphetamines	9 (2.6)
Tranquillizers or benzodiazepines, without medical prescription	20 (5.9)
Opioids, without medical prescription	4 (1.2)
Antecedent of parenteral drug use	12 (3.5)

model for this illness has been implemented in our society (Nascetti et al., 2001) as also occurred for others, such as HIV/AIDS (Sobrino-Vegas et al., 2011) and thromboembolism (Nieto & Monreal, 2004); all of these have notably increased knowledge through an excellent scientific production in their respective knowledge areas.

Several cohort studies have been developed on alcohol use and drug addiction in our country. Worth mentioning, for example, are a cohort of 850 patients who sought treatment for alcohol abuse at the end of the 1980s (Gual, Lligona, & Colom, 1999; Gual, Lligoña, Costa, Segura, & Colom, 2004), the Itinere cohort with patients who were heroin and cocaine users (Pulido et al., 2009) or the study with almost 6,000 patients hospitalised in Hospital Detoxification Units in Barcelona and its metropolitan area, 1,200 of these for alcohol dependency (Rivas et al., 2013; Sanvisens et al., 2014).

The CohRTA project is specifically designed to analyse patients with alcohol use disorder seeking treatment for the disorder for the first time; the study is nested in first-line treatment centres, is rich in clinical and biological data, is patient-centred, and is focused on detecting the mid and long-term impact of alcoholism. However, these types of studies imply several limitations, the main one of which derives of its longitudinal nature. Longitudinal studies are expensive, require special dedication for follow-up of all cases over a long period of time and qualified personnel for data updates and statistical analysis. Secondly, this study's multicentre feature may incorporate an inter-observer bias for certain variables requiring interpretation (i.e., clinical and psychiatric comorbidity), though efforts are made to minimise this aspect through the publication of sufficiently detailed guides on data collection.

Nevertheless, the scientific level of the groups participating in CohRTA, whether in treatment for the disorder (Gual & Miquel, 2015; López-Pelayo et al., 2014), neuroinflammation and brain damage (Montesinos et al., 2015; Pascual, Baliño, Aragón, & Guerri, 2015), immunity and genetics associated with alcoholic hepatitis (Chamorro et al., 2014; Novo-Veleiro et al., 2014), comorbidity and mortality (Rivas et al., 2013; Sanvisens et al., 2014) or the Public Health perspective of the problem (Bosque-Prous et al., 2014; Villalbí, Bosque-Prous, Gili-Miner, Espelt, & Brugal, 2014) guarantee the project's viability.

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Appendix

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References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.).* Wasington, DC: American Psychiatric Association.

Bagnardi, V., Blangiardo, M., La Vecchia, C. & Corrao, G. (2001). Alcohol consumption and the risk of cancer: a meta-analysis. *Alcohol Research & Health, 25,* 263–270.

Bosque-Prous, M., Espelt, A., Guitart, A. M., Bartroli, M., Villalbí, J. R. & Brugal, M. T. (2014). Association between stricter alcohol advertising regulations and lower hazardous drinking across European countries. *Addiction, 109,* 1634–1643. doi: 10.1111/add.12562.

Castillo, C., Bulbena, A., Serras, E., Torrens, M., López-Colomés, J. L., Martínez, M. A. & Politinska, B. (2004). Medical assessment in drug addicts: reliability and validity of the Cumulative Illness Rating Scale (Substance Abuse version). *European Addiction Research, 10,* 112–117. doi: 10.1159/000077699.

Chamorro, A. J., Torres, J. L., Mirón-Canelo, J. A., González-Sarmiento, R., Laso, F. J. & Marcos, M. (2014). Systematic review with meta-analysis: the I148M variant of patatin-like phospholipase domain-containing 3 gene (PNPLA3) is significantly associated with alcoholic liver cirrhosis. *Alimentary Pharmacology & Therapeutics, 40,* 571–581. doi: 10.1111/apt.12890.

Connor, J. P., Haber, P. S. & Hall, W. D. (2016). Alcohol use disorders. *Lancet, 387,* 988–998. doi: 10.1016/S0140-6736(15)00122-1

Fuster, D., Sanvisens, A., Bolao, F., Serra, I., Rivas, I., Tor, J. & Muga, R. (2015). Impact of hepatitis C virus infection on the risk of death of alcohol-dependent patients. *Journal of Viral Hepatitis, 22,* 18–24. doi: 10.1111/jvh.12290.

Gandek, B., Ware, J. E., Aaronson, N. K., Apolone, G., Bjorner, J. B., Brazier, J. E.,… Sullivan, M. (1998). Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *Journal of Clinical Epidemiology, 51,* 1171–1178.

Gossop, M., Manning, V. & Ridge, G. (2006). Concurrent use and order of use of cocaine and alcohol: behavioural differences between users of crack cocaine and cocaine powder. *Addiction, 101,* 1292–1298. doi: 10.1111/j.1360-0443.2006.01497.x.

Gual, A., Lligona, A. & Colom, J. (1999). Five-year outcome in alcohol dependence. A naturalistic study of 850 patients in Catalonia. *Alcohol and Alcoholism, 34,* 183–192.

Gual, A., Lligoña, A., Costa, S., Segura, L. & Colom, J. (2004). Tratamiento del alcoholismo y su impacto a largo plazo. Resultados a 10 años de un estudio longitudinal prospectivo de 850 pacientes. *Medicina Clínica (Barcelona), 123,* 364–369.

