Adicciones

SOCIDROGALCOHOL Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

ISSN 0214-4840

FUNDED BY:

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

2021 | Vol. 33 | n.1

FUNDED BY:

adicciones

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

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
SECRETARÍA DE ESTADO DE SERVICIOS SOCIALES E IGUALDAD
DELEGACIÓN DEL GOBIERNO PARA EL PLAN NACIONAL SOBRE DROGAS

PUBLISHER: **SOCIDROGALCOHOL** (Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías)

I.S.S.N.: 0214-4840 • **SVPF:** 89010R • **LEGAL DEP.:** V-1543-1989

printing: MARTIN IMPRESORES, S.L., Pintor Jover, 1, 46013 VALENCIA • Papel permanente según normas ISO 9706

send correspondence to: SOCIDROGALCOHOL • Avda. de Vallcarca, 180 • 08023 Barcelona
Phone: (+34) 932103854 • E-mail: socidrogalcohol@socidrogalcohol.org • www.socidrogalcohol.org

INDEXED IN: ADDICTION ABSTRACTS, C.A.N., C.I.C., CVDD, EMBASE/EXCERPTA MEDICA, ETOH (NIAAA), FAMILY STUDIES DATABASE (NISC), IBECS, I.M.E., INDID, INIST-CNRS, ISOC, MEDLINE, PSICODOC, PSYCINFO, REDALYC, SOCIAL SCIENCES CITATION INDEX (SSCI) Y SCIENCE CITATION INDEX EXPANDED (SCIE).TOBACCO AND HEALTH ABSTRACTS (NISC), TOXIBASE

editorial

originals / originales

letters to the editor / cartas al editor

FUNDED BY:
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
SECRETARÍA DE ESTADO DE SERVICIOS SOCIALES E IGUALDAD
DELEGACIÓN DEL GOBIERNO PARA EL PLAN NACIONAL SOBRE DROGAS

boletín de suscripción:

■ DATOS PERSONALES:

Nombre y apellidos .....

NIF ..... Profesión .....

Dirección ..... Nº ..... Piso .....

Tel. ..... Población ..... D.P. ..... Provincia .....

E-mail .....

■ SUSCRIBANME A: «Adicciones». Año 2021

España	4 ejemplares y suplementos	50,00 €		suscripción particular
	4 ejemplares ,,	130,00 €		suscripción instituciones
	1 ejemplar	15,00 €		
	1 monográfico	20 €		
Extranjero	4 ejemplares y suplementos	90 €	90 $	suscripción particular
	4 ejemplares ,,	200 €	200 $	suscripción instituciones
	1 ejemplar	19 €	19 $	

Las suscripciones se entenderán por los cuatro ejemplares del año natural en que se realice la suscripción, sea cual sea el momento del año en que ésta se efectúe.

■ PAGARÉ:

A) **Por domiciliación bancaria (rellenar para ello la orden de pago que está a continuación y enviarnos el original por correo).**

B) Mediante cheque nº. ..... que adjunto a nombre de «Adicciones».

C) Transferencia bancaria a BANCO SABADELL ATLÁNTICO - Ag. Ganduxer, Vía Augusta, 246 - Barcelona - IBAN: ES81 0081 0653 7300 0116 0017
(Es importante que en la orden de transferencia conste claramente el ordenante de la transferencia para poderla identificar adecuadamente).

..... de ..... de 20 .....
(Firma)

ORDEN DE PAGO POR DOMICILIACION BANCARIA:

Nombre del titular de la cuenta .....

Nombre del Banco o Caja de Ahorros .....

Número Cuenta Corriente o Libreta **(ATENCIÓN: DEBE CONSTAR DE 20 DÍGITOS):**

Entidad ☐☐☐☐ Oficina ☐☐☐☐ D.C. ☐☐ Nº ☐☐☐☐☐☐☐☐☐☐

Dirección Banco o C.A.:

Calle o Pza.: .....

Código Postal ..... población ..... Provincia .....

Ruego a Vds. Se sirvan tomar nota de que, hasta nuevo aviso, deberán adedudar en mi cuenta los efectos que les sean presentados para su cobro por "Adicciones, Socidrogalcohol"

..... de ..... de 20 .....

Atentamente (firma del titular)

ENVIAR EL ORIGINAL DE ESTA DOMICILIACIÓN POR CORREO POSTAL

ENVIAR ESTE BOLETIN A:

SOCIDROGALCOHOL – Avda. Vallcarca, 180. 08023 Barcelona (España)
Tel/Fax. +34 932 103 854. E-mail: socidrogalcohol@socidrogalcohol.org

La revista es gratuita para los socios de Socidrogalcohol

adicciones
revista de socidrogalcohol

Paradigm shift in the relationship between alcohol and health: the less, the better

Cambio de paradigma en la relación alcohol y salud: cuanto menos, mejor

Rodrigo Córdoba-García*, Xisca Sureda**,***,****,*****,
Luis Sordo******,*******, Antoni Gual********,*********,**********.

* Departamento de Medicina, Facultad de Medicina. Centro de Salud Universitario Delicias Sur, Zaragoza.
** Grupo de Investigación en Salud Pública y Epidemiología, Facultad de Medicina. Universidad de Alcalá, Madrid.
*** Departamento de Epidemiología y Bioestadística. Escuela Graduada de Salud Pública, City University of New York, N.Y.
**** Institut d'Investigació Biomèdica de Bellvitge-IDIBELL. L'Hospitalet de Llobregat, Barcelona.
***** Consorcio de Investigación Biomédica en Enfermedades Respiratorias,
CIBER en Enfermedades Respiratorias (CIBERES), Madrid.
****** Departamento de Salud Pública y Materno-Infantil, Facultad de Medicina. Universidad Complutense de Madrid.
******* CIBER en Epidemiología y Salud Pública (CIBERESP).
******** Unidad de Conductas Adictivas. Hospital Clínic, Barcelona.
********* IDIBAPS, Barcelona.
********** Red de Trastornos Adictivos. I. Carlos III, Madrid.

The consumption of alcoholic beverages is deeply rooted in Western culture and plays a part in most traditions and celebrations. However, this consumption is not without risks, depending on the amount, frequency and pattern of consumption, as well as the characteristics of the consumer, such as age, sex and some health conditions. Despite the accumulation of evidence in scientific research regarding the toxicity of alcohol, the pressure to drink continues to increase. This requires a redefinition of the limits of low-risk consumption by the health authorities.

Alcoholic drinks are consumed daily by 7.4% of the Spanish adult population (Observatorio Español de las Drogas y las Adicciones, 2019). Alcohol is an addictive substance capable of causing dependence and is related to over 200 health problems (Rehm et al., 2017; World Health Organization, 2018). Alcohol use is the seventh biggest risk factor for both death and loss of disability-adjusted years of life. The only alcohol use that minimizes loss of health is zero (GBD 2016 Risk Factors Collaborators, 2017).

Alcohol and cardiovascular risk

Although low doses of alcohol have been shown to have a beneficial effect in ischemic heart disease and thrombotic stroke, most of the studies reporting this are observational and do not contextualize this effect within the consequences that alcohol use has on global health (Brien, Ronksley, Turner, Mukamal & Ghali, 2011). The relationship between drinking and cardiovascular risk is complex and multifactorial, with various biases described in the literature of how this relationship may be modified. Indeed, we know that binge drinking increases the risk of heart attack (Leong et al., 2014) and that drinking over 30g/day increases the risk of other cardiovascular diseases such as arterial hypertension, atrial fibrillation, alcoholic cardiomyopathy or heart failure (Mukamal & Lazo, 2017). A study published in 2015 revealed that with doses above 10 g/day in women or 20 g/day in men, the risk of heart attack fell by 24%, but the risk of cancer rose by 51% (Smyth et al., 2015). The possible cardiovascular benefit does not come close to offsetting mortality from all causes (Wood et al., 2018).

Received: June 2020; Accepted: October 2020.

Corresponding author: Xisca Sureda Llull, BPharm, MPH, PhD.
Universidad de Alcalá. Crta. de Madrid-Barcelona, Km. 33.600. Alcalá de Henares, Madrid, 28871 España. Tel: +34 918854573.
E-mail: francisca.sureda@uah.es.

Alcohol and cancer

As cancer is one of the main causes of morbidity and mortality, it is essential to take into account studies on alcohol and cancer if the complexity of the alcohol-disease relationship is to be understood. Small amounts of alcohol increase the risk of some of the most common cancers in the general population, such as colon (Cho, Lee, Rimm, Fuchs & Giovannucci, 2012), esophagus (Matejcic, Gunter & Ferrari, 2017) or breast cancer (Shield, Soerjomataram & Rehm, 2016). Some studies reporting a possible "beneficial" effect of alcohol on certain cardiovascular diseases actually hide the carcinogenic effect of the main metabolite of alcohol, acetaldehyde, in relation to the appearance of various types of cancer (Singh, Arcaroli, Thompson, Messersmith & Vasiliou, 2015). It is estimated that the risk of digestive cancer increases 10-30% for every 20 g/day of alcohol use. Evidence also indicates that 10% of cancers in men and 3% in women are alcohol-related, with the median 5-year survival rate for such cancers being 50%. The IARC (International Agency for Research on Cancer) lists alcohol as a Group A carcinogen for which there is no safe level of exposure (International Agency for Research on Cancer, 2012).

Limitations of systematic reviews on alcohol and mortality

Some meta-analyses indicate a positive association between mortality and low alcohol-use thresholds. However, such results cannot be interpreted without taking into account many of the limitations of the primary studies on which they are based (Stockwell et al., 2016): 1) Classification bias (combining ex-drinkers and non-drinkers); 2) Bias by omitting binge drinking; 3) Bias by omitting confounding variables (socioeconomic level, physical activity and diet); 4) Selection and generalization bias (confusing disease mortality with global mortality); 5) Publication bias (in the representation of cardiovascular risk studies) and 6) Bias due to industry-sponsored publication (conflicts of interest). Furthermore, many studies are based on samples which are not very representative of the general population. Because of the difficulties in follow-up that would be involved, they do not include groups at high risk of alcohol-related harm, such as marginalized or institutionalized populations and population strata of very low socioeconomic level. Given all these limitations, only studies free of the above biases should be considered when establishing a low-risk consumption threshold.

The paradigm shift

A review of the most recent bias-free cohort studies indicates that the levels above which a significant increase in mortality risk is evidenced range from 20 to 60 g/day of alcohol for men and 12 to 20 g/day for women (Ministerio de Sanidad, 2020). These data come from a review of studies published between 2015 and 2019 which used people who had never drunk alcohol (excluding ex-drinkers) as the reference population and which provided results adjusted for confounding variables such as smoking, body mass index, and socioeconomic status. Furthermore, the results are similar to the figures given in other countries and are aligned with the recommendations of some of the most relevant articles stating that the levels of low-risk alcohol use for the European cultural environment should be of 15-20 g/day in men and 8-10 g/day in women (Shield et al., 2017). The differences in consumption by sex are determined by differences in alcohol dehydrogenase levels and by metabolic capacity.

A paradigm shift would entail that no professional should recommend the consumption of alcohol for any health reason. Although it may decrease the risk of a particular disease slightly, it will not improve the overall prognosis of the patient. Low risk alcohol consumption limits should be 20 g/day for men and 10 g/day for women, assuming there is no zero risk. The idea must be transmitted to the population that the greatest benefit to health is derived from not drinking alcohol at all or doing so in lower quantities than those accepted to date. In December 1995 the WHO organized a Conference in Paris with the title 'Alcohol, less is better' (World Health Organization. Regional Office for Europe & Anderson, 1996). Twenty-five years later, scientific evidence has accumulated to confirm this and promote this paradigm shift: Alcohol, the less, the better.

Conflicts of interest

The authors declare that there is no conflict of interest.

Bibliography

Brien, S. E., Ronksley, P. E., Turner, B. J., Mukamal, K. J. & Ghali, W. A. (2011). Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: Systematic review and meta-analysis of interventional studies. *BMJ (Clinical Research Ed.), 342*, d636. doi:10.1136/bmj.d636.

Cho, E., Lee, J. E., Rimm, E. B., Fuchs, C. S. & Giovannucci, E. L. (2012). Alcohol consumption and the risk of colon cancer by family history of colorectal cancer. *The American Journal of Clinical Nutrition, 95*, 413-419. doi:10.3945/ajcn.111.022145.

GBD 2016 Risk Factors Collaborators, G. 2016 R. F. (2017). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease

Study 2016. *Lancet*, *390*, 1345-1422. doi:10.1016/S0140-6736(17)32366-8.

International Agency for Research on Cancer. (2012). *IARC monographs on the evaluation of carcinogenic risks to humans, volume 100E. Consumption of Alcoholic Beverages*. Lyon, France. Retrieved at http://monographs.iarc.fr/ENG/Monographs/.

Leong, D. P., Smyth, A., Teo, K. K., McKee, M., Rangarajan, S., Pais, P., … Yusuf, S. (2014). Patterns of alcohol consumption and myocardial infarction risk: Observations from 52 countries in the INTERHEART case-control study. *Circulation*, *130*, 390-398. doi:10.1161/CIRCULATIONAHA.113.007627.

Matejcic, M., Gunter, M. J. & Ferrari, P. (2017). Alcohol metabolism and oesophageal cancer: A systematic review of the evidence. *Carcinogenesis*, *38*, 859-872. doi:10.1093/carcin/bgx067.

Ministerio de Sanidad. (2020). *Límites de Consumo de Bajo Riesgo de Alcohol. Actualización del riesgo relacionado con los niveles de consumo de alcohol, el patrón de consumo y el tipo de bebida*. Madrid.

Mukamal, K. & Lazo, M. (2017). Alcohol and cardiovascular disease. *BMJ (Clinical Research Ed.)*, *356*, j134. doi:10.1136/bmj.j1340.

Observatorio Español de las Drogas y las Adicciones. (2019). *INFORME 2019 Alcohol, tabaco y drogas ilegales en España. Encuesta sobre alcohol y drogas en España (EDADES), 1995-2017*. Retrieved at http://www.pnsd.mscbs.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2019_Informe_EDADES.pdf.

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

Shield, K. D., Gmel, G., Gmel, G., Mäkelä, P., Probst, C., Room, R. & Rehm, J. (2017). Life-time risk of mortality due to different levels of alcohol consumption in seven European countries: implications for low-risk drinking guidelines. *Addiction*, *112*, 1535-1544. doi:10.1111/add.13827.

Shield, K. D., Soerjomataram, I. & Rehm, J. (2016). Alcohol Use and Breast Cancer: A Critical Review. *Alcoholism: Clinical and Experimental Research*, *40*, 1166-1181. doi:10.1111/acer.13071.

Singh, S., Arcaroli, J., Thompson, D. C., Messersmith, W. & Vasiliou, V. (2015). Acetaldehyde and retinaldehyde-metabolizing enzymes in colon and pancreatic cancers. *Advances in Experimental Medicine and Biology*, *815*, 281-294. doi:10.1007/978-3-319-09614-8_16.

Smyth, A., Teo, K. K., Rangarajan, S., O'Donnell, M., Zhang, X., Rana, P., … Yusuf, S. (2015). Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: A prospective cohort study. *Lancet*, *386*, 1945-1954. doi:10.1016/S0140-6736(15)00235-4.

Stockwell, T., Zhao, J., Panwar, S., Roemer, A., Naimi, T. & Chikritzhs, T. (2016). Do "moderate" drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *Journal of Studies on Alcohol and Drugs*, *77*, 185-198. doi:10.15288/jsad.2016.77.185.

Wood, A. M., Kaptoge, S., Butterworth, A., Nietert, P. J., Warnakula, S., Bolton, T., … Thompson, S. (2018). Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet*, *391*, 1513-1523. doi:10.1016/S0140-6736(18)30134-X.

World Health Organization. Regional Office for Europe & Anderson, P. (1996). *Alcohol: less is better: report of the WHO European Conference - Health, Society and Alcohol, Paris, 12-14 December 1995*. World Health Organization. Regional Office for Europe.

World Health Organization. (2018). Global status report on alcohol and health 2018. Retrieved at https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf?ua=1.

Visual and auditory contextual cues differentially influence alcohol-related inhibitory control

Los estímulos contextuales visuales y auditivos impactan de manera diferenciada el control inhibitorio relacionado con el alcohol

Adam Qureshi*, Rebecca L. Monk*, Charlotte R. Pennington**, Xiaoyun Li*, Thomas Leatherbarrow*, Jennifer R Oulton*.

* Edge Hill University, Ormskirk. UK. ** University of the West of England, Bristol. UK.

Abstract

Representing a more immersive testing environment, the current study exposed individuals to both alcohol-related visual and auditory cues to assess their respective impact on alcohol-related inhibitory control. It examined further whether individual variation in alcohol consumption and trait effortful control may predict inhibitory control performance. Twenty-five U.K. university students (*M*age = 23.08, *SD* = 8.26) completed an anti-saccade eye-tracking task and were instructed to look towards (pro) or directly away (anti) from alcohol-related and neutral visual stimuli. Short alcohol-related sound cues (bar audio) were played on 50% of trials and were compared with responses where no sounds were played. Findings indicate that participants launched more incorrect saccades towards alcohol-related visual stimuli on anti-saccade trials, and responded quicker to alcohol on pro-saccade trials. Alcohol-related audio cues reduced latencies for both pro- and anti-saccade trials and reduced anti-saccade error rates to alcohol-related visual stimuli. Controlling for trait effortful control and problem alcohol consumption removed these effects. These findings suggest that alcohol-related visual cues may be associated with reduced inhibitory control, evidenced by increased errors and faster response latencies. The presentation of alcohol-related auditory cues, however, appears to enhance performance accuracy. It is postulated that auditory cues may re-contextualise visual stimuli into a more familiar setting that reduces their saliency and lessens their attentional pull.

Keywords: Alcohol consumption; Inhibitory control; Context effects; Anti-saccade; Effortful control.

Resumen

Con el objetivo de crear un entorno de evaluación más ajustado a la realidad, en este estudio se expuso a los participantes a estímulos visuales y auditivos relacionados con el alcohol para evaluar su impacto en el control inhibitorio relacionado con el alcohol. Además, se examinó si las diferencias individuales en el consumo de alcohol y el rasgo autorregulación predecían el rendimiento del control inhibitorio. Veinticinco estudiantes universitarios del Reino Unido (edad media = 23,08 años; SD = 8,26) llevaron a cabo una tarea anti-sacádica de seguimiento ocular, en la que se les pedía que miraran hacia (pro), o directamente en la dirección contraria (anti), estímulos visuales tanto relacionados con el alcohol como neutros. Además, en el 50% de los ensayos se reprodujeron estímulos auditivos breves relacionados con el alcohol (sonido de bar), y las respuestas se compararon con las que se producían en la ausencia de sonidos. Los resultados indican que los participantes dirigieron más movimientos sacádicos incorrectos hacia los estímulos visuales relacionados con el alcohol en los ensayos anti-sacádicos, y que respondieron más rápido al alcohol en los ensayos pro-sacádicos. Los estímulos auditivos relacionados con el alcohol redujeron la latencia de respuesta tanto para los ensayos pro- como anti-sacádicos, y redujeron la tasa de errores anti-sacádicos en los estímulos relacionados con el alcohol. Sin embargo, estos efectos se eliminaron al controlar el rasgo autorregulación y el consumo problemático de alcohol. Estos resultados sugieren que los estímulos visuales relacionados con el alcohol pueden estar asociados con una reducción del control inhibitorio, lo cual se pone de manifiesto en el aumento de errores y en unas latencias de respuesta más rápidas. Sin embargo, la presentación de estímulos auditivos relacionados con el alcohol parece aumentar la precisión en la tarea. Se propone que los estímulos auditivos pueden recontextualizar los estímulos visuales en un contexto más familiar que reduce su prominencia y disminuye su capacidad de captar la atención.