Gual, A. & Miquel, L. (2015). Nuevas perspectivas para el tratamiento del alcoholismo. *Medicina Clínica (Barcelona), 144,* 24–25. doi: 10.1016/j.medcli.2014.07.020.

Heather, N. (2014). The two forms of alcohol brief intervention: an uneasy coalition. *Addiction, 109,* 1059–1060. doi: 10.1111/add.12443.

López-Pelayo, H., Wallace, P., Segura, L., Miquel, L., Díaz, E., Teixidó, L.,… Gual, A. (2014). A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website (EFAR Spain): the study protocol. *BMJ Open, 4,* e007130. doi: 10.1136/bmjopen-2014-007130.

McKee, P. A., Castelli, W. P., McNamara, P. M. & Kannel, W. B. (1971). The natural history of congestive heart failure: the Framingham study. *The New England Journal of Medicine, 285,* 1441–1446. doi: 10.1056/NEJM197112232852601.

Mdege, N. D., Fayter, D., Watson, J. M., Stirk, L., Sowden, A. & Godfrey C. (2013). Interventions for reducing alcohol consumption among general hospital inpatient heavy alcohol users: a systematic review. *Drug and Alcohol Dependence, 131,* 1–22. doi: 10.1016/j.drugalcdep.2013.01.023.

Montesinos, J., Pascual, M., Pla, A., Maldonado, C., Rodríguez-Arias, M., Miñarro, J. & Guerri, C. (2015). TLR4 elimination prevents synaptic and myelin alterations and long-term cognitive dysfunctions in adolescent mice with intermittent ethanol treatment. *Brain, Behavior and Immunity, 45*, 233–244. doi: 10.1016/j.bbi.2014.11.015.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K. & Marks, J. S. (2003). Binge drinking among US adults. *JAMA, 289,* 70–75.

Nascetti, S., Elosua, R., Pena, A., Covas, M. I., Senti, M. & Marrugat, J. (2001). Variables associated with fibrinogen in a population-based study: interaction between smoking and age on fibrinogen concentration. *European Journal of Epidemiology, 17,* 953–958.

Nieto, J. A. & Monreal, M. (2004). Recurrent venous thromboembolism in men and women. *The New England Journal of Medicine, 351,* 2015–2018.

Nilsen, P., Baird, J., Mello, M. J., Nirenberg, T., Woolard, R., Bendtsen, P. & Longabaugh, R. (2008). A systematic review of emergency care brief alcohol interventions for injury patients. *Journal of Substance Abuse Treatment, 35,* 184–201. doi:10.1016/j.jsat.2007.09.008.

Novo-Veleiro, I., González-Sarmiento, R., Cieza-Borrella, C., Pastor, I., Laso, F. J. & Marcos, M. (2014). A genetic variant in the microRNA-146a gene is associated with susceptibility to alcohol use disorders. *European Psychiatry, 29,* 288–292. doi: 10.1016/j.eurpsy.2014.02.002.

Observatorio Español sobre Drogas, Delegación del Gobierno para el Plan Nacional sobre Drogas. (2011). *Informe 2011. Situación y tendencias de los problemas de drogas en España.* Madrid: Ministerio de Sanidad, Política Social e Igualdad.

Pascual, M., Baliño, P., Aragón, C. M. G. & Guerri, C. (2015). Cytokines and chemokines as biomarkers of ethanol-induced neuroinflammation and anxiety-related behavior: role of TLR4 and TLR2. *Neuropharmacology, 89,* 352–359. doi: 10.1016/j.neuropharm.2014.10.014.

Pennings, E. J. M., Leccese, A. P. & de Wolff, F. A. (2002). Effects of concurrent use of alcohol and cocaine. *Addiction, 97,* 773–783.

Pons, J. M. V., Rodés, J., Andreu, A. & Arenas, J. (2013). La olvidada investigación clínica. *Medicina Clínica (Barcelona), 140,* 325–331. doi: 10.1016/j.medcli.2012.10.011.

Pulido, J., Brugal, M. T., de la Fuente, L., Ballesta, R., Barrio, G., Bravo, M. J.,… Fernández, F. (2009). Metodología de reclutamiento y características de una cohorte de jóvenes consumidores habituales de cocaína de tres ciudades españolas. *Gaceta Sanitaria, 23,* 200–207. doi: 10.1016/j.gaceta.2008.05.003.

Rivas, I., Sanvisens, A., Bolao, F., Fuster, D., Tor, J., Pujol, R.,… Muga, R. (2013). Impact of medical comorbidity and risk of death in 680 patients with alcohol use disorders. *Alcoholism, Clinical and Experimental Research, 37 Suppl 1,* E221–E227. doi: 10.1111/j.1530-0277.2012.01861.x.

Roerecke, M. & Rehm, J. (2013). Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction, 108,* 1562–1578. doi: 10.1111/add.12231.

Salyers, M. P., Bosworth, H. B., Swanson, J. W., Lamb-Pagone, J. & Osher, F. C. (2000). Reliability and validity of the SF-12 health survey among people with severe mental illness. *Medical Care, 38,* 1141–1150.

Sanvisens, A., Vallecillo, G., Bolao, F., Rivas, I., Fonseca, F., Fuster, D.,… Muga, R. (2014). Temporal trends in the survival of drug and alcohol abusers according to the primary drug of admission to treatment in Spain. *Drug and Alcohol Dependence, 136,* 115-120. doi: 10.1016/j.drugalcdep.2013.12.022.

Sobrino-Vegas, P., Gutiérrez, F., Berenguer, J., Labarga, P., García, F., Alejos-Ferreras, B.,… del Amo, J. (2011). La cohorte de la red española de investigación en Sida y su biobanco: organización, principales resultados y pérdidas de seguimiento . *Enfermedades Infecciosas y Microbiología Clínica, 29,* 645–653. doi: 10.1016/j.eimc.2011.06.002.

Thomas, D. L., Astemborski, J., Rai, R. M., Anania, F. A., Schaeffer, M., Galai, N.,… Vlahov, D. (2000). The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA, 284,* 450–456.

Villalbí, J. R., Bosque-Prous, M., Gili-Miner, M., Espelt, A. & Brugal, M. T. (2014). Políticas para prevenir los daños causados por el alcohol. *Revista Española de Salud Pública, 88,* 515–528. doi: 10.4321/S1135-57272014000400006.

World Health Organization. (2010). *Global Status Report on Alcohol.* Ginebra: World Health Organization.

Quality of life role in risky alcohol use research: should it be a more relevant outcome in any study?

Rol de la calidad de vida en el consumo de riesgo de alcohol: ¿debe ser una variable más relevante en cualquier investigación en este campo

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Dear Editor:

In recent years, treatment for patients with alcohol-related problems has evolved from a paradigm based on abstinence to a paradigm that places greater emphasis on reducing alcohol consumption in mild and moderate cases as an attainable goal of the therapeutic strategy, and that is coherent with the ethics of our profession (Barrio & Gual, 2016; Bradley & Kivlahan, 2014; Luquiens & Aubin, 2014). Furthermore, we are aware that a patient's self-evaluation of alcohol consumption is not exempt of minimisations as regards amounts and frequencies, likely due to a cognitive bias more so than the conscious desire to falsify the results of one's progress (Gual et al., 2017). In this sense, we questioned whether it would be correct, from a methodological perspective, to evaluate our patients' progress in relation to the changes in their quality of life as a result of treatment (Baumeister et al., 2014). In addition, we must mention that alcohol users as primary care patients, especially in their dependency patterns, usually present a greater risk of comorbidities, with the resulting impact on their quality of life (Barrio et al., 2016). Our goal was to explore the validity of this variable.

In the EFAR-Spain study (a randomised, controlled, non-inferiority trial of primary care-based facilitated access to an alcohol reduction website) (López-Pelayo et al., 2014) for the validation of a brief, on-line intervention with risky alcohol use patients, the EQ-5D-5L was used to collect quality of life as a secondary variable (Badia, Schiaffino, Alonso & Herdman, 1998). The AUDIT was used to collect sociodemographic data and alcohol consumption patterns (Saunders, Aasland, Babor, de la Fuente & Grant, 1993). The purpose of our study was to explore the relationship between quality of life and alcohol consumption pattern. For this purpose, we use the total quality of life score and its six different dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression, visual analogue scale) as the main dependent variable, and AUDIT score and sociodemographic data as independent variables.

The final sample was comprised of 320 risky drinkers. The mean age was 47.7 years, the majority were male (65%), married (62.5%), with children (65.2%), had a primary school education (42.8%) and were of Spanish nationality (90.1%). At baseline, there was a negative correlation (Pearson's test) between AUDIT and EQ-5D-5L scores, as regards both their global score ($r = -0.223$, $p < .05$) and their visual analogue scale for health ($r = -0.244$; $p < .05$). For the mental health dimension (anxiety/depression) of the EQ-5D-5L, the model was statistically significant ($\chi2(8) = 36.805$; $p < .005$). The remaining subscales were unrelated with AUDIT score. The multivariate analysis (Table 1) confirmed the statistical association of the total score for quality of life (linear regression: b = - 0.25; CI 95%: - .01 to -.004), the anxiety/depression subscale (linear regression: OR = 1.14; CI 95%: 1-08-1.22), and the visual analogue scale (linear regression: b = -0.27; CI 95%: -1,25 to -.500) with

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the AUDIT total score independent of sociodemographic factors.

In conclusion, in a clinical setting that is so key for the treatment of risky alcohol drinkers as is primary care (O'Donell et al., 2014), quality of life, especially in its mental health dimension, is transversally related to the severity of the alcohol consumption pattern, as per AUDIT. The EQ-5D-5L instrument has potential for evaluating the progress of primary care patients with risky alcohol consumption in treatment to reduce their alcohol consumption, though longitudinal studies are necessary to confirm this hypothesis, given that the data available to date only enables establishing a statistical association.