Palabras clave: Consumo de alcohol; Control inhibitorio; Efectos contextuales; Anti-sacádico; Autorregulación.

Received: December 2017; Accepted: July 2018.

Send correspondence to:
Adam W. Qureshi. Department of Psychology, Edge Hill University, St Helens Road, Ormskirk, L39 4QP.
Tel: +44 (0)1695 584 498. Fax: +44 (0)1695 579 997. E-mail: qureshia@edgehill.ac.uk.

Exposure to alcohol-related stimuli, environments, and paraphernalia has been shown to impair inhibitory control in both clinical and non-clinical populations (e.g. Field, Wiers, Christiansen, Fillmore & Verster, 2010; Fleming & Bartholow, 2014; Kreusch, Vilenne & Quertemont, 2013; Papachristou, Nederkoorn, Havermans, van der Horst & Jansen, 2012). Individuals with low sensitivity to the acute effects of alcohol exhibit automatic approach biases towards alcohol-related visual stimuli, and experience more conflict when attempting to inhibit alcohol-cued compared to non-alcohol cued responses (Fleming & Bartholow, 2014). Non-problem drinkers also appear to show disinhibition towards alcohol-related visual stimuli, responding with significantly more errors and quicker reaction times towards alcohol-related stimuli on the Cued Go/No-Go task (Kreusch et al., 2013) and anti-saccade task (Jones & Field, 2015; King & Byers, 2004; Laude & Fillmore, 2015; McAteer, Curran & Hanna, 2015). This heightened approach bias towards alcohol-related stimuli is theorised to reflect the salience of such cues to individuals who consume alcohol (Grant & Macdonald, 2005; Rose & Duka, 2008).

Through the process of conditioning, alcohol-related cues are associated with the perceived positive expectancies of drinking and become increasingly attractive (c.f., Jones, Hogarth, Christiansen, Rose, Martinovic & Field, 2012; Tuenissen, Spijkerman, Schoenmakers, Vohs & Engels, 2012). Resultantly, attention is drawn to alcohol-related cues (Tuenissen et al., 2012) which, in turn, may lead to an increase in craving (Manchery, Yarmush, Luehring-Jones & Erblich., 2017) and consumption (e.g., Weafer & Fillmore, 2013). Inhibition is proposed to control the strength of alcohol-related attentional biases (Field & Cox 2008) by moderating processes such as automatic approach tendencies (e.g., Wiers et al., 2007), as well as implicit associations (e.g., Houben & Wiers, 2009). For this reason, inhibitory control is theorised to be an important driver of consumption behaviours (Cooney, Gillespie, Baker & Kaplan, 1987; Nees, Diener, Smolka & Flor, 2012). Indeed, it has been found that both automatic approach tendencies and impulsivity (decision-making and inhibitory control) predict alcohol consumption behaviour (Christiansen, Cole, Goudie & Field, 2012).

Research has also found that trait effortful control and self-reported consumption are important in the study of inhibitory control and attentional bias towards alcohol-related cues. For example, McAteer and colleagues (2015) revealed that alcohol use was significantly correlated with fixation times to alcohol stimuli. Specifically, adolescent social drinkers spent more time fixating on alcoholic stimuli compared to abstainers. These results were interpreted to suggest that alcohol-related attentional bias is driven by experiences with, and positive expectancies, surrounding alcohol, which may have implications of interventions seeking to reduce consumption (ibid). Indeed, research consistently reveals that inhibitory control and attentional bias vary across populations with differing levels of alcohol consumption (e.g., Goudriaan, Oosterlaan, De Beurs & van den Brink, 2006; Murphy & Garavan, 2011; Nederkoorn, Baltus, Guerrieri & Wiers, 2009; Qureshi, Monk, Pennington, Li & Leatherbarrow, 2017), with more problematic alcohol consumption related to heightened approach biases towards alcohol-related stimuli (Albery, Sharma, Noyce, Frings & Moss, 2015; Field, Marhe & Franken, 2014; McAteer et al., 2015; Roberts, Miller, Weafer & Fillmore, 2014).

Moreover, there is some evidence supporting a relationship between elevated trait impulsivity and increased alcohol consumption and problem drinking (Gunnarsson, Gustavsson, Tengström, Franck & Fahlke, 2008; McAdams & Donnellan, 2009; Von Diemen, Bassani, Fuchs, Szobot & Pechansky, 2008). Indeed, higher trait self-control – the ability to override impulsive responding – enables individuals to disengage attention from alcoholic cues (Teunissen, Spijkerman, Schoenmakers, Vohs & Engels, 2012; Qureshi et al., 2017). More recent research utilising behavioural measures has suggested, however, that impulsivity fluctuates within the individual and is susceptible to the influences of external factors (e.g., context). For example, Qureshi et al. (2017) found that higher effortful control facilitates performance on an alcohol-related Go/No-Go Task. Taken together, these findings suggest that self-reported alcohol consumption and trait effortful control also warrant careful consideration during the assessment of how alcohol-related cues may impact inhibition.

Stein and colleagues (2000) note that research has focused on the way in which alcohol-related visual, auditory and tactile cues shape alcohol-related thoughts and behaviours. Indeed, previous studies have provided plentiful evidence for the impact of visual alcohol-related stimuli on inhibitory control mechanisms (e.g., Kreusch et al., 2013; Weafer & Fillmore, 2012), yet relatively less research has examined the impact of alcohol-related auditory stimuli on these processes. As an exception, one study has shown that alcohol-related visual cues impede processing of simultaneously presented auditory signals on a multisensory perception task (Monem & Fillmore, 2016). Other research beyond the focus of substance misuse asserts that the impact of auditory cues on visual attention may be contingent upon their relevance to the task at hand (Leiva, Parmentier, Elchlepp & Verbruggen, 2015). Specifically, Leiva et al. (2015) found that inhibitory control performance was facilitated when participants' perceived auditory cues to be relevant to visually presented targets (i.e., a tone which indicated to participants that they should respond). Conversely, novel, unexpected sounds (i.e., environmental

sounds) impaired performance because participants could not identify their relation to the task requirements[1]. Given that there is a semantic linkage between alcohol-related sounds[2] (i.e., bar-related sounds, such as the opening of beer bottles) and the presentation of alcohol-related visual stimuli, we therefore speculate that inhibitory control performance may be facilitated, rather than impaired, under such conditions.

Building upon these early findings, the current research examined the influence of contextually relevant alcohol-related visual (e.g., a bottle of liquor) and auditory cues (e.g., opening of alcohol) on inhibitory control mechanisms. Employing the anti-saccade eye-tracking task (a direct measure of inhibition; Munoz & Everling, 2004), participants were instructed to fixate on a central point and launch eye movements either towards (pro) or away (anti) from a peripherally placed alcohol-related or neutral target. Within this task, auditory cues that were semantically related to alcohol were presented during 50% of the trials, prior to the alcohol-related visual targets. In line with previous research (Jones & Field, 2015; McAteer et al., 2015), it was predicted that participants would respond faster to alcohol-related relative to neutral visual stimuli on pro-saccade trials. It was also predicted that they would launch a greater proportion of incorrect saccades towards alcohol-related stimuli during anti-saccade trials, demonstrating enhanced attentional bias. Moreover, it was expected that participants would be more accurate and quicker to respond to alcohol-related visual stimuli on pro-saccade trials when they were exposed to short bar-related auditory cues (as per Leiva et al., 2015). However, during anti-saccade trials, we predicted that alcohol-related auditory cues would interfere with goal-directed performance and impair inhibitory control towards visual alcohol-related stimuli (c.f., Monem & Fillmore, 2016). This was underpinned by the rationale that hearing alcohol-related sound (i.e., audio from a bar environment) should make alcohol-related cues more salient to the individual, attracting their attention.

As a second aim, we also investigated whether individual differences in alcohol consumption and trait effortful control could explain the influence that alcohol-related visual and auditory stimuli exert on inhibitory control. We predicted that participants with lower trait effortful control would launch more incorrect saccades and have faster response latencies to both types of visual stimuli, and within those participants, individuals with higher level of problematic alcohol consumption would show greater response impairment to alcohol-related stimuli (specifically when alcohol-related auditory cues and visual stimuli were paired).

Method

Participants

This experimental study follows the international agreements on human experimentation and was approved by the ethics committee at Edge Hill University (UK). Twenty-five participants (15 female, *M*age = 23.08, *SD* = 8.26; age range 18-53) were recruited via opportunity sampling. The minimum number of participants was determined by an a-priori power analysis, based on pilot studies, and indicated that a minimum sample size of 12 participants was required to detect a predicted effect size of = .17 with 80% power. In order to ensure sufficient statistical power, this recommended sample size was doubled and 25 participants were recruited. This sample size and gender ratio is consistent with that reported in previous research (Monem & Fillmore, 2016, $n = 25$, $n = 13$ females; Leiva et al., 2015, $n = 20$, $n = 15$ females; Vorstius, Radach, Lang & Riccardi, 2008; $n = 24$, $n = 12$ females). Participants were required to be over the legal age of drinking to take part (18 years old in the U.K.) and reported no visual acuity or auditory deficits.

Measures

Alcohol Consumption. The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, De la Fuente & Grant, 1993) was used to assess alcohol consumption and drinking behaviours. Participants respond to this 10-item questionnaire on a Likert response scale anchored between 0 (Never) and 4 (4 or more times). Responses to this questionnaire showed excellent internal consistency, Cronbach's $a = 0.80$, with a mean of 6.26 ($SD = 3.82$).

Effortful Control. The effortful control sub-section of the Adult Temperament Questionnaire (ATQ; Rothbart, Ahadi & Evans, 2000) was used to measure trait effortful control. This 35-item sub-scale includes three sub-components of attentional control (capacity to voluntarily focus as well as shift attention), inhibitory control (capacity to suppress inappropriate approach behavior), and activation control (capacity to perform activities that one would rather avoid). Participants responded to questions on a Likert scale anchored between 1 (Extremely untrue of you) and

1 Here, it may be postulated that the processing of a novel stimuli divides attention, reducing the resources allocated to inhibitory control, thus impairing performance.

2 According to relational frame theory, related concepts are stored in memory and exposure to one concept can lead to a process of spreading activation, where related constructs are also activated. There are therefore theoretical grounds to propose a semantic link between alcohol-related sights and sounds, with the processes evident upon exposure to alcohol-related visuals also elicited by other sensory cues (Riecke, Schulte-Pelkum, Caniard, & Bülthoff, 2005).

7 (extremely true of you). Responses to this questionnaire also showed excellent internal consistency, $a = 0.90$, with a mean of 50.97 ($SD = 10.20$).

Anti-saccade task. Participants completed an anti-saccade task to measure their inhibitory control performance. Throughout this task, participants' eye-movements were recorded using a video-based pupil-tracking system (EyeLink 1000; SR Research Ltd), and their heads were stabilised by a chin rest situated 57cm from the computer.

Visual Stimuli. For the alcohol-related visual stimulus, a bottle of unbranded liqueur was used, whilst the neutral stimulus was a green rectangle, matched for size and luminosity. Given the size of the stimuli and the short duration of presentation, the study needed to use stimuli that were recognisably alcohol related and non-alcohol related. Previous research has revealed that the use of alcoholic and non-alcoholic appetitive stimuli (e.g. alcoholic versus soft drinks – Cavanagh & Obasi, 2015) or alcoholic versus neutral stimuli (Kreusch et al., 2013) has yielded mixed results, so the decision was made to use explicitly alcohol-related and non-alcohol related visual cues.

Auditory Stimuli. A series of pilot studies were conducted to establish the optimum audio cues (See Supporting Information File 1). Participants heard bar-related cues of short duration (48 kHz), which were presented randomly on 50% of trials[3]. On the remaining 50% of trials, no sound was heard. Auditory cues were presented randomly after the onset of a fixation cross for the remaining duration of the trial (see Figure 1).

Procedure

Participants were asked to refrain from consuming alcohol 12 hours before taking part in the study. On arrival, they first completed the anti-saccade task and then the AUDIT and ATQ to avoid alcohol-related priming of the questionnaire content (in line with McAteer et al., 2015). Participants sat in a quiet room in front of a computer screen and were asked to wear headphones. Eye movements were validated using a nine-point calibration system.

Within both pro- and anti-saccade trials, participants were instructed to fixate on a black cross, presented on a white background. This was followed by an auditory cue with a stimulus onset asynchrony of 800 or 1000ms after fixation cross presentation (randomised) on 50% of trials. This fixation point then changed to a coloured dot after 1500ms,informing the participant to perform an anti- (red) or pro-saccade (blue). Alcohol-related (a bottle of unbranded liquor) or neutral stimuli (a green rectangle) were then presented randomly on either the left or right side of the computer screen for 1500 ms. During pro-saccade trails, participants were required to look directly at the target as quickly and accurately as possible. During anti-saccade trials, participants were instructed to look directly away from the target, to its mirror position. The auditory cue lasted until the end of the trial and the inter-trial interval was 1500 ms. Figure 1 provides an overview of the trial procedure.

The experiment was organised into eight blocks of four anti-saccade and four pro-saccade trials, and block order (pro or anti) was randomised for each participant. There were a total of 224 trials, with 28 trials per block. The alcohol-related and neutral visual stimuli order and position were randomised within blocks, and were balanced equally within blocks and overall. The first eight trials in each block were treated as practice trials and removed from the final analyses (as per Umiltà & Moscovitch, 1994).

Data Analysis

Saccades with initial latencies of 80-600ms and amplitudes more than 2° were included (c.f. Kanjee, Yücel, Steinbach, González & Gupta, 2012), resulting in 3798 valid trials (91.3%), a similar proportion to other saccade experiments (e.g. Vorstius et al., 2008). The initial saccades that met these parameters and were also classified as 'full' saccades towards (pro) or away (anti) from the stimuli were included in the final analyses. This was achieved using 'barriers' set at $x = 412$ for the left of the screen and $x = 612$ for the right of the screen. Specifically, saccade end-points were included if they were beyond the appropriate barrier (for example, a pro-saccade trial to the right-hand side of the screen would need to exceed 612), and met the latency parameters. For error rates, the barrier was used to assess if saccades ended past the barrier on the incorrect side.

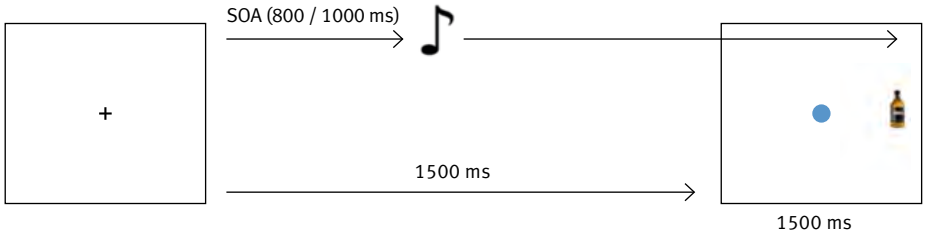
A series of two-way repeated measures Analysis of Variance tests (ANOVA) were conducted for response latencies and error rates on anti- and pro-saccade trials to examine the effect of visual stimuli (alcohol-related or neutral images) and auditory cue type (alcohol-related and none). Analyses of Covariance (ANCOVA), including follow-up simple main effect analyses, were then conducted to elucidate any moderating role of alcohol consumption (AUDIT) and trait effortful control (ATQ; in accordance with Judd, Kenny & McClelland, 2001).

Results

Saccadic Latencies

Pro-saccade trials. There was a significant main effect of visual stimuli, with faster latencies to alcohol stimuli (*M*

3 After completing the task, participants were asked what they thought the auditory cues represented. All stated that the cues were bar-related.



Duration of auditory cue=from SOA (800/1000ms from fixation cross) until end of trial.

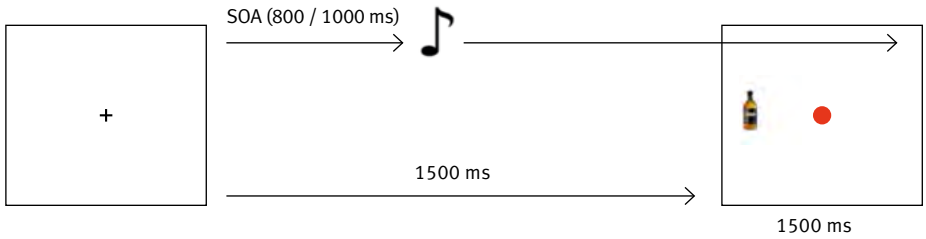


Figure 1. Example pro-saccade (top) and anti-saccade (bottom) trial procedures.

= 232.59, *SD* = 46.77) compared to neutral stimuli (*M* = 249.18, *SD* = 50.50), $F(1, 24) = 9.75$, $p < .01$, $\eta^2_p = .29$. There was also a significant main effect of auditory cue type, with bar-related sound cues facilitating responses (*M* = 229.96, *SD* = 45.23) compared to no sound cue (*M* = 251.82, *SD* = 52.18) across both visual stimuli types, $F(1, 24) = 15.53$, $p < .01$, $\eta^2_p = .39$. There was no significant interaction between visual and auditory stimuli, $p > .05$. Adding AUDIT and trait effortful control as covariates resulted in no significant main effects or interactions (all *p*'s > .19).

Anti-saccade trials. There was no significant main effect of visual stimuli ($p = .46$), and no interaction between visual stimuli and auditory cue type ($p = .64$). A significant main effect of auditory cue type indicated that bar-related cues facilitated response latencies (*M* = 280.57, *SD* = 53.65) compared to when there was no cue (*M* = 319.37, *SD* = 53.00) for both visual stimuli types, $F(1, 24) = 33.18$, $p < .01$, $\eta^2_p = .58$. Adding AUDIT and trait effortful control as covariates resulted in no significant main effects or interactions (all *p*'s > .06). Latencies by saccade type, visual stimuli and auditory cue type are shown in Table 1.

Error rate (anti-saccade only)

There was a significant main effect of visual stimuli with more errors to alcohol stimuli (*M* = 0.19, *SD* = 0.16) relative to neutral stimuli (*M* = 0.13, *SD* = 0.11), $F(1, 24) = 10.44$, $p < .01$, $\eta^2_p = .30$. There was also a significant main effect of auditory cue type with participants making fewer errors when they were cued with bar-related sounds (*M* = 0.12, *SD* = 0.11) compared to no sound (*M* = 0.20, *SD* = 0.15), $F(1, 24) = 14.45$, $p < .01$, $\eta^2_p = .38$. There was a significant interaction between visual stimuli and auditory cue type, $F(1, 24) = 20.48$, $p < .01$, $\eta^2_p = .46$. Simple main effects showed that error rates were significantly higher for alcohol-related visual stimuli compared to neutral stimuli when there was no auditory cue ($p < .01$); however there was no difference in error rates between the visual stimuli when hearing bar-related cues ($p = .57$). Error rates were significantly lower for alcohol-related visual stimuli when there was a bar-related cue compared to no cue ($p < .01$), yet there was no significant difference between auditory cue type for neutral visual stimuli ($p = .77$). See Figure 2.

Adding AUDIT and trait effortful control as covariates resulted in a significant main effect of trait effortful control with overall error rates reducing as trait effortful control increased, $F(1, 20) = 6.55$, $p < .05$, $\eta^2_p = .25$. There was no relationship with AUDIT, $p > .05$. There was also a significant interaction between visual stimuli and auditory cue type, $F(1, 20) = 8.28$, $p < .01$, $\eta^2_p = .29$. Simple main effects showed that while there was no difference in error rate between visual stimuli when hearing bar-related cues ($p = 0.76$), there was a significantly higher error rate for alcohol visual stimuli compared to neutral visual stimuli when there was no auditory cue ($p < .01$). For neutral visual stimuli, there was no difference in error rate between auditory cue type ($p = .77$), but error rates were significantly higher for alcohol visual stimuli when there was no cue compared to when the bar cue was heard ($p < .01$).

Table 1. *Means (and corresponding standard deviations) for pro- and anti-saccade response latencies as a function of visual stimuli and auditory cue.*

		Anti-saccade	
	Alcohol-Related Stimuli	Neutral Stimuli	Visual Stimuli collapsed
Alcohol auditory cue	278.20 (52.29)	282.94 (56.77)	280.57 (53.65)
No cue	318.79 (52.29)	319.95 (58.39)	319.37 (53.00)
Audio cue collapsed	298.50 (55.67)	301.44 (59.98)	--
		Pro-saccade	
	Alcohol-Related Stimuli	Neutral Stimuli	Visual Stimuli collapsed
Alcohol auditory cue	223.65 (45.01)	236.27 (49.20)	229.96 (45.23)
No cue	241.54 (52.76)	262.10 (57.66)	251.82 (52.18)
Audio cue collapsed	232.59 (46.77)	249.18 (50.50)	--

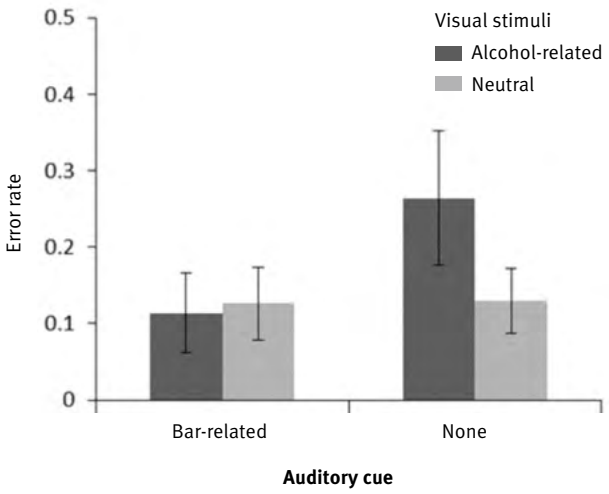


Figure 2. Mean error rates (and confidence intervals) by visual stimuli (alcohol-related*neutral) and auditory cue (bar-related*none).

Discussion

The current research examined the impact of alcohol-related visual stimuli and auditory cues on inhibitory control. Consistent with predictions, participants were significantly quicker to respond to alcohol-related visual stimuli on pro-saccade trials. Moreover, they made more errors when responding to alcohol-related relative to neutral visual stimuli on anti-saccade trials. This is in line with previous research suggesting that individuals show greater attentional bias to alcohol-related relative to neutral stimuli (e.g. Albery et al., 2015; Field et al., 2014; Weafer & Fillmore, 2012). Findings also revealed that individual variation in trait effortful control was predictive of inhibitory control performance, with error rates decreasing as effortful control increased. The ability to withhold responses may therefore enhance inhibitory control performance towards alcohol-related stimuli (Qureshi et al., 2017), which in the current study was shown irrespective of self-reported drinking behaviour.

Findings also indicate that participants made fewer errors when alcohol-related auditory cues were presented compared to when no sound cue was presented. However, this facilitatory effect only occurred when bar sounds coincided with the presentation of alcohol-related visual cues, and not neutral visual cues. These findings are consistent with that of Leiva et al. (2015), who found that inhibitory performance was facilitated when participants heard auditory sounds that were relevant to the visual stimuli, whereas task irrelevant auditory cues impaired performance. In the current task, participants recognised that the auditory cue represented sounds played in an alcohol-related environment, and therefore the relevance

of these sounds may have enhanced performance when participants responded to alcohol-related visual stimuli. Conversely, bar-related sounds did not appear to facilitate responding for neutral stimuli, perhaps because participants deemed such auditory cues to be irrelevant to the target. Such findings may indicate that the introduction of alcohol-related auditory cues may effectively re-contextualise alcohol-related visual stimuli, causing them to have less attentional pull. Whilst speculative, this effect may result from the process of evaluative conditioning, whereby an attitude towards one stimulus is changed through its pairing with another (Jones, Olson & Fazio 2010). In other words, when bar-related auditory cues are paired with alcohol-related visual stimuli, the overall effect may be to associate the visual stimuli with a familiar context, lessening their novelty and reducing any impact on inhibitory control.

Whilst further research in this domain remains prudent, these findings may have a number of important implications. First, they may suggest that attentional bias to alcohol-related visual cues in the laboratory may not be observed consistently, or to the same degree, when testing occurs in different environments and/or during exposure to a more diverse array of cues. Previous research which only employs alcohol-related visual targets may therefore exaggerate the effect of alcohol-related attentional biases by studying them in relative isolation from other ecologically valid contextual cues. Second, interventions which seek to draw upon such paradigms as a means of effectively re-training inhibitory control (e.g. Jones & Field, 2013) should be aware of the variable dis-inhibitory effect of different alcohol-related stimuli modalities targeting different senses (c.f. Monk, Sunley, Qureshi & Heim, 2016). This may have important implications when it comes to the effective implementation of such training in the real world, where individuals are surrounded by a variety of sights and sounds associated with alcohol.

Limitations

As an explorative study, the current study is the first of its kind to examine the effect of introducing alcohol-related auditory cues into the more traditional examination of alcohol-related ocular inhibition. However, there are limitations in the scope and generalisability of the current findings and future research: First, increasing the number of alcoholic and non-alcoholic stimuli included within the anti-saccade task and assessing their respective valence and arousal would be advisable to control for any familiarisation or practice effects. Presently, we accept that the alcohol-related stimulus may have been more visually attractive than the neutral cue (a green rectangle), meaning that it drew attention regardless of its association with alcohol. If this were the case, however, both slower anti-saccade latencies and higher error rates for the alcohol-related stimuli would be expected. On the contrary, the findings indicate that only error rates were higher for the alcohol-related stimulus, but participants were quicker to launch anti-saccades away from alcohol-related visual stimuli. As such, there are reasonable grounds on which to assert that this performance difference can be attributed to the alcohol-related nature of the stimuli, rather than any inherent differences in the visual attractiveness of the stimuli. Moreover, future research may benefit from employing other appetitive control stimuli. Such comparisons between alcohol-related appetitive and neutral non-appetitive cues are present in the majority of studies in this field (e.g. Kreusch et al., 2013; c.f. Monk, Qureshi, Pennington & Hamlin, 2017 for related discussion). Yet, this means that researchers cannot assuredly separate attentional biases to alcohol-related appetitive cues from other non-alcohol-related appetitive cues (c.f., Adams, Ataya, Attwood, & Munafò 2013).

Based on pilot studies, the current research compared an alcohol-related auditory cue to no sound, in order to simplify the study design, maintain statistical power, and provide an absolute contrast to the alcohol-related stimuli. However, bar-related auditory cues were found to facilitate response latencies to both alcohol-related and neutral visual targets, suggesting that short bursts of sound may therefore arouse participants and trigger a response. Further exploration of the comparable effect of varying auditory cues is therefore recommended.

Research has demonstrated that differences in inhibitory control emerge between intoxicated relative sober individuals (c.f., De Wit, 1996; Roberts et al., 2014). Whilst participants were asked to remain abstinent from alcohol prior to participating in the current study, we did not verify this using an objective breathalyser reading. It must therefore be noted that although the admittance of intoxicated individuals was highly unlikely in this study, any inadvertent inclusion of non-sober participants would have the capacity to impact the validity of the results. Finally, the participant sample was predominantly university students, who are immersed typically in a social, pub-based drinking culture (Straus & Bacon, 1953). As such, context-related cueing might be particularly likely (Rumelhart & Todd, 1993) and future research beyond this sample is recommended.

Conclusion

The current findings are the first to indicate that visual and auditory alcohol-related cues differentially impact inhibitory control performance. Specifically, auditory cues may re-contextualise visual stimuli into a more familiar setting that reduces their saliency and lessens their attentional pull. Moreover, trait effortful control may predict an individual's ability to respond to external stimuli, with greater effortful control facilitating inhibitory performance. These

findings suggest that inhibitory control levels may vary in real-world alcohol-related environments where individuals are surrounded by associated sights and sounds, and this may impact their ability to control consumption behaviour. Such findings may have implications for alcohol interventions, which in order to be effective, must be capable of taking into account such contextual and individual variations in inhibitory control.

Declaration of Competing Interests

There are no potential conflicts of interest associated with this article.

Funding

This research was supported by an Alcohol Research UK small grant (SG 14/15 203). The funders had no role other than financial support.

References

Adams, S., Ataya, A. F., Attwood, A. S. & Munafò, M. R. (2013). Effects of alcohol on disinhibition towards alcohol-related cues. *Drug & Alcohol Dependence. 127*, 137-142. doi:10.1016/j.drugalcdep.2012.06.025.

Albery, I., Sharma, D., Noyce, S., Frings, D. & Moss, A. (2015). Testing a frequency of exposure hypothesis in attentional bias for alcohol-related stimuli amongst social drinkers. *Addictive Behaviors Reports*, *1*, 68-72. doi:10.1016/j.abrep.2015.05.001.

Cavanagh, L. & Obasi, E. M. (2015). The moderating role of implicit alcohol-related cognitions in hazardous alcohol use. *Addiction, Research & Theory, 23,* 380-390. doi:10.3109/16066359.2015.1011624.

Christiansen, P., Cole, J. C., Goudie, A. J. & Field, M. (2012). Components of behavioural impulsivity and automatic cue approach predict unique variance in hazardous drinking. *Psychopharmacology, 219*, 501-510. doi:10.1007/s00213-011-2396-z.

Cooney, N., Gillespie, R., Baker, L. & Kaplan, R. (1987). Cognitive changes after alcohol cue exposure. *Journal of Consulting and Clinical Psychology, 55*, 150-155.

De Wit, H. (1996). Priming effects with drugs and other reinforcers. *Experimental and Clinical Psychopharmacology, 4*, 5-10. doi:10.1037/1064-1297.4.1.5.

Field, M., Marhe, R. & Franken, I. (2014). The clinical relevance of attentional bias in substance use disorders. *CNS Spectrums*, *19*, 225-230. doi:10.1017/S1092852913000321.

Field, M. & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence, 97,* 1-20. doi:10.1016/j.drugalcdep.2008.03.030.

Field, M., Wiers, R. W., Christiansen, P., Fillmore, M. T. & Verster, J. C. (2010). Acute alcohol effects on inhibitory control and implicit cognition: Implications for loss of control over drinking. *Alcoholism: Clinical and Experimental Research, 34*, 1346-1352. doi:10.1111/j.1530-0277.2010.01218.x.

Fleming, K. A. & Bartholow, B. D. (2014). Alcohol cues, approach bias, and inhibitory control: Applying a dual process model of addiction to alcohol sensitivity. *Psychology of Addictive Behaviors, 28*, 85-96. doi:10.1037/a0031565.

Goudriaan, A. E., Oosterlaan, J., De Beurs, E. & Van Den Brink, W. (2006). Neurocognitive functions in pathological gambling: A comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction, 101*, 534-547. doi:10.1111/j.1360-0443.2006.01380.x.

Gunnarsson, M., Gustavsson, J.P., Tengström, A., Franck, J. & Fahlke, C. (2008). Personality traits and their associations with substance use among adolescents. *Personality and Individual Differences, 45*, 356-360. doi:10.1016/j.paid.2008.05.004.

Grant, N. K. & Macdonald, T. K. (2005). Can alcohol lead to inhibition or disinhibition? Applying alcohol myopia to animal experimentation. *Alcohol and Alcoholism*, *40*, 373-378. doi:10.1093/alcalc/agh177.

Houben, K. & Wiers, R. W. (2009). Response inhibition moderates the relationship between implicit associations and drinking behavior. *Alcoholism: Clinical and Experimental Research, 33*, 626-633. doi:10.1111/j.1530-0277.2008.00877.x.

Jones, A. & Field, M. (2015). Alcohol-related and negatively valenced cues increase motor and oculomotor disinhibition in social drinkers. *Experimental and Clinical Psychopharmacology*, *23*, 122-129. doi:10.1037/pha0000011.

Jones, A. & Field, M. (2013). The effects of cue-specific inhibition training on alcohol consumption in heavy social drinkers. *Experimental and Clinical Psychopharmacology*, *21*, 8-16. doi:10.1037/a0030683.

Jones, A., Hogarth, L., Christiansen, P., Rose, A. K., Martinovic, J. & Field, M. (2012). Reward expectancy promotes generalized increases in attentional bias for rewarding stimuli. *Quarterly Journal of Experimental Psychology, 65,* 2333-2342. doi:10.1080/17470218.2012.686513.

Jones, C. R., Olson, M. A. & Fazio, R. H. (2010). Evaluative conditioning: The "how" question. *Advances in Experimental Social Psychology, 43*, 205-255. doi:10.1016/S0065-2601(10)43005-1.

Judd, C. M., Kenny, D. A. & McClelland, G. H. (2001). Estimating and testing mediation and moderation in within-subjects designs. *Psychological Methods*, *6*, 115-134. doi:10.1037//1082-989X.6.2.115.

Kanjee, R., Yücel, Y. H., Steinbach, M. J., González, E. G. & Gupta, N. (2012). Delayed saccadic eye movements in glaucoma. *Eye and Brain, 4,* 63-68. doi:10.2147/EB.S38467.

King, A. & Byers, J. (2004). Alcohol-induced impairment in heavy episodic and light social drinkers. *Journal of Studies on Alcohol, 65*, 27-36. doi:10.15288/jsa.2004.65.27.

Kreusch, F., Vilenne, A. & Quertemont, E. (2013). Response inhibition toward alcohol-related cues using an alcohol go/no-go task in problem and non-problem drinkers. *Addictive Behaviors, 38*, 2520-2528. doi:10.1016/j.addbeh.2013.04.007.

Laude, J. & Fillmore, M. (2015). Alcohol cues impair learning inhibitory signals in beer drinkers. *Alcoholism: Clinical and Experimental Research, 39*, 880-886. doi:10.1111/acer.12690.

Leiva, A., Parmentier, F. B. R., Elchlepp, H. & Verbruggen, F. (2015). Reorienting the mind: The impact of novel sounds on go/no-go performance. *Journal of Experimental Psychology: Human Perception & Performance. 41*, 1197-1202. doi:10.1037/xhp0000111.

Manchery, L., Yarmush, D. E., Luehring-Jones, P. & Erblich, J. (2017). Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. *Addictive Behaviors, 70,* 14-17. doi:10.1016/j.addbeh.2017.01.035.

McAdams, K. K. & Donnellan, M. B. (2009). Facets of personality and drinking in first-year college students. *Personality and Individual Differences, 46*, 207-212. doi:10.1016/j.paid.2008.09.028.

McAteer, A., Curran, D. & Hannah, D. (2015). Alcohol attention bias in adolescent social drinkers: An eye tracking study. *Psychopharmacology, 232,* 3183-3191. doi:10.1007/s00213-015-3969-z.

Monem, R. & Fillmore, M. (2016). Alcohol-related visual cues impeded the ability to process auditory information: Seeing but not hearing. *Psychology of Addictive Behaviours, 30*, 12-17. doi:10.1037/adb0000140.

Monk, R., Sunley, J., Qureshi, A. & Heim, D. (2016). Smells like inhibition: The effects of olfactory and visual alcohol cues on inhibitory control. *Psychopharmacology, 233,* 1331-1337. doi:10.1007/s00213-016-4221-1.

Monk, R. L., Qureshi, A., Pennington, C. R. & Hamlin, I. (2017). Generalised inhibitory impairment to appetitive cues: From alcoholic to non-alcoholic visual stimuli. *Drug and Alcohol Dependence, 1,* 26-32. doi:10.1016/j.drugalcdep.2017.07.038.

Munoz, D. & Everling, S. (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5*, 218-228. doi:10.1038/nrn1345.

Murphy, P. & Garavan, H. (2011). Cognitive predictors of problem drinking and AUDIT scores among college students. *Drug and Alcohol Dependence, 115*, 94-100. doi:10.1016/j.drugalcdep.2010.10.011.

Nederkoorn, C., Baltus, M., Guerrieri, R. & Wiers, R. W. (2009). Heavy drinking is associated with deficient response inhibition in women but not in men. *Pharmacology Biochemistry and Behavior, 93*, 331-336. doi:10.1016/j.pbb.2009.04.015.

Nees, F., Diener, C., Smolka, M. & Flor, H. (2012). The role of context in the processing of alcohol-relevant cues. *Addiction Biology, 17,* 441-451. doi:10.1111/j.1369-1600.2011.00347.x.

Papachristou, H., Nederkoorn, C., Havermans, R., van der Horst, M. & Jansen, A. (2012). Can't stop the craving: the effect of impulsivity on cue-elicited craving for alcohol in heavy and light social drinkers. *Psychopharmacology, 219*, 511-518. doi:10.1007/s00213-011-2240-5.

Qureshi, A. W., Monk, R. L., Pennington, C. R., Li, X. & Leatherbarrow, T. (2017). Context and alcohol consumption behaviors affect inhibitory control. *Journal of Applied Social Psychology, 47,* 625-633. doi:10.1111/jasp.12465.

Riecke, B. E., Schulte-Pelkum, J., Caniard, F. & Bülthoff, H. H. (2005). Influence of auditory cues on the visually-induced self-motion illusion (circular vection) in virtual reality. *Proceedings of 8th International Workshop on Presence*, 49-57.

Roberts W., Miller, M., Weafer, J. & Fillmore, J. (2014). Heavy drinking and the role of inhibitory control of attention. *Experimental and Clinical Psychopharmacology, 22,* 133-140. doi:10.1037/a0035317.

Rose, A. & Duka, T. (2008). Effects of alcohol on inhibitory processes. *Behavioural Pharmacology, 19*, 284-291. doi:10.1097/FBP.0b013e328308f1b2.

Rothbart, M., Ahadi, S. & Evans, D. (2000). Temperament and personality: Origins and outcomes. *Journal of Personality and Social Psychology, 78*, 122-135. doi:10.1037//0022-3514.78.1.122.

Rumelhart, D. & Todd, P. (1993). Learning and connectionist representations. In D. Meyer and S. Kornblum (Eds.), *Attention and performance XIV: Synergies in experimental psychology, artificial intelligence, and cognitive neuroscience*. Cambridge: MIT Press. pp. 3-30.

Saunders, J. B., Aasland, O. G., Babor, T. F., De la Fuente, J. R. & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88,* 791-804. doi:10.1111/j.1360-0443.1993.tb02093.x.

Stein, K. D., Goldman, M. S. & Del Boca, F. K. (2000). The influence of alcohol expectancy priming and mood manipulation on subsequent alcohol consumption. *Journal of Abnormal Psychology, 109*, 106-115. doi:10.1037/0021-843X.109.1.106.

Straus, R. & Bacon, S. (1953). *Drinking in college*. New York: Yale University Press.

Teunissen, H. A., Spijkerman, R., Schoenmakers, T. M., Vohs, K. D. & Engels, R. C. M. E. (2012). The effect of self-control on attentional bias for alcohol cues in male heavy drinkers. *Journal of Applied Social Psychology, 42,* 776-792. doi:10.1111/j.1559-1816.2011.00800.x.

Umiltà, C. & Moscovitch, M. (1994). *Attention and Performance XV: Conscious and Nonconscious Information Processing*. Massachusetts, USA: MIT Press.

Von Diemen, L., Bassani, D. G., Fuchs, S. C., Szobot, C. M. & Pechansky, F. (2008). Impulsivity, age of first alcohol use and substance use disorders among male adolescents: A population based case-control study. *Addiction, 103*, 1198-1205. doi:10.1111/j.1360-0443.2008.02223.x.