Table 1. *Logistic regression (dependent variable: presence of anxiety/depression in the EQ-5D-5L) and linear regression (dependent variable: total score in the EQ-5D-5L and Visual Analogue Scale of the EQ-5D-5L)*

Dependent variable: Total score	**Beta (CI 95%)**	**p**
AUDIT score	-0.25 (-0.01; -0.004)	‹ .001
Sex (male)	0.05 (-0.20; 0.05)	0.372
Age	0.06 (-0.01; 0.02)	0.466
Studies (university vs. others)	-0.01 (-0.19; 0.85)	0.847
Marital status (married vs. others)	-0.07 (-0.05; 0.02)	0.312
Use of technology (high)	-0.03 (-0.03; 0.02)	0.654
Children (yes)	-0.02 (-0.05; 0.04)	0.754
Country of origin (Spain)	-0.01 (0.04; 0.30)	0.838
Dependent variable: Visual Analogue Scale	**Beta (CI 95%)**	**p**
AUDIT score	-0.27 (-1.25; -0.50)	‹ .001
Sex (male)	0.06 (1.82; 5.77)	0.307
Age	-0.04 (-0.22; 0.14)	0.657
Studies (university vs. others)	0.01 (-0.01; 0.02)	0.810
Marital status (married vs. others)	-0.10 (-5.59; 0.76)	0.135
Use of technology (high)	0.64 (-2.67; 1.56)	0.604
Children (yes)	0.40 (-6.50; 2.57)	0.395
Country of origin (Spain)	0.01 (-3.14; 3.83)	0.847
Dependent variable: Presence of anxiety/depression (P5 EQ5D5L)	**OR (CI 95%)**	**p**
AUDIT score	1.14 (1.08; 1.22)	‹ .001
Sex (male)	0.78 (0.44; 1.37)	0.385
Age	0.99 (0.96; 1.01)	0.269
Studies (university vs. others)	1.01 (0.89; 1.15)	0.874
Marital status (married vs. others)	1.56 (0.98; 2.49)	0.062
Use of technology (high)	1.00 (0.72; 1.40)	0.996
Children (yes)	1.04 (0.49; 2.20)	0.928
Country of origin (Spain)	1.28 (0.74;2.20)	0.376

Note. CI 95% = Confidence Interval of 95%. OR = Odds Ratio

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References

Badia, X., Schiaffino, A., Alonso, J. & Herdman, M. (1998). Using the EuroQoL 5-D in the Catalan general population: Feasibility and construct validity. *Quality of Life Research, 7*, 311-322. doi:10.1023/A:1008894502042.

Barrio, P. & Gual, A. (2016). Patient-centered care interventions for the management of alcohol use disorders: A systematic review of randomized controlled trials. *Patient Preference and Adherence, 10*, 1823-1845. doi:10.2147/PPA.S109641.

Barrio, P., Miquel, L., Moreno-España, J., Martínez, A., Ortega, L., Teixidor, L.,… Gual, A. (2016). Alcohol in Primary Care. Differential characteristics between alcohol-dependent patients who are receiving or not receiving treatment. *Adicciones, 28*, 116–122. doi:10.20882/adicciones.779.

Baumeister, S. E., Gelberg, L., Leake, B. D., Yacenda-Murphy, J., Vahidi, M. & Andersen, R. M. (2014). Effect of a primary care based brief intervention trial among risky drug users on health-related quality of life. *Drug and Alcohol Dependence, 142*, 254-261. doi:10.1016/j.drugalcdep.2014.06.034.

Bradley, K. A. & Kivlahan, D. R. (2014). Bringing patient-centered care to patients with alcohol use disorders. *JAMA, 311*, 1861-1862. doi:10.1001/jama.2014.3629.

Gual, A., Arbesú, J., Zarco, J., Balcells-Oliveró, M. M., López-Pelayo, H., Miquel, L. & Bobes, J. (2017). Risky drinkers underestimate their own alcohol consumption. *Alcohol and Alcoholism, 52*, 516-517. doi:10.1093/alcalc/agx029.

López-Pelayo, H., Wallace, P., Segura, L., Miquel, L., Díaz, E., Teixidó, L.,... Gual, A. (2014). A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website (EFAR Spain): The study protocol. *British Medical Journal Open, 4* (12). doi:10.1136/bmjopen-2014-007130.

Luquiens, A. & Aubin, H. J. (2014). Patient preferences and perspectives regarding reducing alcohol consumption: Role of nalmefene. *Patient Preference and Adherence, 8*, 1347–1352. doi:10.2147/PPA.S57358.

O'Donell, A., Anderson, P., Newbury-Birch, D., Schulte, B., Schmidt, C., Reimer, J. & Kaner, E. (2014). The impact of brief alcohol interventions in primary healthcare: A systematic review of reviews. *Alcohol and Alcoholism, 49*, 66-78. doi:10.1093/alcalc/agt170.

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R. & Grant, M. (1993). Development of the Alcohol Use Disorders Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction, 88*, 791-804.

The influence of cigarette-smoking when choosing a partner for a casual, intimate relationship

La influencia de fumar cigarrillos en la elección de pareja para una relación íntima y ocasional

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Dear Editor,

The study of the effect that smoking may have on casual, intimate relationships is of great interest as it may prove to be a useful tool in the prevention and treatment of smoking. Traditionally, smoking cigarettes has been considered a useful tool when approaching the opposite sex (Baek and Mayer, 2010). However, over the last years, educational campaigns and changes in legislation may have altered perception of the effect of tobacco on the quality and healthiness of the relationship between a couple.