Vorstius, C., Radach, R., Lang, A. R. & Riccardi, C. J. (2008). Specific visuomotor deficits due to alcohol intoxication: evidence from the pro-and antisaccade paradigms. *Psychopharmacology, 196*, 201-210. doi:10/1007/s00213-007-0954-1.

Weafer, J. & Fillmore, M. (2012). Alcohol-related stimuli reduce inhibitory control of behaviour in drinkers. *Psychopharmacology, 222,* 489-498. doi:10.1007/s00213-012-2667-3.

Weafer, J. & Fillmore, M. T. (2013). Acute alcohol effects on attentional bias in heavy and moderate drinkers. *Psychology of Addictive Behaviors, 27*, 32-41. doi:10.1037%-2Fa0028991.

Weafer, J. & Fillmore, M. T. (2015). Alcohol-related cues potentiate alcohol impairment of behavioural control in drinkers. *Psychology of Addictive Behaviours, 29,* 290-299. doi:10.1037/adb0000013.

Wiers, R. W., Bartholow, B. D., van, d. W., Thush, C., Engels, R. C. M. E., Sher, K. J., … Stacy, A. W. (2007). Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. *Pharmacology, Biochemistry and Behavior, 86*, 263-283. doi:10.1016/j.pbb.2006.09.021.

Supporting Information File 1

Validation of sound cues utilised in the final study.

Pilot Study 1. In a first pilot study ($n = 10$), participants were asked to listen to a series of auditory clips containing social alcohol-related (e.g., sounds of a pub) and neutral social sounds (e.g., sounds of an office/work environment). They were then asked to rate these in terms of how representative they were of the intended environment (1 = sound file accurately portrayed the intended sound; 10 = sound file did not accurately portray the intended sound). The highest rated clips for the pub environments were used in the final presented study.

Pilot Study 2. A second pilot study ($n = 66$) of the anti-saccade task was conducted which introduced an additional audio cue of supermarket noise (a neutral noise). This cue was found to affect latencies differentially from both alcohol-related (bar) and no cues; more errors were made in the anti-saccade task, and there were more errors to alcohol images when the supermarket cue was played. However, less errors were made towards alcohol images when the bar cue was played. This suggested that the observed differences in inhibitory control-related performance were not the product of drawing comparisons between any noise and no noise; rather, it reflected the contextual influence of alcohol-related auditory cues. Accordingly, in the final study presented here, the neutral cue was removed to simplify the study design.

Relationship between substance use and schizotypal traits in school-aged adolescents

Relación entre consumo de sustancias y rasgos esquizotípicos en adolescentes escolarizados

Mª de los Ángeles Sánchez-García*, Javier Ortuño-Sierra*, Mercedes Paino**, Eduardo Fonseca-Pedrero*,***.

* Departamento de Ciencias de la Educación. Universidad de La Rioja, Logroño. España.
** Departamento de Psicología. Universidad de Oviedo, Oviedo. España.
*** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo. España.

Abstract

Goal: The main goal of the present study was to analyze the relationship between substance use (tobacco, alcohol, cannabis) and schizotypal traits in a representative sample of school-aged adolescents from the general population. Method: cross-sectional, descriptive survey 1,588 students (M = 16.13 years, SD = 1.36), 739 male (46.5%), selected by random stratified cluster sampling, participated in the study. The instruments administered were the Oviedo Questionnaire for Schizotypy Assessment, the Modified Substance Use Questionnaire, the Strengths and Difficulties Questionnaire, the Penn Matrix Reasoning Test, the Family Affluence Scale-II, and the Oviedo Infrequency Scale. Results: Controlling for the effects of multiple covariates (gender, age, IQ, socio-economic level, psychopathology and consumption), the results showed that, compared with non-users, alcohol drinkers reported higher average scores in the Social Disorganization dimension. Cigarette smokers, differentiated by frequency, reported higher average scores in the Anhedonia and Social Disorganization dimensions than non-smokers. No statistically significant differences between users and non-users of cannabis were found in terms of schizotypal traits. Conclusion: controlling for the effects of multiple covariates, adolescents who use tobacco and alcohol reported higher scores – depending on frequency of use – in schizotypal traits. Future studies should continue to analyze the role of substance use in individuals at risk of psychosis and determine its role in the transition to serious mental disorders, like psychosis, using new methodologies such as ambulatory assessment.

Keywords: Adolescence; Substance consumption; Drugs; Schizotypy; Schizotypal traits.

Resumen

Objetivo: analizar la posible relación entre el consumo de sustancias psicoactivas (en concreto, tabaco, alcohol y cannabis) y los rasgos esquizotípicos en una muestra representativa de adolescentes escolarizados de la población general. Método: diseño transversal descriptivo tipo encuesta. La muestra se compuso por 1.588 estudiantes (M = 16,13 años; DT = 1,36; 739 varones, 46,5%), seleccionados mediante muestreo aleatorio estratificado por conglomerados. Los instrumentos administrados fueron el Cuestionario Oviedo para la Evaluación de la Esquizotipia, el Cuestionario de Consumo de Sustancias Modificado, el Cuestionario de Capacidades y Dificultades, el *Penn Matrix Reasoning Test*, la *Family Affluence Scale*-II y la Escala Oviedo de Infrecuencia de Respuesta. Resultados: una vez controlado el efecto de múltiples covariables (género, edad, cociente intelectual, nivel socio-económico, psicopatología previa y consumo de sustancias), los consumidores de alcohol, comparados con los no consumidores, informaron de mayores puntuaciones medias en la dimensión Desorganización Social. Los consumidores de tabaco, comparados con los no consumidores, informaron de mayores puntuaciones medias en las dimensiones de esquizotipia de Anhedonia y Desorganización Social. Con respecto al consumo de cannabis, no se hallaron diferencias estadísticamente significativas entre consumidores y no consumidores en las dimensiones esquizotípicas. Conclusiones: controlando el efecto de múltiples variables de confundido, los adolescentes consumidores de tabaco y alcohol –según su frecuencia– informaron de mayores puntuaciones en rasgos esquizotípicos. Futuros estudios podrían continuar analizando el papel del consumo de sustancias en la aparición de trastornos mentales, como la psicosis, mediante nuevas metodologías como la evaluación ambulatoria.

Palabras clave: Adolescencia; Consumo sustancias; Drogas; Esquizotipia; Rasgos esquizotípicos.

Received: July 2018; Accepted: July 2019.

Send correspondence to: Eduardo Fonseca-Pedrero.
Universidad de La Rioja. Dpto. Ciencias de la Educación. C/ Luis de Ulloa, 2. 26004 Logroño-España. Tlf: +34 941 299 236. Fax +34 941 299 333.
E-mail: eduardo.fonseca@unirioja.es.

Schizotypy is defined as the latent predisposition to schizophrenia-spectrum disorders (Meehl, 1962). Most current etiological models consider that this vulnerability to psychosis is expressed along a severity continuum ranging from non-clinical expression (schizotypal features, psychotic-like experiences experiences) through a subthreshold level (attenuated psychotic symptoms) to a clinical level of psychosis and the need for treatment (Barrantes-Vidal, Grant & Kwapil, 2015; Fonseca-Pedrero, 2018; Fonseca-Pedrero & Debbané, 2017; Fumero, Marrero & Fonseca-Pedrero, 2018). Psychotic-like experiences and schizotypal traits are normally distributed in the general population, without necessarily being associated with distress, impairment, and/or disability (Linscott & Van Os, 2013; Van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam, 2009). For example, the prevalence rates of attenuated psychotic experiences among children are 17% for 9 to 12-year-olds and 7.5% for adolescents between 13 and 18 (Kelleher, Connor & Clarke, 2012). In addition, both psychotic-like experiences experiences and schizotypal traits are seen as markers of vulnerability to psychotic spectrum disorders in general and to schizophrenia in particular (Debbané et al., 2015). An analysis of these phenomena may allow us to understand the possible etiological mechanisms involved in the transition to a psychotic disorder in order to establish preventive treatments (Fonseca-Pedrero e Inchausti, 2018).

In the proneness-persistence-impairment model of psychosis (Van Os et al., 2009), schizotypal traits or psychotic-like experiences experiences may reflect underlying behavioural vulnerability, which increases the risk of psychotic disorder (Ericson, Tuvblad, Raine, Young-Wolff & Baker, 2011; Morton et al., 2017; Shakoor et al., 2016). This may be influenced by factors such as, for example, childhood trauma (Abajobir et al., 2017; Arseneault et al., 2011), self-harm and suicidal behaviour, negative affective states (Fonseca-Pedrero & Debbané, 2017; Najolia, Buckner & Cohen, 2012), and/or the use of substances such as cannabis (Hides et al., 2009; Malone, Hill & Rubino, 2010; Saha et al., 2011; Schubart et al., 2011). Genetic factors could determine the specific sensitivity of each individual to different environmental (e.g., obstetric complications, cannabis use, trauma experiences), and/or psychological risk factors (e.g., dysfunctional cognitive schemes, hyper-reflexivity), so that the most vulnerable individuals would be more at risk of developing psychosis or some of its symptoms when exposed to one or more risk factors. Likewise, multiple environmental impacts at different time points could lead to psychotic-like experiences experiences and schizotypal traits, becoming persistent in vulnerable people and exceed the clinical threshold, leading to disability and the need for treatment (Fonseca-Pedrero, 2018; Linscott & Van Os, 2013).

Recent decades have seen a considerable increase in research examining the relationship between drug use and mental health problems (Casajuana Kögel, López-Pelayo, Balcells-Olivero, Colom & Gual, 2018; Cohn, Johnson, Ehlke & Villanti, 2016; Gonzalvo, Barral & Roncero, 2011; Rial et al., 2018). One of the groups of mental disorders attracting most attention has been the spectrum of psychosis. Various meta-analyses or reviews confirm the relationship between cannabis use and the clinical and subclinical psychosis phenotype (Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2020; Kraan et al., 2016; Large, Sharma, Compton, Slade & Nielssen, 2011; Marconi, Di Forti, Lewis Murray & Vassos, 2016; Moore et al., 2007; Szoke et al., 2014). For example, Marconi et al. (2016) found that high levels of cannabis use increased the risk of psychosis, confirming a dose-response relationship between the level of use and the risk of psychosis. In another study, Saha et al. (2011) revealed that, at an early age (16 years or younger), cannabis users were approximately ten times more likely to have delusional-like experiences than non-users.

Previous research has analyzed the relationship between cannabis use and schizotypal traits, suggesting that greater use of cannabis is linked to higher scores in the positive dimension (reality distortion) (Cohen, Buckner, Najolia & Stewart, 2011; Hides et al., 2009; Schubart et al., 2011), although it is true that there are also studies which have not found a statistically significant association (Barkus, 2008; Van Gastel et al., 2012). What is more, results for the negative dimension are not convincing: some studies have found an association between greater use and higher scores in anhedonia (Cohen et al., 2011; Schubart et al., 2011; Verdoux & Van Os, 2002), while such an association was not reported in other studies (Hides et al., 2009; Najolia et al., 2012; Schubart et al., 2011). For example, Najolia et al. (2012), in their study with young non-clinical adults, revealed that cannabis use was associated with higher rates of positive and disorganized schizotypal traits, but not with negative schizotypal traits.

A further concern is that polydrug use is rather common among drug users; its adverse effects impact cognitive, affective, and behavioural aspects in a way that increases the risk of social and mental health problems (Moreno, 2018). Alcohol and cigarettes are considered the "gateway" to other illegal drugs (Vázquez & Becoña, 2000). The literature also notes that young people who engage in heavy alcohol consumption are more likely to be involved in risky behaviours such as violence, unplanned sexual activity, truancy, dangerous driving (Maturana, 2011), attempting or committing suicide (Pérez Gálvez, 2015), and binge drinking (Sendino et al., 2016). Thus, several studies have concluded that adolescents who are more vulnerable to alcohol, cigarettes, and cannabis, could be subject to greater clinical risk (Auther et al., 2012; Buchy, Perkins, Woods,

Liu & Addington, 2014; Fonseca-Pedrero, Ortuño-Sierra, Paino & Muñiz, 2016; Fumero, Santamaría & Navarrete, 2009). For instance, in a sample of students, it was corroborated that schizotype scores correlated positively with the consumption of alcohol and cannabis (García Montes, Zaldívar Basurto, Moreno Montoya & Flores Cubos, 2013). Analyzing schizotypal traits and smoking, it was found that individuals with schizotypy were twice as likely to smoke, and smokers reported more severe symptoms of disorganization and less serious negative schizotypal symptoms (Stewart, Cohen & Copeland, 2010).

In addition, as shown by the Spanish national survey on drug use in secondary education (ESTUDES 2016-17), 75.6% of these high-school students had drunk alcohol, 34.7% had smoked cigarettes, and 26.3% had used cannabis in the previous year. In this survey, a significant finding was that there was a delay in the average age of onset of these substances until the age of 14. Recent data indicate that the percentage of problematic cannabis users stands at 13.3% (Moreno, 2018). The prevalence of tobacco, alcohol, and cannabis use among young people is already high and is associated with morbidity and mortality, as well as multiple costs at personal and social health levels.

Substance use is a risk factor and/or a marker of vulnerability which can precipitate the development of clinical and subclinical psychotic experiences (Hall & Degenhardt, 2008). Given the accepted complex relationship between the risk of psychosis and substance use in young people and the negative impact they can cause during this period of human development, new studies are needed to understand their association in order to implement measures promoting emotional well-being and the prevention of mental disorders.

To date, there have not been many studies attempting to analyze the relationship between substance use and risk of psychosis (as estimated by the schizotypy construct) in representative samples of the adolescent population internationally, and more particularly in Spain. In addition, few previous studies have analyzed this relationship while controlling for the effects of multiple confounding variables (e.g., IQ, socio-economic level) with assessment instruments specifically designed for this sector of the population.

Within this research context, the main objective of the study was to explore the relationship between substance use, specifically alcohol, tobacco and cannabis, and schizotypal features in a sample of Spanish secondary school students, and controlling for the effect of multiple confounding variables. It is hypothesized that, in line with the literature, those adolescents who report greater use of substances will have higher scores on schizotypal personality traits.

Method

Participants

The study is of a survey-type descriptive cross-sectional design. Random stratified cluster sampling was performed at the classroom level in a population of approximately 15,000 selected students from the Autonomous Community of La Rioja. The students came from a range of schools (public and publicly-funded private) and vocational training courses (basic, middle and upper). The strata were created according to school type (public/private) and stage (compulsory secondary, higher secondary and vocational training), where the likelihood of being selected depended on the number of students in the school.

The initial sample comprised 1,881 students. Those scoring high on the Oviedo Infrequency Response Scale (3 points or higher) (n = 104), aged over 19 (n = 113) or not completing the test (n = 76) were excluded. A final total of 1,588 students, 739 male (46.5%) and 849 female (53.5%), from 34 schools and 98 classrooms participated in the study. The average age was 16.13 years (SD = 1.36), ranging from 14 to 19 (14, n = 213; 15, n = 337; 16, n = 400; 17, n = 382, 18, n = 180; 19, n = 76).

The distribution of participant nationalities was as follows: 89.9% Spanish, 3.7% Latin American (Bolivia, Argentina, Colombia and Ecuador), 0.7% Portuguese, 2.4% Romanian, 1% Moroccan, 0.7% Pakistani, and 2% other nationalities.

Instruments

Oviedo Schizotypy Assessment Questionnaire-Revised (ESQUIZO-Q) (Fonseca-Pedrero, Lemos, Muñiz, Paino & Villazón, 2010). This is a self-report measure composed of 62 items developed for the assessment of schizotypal traits in adolescents, which can also be used for epidemiological purposes. The items of the ESQUIZO-Q were selected from an exhaustive review of the schizotypal personality literature, with a 5-point Likert-type response format (from 1 'completely disagree' to 5 'completely agree'). The self-report consists of a total of 10 subscales derived empirically by exploratory factor analysis, which, in turn, are grouped into three general dimensions: Positive (which includes the Referential Ideation, Magical Thought, Unusual Perceptual Experiences and Paranoid Ideation subscales); Anhedonia (Physical Anhedonia and Social Anhedonia); and Social Disorganization (Odd Thought and Language, Odd Behavior, Lack of Intimate Friends and Excessive Social Anxiety).

The psychometric properties of the ESQUIZO-Q have been widely analyzed in previous studies (Fonseca-Pedrero, Lemos-Giráldez, Paino, Sierra-Baigrie, Santarén-Rosell & Muñiz, 2011; Fonseca-Pedrero, Paino, Lemos-Girádez & Muñiz, 2011).

Modified Substance Use Questionnaire (Fonseca-Pedrero et al., 2020). The substance use questionnaire used in this research is an abbreviated modification of the World Health Organization's *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST v3.0) (WHO *Assist Working Group,* 2002). ASSIST is an interview-format screening tool developed by the World Health Organization for the identification of drug users. It consists of different items which assess, among other aspects, the frequency with which different substances (alcohol, tobacco, cannabis, cocaine, etc.) are used in the three months prior to the completion of the questionnaire.

In this study, we used two of the ASSIST questions, which were applied in a self-report format. Item 1 asked: "In your life, which of the following substances have you ever used?" Participants responded in a dichotomous response format Yes/No for the following substances: a) tobacco (cigarettes, cigars, chewing tobacco, pipe, etc.); b) alcoholic drinks (beer, wine, liquors, spirits, etc.); c) cannabis (marijuana, pot, grass, hashish, etc.); and d) others (e.g., cocaine, amphetamines, inhalants, hallucinogens, opiates, etc.). In the case of an affirmative answer to any substances in Item 1, participants were asked in Item 2 about the frequency of use in the last three months (0 = "Never"; 1 = "Once or twice"; 2 = "Every month"; 3 = "Every week"; 4 = "Daily or almost daily").

ASSIST has been translated and validated in Spanish (Soto-Brandt et al., 2014), and its modified version has been used with Spanish adolescents (Fonseca-Pedrero et al., 2020).

Strengths and Difficulties Questionnaire - Self-Report version (SDQ-SR) (Goodman, 1997). The SDQ is a measurement instrument used for the detection of behavioural and emotional difficulties, as well as for the assessment of prosocial skills (Fonseca-Pedrero et al., 2011). It has also been used as a screening tool and for the epidemiological analysis of mental health status in children and adolescents (Ortuño-Sierra, Fonseca-Pedrero, Inchausti & Sastre i Riba, 2016).

The SDQ comprises 25 items using a Likert-type response format with three options (0 = "No, never"; 1 = "Sometimes"; 2 = "Yes, always"). The items are grouped into five dimensions (with five items each): Emotional Symptoms, Behavioural Problems, Hyperactivity, Peer Problems, and Prosocial Behaviour. The first four subscales form a Total Difficulties score. The higher the score, the greater the level of emotional and behavioural difficulties, except for the Prosocial Behaviour subscale, where a lower score corresponds to worse adjustment.

The psychometric properties of the SDQ have been analyzed in previous national studies (Ortuño-Sierra et al., 2016; Ortuño-Sierra, Fonseca-Pedrero, Paino, Sastre I Riba & Muñiz, 2015).

Penn Matrix Reasoning Test (PMRT) (Gur et al., 2012; Moore, Reise, Gur, Hakonarson & Gur, 2015). This is one of the tasks on the children's version of the Penn Computerized Neurocognitive Battery, and was developed to measure nonverbal reasoning (using matrix reasoning problems as used in the Raven Progressive Matrices Test). This task, comprising 20 elements, can be considered an indirect estimate of IQ. The test has been used in previous studies with Spanish adolescents (Fonseca-Pedrero et al., 2020).