The aim of this study is to analyse whether the fact that the potential partner is or is not a smoker affects intentions to maintain a casual, intimate relationship. Gender and age influence choice of a sporadic partner is also analysed.

The participants were 597 subjects (293 non-smokers, 163 ex-smokers and 141 smokers). The mean age of the total sample was 26 (25 for smokers and non-smokers, and 28 for ex-smokers). Age range was from 16 to 68 years of age. Sixty-two percent were women and 38% men. Fifty-nine percent had basic secondary studies, 30% had finished school or were at university and 11.40% had university degrees.

Three different *ad hoc* questionnaires were used for each of the groups of participants. They included questions about sociodemographic characteristics and about the effect of cigarrette-smoking when choosing a partner for a casual, intimate relationship. The Questionnaires were applied over the Internet, through the "snowball method", using Google Forms and sent via the social networks Facebook and WhatsApp. The survey was totally anonymous and participation voluntary, as this method guarantees.

The results showed that 3.5% of the smokers, 26.8% of the ex-smokers and 41.6% of the non-smokers affirmed that the fact that a person smoked would have a negative influence on them when it came to initiating a casual, intimate relationship. Eleven percent of the smokers, 6.2% of the non-smokers and 9.1% of the ex-smokers affirmed that they would prefer a smoker when maintaining a casual, intimate relationships. There are statistically significant differences between smokers and non-smokers (χ^2=66.72, p<0.001), between ex-smokers and non-smokers (χ^2=30.74, p<0.001), and between smokers and ex-smokers (χ^2=9.70, p=0.002) regarding their negative attitude towards maintaining a casual, intimate relationship with a person who smokes. The analyses of a negative attitude towards smokers in relation to sex and age (over and under 30 years of age) did not show statistically significant differences (p> .05).

This is the first study to analyse whether the fact that a person smokes plays a role in the likelihood of that person being chosen as a partner for a casual, intimate relationship. The results showed that, in comparison to smokers, non-smokers and ex-smokers were more reluctant to maintain casual, intimate relationships with people who smoke. The negative attitude towards smoking was similar across gender and age. Preference for smokers when maintaining

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a casual intimate relationship was very low and similar in all groups of participants. Less than 11% of participants preferred a smoker, even if they were smokers themselves.

With regard to the reasons given by non-smokers and ex-smokers to justify their initial negative attitude towards maintaining casual relationships with someone who smoked, 88.2% indicated that what most bothered them was bad breath, followed by 78.7% who referred to the smell of tobacco, 25% to tobacco smoke and 6% to having to go outside premises to smoke.

These results underline how smoking, which for many years was considered to have a certain sex appeal, as the publicity was keen to show (Baek and Mayer, 2010), now appears not only to be beginning to lose this value but, furthermore, is starting to be perceived as an obstacle as far as intimate relationships are concerned. Smoking is no longer regarded to be attractive. Hygiene (the smell of tobacco, bad breath), and also social reasons (having to accompany the smoker outside a premises to smoke) explain this trend. The results also showed that the reluctance to maintain relationships with people who smoke was similar in men and women.

This study has direct implications for prevention and treatment of smoking. It is important that adolescents should be made aware of this issue, and the fact that smoking impedes the establishing of casual intimate relationships could be incorporated into the list of drawbacks associated with smoking.

Limitations of this study are that the sample was limited to over-18-year-olds and did not include adolescents, and that the snowball method does not always guarantee that the sample will be sufficiently representative.

Even with these limitations,, the results of this study show the existence of a further argument that can be used in the fight against smoking, based on the potential rejection that smoking appears to cause with regard to initiating intimate relationships.

Conflict of Interest

No conflict declared.

References

Baek, T. H. & Mayer, M. (2010). Sexual Imagery in Cigarette Advertising Before and After the Master Settlement Agreement. *Health Communication, 25,* 747-757. doi:10.1080/10410236.2010.521917.

Demotivating outcome of asymmetrical Nucleus Accumbens disconnection for cocaine related disorder: a translational point of view

Desmotivadora evolución de la desconexión asimétrica del Núcleo Accumbens en el trastorno por consumo de cocaína: un punto de vista traslacional

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Dear Editor,

Neuroanatomical disconnection used in animals reveal that cortico-limbic-striatal circuit involving the medial prefrontal cortex (mPFC), the basolateral amygdala (BLA), and nucleus accumbens (Nacb) mediate decision-making processes (Salamone & Correa, 2012; Salamone, Yohn, López-Cruz, San Miguel & Correa, 2016). BLA projections modulate Nacb activity, and influence the direction of behavior toward relevant stimuli (Floresco, Blaha, Yang & Phillips, 2001). Disruption of activity in both the Nacb and BLA, as well as their communication, reduces preference for more effortful options, increases for riskier ones, with less motivated behavior (Salamone & Correa, 2012; Salamone et al., 2016).

With this letter, the authors present the history of a patient after extensive psychosurgery, including neuroimaging and neuropsychological assessment, and discussion from a translational point of view.