Family Affluence Scale-II (FAS-II) (Boyce, Torsheim, Currie & Zambon, 2006). The FAS-II provides an indirect estimation of socioeconomic level through four items with a Likert-type response format. It has proven useful in adolescent populations. Previous international studies have shown its satisfactory psychometric properties (Boyce, Torsheim, Currie & Zambon, 2006). The FAS-II, in its Spanish version has, been used in previous studies (Fonseca-Pedrero et al., 2020).

Oviedo Infrequency Response Scale (INF-OV) (Fonseca-Pedrero, Paino-Piñeiro, Lemos-Giráldez, Villazón-García & Muñiz, 2009). The INF-OV was developed to detect participants who respond in a random, pseudo-random or untruthful way to the measurement instruments used. The INF-OV is a self-report type assessment tool comprising 12 items in a Likert-type format with five categories showing the degree of adherence (from 1 = "Completely disagree" to 5 = "Strongly agree"). Once the items have been dichotomized, students scoring more than two items of the INF-OV incorrectly are eliminated from the study. The INF-OV has been used in previous studies (Fonseca-Pedrero et al., 2011; Fonseca-Pedrero et al., 2009)

Procedure

The present research was approved by the General Directorate of Education of the Government of La Rioja and the Clinical Research Ethics Committee of La Rioja (CEICLAR). Contact with schools was made by telephone, e-mail or by regular post. The initial contact with a school was with the director, the head of studies or the orientation department.

In order to standardize the administration process, all the researchers were given a protocol and guidelines to be carried out before, during, and after the administration of the measurment instruments. Questionnaires were administered by computer and collectively in groups of between 10 and 30 participants.

Participants were informed at all times that their responses would remain confidential, and that participation was voluntary; collaboration in the study was not remunerated in any way. Since many of the participants were minors, parental consent was requested to authorize the participation of the adolescent in the investigation. This

study is part of a larger project on the early detection of mental health problems.

Data analysis

The following analyses were carried out to investigate the proposed objectives.

First, we analyzed the percentage of participants who reported substance use, specifically tobacco, alcohol, and cannabis.

Secondly, to examine the relationship between substance use and the three dimensions of schizotypal traits (Positive, Anhedonia and Social Disorganization), various Multivariate Analyses of Covariance (MANCOVA) were performed. The schizotypy dimensions were considered as dependent variables, and substance use (tobacco, alcohol and cannabis) as a fixed factor. Each MANCOVA initially analyzed the effect at the level of lifetime prevalence (having used the substance at some time in their life) followed by the frequency level. Given that gender, age, socio-economic level, IQ, and/or emotional and behavioural problems may affect the expression of the relationship between schizotypal traits and substance use, these factors were considered as covariables. Substance use was also taken as a covariate, depending on the type of substance in question. Thus, when analyzing the effect of cannabis on schizotypal dimensions, the effects of alcohol and cigarettes use was controlled for. When analyzing the effect of cigarette smoking on the schizotypal dimensions, the effects of alcohol and cannabis use was controlled for. When analyzing the effect of alcohol on the schizotypal dimensions, the effect of cannabis use and cigarette smoking was controlled for. The partial squared eta statistic (partial η^2) was used to calculate the effect size.

The data analyses were performed with the SPSS v22 statistical package (IBM *Corp Released,* 2013).

Results

Prevalence of substance use

Lifetime prevalence (having used the substance at some time in their life) was 40.6% for cigarettes, 79.4% for alcohol and 23.6% for cannabis. Drinking alcohol every week was reported by 15.7% of the sample. In addition, 2.9% of the participants reported a frequency of monthly cannabis use, while 2% presented a pattern of weekly use. Table 1 shows the prevalence rates of substance use; in addition, data on the frequency of use of the three substances over the last three months are also provided.

Relationship between alcohol consumption and schizotypal traits

First, we analyzed the relationship between the lifetime prevalence of alcohol use and the ESQUIZO-Q scores, and then between the frequency of use and ESQUIZO-Q scores. The effects of gender, age, IQ, socio-economic level, psychopathology, and cannabis and tobacco use were controlled for.

Based on the lifetime prevalence of alcohol use, MANCOVA did not reveal the existence of statistically significant differences ($\lambda = 0.998$; $F_{(3,1577)} = 1.110$, $p = 0.334$). Compared with non-users, alcohol drinkers did not report higher mean scores in any of the ESQUIZO-Q dimensions. Table 2 shows the mean scores for the two groups.

Based on the frequency of alcohol use (in the last 3 months), MANCOVA revealed the existence of statistically significant differences ($\lambda = 0.985$; $F(12, 3783) = 1.842$, $p = 0.037$). Those who reported more frequent drinking, compared with non-users, also reported higher average scores in the Social Disorganization dimension. Statistically significant differences were found in particular between group 1 ("once or twice") and 3 ("every week"). Mean scores for the groups are shown in Table 3.

Table 1. *Prevalence and frequency of substance use in the total sample.*

		Alcohol		Cigarettes		Cannabis	
		n	%	n	%	n	%
Prevalence	No	327	20.6	947	59.6	1211	76.3
	Yes	1261	79.4	641	40.4	377	23.7
Frequency	Never (0)	208	13.1	783	49.3	1047	65.9
	Once or twice (1)	494	31.1	312	19.6	239	15.1
	Each month (2)	478	30.1	77	4.8	46	2.9
	Each week (3)	250	15.7	61	3.8	29	1.8
	Daily or almost daily (4)	14	0.9	163	10.3	29	1.8
	Total	1444	90.9	1396	87.9	1390	87.5
	No answer	144	9.1	192	12.1	198	12.5

Note. Prevalence: indication by participants whether or not they have used the substances at some time in their life.

Table 2. *Relationship between alcohol use (lifetime prevalence) and schizotypal traits.*

	Non-use		Use				
Dimension	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	33.51	11.69	34.65	11.91	0.4	0.527	0
Negative	34.52	7.33	33.44	6.54	1.99	0.159	0.001
Disorganization	57.47	15.81	58.85	15.23	0.554	0.457	0

Table 3. *Relationship between alcohol use (frequency) and schizotypal traits.*

	0		1		2		3		4				
Dimension	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	33.80	11.19	34.50	11.90	34.50	11.28	35.06	12.19	40.50	24.42	0.718	0.579	0.002
Negative	34.02	7.26	33.59	6.75	32.92	6.24	33.90	6.54	34.29	7.34	0.494	0.74	0.001
Disorganization	57.38	15.73	59.92	15.31	58.26	14.71	57.87	14.87	57.50	26.39	2.676	0.031	0.007

Note. Never = 0; Once or twice = 1; Each month = 2; Each week = 3; Daily or almost daily = 4.

Relationship between cigarette smoking and schizotypal traits

The MANCOVA used to analyze the relationship between the use or non-use of tobacco (lifetime prevalence) and ESQUIZO-Q scores, controlling for the effect of gender, age, IQ, socio-economic level, psychopathology, and cannabis and alcohol use, revealed the existence of statistically significant differences ($\lambda = 0.991$; $F_{(3,1577)} = 4.995$, $p = 0.002$), particularly in the Anhedonia and Social Disorganization dimensions. Compared with non-smokers, cigarette smokers reported higher mean scores in these two ESQUIZO-Q dimensions. The mean scores for the two groups are shown in Table 4.

Next, a new MANCOVA was performed taking the frequency variable of smoking into account as a fixed factor, the ESQUIZO-Q dimensions as dependent variables, and controlling for the effects of the same covariates. In this case, MANCOVA revealed the existence of statistically significant differences ($\lambda = 0.973$; $F_{(12,\ 3656)} = 3.143$, $p < 0.001$). Compared with non-smokers, cigarette smokers, differentiated by frequency, reported higher average scores in the Anhedonia and Social Disorganization dimensions of the ESQUIZO-Q. Statistically significant differences were found specifically between group 0 and 1 in Anhedonia, and between groups 0-1, 0-4 and 2-4 (where never = 0, once or twice = 1, every month = 2; every week = 3; daily or almost daily = 4) in the schizotypal factor of Disorganization. The mean scores for smoking frequency groups are shown in Table 5.

Table 4. *Relationship between cigarette smoking (lifetime prevalence) and schizotypal traits.*

	Non-use		Use				
Dimension	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	33.81	11.54	35.31	12.30	1.132	0.287	0.001
Negative	33.95	6.87	33.24	6.47	5.707	0.017	0.004
Disorganization	58.14	15.26	59.20	15.49	11.93	0.001	0.007

Table 5. *Relationship between cigarette smoking (frequency) and schizotypal traits.*

	0		1		2		3		4				
Dimension	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	34.14	11.68	34.40	11.46	36.32	12.14	36.84	11.02	35.61	13.49	1.638	0.162	0.005
Negative	33.74	6.78	32.66	6.33	32.16	6.12	33.77	6.95	34.24	6.53	2.888	0.021	0.008
Disorganization	58.31	15.14	58.63	14.52	60.06	13.78	60.97	16.76	58.86	16.87	6.444	<0.001	0.018

Note. Never = 0; Once or twice = 1; Each month = 2; Each week = 3; Daily or almost daily = 4.

Relationship between cannabis use and schizotypal traits

The MANCOVA analyzing the relationship between lifetime prevalence of cannabis use and the schizotypy dimensions, while controlling for the effects of gender, age, IQ, socio-economic level, psychopathology, and alcohol and tobacco use covariates, did not reveal the existence of statistically significant differences ($\lambda = 0.998$; $F_{(3,1577)} = 1.146$, $p = 0.329$). Cannabis users, compared with non-users, did not report higher average scores in any of the ESQUIZO-Q dimensions. The results are presented in Table 6.

Looking at frequency of use, the MANCOVA performed, which considered the variable frequency of cannabis use as a fixed factor and the ESQUIZO-Q scores as dependent variables, and controlled for the effects of the same covariates, did not reveal the existence of statistically significant differences ($\lambda = 0.991$; $F_{(12, 3640)} = 1.014$, $p = 0.433$). Table 7 shows the mean scores for the different cannabis use frequency groups.

Table 6. *Relationship between cannabis use (lifetime prevalence) and schizotypal traits.*

	Non-use		Use				
Dimension	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	33.79	11.43	36.43	13.01	1.743	0.187	0.001
Negative	33.57	6.73	33.95	6.70	1.377	0.241	0.001
Disorganization	58.03	15.16	60.29	15.88	0.042	0.838	0

Table 7. *Relationship between cannabis use (frequency) and schizotypal traits.*

	0		1		2		3		4				
Dimension	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	*partial* η^2
Positive	33.99	11.41	36.04	12.77	37.22	11.50	35.31	12.04	38.55	17.82	0.788	0.533	0.002
Negative	33.31	6.66	33.31	6.38	35.09	8.28	35.31	5.50	35.14	6.96	0.43	0.787	0.001
Disorganization	58.07	14.96	59.67	15.50	62.70	15.54	59.86	16.36	59.76	20.12	1.266	0.0281	0.004

Note. Never = 0; Once or twice = 1; Each month = 2; Each week = 3; Daily or almost daily = 4.

Discussion

The main aim of this study was to analyze the relationship between substance use (tobacco, alcohol and cannabis) and the risk of psychosis, estimated by schizotypal traits, in a representative sample of Spanish school-aged adolescents.

Firstly, lifetime prevalence rates of alcohol, tobacco, and cannabis use were analyzed. The results show a lifetime prevalence of 40.4% for tobacco, 79.4% for alcohol and 23.7% for cannabis. These results are similar to those obtained in the Spanish national survey on drug use in secondary education, ESTUDES 16-17 (34.7% for tobacco, 76.9% alcohol, and 31.1% for cannabis). Of the sample, 10.3% of adolescents reported that they smoked cigarettes every day or almost daily; according to the Spanish Observatory on Drugs, 8.8% of young people reported smoking cigarettes daily (Moreno, 2018). Alcohol was drunk by 30.1% every month, data similar to high school students (ESTUDES 16-17). Three out of four youths admit to having drunk alcohol in the last 30 days. Finally, 2.9% reported smoking cannabis monthly, a figure that differs from that of secondary education students aged 14 to 18 (ESTUDES 16-17) where cannabis use of 18.3% in the last 30 days is confirmed. Data from a recent study reveal that the percentage of adolescents who smoke cigarettes and cannabis is higher nowadays than that of cigarettes only (12.7% vs. 10.5%), and that this not only implies a greater probability of using other illegal substances, but also of developing a pattern of risky alcohol use (Rial et al., 2018). According to a variety of studies, young people are not aware of the risky behaviours that lead to drug use because of the low perception of risk; they consider sporadic use as harmless, which makes them more vulnerable (Barrett & Bradley, 2016; López-Quintero & Neumark, 2010; Rowe, Santos, Behar & Coffin, 2016).

Secondly, the schizotypy dimensions (Positive, Negative and Disorganization) were analyzed in terms of use - at the levels of lifetime prevalence and frequency - controlling for the effect of the covariates (gender, age, IQ, socio-economic level, psychopathology, and use of other substances). Compared with non-users, alcohol users reported higher scores in the Social Disorganization dimension, findings which concur with a current review of the effects of binge drinking in young people, which links such use to neurocognitive deficits (dimished sustained attention and visuospatial working memory; deficits in decision-making, cognitive flexibility and executive functions) (López-Cane-

da et al., 2014). The Positive and Anhedonia schizotypal dimensions did not show statistically significant differences when the effects of these covariates were controlled for. Along similar lines to our research, Auther et al. (2012) stated that adolescents with early onset (aged 17 or less) of alcohol use were significantly more likely to have schizotypal experiences. However, the pattern of association between alcohol use, dependency disorder and schizotypal traits was less consistent when adjusted for the presence of other substance use disorders, even though more severe symptoms are also associated with higher levels of substance use.

Cigarette smokers reported higher scores on the Anhedonia and Social Disorganization dimensions. The results of the present study reflect that both the presence (yes/no) and the frequency of cigarette smoking are associated with higher scores in negative traits and social disorganization. Anhedonia is linked to the habit of smoking to relieve these effects (Leventhal et al, 2013), and is considered a risk marker for psychosis (Docherty & Sponheim, 2014; Meehl, 1962). Several prospective studies link smoking to psychotic symptoms (Gurillo et al., 2015; Munafò, Larsson Lönn, Sundquist, Sundquist & Kendler, 2016; Riala, Hakko, Isohanni, Pouta & Räsänen, 2005; Zammit et al., 2003). For example, Gurillo et al., (2015) emphasize that daily smoking is associated with an increased risk of psychosis in case-control studies, and also indicate that smoking is linked to earlier onset of psychotic disorder. Similarly, Weiser et al. (2004) state that the rate of cigarette smoking in male adolescents was significantly linked to the risk of schizophrenia. However, the possibility of a causal link between tobacco use and psychosis merits a more detailed examination.

Regarding the influence of cannabis, no statistically significant differences were found, either in terms of prevalence or frequency of use in the schizotypal dimensions, when the effect of confounding variables was controlled for. The results yielded do not reveal a statistically significant link, after adjustment for confounding values, which suggests the possible existence of underlying factors that can better explain the association. However, a study in Spain found that patients who had a first episode of psychosis (average age 15.5 years) had a higher rate of positive symptoms and fewer negative symptoms if they were cannabis users, compared with those who did not use cannabis (Baeza et al., 2009). The association between cannabis use and psychosis has been analyzed in a large number of previous studies (Fergusson, Horwood & Ridder, 2005; Fonseca-Pedrero, Ortuño-Sierra, Paino & Muñiz, 2016; Gage, Hickman & Zammit, 2016; Hides et al., 2009; Kelleher et al., 2012; Marconi et al., 2016; Moore et al., 2007). In general, research in the field of schizotypy indicates that the relationships established with cannabis use are complex and bidirectional, with different variables possibly playing a mediating or moderating role (Fonseca-Pedrero et al., 2020). For example, Schubart et al. (2011), analyzed the association between onset age and level of cannabis use and psychotic experiences in three symptom dimensions (positive, negative and depressive) in a sample of the Dutch population comprising more than 17,500 participants, with an average age of 21. This study revealed that the onset age of cannabis use is strongly associated with current psychotic experiences, and that the level of cannabis use is similarly related to positive, negative, and depressive symptoms.

There is copious literature linking substance use to psychosis, although establishing causality from these investigations is problematic. As Minozzi et al. (2009) claim, reverse causality and residual confounding cannot be excluded. The interaction with other environmental and genetic factors is difficult to determine. This should not alter the public health message that cannabis can be harmful and that dependence on cannabis should be avoided (Gage et al., 2016). In fact, perhaps an interesting line of action in the field of psychosis may lie, rather than reducing the risk of psychosis or latent vulnerability in itself, in preventing or reducing relevant risk factors which are closely related to the etiology of psychosis, such as, for example, cannabis use or trauma experiences (Radua et al., 2018).

When interpreting the results obtained in the present work, some limitations need to be borne in mind. First, the conclusions are limited by the measurement instruments used, of the self-report type, with the corresponding corollaries of this type of tool (possible lack of comprehension, misinterpretation of the items, or response biases). The multi-informant system would have been particularly relevant in the assessment of the study variables. Second, the sample comes from a Spanish Autonomous Community (La Rioja), an aspect which, despite random stratified cluster sampling, partially limits the generalizability of results to the whole of Spain. Third, it is a cross-sectional study, so that cause-and-effect relationships cannot be established. Fourth, no information on possible psychiatric morbidity was collected, either from participants or from close relatives, which could affect the study's results.

In conclusion, during adolescence schizotypal traits were associated with tobacco and alcohol use, but not cannabis. This study aimed to shed light on the link between experiences of substance use and schizotypal traits in adolescence. It is necessary to identify the mechanisms underlying this association in vulnerable groups of at-risk young people if prevention strategies are to be improved. Future research could continue to analyze the role of risk and protective factors related to the transition to different psychological problems in longitudinal and gene-environment interaction studies. In the same way, it would be extremely interesting to incorporate new assessment and measurement techniques, such as the experience-sampling meth-

od, which allows a more ecological, contextual, etiological, personalized, and accurate analysis of human behaviour.

Acknowledgment

This research has been funded by the Ministry of Science and Innovation of Spain (MICINN) (reference PSI2014-56114-P), by the Carlos III Institute, Center for Biomedical Research in the Mental Health Network (CIBERSAM), by the 2015 Call for Proposals "BBVA Foundation helps researchers and cultural creators", for the "BBVA Foundation Aids to Scientific Research Teams 2017", by the Ministry of Economy and Competitiveness (MINECO) (reference PSI 2016-79524-R) and co-financed with FEDER funds in the FEDER PO of La Rioja 2014-2020 (SRS 6FRSABC026).

Conflict of interests

The authors declare no conflicts of interest.

References

Abajobir, A. A., Kisely, S., Scott, J. G., Williams, G., Clavarino, A., Strathearn, L. & Najman, J. M. (2017). Childhood maltreatment and young adulthood hallucinations, delusional experiences, and psychosis: a longitudinal study. *Schizophrenia Bulletin, 43,* 1045–1055. doi:10.1093/schbul/sbw175.

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E. & Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *American Journal of Psychiatry, 168,* 65–72. doi:10.1176/appi.ajp.2010.10040567.

Auther, A. M., McLaughlin, D., Carrión, R. E., Nagachandran, P., Correll, C. U. & Cornblatt, B. A. (2012). Prospective study of cannabis use in adolescents at clinical high risk for psychosis: impact on conversion to psychosis and functional outcome. *Psychological Medicine, 42,* 2485–2497. doi:10.1017/S0033291712000803.

Baeza, I., Graell, M., Moreno, D., Castro-Fornieles, J., Parellada, M., González-Pinto, A., … Arango, C. (2009). Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). *Schizophrenia Research, 113,* 129–137. doi:10.1016/j.schres.2009.04.005.