The patient was adopted few days after being born with dystocia. The biological-family history is unknown. His adoptive parents suffered from cocaine and alcohol-related disorder. During childhood, the patient had most symptoms of Attention Deficit Hyperactive Disorder (ADHD). He was described as an aggressive child and had a diagnostic of conduct disorder. At 14, he started cocaine consumption. At 16, he was diagnosed of "non-specified impulse control disorder" and cocaine-related disorder. His intelligence Quotient was 85. At 17, a psychiatrist diagnosed the patient with a "mental disorder secondary to dystocia". Magnetic resonance image (MRI) indicated atrophy of the left hemisphere. Positron emission tomography (PET) showed a moderate general reduction in brain metabolism. Based upon last diagnose and neuroimaging study, a neurosurgeon diagnosed the patient from "impulse control dysfunction" and "limbic dysfunction syndrome", prescribing psychosurgery for the control of aggressiveness.

The neurosurgery consisted in thermal coagulation lesions induced by radiofrequency. The target regions were anterior cingulate (AC), anterior capsula, and stria terminalis of left hemisphere and anterior capsula and the amygdala of right hemisphere. A second surgery extending the lesions in left anterior capsula and right AC was performed two months later given a relapse in aggressiveness.

After psychosurgery, the aggressiveness persisted, and the patient started to have delusions. The patient alternated periods of cocaine and heroin consumption, with periods of permanence in penitentiary centers. He was diagnosed with paranoid schizophrenia without treatment adherence. At the age of 27, he showed predominant cognitive deficits and negative psychotic symptomatology.

Fifteen years after psychosurgery, at 32, a more thorough neuroimage exploration was performed (Figure 1). MRI showed abnormal cavities in right putamen, left Nacb, internal capsule and AC of both hemispheres. Tractography showed major impact on the connections among AC, Nacb and amygdala. Morphological analyses show a

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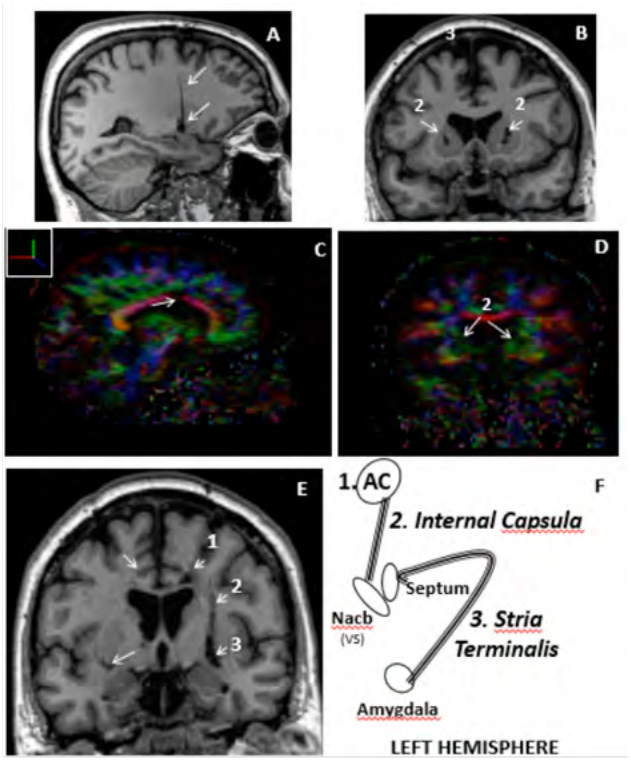

Figure 1.

MRI test performed 15 years after surgery (A, B and E). Tractography images showing impact on corpus callosum (C) and internal capsule fibers (D). (F) Schematic with the neurosurgery targets. The goal of the surgery was to inactivate AC and to disconnect it from ventral striatum (VS) and amygdala in both hemispheres, as well as to produce a lesion of the amygdala in the right hemisphere and disconnect amygdala output fibers in the left hemisphere.

marked reduction in the volume of parietal cortices and medial PFC, including ventromedial and orbital cortex. Furthermore, neuropsychological assessment (BIS-11, LSRP, IOWA gambling task and Tower of London) showed impairment of planning processes, difficulties in cost/benefit decision-making, psychopathic traits and high motor impulsivity.

Combined unilateral lesions of the mPFC and the Nacb in opposite hemispheres (disconnection) in animals reduced selection of effortful options and produced perseveration of behavior without integrating information from affective feedback (Salamone & Correa, 2012; Hauber & Sommer, 2009). Moreover, disconnection between mPFC and other striatal regions (e.g. medial caudate-putamen) impairs aspects of attentional function and habit-based memories (Phillips & Carr, 1988; Packard, Hirsh & White, 1989). In humans, functional connectivity between the AC and the Nacb, as well as, between AC and amygdala is relevant for decision-making and reward anticipation, respectively (Cohen, Heller & Ranganath, 2005; Marsh, Blair, Vythilingam, Busis & Blair, 2007). In addition, non-routine tasks, which require constant monitoring of new information to plan appropriate responses, are particularly susceptible to PFC damage. The patient has been reported to have difficulties in acquiring new habits and shows difficulties in sustaining attention. Furthermore, neuropsychological assessment suggests impairment of planning processes and difficulties in cost/benefit decision-making. Hence, these behavioral patterns are consistent with the lesions performed during the surgery and the resulting damage observed in the recent images.

Barcia et al (2007) and Leiphart & Valone-III (2010) recognized that the most frequent psychosurgeries are anterior capsulotomy, which have been shown beneficial for general anxiety and obsessive-compulsive disorders, and anterior cingulotomy, which have shown improvements for depression, bipolar and schizoaffective disorders. However, addiction and schizophrenia had the lowest reported improvements, and there is evidence that combining more than one brain target may make the outcomes worse.