Barkus, E. (2008). Personality and cannabis use. *Advances in Schizophrenia and Clinical Psychiatry, 3,* 84–89.

Barrantes-Vidal, N., Grant, P. & Kwapil, T. R. (2015). The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophrenia Bulletin, 41,* 408–416. doi:10.1093/schbul/sbu191.

Barrett, P. & Bradley, C. (2016). Attitudes and perceived risk of cannabis use in Irish adolescents. *Irish Journal of Medical Science, 185,* 643–647. doi:10.1007/s11845-015-1325-2.

Boyce, W., Torsheim, T., Currie, C. & Zambon, A. (2006). The Family Affluence Scale as a measure of national wealth: validation of an adolescent self-report measure. *Social Indicators Research, 78,* 473–487. doi:10.1007/s11205-005-1607-6.

Buchy, L., Perkins, D., Woods, S. W., Liu, L. & Addington, J. (2014). Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. *Schizophrenia Research, 156,* 277–280. doi:10.1016/j.schres.2014.04.021.

Casajuana Kögel, C., López-Pelayo, H., Balcells-Olivero, M. M., Colom, J. & Gual, A. (2018). Psychoactive constituents of cannabis and their clinical implications: a systematic review constituyentes psicoactivos del cannabis & sus implicaciones clínicas: una revisión sistemática. *Adicciones, 30,* 140–151. doi:10.20882/adicciones.858.

Cohen, A. S., Buckner, J. D., Najolia, G. M. & Stewart, D. W. (2011). Cannabis and psychometrically-defined schizotypy: use, problems and treatment considerations. *Journal of Psychiatric Research, 45,* 548–554. doi:10.1016/j.jpsychires.2010.08.013.

Cohn, A., Johnson, A., Ehlke, S. & Villanti, A. C. (2016). Characterizing substance use and mental health profiles of cigar, blunt, and non-blunt marijuana users from the National Survey of Drug Use and Health. *Drug and Alcohol Dependence, 160,* 105–111. doi:10.1016/j.drugalcdep.2015.12.017.

Debbané, M., Eliez, S., Badoud, D., Conus, P., Fluckiger, R. & Schultze-Lutter, F. (2015). Developing psychosis and its risk states through the lens of schizotypy. *Schizophrenia Bulletin, 41,* 396–407. doi:10.1093/schbul/sbu176.

Ericson, M., Tuvblad, C., Raine, A., Young-Wolff, K. & Baker, L. A. (2011). Heritability and longitudinal stability of schizotypal traits during adolescence. *Behavior Genetics, 41,* 499–511. doi:10.1007/s10519-010-9401-x.

Fergusson, D. M., Horwood, L. J. & Ridder, E. M. (2005). Tests of causal linkage between cannabis use and psychotic symptoms. *Addiction, 100,* 354–366. doi:10.1111/j.1360-0443.2005.001001.x.

Fonseca-Pedrero, E., Lemos, S., Muñiz, J., Paino, M. & Villazón, U. (2010). ESQUIZO-Q. Cuestionario Oviedo para la Evaluación de la Esquizotipia. Madrid: TEA Ediciones.

Fonseca-Pedrero, E. (coord). (2018). Evaluación de los trastornos del espectro psicótico. Madrid: Pirámide.

Fonseca-Pedrero, E. & Debbané, M. (2017). Schizotypal traits and psychotic-like experiences during adolescence: an update. *Psicothema, 29,* 5–17. doi:10.7334/psicothema2016.209.

Fonseca-Pedrero, E. e Inchausti, F. (2018). Update on the prevention of psychotic spectrum disorders. *Papeles del Psicologo, 39,* 127–139. doi:10.23923/pap.psicol2018.2860.

Fonseca-Pedrero, E., Lucas-Molina, B., Pérez-Albéniz, A., Inchausti, F. & Ortuño-Sierra, J. (2020). Psychotic-like experiences and cannabis use in adolescents from the general population. *Adicciones, 32*, 41-51. doi:10.20882/adicciones.1149.

Fonseca-Pedrero, E., Ortuño-Sierra, J., Paino, M. & Muñiz, J. (2016). Psychotic-like experiences and substance use in college students. *Adicciones, 28,* 144–153. doi:10.20882/adicciones.781.

Fonseca-Pedrero, E., Paino-Piñeiro, M., Lemos-Giráldez, S., Villazón-García, U. & Muñiz, J. (2009). Validation of the Schizotypal Personality Questionnaire-Brief form in adolescents. *Schizophrenia Research, 111,* 53–60. doi:10.1016/j.schres.2009.03.006.

Fonseca-Pedrero, E., Paino, M., Lemos-Giráldez, S. & Muñiz, J. (2011a). Prevalencia de la sintomatología emocional y comportamental en adolescentes Españoles a través del Strengths and Difficulties Questionnaire (SDQ). *Revista de Psicopatologia y Psicologia Clinica, 16,* 15–25. doi:10.5944/rppc.vol.16.num.1.2011.10348.

Fonseca-Pedrero, E., Paino, M., Lemos-Giráldez, S. & Muñiz, J. (2011b). Schizotypal traits and depressive symptoms in nonclinical adolescents. *Comprehensive Psychiatry, 52,* 293–300. doi:10.1016/j.comppsych.2010.07.001.

Fonseca-Pedrero, E., Paino, M., Lemos-Giráldez, S., Sierra-Baigrie, S., Ordóñez-Camblor, N. & Muñiz, J. (2011). Early psychopathological features in Spanish adolescents. *Psicothema, 23,* 87–93.

Fumero, A., Marrero, R. J. & Fonseca-Pedrero, E. (2018). Well-being in schizotypy: the effect of subclinical psychotic experiences. *Psicothema, 30,* 177–182. doi:10.7334/psicothema2017.100.

Fumero A., Santamaría, C. & Navarrete, G. (2009). Predisposición al consumo de alcohol y drogas en personas vulnerables a la esquizofrenia. *Revista de Neurologia, 49,* 8–12. doi:10.33588/rn.4901.2008672.

Gage, S. H., Hickman, M. & Zammit, S. (2016). Association between cannabis and psychosis: epidemiologic evidence. *Biological Psychiatry, 79,* 549–556. doi:10.1016/j.biopsych.2015.08.001.

García Montes, J. M., Zaldívar Basurto, F., Moreno Montoya, M. & Flores Cubos, P. (2013). Relaciones entre el consumo de drogas y variables de riesgo psicopatológicas en jóvenes universitarios. *Psicothema, 25,* 433–439. doi:10.7334/psicothema2013.20.

Gonzalvo, B., Barral, C. & Roncero, O. E. C. (2011). Comorbilidad psiquiátrica en adolescentes consumidores de cannabis. *Trastornos Adictivos, 13,* 109–112. doi:10.1016/S1575-0973(11)70023-X.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: a research note. *Journal of Child Psychology and Psychiatry, 38,* 581–6. doi:10.1111/j.1469-7610.1997.tb01545.x.

Gur, R. C., Richard, J., Calkins, M. E., Chiavacci, R., Hansen, J. A., Bilker, W. B., … Gur, R. E. (2012). Age group and sex differences in performance on a computerized neurocognitive battery in children age 8-21. *Neuropsychology, 26,* 251–265. doi:10.1037/a0026712.

Gurillo, P., Jauhar, S., Murray, R. M. & MacCabe, J. H. (2015). Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry, 2,* 718–725. doi:10.1016/S2215-0366(15)00152-2.

Hall, W. & Degenhardt, L. (2008). Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry, 7,* 68–71.

Hides, L., Lubman, D. I., Buckby, J., Yuen, H. P., Cosgrave, E., Baker, K. & Yung, A. R. (2009). The association between early cannabis use and psychotic-like experiences in a community adolescent sample. *Schizophrenia Research, 112,* 130–135. doi:10.1016/j.schres.2009.04.001.

IBM Corp Released. (2013). *IBM SPSS Statistics for Windows, Version 22.0*. Armonk, NY: IBM Corp.

Kelleher, I., Connor, D. & Clarke, M. C. (2012). Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta- analysis of population-based studies. *Psychological Medicine, 42,* 1857-1863. doi:10.1017/S0033291711002960.

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H. K., van den Berg, D., … Van der Gaag, M. (2016). Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. *Psychological Medicine, 46,* 673–681. doi:10.1017/S0033291715002329.

Large, M., Sharma, S., Compton, M. T., Slade, T. & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry, 68,* 555–561. doi:10.1001/archgenpsychiatry.2011.5.

Leventhal, A. M., Greenberg, J. B., Trujillo, M. A., Ameringer, K. J., Lisha, N. E., Pang, R. D. & Monterosso, J. (2013). Positive and negative affect as predictors of urge to smoke: temporal factors and mediational pathways. *Psychology of Addictive Behaviors, 27,* 262–267. doi:10.1037/a0031579.

Linscott, R. J. & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine, 43,* 1133–1149. doi:10.1017/S0033291712001626.

López-Caneda, E., Mota, N., Crego, A., Velásquez, T., Corral, M., Holguín, S. R. & Cadaveira, F. (2014). Anomalías neurocognitivas asociadas al consumo intensivo de alcohol (binge drinking) en jóvenes y adolescentes: Una revisión. *Adicciones, 26*, 334–359. doi:10.20882/adicciones.39.

López-Quintero, C. & Neumark, Y. (2010). Effects of risk perception of marijuana use on marijuana use and in-

tentions to use among adolescents in Bogotá, Colombia. *Drug and Alcohol Dependence, 109,* 65–72. doi:10.1016/j.drugalcdep.2009.12.011.

Malone, D. T., Hill, M. N. & Rubino, T. (2010). Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. *British Journal of Pharmacology, 160,* 511–522. doi:10.1111/j.1476-5381.2010.00721.x.

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.

Maturana, A. (2011). Consumo de alcohol y drogas en adolescentes. *Revista Médica Clínica Las Condes, 22,* 98–109. doi:10.1016/S0716-8640(11)70397-2.

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist, 17,* 827–838. doi:10.1037/h0041029.

Minozzi, S., Davoli, M., Bargagli, A. M., Amato, L., Vecchi, S. & Perucci, C. A. (2009). An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. *Drug and Alcohol Review, 29,* 304–317. doi:10.1111/j.1465-3362.2009.00132.x.

Moore, T. H. M., Zammit, S., Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M. & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370,* 319–28. doi:10.1016/S0140-6736(07)61162-3.

Moore, T. M., Reise, S. P., Gur, R. E., Hakonarson, H. & Gur, R. C. (2015). Psychometric properties of the penn computerized neurocognitive battery. *Neuropsychology, 29,* 235–246. doi:10.1037/neu0000093.

Moreno, L. M. (2018). Informe ESTUDES 2018: Alcohol, tabaco y drogas ilegales en España.

Morton, S. E., O'Hare, K. J. M., Maha, J. L. K., Nicolson, M. P., Machado, L., Topless, R., … Linscott, R. J. (2017). Testing the validity of taxonic schizotypy using genetic and environmental risk variables. *Schizophrenia Bulletin, 43,* 633–643. doi:10.1093/schbul/sbw108.

Munafò, M. R., Larsson Lönn, S., Sundquist, J., Sundquist, K. & Kendler, K. (2016). Snus use and risk of schizophrenia and non-affective psychosis. *Drug and Alcohol Dependence, 164,* 179–182. doi:10.1016/j.drugalcdep.2016.04.035.

Najolia, G. M., Buckner, J. D. & Cohen, A. S. (2012). Cannabis use and schizotypy: The role of social anxiety and other negative affective states. *Psychiatry Research, 200,* 660–668. doi:10.1016/j.psychres.2012.07.042.

Ortuño-Sierra, J., Fonseca-Pedrero, E., Inchausti, F. & Sastre I Riba, S. (2016). Evaluación de dificultades emocionales y comportamentales en población infanto-juvenil: el cuestionario de capacidades y dificultades (SDQ). *Papeles del Psicologo, 37,* 14–26.

Ortuño-Sierra, J., Fonseca-Pedrero, E., Paino, M., Sastre I Riba, S. & Muñiz, J. (2015). Screening mental health problems during adolescence: psychometric properties of the Spanish version of the strengths and difficulties Questionnaire. *Journal of Adolescence, 38,* 49-56. doi:10.1016/j.adolescence.2014.11.001.

Pérez Gálvez, M. (2015). Prevención e intervención de la conducta suicida en personas consumidoras de alcohol. En Andoni Aseán (ed.), *Manual de prevención, intervención y postvención de la conducta suicida* (pp. 611–630). Madrid: Fundación Salud Mental España.

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., … Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry, 17,* 49–66. doi:10.1002/wps.20490.

Rial, A., Burkhart, G., Isorna, M., Barreiro, C., Varela, J. & Golpe, S. (2018). Cannabis use among adolescents: Risk pattern, implications and possible explanatory variables. *Adicciones, 31,* 64-77. doi:10.20882/adicciones.1212.

Riala, K., Hakko, H., Isohanni, M., Pouta, A. & Räsänen, P. (2005). Is initiation of smoking associated with the prodromal phase of schizophrenia? *Journal of Psychiatry y Neuroscience, 30,* 26–32. doi:10.1016/j.psychres.2005.07.014.

Rowe, C., Santos, G.-M., Behar, E. & Coffin, P. O. (2016). Correlates of overdose risk perception among illicit opioid users. *Drug and Alcohol Dependence, 159,* 234–239. doi:10.1016/j.drugalcdep.2015.12.018.

Saha, S., Scott, J. G., Varghese, D., Degenhardt, L., Slade, T. & McGrath, J. J. (2011). The association between delusional-like experiences, and tobacco, alcohol or cannabis use: a nationwide population-based survey. *BMC Psychiatry, 11,* 202. doi:10.1186/1471-244X-11-202.

Schubart, C. D., Van Gastel, W. A., Breetvelt, E. J., Beetz, S. L., Ophoff, R. A., Sommer, I. E. C., … Boks, M. P. M. (2011). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine, 41,* 1301–1310. doi:10.1017/S003329171000187X.

Sendino, R., Álvares, E., Brime, B., Llorens, N., Ruiz, A. & Sánchez, E. (2016). Informe 2016: alcohol, tabaco y drogas ilegales en España. *Observatorio Español de La Droga y Las Toxicomanias. Ministerio de Sanidad y Servicios Sociales, 72.* doi:10.1007/s13398-014-0173-7.2.

Shakoor, S., Zavos, H. M. S., Haworth, C. M. A., McGuire, P., Cardno, A. G., Freeman, D. & Ronald, A. (2016). Association between stressful life events and psychotic experiences in adolescence: evidence for gene-environment correlations. *British Journal of Psychiatry, 208,* 532–538. doi:10.1192/bjp.bp.114.159079.

Soto-Brandt, G., Portilla Huidobro, R., Huepe Artigas, D., Rivera-Rei, A., Escobar, M. J., Salas Guzman, N., … Castillo-Carniglia, A. (2014). Validity evidence of the Al-

cohol, Smoking and Substance Involvement Screening Test (ASSIST) in Chile. *Adicciones, 26,* 291–302.

Stewart, D. W., Cohen, A. S. & Copeland, A. L. (2010). Cigarette smoking across the schizotypy spectrum. *Psychiatry Research, 179,* 113–115. doi:10.1016/J.PSYCHRES.2010.04.038.

Szoke, A., Galliot, A. M., Richard, J. R., Ferchiou, A., Baudin, G., Leboyer, M. & Schürhoff, F. (2014). Association between cannabis use and schizotypal dimensions - A meta-analysis of cross-sectional studies. *Psychiatry Research, 219,* 58–66. doi:10.1016/j.psychres.2014.05.008.

Van Gastel, W. A., Wigman, J. T. W., Monshouwer, K., Kahn, R. S., Van Os, J., Boks, M. P. M. & Vollebergh, W. A. M. (2012). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey. *Addiction, 107,* 381–387. doi:10.1111/j.1360-0443.2011.03626.x.

Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P. & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine, 39,* 179–195. doi:10.1017/S0033291708003814.

Vázquez, F. & Becoña, E. (2000). Factores de riesgo y escalada cannabinoide. *Adicciones, 12 (Suppl. 2),* 175–184. doi:10.20882/adicciones.680.

Verdoux, H. & Van Os, J. (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia Research, 54,* 59–65. doi:10.1016/S0920-9964(01)00401-7.

Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., … Davidson, M. (2004). Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. *American Journal of Psychiatry, 161,* 1219–1223. doi:10.1176/appi.ajp.161.7.1219.

WHO Assist Working Group. (2002). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction, 97,* 1183-1194. doi:10.1046/j.1360-0443.2002.00185.x.

Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingsson, T. & Lewis, G. (2003). Investigating the association between cigarette smoking and schizophrenia in a cohort study. *American Journal of Psychiatry, 160,* 2216–2221. doi:10.1176/appi.ajp.160.12.2216.

The relationship between motivations for cannabis consumption and problematic use

Relación entre las motivaciones para consumir y el consumo problemático de cannabis

Cristina Casajuana-Kögel*, Hugo López-Pelayo*, Clara Oliveras*, Joan Colom**, Antoni Gual*, María Mercedes Balcells-Oliveró*.

* Grup de Recerca en Addiccions Clínic (GRAC-GRE). Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Hospital Clínic i Universitari de Barcelona. Universitat de Barcelona, Barcelona. España. ** Agència de Salut Pública de Catalunya, Sub-direcció general de drogodependències, Departament de Salut. Generalitat de Catalunya. España.

Abstract

Introduction. Systematic screening of problematic cannabis use does not include the motivations that lead to consumption, although from a person-centered perspective this is fundamental. The present study explores the motivations for cannabis use in adults and its relationship with cannabis use patterns and problematic use. *Method.* Adult cannabis users (previous 60 days) were recruited in the province of Barcelona (n = 468). Information on their sociodemographic data, cannabis use pattern, Cannabis Abuse Screening Test (CAST) and the main motivation for use were collected. Motivations were categorized a posteriori according to the *Marijuana Motives Measures (MMM).* A descriptive and inferential analysis was carried out to link the motivations to sociodemographic variables, consumption pattern and probability of suffering problematic cannabis use (CAST). *Results.* Using cannabis to heighten positive feelings (35%), out of habit (29%) and to cope with negative feelings (25%) were the most frequent motivations. In comparison to other motivations, coping is related to a greater quantity of cannabis used (4 vs 3 joints per day, p = 0.005), higher probability of problematic cannabis use (77% vs 64%, p = 0.05), and greater social vulnerability (unemployment 56% vs 37%, p = 0.001; and low educational level 14% vs 8%, p = 0.042). *Conclusions.* Coping as a motivation for cannabis use is present in one out of four users and is a marker of social vulnerability, greater quantity of cannabis used and higher risk of problematic use. Patient-centered care together with preventive (emotional and social education) and clinical strategies (psychotherapy) can be useful for this population at higher risk.

Key Words: Patient-centered care; Cannabis; Motivations for cannabis use; Problematic cannabis use.