In this letter, we suggest that "impulse control dysfunction" and "limbic dysfunction syndrome" when the patient was adolescent could had been better defined as ADHD, conduct and cocaine-related disorders. These disorders have specific and effective non-surgical treatments. Fifteen years after psychosurgery, he developed Schizophrenia and aggressiveness persists. Furthermore, the patient presents increased choice of riskier options, an inability to integrate information related to affective feedback (punishment or reward), difficulties in acquiring new habits, and difficulties in sustaining attention. Taking into account the animal models, these functional impairments are partly due to the psychosurgery, which suggests an irreversible and demotivating prognosis.

Conflicts of interest

There are no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Fundación de investigación del Hospital Provincial de Castellón has supported the open access. All authors contributed equally.

Ethical aspects

The ethical committee of Castellón Provincial Hospital Consortium approved the study, and an informed consent was obtained from the legal tutor and from the participant for experimentation (neuroimages and neuropsychological tests) and publication.

References

Barcia, J.A., Bertolín-Guillén, J.M., Barcia-González, J., Campos, J. & Hernández, M.E. (2007). Estado actual de la psicocirugía en España. *Neurocirugía, 18,* 301-311.

Cohen, M.X., Heller, A.S. & Ranganath. C. (2005). Functional connectivity with anterior cingulate and orbitof-

rontal cortices during decision-making. *Brain Research. Cognitive Brain Research, 23,* 61-70. doi:10.1016/j.cogbrainres.2005.01.010.

Floresco, S.B., Blaha, C.D., Yang, C.R. & Phillips, A.G. (2001). Dopamine D1 and NMDA receptors mediate potentiation of basolateral amygdala-evoked firing of nucleus accumbens neurons. *The Journal of Neuroscience, 21*, 6370-6376.

Hauber, W. & Sommer, S. (2009). Prefrontostriatal circuitry regulates effort-related decision making. *Cerebral Cortex, 19,* 2240-2247. doi:10.1093/cercor/bhn241.

Leiphart, J.W. & Valone-III, F.H. (2010). Stereotactic lesions for the treatment of psychiatric disorders. *Journal of Neurosurgery, 113,* 1204-1211.

Marsh, A.A., Blair, K.S., Vythilingam, M., Busis, S. & Blair, R.J. (2007). Response options and expectations of reward in decision-making: the differential roles of dorsal and rostral anterior cingulate cortex. *Neuroimage, 35,* 979-988. doi:10.1016/j.neuroimage.2006.11.044.

Packard, M.G., Hirsh, R. & White, N.M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. *Journal of Neurosurgery, 9,* 1465-1472.

Phillips, A.G. & Carr, G.D. (1988). Cognition and the basal ganglia: a possible substrate for procedural knowledge. *The Canadian Journal of Neurological Sciences, 14,* 381-385.

Salamone, J.D. & Correa. M. (2012). The mysterious motivational functions of mesolimbic dopamine. *Neuron, 76,* 470-485. doi:10.1016/j.neuron.2012.10.021.

Salamone, J.D., Yohn, S.E., López-Cruz, L., San Miguel, N. & Correa, M. (2016). Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology. *Brain, 139,* 1325-1347. doi:10.1093/brain/aww050.

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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

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

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

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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.

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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.

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

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

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

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

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

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Medidas para evitar la omisión de dosis.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. *Omisión de la segunda dosis de iniciación (<4 semanas desde la primera inyección).* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: *Para los pacientes estabilizados con dosis de 25 a 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada > 65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥ 50 a < 80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada 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. 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. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos $<1x10^9$/L) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con Xeplion se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia 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 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 2000 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 los enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro* ni *in vivo* de que esas isoenzimas desempeñen un papel 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_{ss} 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. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10); *frecuentes* (≥1/100 a <1/10); *poco frecuentes* (≥1/1.000 a <1/100); *raras* (≥1/10.000 a <1/1.000); *muy raras* (<1/10.000); y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

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

Trastornos 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[c], ginecomastia, disfunción sexual, dolor de mamas	malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[a], aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección	disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

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

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

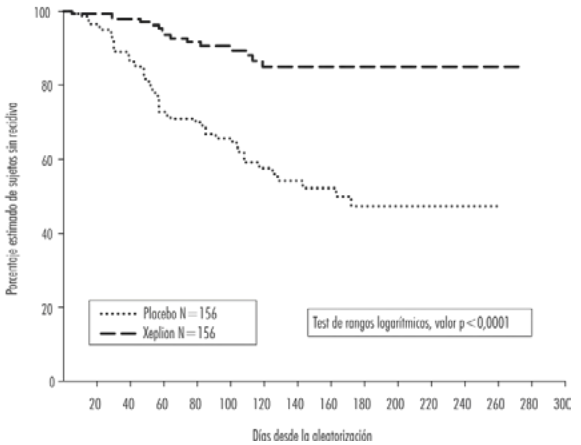
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 estos 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 (días 8 y 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 los de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (ClCr=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (ClCr =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{inf}) 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 mayoritariamente 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.** Poliisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Período de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefino-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: 171,61 €; PVP: 217,52 €; PVP (IVA): 226,22 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 223,08 €; PVP: 273,99 €; PVP (IVA): 284,95 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 274,59 €; PVP: 325,50 €; PVP (IVA): 338,52 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 411,88 €; PVP: 462,79 €; PVP (IVA): 481,30 €. **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.** 11/2016. 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. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. COMPOSICION CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de paliperidona equivalentes a 175 mg de paliperidona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de paliperidona equivalentes a 263 mg de paliperidona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de paliperidona equivalentes a 350 mg de paliperidona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de paliperidona equivalentes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a TREVICTA. 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.* TREVICTA se debe usar solo después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se deben tener en cuenta sus características de liberación prolongada. *Cambio desde TREVICTA a palmitato de paliperidona inyectable mensual.* Para cambiar desde TREVICTA a palmitato de paliperidona inyectable mensual, este se administrará en el momento en que se deba administrar la dosis siguiente de TREVICTA, dividiendo la dosis por 3,5 según se indica en la tabla siguiente. No es necesaria la dosis de inicio según se describe en la ficha técnica de palmitato de paliperidona inyectable mensual. El palmitato de paliperidona inyectable mensual se seguirá administrando una vez al mes tal como se describe en su ficha técnica.

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

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

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

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

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

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

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

Dosis omitidas

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

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

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

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

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en Insuficiencia renal las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado de manera sistemática 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 necesaria 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. 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. Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos <1 x 10^9/l) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **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 esos isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de C_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. **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. 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[d]	agitación, depresión, ansiedad	trastornos del sueño, manía, disminución de la líbido, nerviosismo, pesadillas	estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[e], acatisia[e], sedación[f]/somnolencia, distonía[e], mareo, discinesias[e], 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[g], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolia pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión respiratoria, sibilancias, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía

Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, disfagia, 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, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales					síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastornos de la eyaculación, trastornos menstruales[c], ginecomastia, disfunción sexual, dolor mamario	hinchazón o malestar mamario, aumento del tamaño de las mamas, flujo vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		fiebre, astenia, fatiga, reacciones en el lugar de inyección	edema facial, edema[a], aumento de la temperatura corporal, alteraciones de la marcha, dolor torácico, molestias en el pecho, malestar general, induración	hipotermia, escalofríos, polidipsia, síndrome de abstinencia de fármacos/drogas, abscesos en el lugar de inyección, celulitis en el lugar de inyección, quistes en el lugar de inyección, hematomas en el lugar de inyección	descenso de la temperatura corporal, necrosis en el lugar de inyección, úlceras en el lugar de inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica*. Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección*. En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP)*. En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, emprostótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo bucofaringeo, 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 los monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual 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%]).

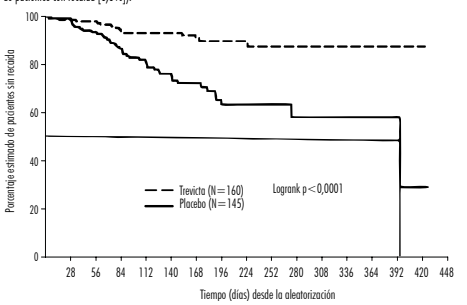


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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 período de 48 semanas. Los pacientes recibieron TREVICTA una vez cada 3 meses y una medicación inyectable placebo durante los meses restantes para mantener el ciego. En este estudio, el criterio de valoración de la eficacia principal era el porcentaje de pacientes sin recaída al final de la fase doble ciego de 48 semanas, basado en la estimación de Kaplan-Meier de las 48 semanas (TREVICTA: 91,2%, palmitato de paliperidona inyectable mensual: 90,0%). No fue posible calcular la mediana de tiempo hasta la recaída en ninguno de los grupos, dado el escaso porcentaje de pacientes con recaídas. La diferencia (IC 95%) entre los grupos de tratamiento fue del 1,2% (-2,7%, 5,1%), lo que satisface el criterio de no inferioridad basado en un margen de -10%. Por tanto, el grupo de tratamiento con TREVICTA fue no inferior al grupo tratado con palmitato de paliperidona inyectable mensual. Las mejorías funcionales, determinadas según la Escala de Funcionamiento Personal y Social (PSP), que se observaron durante la fase de estabilización abierta se mantuvieron durante la fase de doble ciego en ambos de tratamiento.

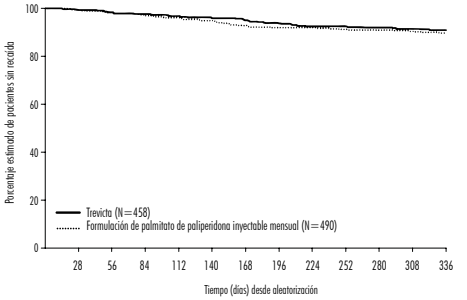


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{max}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la 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 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un período de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{∞}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. Raza. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. Sexo. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. Tabaquismo. Según estudios in vitro realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS 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: 515,00 €; PVP: 570,91 €; PVP (IVA): 593,75 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 670,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 824,00 €; PVP: 879,91 €; PVP (IVA): 915,11 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.236,00 €; PVP: 1.291,91 €; PVP (IVA): 1.343,59 €. 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 AUTORIZACION/RENOVACIÓN DE LA AUTORIZACION.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 05/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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