Resumen

Introducción. El cribado sistemático del consumo problemático de cannabis no incluye las motivaciones que llevan al consumo, aunque desde una perspectiva de atención centrada en la persona, este dato sea fundamental. El presente estudio explora las motivaciones de consumo de cannabis en adultos y su relación con el patrón de consumo y consumo problemático. *Método.* Consumidores adultos de cannabis (en los últimos 60 días) fueron reclutados en la provincia de Barcelona (n=468). Se pasó un cuestionario para explorar datos sociodemográficos, patrón de uso, la Cannabis Abuse Screening Test (CAST) y la motivación principal para el consumo. Los motivos de consumo se categorizaron a posteriori según la *Marijuana Motives Measures (MMM). S*e realizó un análisis descriptivo e inferencial para explorar la relación entre la motivación categorizada y variables sociodemográficas, patrón de consumo y puntuaciones de la CAST. *Resultados.* Consumir cannabis para mejorar las emociones positivas (35%), por costumbre (29%) y para afrontar emociones negativas (25 %) fueron las motivaciones más frecuentes. Respecto a otras motivaciones, el "afrontamiento" se relaciona con mayor cantidad consumida (4 vs 3 porros/día, p = 0,005), mayor probabilidad de tener un consumo problemático (77% vs 64%, p = 0,05), y mayor vulnerabilidad social (desempleo 56% vs 37%, p = 0,001; y bajo nivel de estudios (14% vs 8%, p = 0,042)). *Conclusiones.* El afrontamiento está presente en uno de cada cuatro usuarios de cannabis, es un marcador de vulnerabilidad social y de mayor cantidad de consumo de cannabis y probabilidad de consumo problemático. Una atención centrada en la persona junto con estrategias preventivas (educación emocional y social) y clínicas (psicoterapia) pueden ser de utilidad en esta población de mayor riesgo.

Palabras clave: Atención centrada en la persona; Cannabis; Motivación para el consumo; Consumo problemático de cánnabis.

Received: August 2018; Accepted: January 2019.

Send correspondence to:
Cristina Casajuana Kögel. C/ Villarroel 170, 08036 Barcelona (Spain).
E-mail: cristina.casajuana@gencat.cat.

Introduction

It is estimated that one in three Spanish people has used cannabis at some point during their life and that 2% of the population uses it daily (Observatorio Español de la Droga y las Toxicomanías, 2017). Over recent years, evidence of the risks and organic, psychological and social consequences associated with its use is increasingly robust. (López Pelayo, Miquel De Montagut, Casajuana Kögel & Balcells Oliveró, 2018; Volkow et al., 2016; World Health Organization, 2016). However, cannabis is probably the illicit drug whose image has improved most over recent years, with growing social acceptance and a fading perception of the risks related to its use (Okaneku, Vearrier, McKeever, LaSala & Greenberg, 2015). Given this trend, an analysis of possible changes in the reasons leading people to start using cannabis would be timely in order to improve approaches towards the associated problems.

At a preventive level, dissuasive measures influencing the accessibility of substances (price increases, vending restrictions, advertising bans) have been shown to be effective in reducing substance use (Anderson, Braddick, Reynolds & Gual, 2012; Meier et al., 2016; Mora, 2018). However, this type of public health measure is focused primarily on the substance involved and less on the individual's behavior. The problem of drug use would benefit from an approach including both angles: the most general - the substance itself - and the personal - knowing the motivations that lead people to put their health at risk (Anderson et al., 2017; Barrio & Gual, 2016).

In 2017, the scientific society of reference in Spain on drug-related issues, Socidrogalcohol, conducted a"Qualitative sociological study on the use of alcohol and cannabis among adolescents and young adults" (Estudio Sociológico cualitativo sobre el consumo de alcohol y cannabis entre adolescentes y jóvenes, Socidrogalcohol, 2017). This study showed what motivated Spanish adolescents and young adults from different autonomous regions to use cannabis. As discussed in this study, many young Spaniards initially use cannabis in order to seek a sense of belonging to the group and out of a sense of transgression. Later, however, their use can turn more towards managing negative emotions, such as dealing with everyday life situations and, therefore, as a way of avoiding negative effects and finding relief from discomfort (Baker, Piper, McCarthy, Majeskie & Fiore, 2004). In this stage, cannabis use can be confused with supposedly therapeutic use, as well as an excuse to alleviate the negative effects of not consuming (Lee, Derefinko, Davis, Milich & Lynam, 2017). At the same time, these motivations can be fed by phenomena such as tolerance, which requires increased doses to achieve the desired effects (Ramaekers et al., 2011). Alongside others, the Socidrogalcohol study highlights the importance of analyzing the motivations for consumption at an early age in order to better address cannabis use in our context from onset, and especially to study their relationship with problematic use. However, this national study involves people aged under 25 and does not offer information about older users in our context, whose use and motivations may have changed over the years.

In a clinical setting, the motivational approach also presents consistent scientific evidence on the treatment of substance use disorder (SUD), including cannabis (Chatters et al., 2016; K. Cooper, Chatters, Kaltenthaler & Wong, 2015). Indeed, the motivational interview in cases of cannabis use disorder has proved efficacious, with positive results achieved in one out of seven treated, and showing a moderate effect size for abstinence/reduced use (Hedge's g 0.26 CI 95% 0.10-0.43) (Lundahl, Kunz, Brownell, Tollefson & Burke, 2010; Walther, Gantner, Heinz & Majić, 2016). In another meta-analysis, the OR for abstinence was 1.99 (95% CI 0.81-4.86) and 3.22 for reduced use. (CI 95% 2.14-4.84) (Lundahl et al., 2013). In other words, receiving treatment with motivational interviewing doubled or even tripled the probability of success with respect to standard treatment. These data are comparable, for example, to the effectiveness of lithium carbonate or aripiprazole in treating bipolar mania (Yildiz, Vieta, Leucht & Baldessarini, 2011). The motivational interview aims to discover the reasons why the patient uses the substance, and as such relies on verbalization; patients need to express the reasons and motivations for using as well as quitting, and discuss any tools they might possess to achieve this. Other necessary principles are the existence of a spirit of collaboration (horizontal relationship between professional and patient), compassion (promoting the patient's well-being) and acceptance (creating an empathic climate, promoting autonomy and affirming the patient's values) (Miller & Rollnick, 2013). In an approach focused on the patient's motivations and scale of values, these play a crucial role as part of a therapeutic strategy.

For all these reasons, a theoretical framework which links patterns of cannabis use to motivations for use in adults in our context seems of great interest in order to better understand and address the different stages of consumption. The recent review by Cooper et al. on motivational models of substance use highlights a minimum of four motivations that vary with consumption *(heightening of positive feelings, coping, social cohesion and avoiding social rejection)* (Cooper, Kuntsche, Levitt, Barber & Wolf, 2015). Similarly, instruments such as the *Marijuana Motives Measure* (MMM) have been designed (Matalí Costa et al., 2018; Simons, Correia, Carey & Borsari, 1998), available in Spanish in an abbreviated version (Mezquita, Ruiz-Valero, Martínez-Gómez, Ibáñez & Ortet, 2019). This instrument proposes six categories of reasons for marijuana use (*promoting social cohesion, avoiding social rejection, increasing awareness and perception, routine, coping, heightening positive feelings*).

Recent studies have analyzed the relationship between specific motivations and the risk of problematic use (Buck-

ner, Walukevich, Zvolensky & Gallagher, 2017; Fox, Towe, Stephens, Walker & Roffman, 2011; Mezquita et al., 2019; Moitra, Christopher, Anderson & Stein, 2015), postulating its potential in forecasting how use may develop. However, the information on the relationship between motivations and problematic use in our context has been focused more on adolescents and less on adults, who have more heterogeneous contexts of use (Patrick, Bray & Berglund, 2016). Moreover, despite scientific evidence to warrant their involvement in the risks associated with cannabis use, motivations for consumption are currently not explored in systematic screening tools for high-risk and problematic users of cannabis. (López-Pelayo, Batalla, Balcells, Colom & Gual, 2015). Therefore, the relationship between the motivations among adults in our context to use cannabis and the patterns of use and problematic use is little explored at present.

The aim of this article is to describe the main motivation for the use of cannabis as reported by adults in a little studied cultural context such as the province of Barcelona, taking into account different environments of use (cannabis associations, universities, mental health outpatient clinics and leisure), and as a second step, to analyze its relationship with consumption patterns and the probability of problematic use. Based on the literature, our hypothesis is that coping motivations will correlate with more frequent and intense use and with a higher risk of problematic use.

Methodology

Sample

Between February 2015 and June 2016, cannabis users were recruited in four clinical and non-clinical environments in the province of Barcelona: university campuses, mental health outpatient clinics, leisure areas and cannabis associations. The selection criteria for participation were: 1) to have used cannabis in the previous 60 days; 2) to give consent for participation; and 3) to be at least 18 years old. Participants were excluded if: 1) they did not declare consent for participation; 2) presented cognitive impairment which would prevent them answering the questionnaire; and 3) presented linguistic barriers.

Recruitment and procedure

The volunteers were recruited on a convenience basis following a naturalistic approach. They were proactively approached in leisure spaces, cannabis associations and universities. In addition, health professionals in outpatient mental health centers referred patients after checking the selection criteria. Before starting the study, the interviewer informed the volunteers about the purpose of the study as well as to the anonymity and confidentiality of their data. In terms of participation, volunteers responded to a printed questionnaire administered by an interviewer, mostly in the context in which they had been approached.

Instruments

For this study, a questionnaire was designed, and as part of its preparation, questions previously used in similar contexts were reviewed (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2013; Delegación del Gobierno para Plan Nacional sobre Drogas, 2015; Villalbí, Suelves, Saltó & Cabezas, 2011). Questions related to the following variables were incorporated: 1) sociodemographic characteristics (sex, age, marital status, higher educational level, employment situation); 2) pattern and habits of cannabis use (frequency of use in the previous 30 days, frequency of use in the previous 12 months, number of joints smoked in the previous 30 days); 3) main motivation for cannabis use; 4) Cannabis Abuse Screening Test (CAST) (Legleye, Karila, Beck & Reynaud, 2007).

The CAST assesses potential problematic use by measuring the frequency of six events in the previous 12 months: 1) "Have you smoked cannabis before midday?", 2) "Have you smoked cannabis when you were alone?"; 3) "Have you had memory problems when you smoked cannabis?"; 4) "Have friends or family members told you that you should reduce or stop cannabis consumption?"; 5) "Have you tried to reduce or stop your cannabis use without succeeding?" and 6) "Have you had problems because of your cannabis use (argument, fight, accident, poor results at school, etc)?". All questions are answered using a scale which in its full version are equivalent to the following scores: "never"=0, "rarely"=1, "from time to time"=2, "fairly often"=3 and "very often"=4. CAST scores can range from 0 to 24 points, and have been linked to the probability of presenting problematic cannabis use as follows: low (≤ 3), moderate (4-6) and high (≥ 7) (Blankers et al., 2014).

To investigate the main motivation for cannabis use, it was decided to explore this variable by means of an open question ("What is your main reason for using cannabis?"). This was part of the heteroadministered questionnaire. For subsequent analysis, responses were categorized based on the categories proposed in the Marijuana Motives Measure (MMM) (Benschop et al., 2015, Simons et al., 1998), which classifies the motivations into six categories (translated into Spanish by Matalí Costa (Matalí Costa, 2015)): *Coping* – using cannabis to deal with negative feelings; *Enhancement* - to heighten positive feelings; *Social* - to improve social cohesion and support; *Conformity* - to avoid social rejection; *Expansion* - to expand awareness and perception; and *Routine* – out of habit or custom. The classification was carried out independently by two researchers (CC and CO). In the case of divergent encodings, the response was examined in order to agree on a single category. If the answer remained ambiguous or corresponded to more than one coding option, it was discarded (missing).

Analysis

First, a descriptive analysis was carried out to determine frequencies and percentages for all qualitative variables collected. For quantitative variables, distributions were explored and, as a second step, means or medians established, along with corresponding standard deviations or interquartile ranges (IQR). Next, possible differences between the variables collected (sociodemographic variables, consumption pattern, quantity consumed and CAST score) by main motivation were described and analyzed. For this, the chi square test was used with categorical variables, while the U Mann-Whitney test was performed with quantitative variables. In a subsequent analysis, we explored how the number of joints smoked per day varied according to the main motivation for use, employing an Omnibus analysis and a Poisson-based distribution analysis to do so. Statistical significance was considered at p values equal to or below 0.05. Statistical analyses were performed with the SPSS program (IBM®, version 19).

Ethical considerations

The study protocol was approved by the Ethics Committee of the Hospital Clínico de Barcelona (HCB / 2014/0770). It was not necessary to obtain written informed consent because participation was anonymous and refusal to give verbal consent was an exclusion criterion. Study procedures were prepared in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013).

Results

Description of the sample

The questionnaire was answered by 468 cannabis users. For 433 participants, the main motivation for use was encoded using the categories proposed in the MMM (92.5% of the answers). Three categories stood out: e*nhancement* (35%), r*outine* (29%) and *coping* (25%). The other three categories (*social cohesion*, c*onformity,* and *expanding awareness and perception*) accounted for 11% in total (Table 1). For the analysis, these three categories were grouped as "other".

Participants were mainly young adults (median age 27 years, IQR 14), mostly men (n = 331, 76%) and single (n = 323, 75%). At the time of the survey, more than half of the sample (n = 307, 71%) said they had completed at least advanced secondary studies and were working (n = 239, 55%). The majority of users (n = 324, 75%) reported having used cannabis on more than 20 days in the previous month. On average, participants said they smoked 3 joints per day (IQR 3.5). According to CAST scores, the probability of presenting problematic use of cannabis was low in 10% of the sample (N = 41), moderate in 23% (N = 100) and high in 67% (N = 290). More details are displayed in Table 1.

The relationship between sociodemographic variables and reasons for use

Table 2 shows how there are statistically significant differences in the various motivations to consume depending on age, educational, employment, frequency of use, number of joints smoked daily, and the likelihood of problematic use (according to CAST). As regards the other participants, those whose main motivation puts them in the "coping" group are unemployed or without income to a greater extent (56% vs 37%, X^2 = 13.949, p = 0.001) and have a lower level of completed education (14% vs. 8%, X^2 = 6.330, p = 0.042) (Table 2). These users also turned out to be older than those who claimed to use cannabis mainly for the other reasons (29 years of age (IQR 14) vs 26 (IQR 16), U = 17144.5, p = 0.033).

The relationship between patterns of use, problematic use and the main motivation to use cannabis

There was a statistically significant difference in the number of joints smoked daily depending on the main motivation for use (Table 2). Regarding the other motivations, users who said they were smoking for coping reasons consumed a greater number of daily joints (3 joints (IQR 3.5) versus 4 joints (IQR 4), U = 15917, p = 0.007). Similarly, the omnibus test suggested a change in this variable according to the main motivation for use (F = 3.784, p = 0.002). The subsequent Poisson distribution test showed that only the 'coping' motivation obtains a statistically different result (p = 0.006) and suggests that this motive would increase daily consumption by 1.06 joints (95% CI 1.02-1.11) (data not shown in the tables).

The likelihood of problematic use according to CAST scores was also statistically different depending on the main reason for consumption (Table 2). In contrast to other motivations, users who reported consuming for 'coping' reasons were less likely to be classified as having a low probability of problematic use (6% vs. 11%), and, on the other hand, were more likely to be classified as having a high probability of problematic use (64% vs 77%) (Table 2).

Discussion

This study describes the use of cannabis by adults in the province of Barcelona, focusing on the main motivation for cannabis consumption in order to understand its involvement in patterns of use and possible problematic use. Three motivations stand out in our context: "heightening positive feelings" (35%), "habit" (29%) and "coping" (25%). For more than two thirds of users, the main reason to use cannabis are habit and positive sensations, but we also find that for 25% of users cannabis is a vehicle to alleviate emotional discomfort. Likewise, using cannabis to deal with emotional distress is the main reason for use among those with more intense and problematic patterns of use.

Table 1. *Descriptive statistics of the main motivation for cannabis use, sociodemographic variables and consumption pattern.*

		Main motivation for cannabis use													
		Coping		Heightening positive feelings		Social		Avoiding rejection		Expanding awareness and perception		Habit		Total	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex	Men	81	75	122	80	18	78	5	100	15	75	90	72	331	76
	Women	27	25	30	20	5	22	0	0	5	25	35	28	102	24
	Total	*108*	*100*	*152*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*125*	*100*	*433*	*100*
Marital status	Single	73	68	119	78	19	83	5	100	11	55	96	77	323	75
	Partner or married	26	24	24	16	4	17	0	0	8	40	23	18	85	20
	Separated / divorced / widowed or other	9	8	9	6	0	0	0	0	1	5	6	5	25	6
	Total	*108*	*100*	*152*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*125*	*100*	*433*	*100*
Highest educational level attained	None or primary	15	14	10	7	0	0	0	0	0	0	16	13	41	9
	Secondary	79	73	110	72	16	70	4	80	13	65	85	68	307	71
	Tertiary	14	13	32	21	7	30	1	20	7	35	24	19	85	20
	Total	*108*	*100*	*152*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*125*	*100*	*433*	*100*
Employment situation	Working	43	40	91	60	15	65	4	80	14	70	72	58	239	55
	Permanent disability	5	5	1	1	0	0	0	0	0	0	7	6	13	3
	Without work or income	60	56	60	39	8	35	1	20	6	30	46	37	181	42
	Total	*108*	*100*	*152*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*125*	*100*	*433*	*100*
Frequency of consumption in the last month	Fewer than 10 days	16	15	23	15	11	48	0	0	1	5	15	12	66	15
	Between 11 and 20 days	9	8	16	11	3	13	0	0	4	20	10	8	42	10
	More than 20 days	82	77	113	74	9	39	5	100	15	75	100	80	324	75
	Total	*107*	*100*	*152*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*125*	*100*	*432*	*100*
Problematic use according to CAST[a]	Low risk	7	6	19	13	6	26	0	0	3	15	6	5	41	10
	Moderate risk	18	17	39	26	11	48	0	0	5	25	27	22	100	23
	High risk	83	77	93	62	6	26	5	100	12	60	91	73	290	67
	Total	*108*	*100*	*151*	*100*	*23*	*100*	*5*	*100*	*20*	*100*	*124*	*100*	*431*	*100*
Age *(median and IQR[b])*		29	16	26	12	28	12	21	5	30	13	29	17	27	15
Joints smoked per day in the last month *(median and IQR[b])*		4.00	4.00	3.00	3.00	2.00	1.50	4.00	6.00	2.00	1.75	3.00	4.00	3.00	3.50

Note. [a] CAST: Cannabis Abuse Screening Test; [b] IQR: Interquartile Range; Missing data correspond to omissions.

In a framework of person- rather than substance-centered care, the motivation for use is an important variable that could improve the approach to cannabis use at the clinical and public health levels in order to minimize negative consequences and the most severe cases deriving from problematic cannabis use.

The relationship between motivations for cannabis use and the probability of presenting problematic use

In our sample, one out of every four users said they used cannabis mainly to cope with discomfort ("coping"). This category was associated with more intense consumption and a higher risk of problematic use. It is, therefore, the motivation for use with the greatest impact on health, and this is consistent with other studies such as that of Moitra et al. (Moitra et al., 2015), which found that US users aged 18 to 25 years who used cannabis to deal with discomfort had a 1.85 times higher probability of being diagnosed with cannabis use disorder, according to DSM-5, compared to those who did so for other reasons (OR = 1.85, 95% CI 1.31, 2.62, p <.01).

Other studies also link coping-related use with increased problematic use of cannabis in adults (Bujarski, Norberg & Copeland, 2012; Johnson, Mullin, Marshall, Bonn-Miller & Zvolensky, 2010) and highlight the modulating role that this motivation can have in users with greater anxiety and

Table 2. *Inferential analysis of the main motivations expressed for cannabis use (dependent variable) and independent qualitative variables (sociodemographic characteristics, consumption pattern and probability of problematic use).*

		Coping				Heightening positive feelings				Habit				Other motivations			
		No		Yes		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Frequency of use in the last month	Fewer than 10 days	50	15	16	15	43	15	23	15	51	17	15	12	54	14	12	25
	Between 11 and 20 days	33	10	9	8	26	9	16	11	32	10	10	8	35	9	7	15
	More than 20 days	242	74	82	77	211	75	113	74	224	73	100	80	295	77	29	60
	Total	325	100	107	100	280	100	152	100	307	100	125	100	384	100	48	100
	X^2	0.312				0.173				2.360				6.185			
	p value	0.856				0.917				0.307				0.045			
Highest educational level attained	None or primary	26	8	15	14	31	11	10	7	25	8	16	13	41	11	0	0
	Secondary studies	228	70	79	73	197	70	110	72	222	72	85	68	274	71	33	69
	Higher education	71	22	14	13	53	19	32	21	61	20	24	19	70	18	15	31
	Total	325	100	108	100	281	100	152	100	308	100	125	100	385	100	48	100
	X^2	6.330				2.378				2.285				8.860			
	p value	0.042				0.304				0.319				0.012			
Employment situation	Working	196	60	43	40	148	53	91	60	167	54	72	58	206	54	33	69
	Permanent disability	8	2	5	5	12	4	1	1	6	2	7	6	13	3	0	0
	Without work or income	121	37	60	56	121	43	60	39	135	44	46	37	166	43	15	31
	Total	325	100	108	100	281	100	152	100	308	100	125	100	385	100	48	100
	X^2	13.949				5.518				5.185				4.855			
	p value	0.001				0.063				0.075				0.088			
Problematic use according to the Cannabis Abuse Screening Test	Low risk	34	11	7	6	22	8	19	13	35	11	6	5	32	8	9	19
	Moderate risk	82	25	18	17	61	22	39	26	73	24	27	22	84	22	16	33
	High risk	207	64	83	77	197	70	93	62	199	65	91	73	267	70	23	48
	Total	323	100	108	100	280	100	151	100	307	100	124	100	383	100	48	100
	X^2	6.005				4.114				5.114				10.246			
	p value	0.050				0.128				0.078				0.006			

Note. Missing data correspond to omissions.

distress (Ecker & Buckner, 2014). Therefore, this motivation for use would not only appear to be a predictor of problematic use (Fox et al., 2011; Patrick et al., 2016) but could also indicate a greater degree of complexity in addressing consumption in specific cannabis users (Buckner et al., 2017).

Our results also show that users who consume mainly in order to cope are more often unemployed and have a lower educational level, which would in turn increase social vulnerability among these users. For this reason, it is relevant to identify these users at an early stage, when a motivational approach can have a great impact on the course of their lives and on their personal development. Studies like those of Matalí Costa show that even at early stages such as adolescence, coping-related use can be an indicator of a faster progression towards regular and more problematic use (Matalí Costa, 2015). This circumstance, added to the fact that cannabis use in adolescence produces greater and potentially irreversible damage to the organism, underlines the importance of early identification and intervention (Hall & Degenhardt, 2014; Patton et al., 2007)

Weaknesses and strengths

Among the potential weaknesses of the study, it should be noted that motivations were not assessed with a structured instrument which also allowed several motivations to be collected simultaneously. At the time of the design of this study, the MMM in Spanish had not yet been validated, so an open question was chosen to gather the main motivation. Although it does not allow for the exploration of motivation from a multidimensional point of view, this is also a strength in the sense that through an open question, the information obtained was less conditioned and more honest, thereby providing a better reflection of a less frequently document-

Table 3. *Inferential analysis of the main motivations expressed for cannabis use (dependent variable) and independent quantitative variables (age and number of joints smoked per day).*

	Coping		Heightening positive feelings		Habit		Other	
	No	Yes	No	Yes	No	Yes	No	Yes
Number of joints per day								
Median	3.00	4.00	3.00	3.00	3.00	3.00	3.00	2.00
IQR	3.50	4.00	3.50	3.00	3.25	4.00	3.50	2.50
Static U	15917		24042		21174		13514	
p value	0.007		0.932		0.728		0.002	
Age								
Median	26	29	28	26	26	29	27	25
IQR	14	16	15	12	14	17	15	10
Static U	17144.5		21929		19528.5		14924	
p value	0.033		0.060		0.074		0.040	

ed variable. To minimize potential interobserver variability, the assessment was carried out by two independent observers and in case of disagreement or ambiguity (less than 10% of the responses) the answers were discarded.

A further possible limitation of the study is that the assessment of cannabis use frequency was not precise enough to determine irregular use, although consumption was explored in the previous 30 days and the previous 12 months, thus matching the questions of other questionnaires applied with similar aims and in similar contexts (Bashford, Flett & Copeland, 2010; Delegación del Gobierno para el Plan Nacional sobre Drogas, 2009). The type of cross-sectional study used is another potential limitation, given that this design prevents the development of the individual's motivations and patterns of use, as well as the temporal relationship between them, from being observed. Finally, this study is part of a project which priority was to understand patterns of use among adults in our context. Therefore, both the procedure and the assessment instruments of this ad-hoc designed study may be more appropriate if the design is specifically aimed at analyzing the motivations for cannabis use. Due to the exploratory nature of the study, our results need to be confirmed with longitudinal studies designed for this purpose.

Strengths include the considerable sample size (> 450 participants), a wide variety of user profiles (recruited in four very different areas), a comprehensive assessment of cannabis use patterns and the likelihood of problematic use according to the validated CAST scale.

Implications of results

From a clinical perspective, our results show that exploring the motivations for cannabis use should be prioritized, especially in the case of coping motivation, since this is a possible indicator for early identification of users with a greater likelihood of suffering problematic use. At a clinical level, early identification of such users could improve their clinical treatment. Motivational interviewing has proven useful in the management of patients using cannabis (Blevins, Banes, Stephens, Walker & Roffman, 2016; Bonsack et al., 2008), with an exploration of the reasons for use playing a key role in this type of approach. The reasons for use, together with possible reasons for quitting, allow the exploration of ambivalence and the application of different strategies to increase the likelihood of change by helping to reduce consumption and its negative consequences. Also, exploring whether cannabis plays a role in alleviating discomfort could help in implementing more effective coping strategies. This user profile could benefit from strategies involving the management of emotions and coping with life events as a theoretical framework, for example, mindfulness (Garland & Howard, 2018; Li, Howard, Garland, McGovern & Lazar, 2017; Witkiewitz et al., 2014) or group therapy (Korshak & Delboy, 2013).

In terms of public health, it is essential to continue working on drug policies governing the accessibility of substances (probably aiming to reduce the number of users who consume out of habit), analogous to what has been done with tobacco, or diversify young people's leisure possibilities (potentially diminishing the number of users who consume to heighten positive emotions). However, our results suggest that such strategies will have less of an effect on those users with a more intense and problematic consumption pattern, mainly motivated by the desire to cope with discomfort. Therefore, an approach that includes emotional management training (*social and emotional learning programs*) as a preventive strategy could be useful for these patients (Hernández-Serrano, Espada & Guillén-Riquelme, 2016; Jones, Greenberg & Crowley, 2015; Payton et al., 2000; Socidrogalcohol, 2017).

Conclusion

The use of cannabis as an "escape route" leads to greater risks to health and greater social vulnerability. A motivational focus centered on the person is essential in particular to address those users for whom cannabis is an aid in coping with discomfort. It must be accompanied by preventive strategies (emotional management training) and therapeutic strategies (for example group therapy or mindfulness).

Finally, when patients report that their cannabis use is motivated by alleviating some type of distress it should set off alarms bells and guide us to a more detailed assessment of their consumption pattern. And inversely, those patients turning to professional help with intense or problematic consumption should be explored to determine whether cannabis plays a role in alleviating distress and should thus be helped with more effective coping strategies.

Contributions

Cristina Casajuana Kögel, Hugo López Pelayo, María Mercedes Balcells Oliveró and Antoni Gual Solé designed the study. Cristina Casajuana Kögel wrote the first version of the manuscript. All other authors contributed to the editing and final revision of the manuscript. All authors approved the final document.

Financing

This study was funded by a Spanish subsidy of the Plan Nacional sobre Drogas, Ministerio de Sanidad y Consumo (PNSD 2013I082, Antoni Gual Solé). Hugo López Pelayo is being funded by the Ministerio de Economía y Competividad; Instituto de Salud Carlos III through a contract, 'Rio Hortega' (CM17/00123, Dr. López-Pelayo), FEDER.

The conclusions of the article are the sole responsibility of the authors and do not necessarily represent the official points of view of the institutions, which played no part in the study design, collection, analysis, and interpretation of the data, nor in the writing of the article, nor in the decision to submit the article for publication.

Conflict of interests

Hugo López Pelayo has received fees and travel grants from Lundbeck, Exeltis and Otsuka. María Mercedes Balcells Oliveró has received fees from Lundbeck. Antoni Gual Solé has received fees, research grants and travel grants from Lundbeck, Janssen, Pfizer, Lilly, Abbvie DyA Pharma and Servier. The aforementioned fees did not influence this article. The other authors declare that they have no potential conflicts of interest.

Thanks

We wish to thank María Estrada, Otger Amatller, Sílvia Gómez and David Tinoco for their participation as interviewers. We would also like to extend our gratitude to the psychiatrists Dr. Blanch, Dr. García-Rizo, Dr. Garrido and Dr. Goikolea and for the support of the Fundació Clínic per la Recerca Biomèdica, el Institut d'Investigacions Biomèdiques August Pi i Sunyer, la Agència de Salut Pública de Catalunya-Generalitat de Catalunya, Energy Control and la Fundació Salut i Comunitat i a CERCA Programme / Generalitat de Catalunya.

Bibliography

Anderson, P., Berridge, V., Conrod, P., Dudley, R., Hellman, M., Lachenmeier, D., … Gual, A. (2017). Reframing the science and policy of nicotine, illegal drugs and alcohol – conclusions of the ALICE RAP Project. *F1000Research*, *6*, 289. doi:10.12688/f1000research.10860.1.

Anderson, P., Braddick, F., Reynolds, J. & Gual, A. (2012). *Alcohol policy in Europe - Evidence from the AMPHORA*. Retrieved at http://amphoraproject.net/view.php?id_cont=45.

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R. & Fiore, M. C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychological Review*, *111*, 33–51. doi:10.1037/0033-295X.111.1.33.

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.

Bashford, J., Flett, R. & Copeland, J. (2010). The Cannabis Use Problems Identification Test (CUPIT): Development, reliability, concurrent and predictive validity among adolescents and adults. *Addiction*, *105*, 615–625. doi:10.1111/j.1360-0443.2009.02859.x.

Benschop, A., Liebregts, N., van der Pol, P., Schaap, R., Buisman, R., van Laar, M., … Korf, D. J. (2015). Reliability and validity of the Marijuana Motives Measure among young adult frequent cannabis users and associations with cannabis dependence. *Addictive Behaviors*, *40*, 91–95. doi:10.1016/j.addbeh.2014.09.003.

Blankers, M., Frijns, T., Belackova, V., Rossi, C., Svensson, B., Trautmann, F. & van Laar, M. (2014). Predicting Cannabis Abuse Screening Test (CAST) Scores: A recursive partitioning analysis using survey data from Czech Republic, Italy, the Netherlands and Sweden. *PLoS ONE*, *9*, e108298. doi:10.1371/journal.pone.0108298.

Blevins, C. E., Banes, K. E., Stephens, R. S., Walker, D. D. & Roffman, R. A. (2016). Change in motives among frequent cannabis-using adolescents: Predicting treatment

outcomes. *Drug and Alcohol Dependence, 167*, 175–181. doi:10.1016/j.drugalcdep.2016.08.018.

Bonsack, C., Montagrin, Y., Gibellini, S., Favrod, J., Besson, J. & Conus, P. (2008). Practice of a motivational intervention for cannabis users with psychosis. *Schweizer Archiv fur Neurologie und Psychiatrie, 159*, 378–385.

Buckner, J. D., Walukevich, K. A., Zvolensky, M. J. & Gallagher, M. W. (2017). Emotion regulation and coping motives serially affect cannabis cessation problems among dually diagnosed outpatients. *Psychology of Addictive Behaviors, 31*, 839–845. doi:10.1037/adb0000310.

Bujarski, S. J., Norberg, M. M. & Copeland, J. (2012). The association between distress tolerance and cannabis use-related problems: The mediating and moderating roles of coping motives and gender. *Addictive Behaviors, 37*, 1181–1184. doi:10.1016/j.addbeh.2012.05.014.

Chatters, R., Cooper, K., Day, E., Knight, M., Lagundoye, O., Wong, R. & Kaltenthaler, E. (2016). Psychological and psychosocial interventions for cannabis cessation in adults: A systematic review. *Addiction Research & Theory, 24*, 93–110. doi:10.3109/16066359.2015.1073719.

Cooper, K., Chatters, R., Kaltenthaler, E. & Wong, R. (2015). Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review short report. *Health Technology Assessment, 19*, 1–130. doi:10.3310/hta19560.

Cooper, M. L., Kuntsche, E., Levitt, A., Barber, L. L. & Wolf, S. (2015). *Motivational models of substance use.* (K. J. Sher, Ed.) (Vol. 1). Oxford University Press. doi:10.1093/oxfordhb/9780199381678.013.017.

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2009). *Consumo problemático de cánnabis en estudiantes españoles de 14-18 años: Validación de escalas.* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved at http://www.pnsd.msssi.gob.es/profesionales/publicaciones/catalogo/bibliotecaDigital/publicaciones/pdf/ConsProblematico_cannabis.pdf.

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2013). *Encuesta estatal sobre el uso de drogas en enseñanzas secundarias (ESTUDES) 2012-2013, España.* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved at http://www.pnsd.msssi.gob.es/noticiasEventos/dossier/pdf/ESTUDES2012_2013.pdf.

Delegación del Gobierno para Plan Nacional sobre Drogas. (2015). *Encuesta sobre alcohol y drogas en España (EDADES) 2013/14.* Madrid: Ministerio de Sanidad Sevicios Sociales e Igualdad. Retrieved at http://www.pnsd.msssi.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/EDADES2013.pdf.

Ecker, A. H. & Buckner, J. D. (2014). Cannabis use behaviors and social anxiety: The roles of perceived descriptive and injunctive social norms. *Journal of Studies on Alcohol and Drugs, 75*, 74–82.

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

Garland, E. L. & Howard, M. O. (2018). Mindfulness-based treatment of addiction: current state of the field and envisioning the next wave of research. *Addiction Science & Clinical Practice, 13*, 14. doi:10.1186/s13722-018-0115-3.

Hall, W. & Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. *Drug Testing and Analysis, 6*, 39–45. doi:10.1002/dta.1506.

Hernández-Serrano, O., Espada, J. P. & Guillén-Riquelme, A. (2016). Relación entre conducta prosocial, resolución de problemas y consumo de drogas en adolescentes. *Anales de Psicología, 32*, 609-616. doi:10.6018/analesps.32.2.204941.

Johnson, K., Mullin, J. L., Marshall, E. C., Bonn-Miller, M. O. & Zvolensky, M. (2010). Exploring the mediational role of coping motives for marijuana use in terms of the relation between anxiety sensitivity and marijuana dependence. *American Journal on Addictions, 19*, 277–282. doi:10.1111/j.1521-0391.2010.00041.x.

Jones, D. E., Greenberg, M. & Crowley, M. (2015). Early social-emotional functioning and public health: The relationship between kindergarten social competence and future wellness. *American Journal of Public Health, 105*, 2283–2290. doi:10.2105/AJPH.2015.302630.

Korshak, S.J. & Delboy, S. (2013). Complementary modalities: Twelve-step programs and group psychotherapy for addiction treatment. *Group, 37*, 273-294. doi:10.13186/group.37.4.0273.

Lee, C. A., Derefinko, K. J., Davis, H. A., Milich, R. & Lynam, D. R. (2017). Cross-lagged relations between motives and substance use: Can use strengthen your motivation over time? *Drug and Alcohol Dependence, 178*, 544–550. doi:10.1016/j.drugalcdep.2017.05.027.

Legleye, S., Karila, L., Beck, F. & Reynaud, M. (2007). Validation of the CAST, a general population Cannabis Abuse Screening Test. *Journal of Substance Use, 12*, 233–242. doi:10.1080/14659890701476532.

Li, W., Howard, M. O., Garland, E. L., McGovern, P. & Lazar, M. (2017). Mindfulness treatment for substance misuse: A systematic review and meta-analysis. *Journal of Substance Abuse Treatment, 75*, 62–96. doi:10.1016/j.jsat.2017.01.008.

López-Pelayo, H., Batalla, A., Balcells, M. M., Colom, J. & Gual, A. (2015). Assessment of cannabis use disorders: A systematic review of screening and diagnostic instruments. *Psychological Medicine, 45*, 1121–1133. doi:10.1017/S0033291714002463.

López Pelayo, H., Miquel De Montagut, L., Casajuana Kögel, C. & Balcells Oliveró, M. (2018). Post-truth Cannabis use: Back to evidence-based medicine. *Adicciones, 30*, 237-242. doi:10.20882/adicciones.1095.

Lundahl, B. W., Kunz, C., Brownell, C., Tollefson, D. & Burke, B. L. (2010). A meta-analysis of motivational interviewing: Twenty-five years of empirical studies. *Research on Social Work Practice, 20*, 137–160. doi:10.1177/1049731509347850.

Lundahl, B. W., Moleni, T., Burke, B. L., Butters, R., Tollefson, D., Butler, C. & Rollnick, S. (2013). Motivational interviewing in medical care settings: A systematic review and meta-analysis of randomized controlled trials. *Patient Education and Counseling, 93*, 157–168. doi:10.1016/j.pec.2013.07.012.

Matalí Costa, J. L. (2015). *Motius de consum de cànnabis dels adolescents amb trastorn dual: relació amb variables clíniques i conseqüències acadèmiques*. Universitat Autònoma de Barcelona. Retrieved at http://www.tesisenred.net/bitstream/handle/10803/321107/jlmc1de1.pdf?sequence=1.

Matalí Costa, J., Simons, J., Pardo, M., Lleras, M., Pérez, A. & Andión, O. (2018). Spanish version validation of the Marihuana Motives Measure in a drug-consuming adolescent sample. *Adicciones, 30*, 282–291. doi:10.20882/adicciones.947.

Meier, P. S., Holmes, J., Angus, C., Ally, A. K., Meng, Y. & Brennan, A. (2016). Estimated effects of different alcohol taxation and price policies on health inequalities: A mathematical modelling study. *PLoS Medicine, 13*, e1001963. doi:10.1371/journal.pmed.1001963.

Mezquita, L., Ruiz-Valero, L., Martínez-Gómez, N., Ibáñez, M. I. & Ortet, G. (2019). Development and Validation of the Marijuana Motives Measure Short Form (MMM-SF). *Adicciones, 31,* 106-116. doi:10.20882/adicciones.979.

Miller, W. R. & Rollnick, S. (2013). *Motivational interviewing : helping people change*. Guilford Press. Retrieved at https://www.guilford.com/books/Motivational-Interviewing/Miller-Rollnick/9781609182274.

Moitra, E., Christopher, P. P., Anderson, B. J. & Stein, M. D. (2015). Coping-motivated marijuana use correlates with DSM-5 cannabis use disorder and psychological distress among emerging adults. *Psychology of Addictive Behaviors, 29*, 627–632. doi:10.1037/adb0000083.

Mora, T. (2018). Acerca de la imposición sobre bebidas alcohólicas en España. *Gaceta Sanitaria, 32*, 176–180. doi:10.1016/j.gaceta.2017.10.017.

Observatorio Español de la Droga y las Toxicomanias. (2017). *INFORME 2017: Alcohol, Tabaco y Drogas ilegales en España. Ministerio de Sanidad y Servicios Sociales.*

Okaneku, J., Vearrier, D., McKeever, R. G., LaSala, G. S. & Greenberg, M. I. (2015). Change in perceived risk associated with marijuana use in the United States from 2002 to 2012. *Clinical Toxicology, 53*, 151–155. doi:10.3109/15563650.2015.1004581.

Patrick, M. E., Bray, B. C. & Berglund, P. A. (2016). Reasons for marijuana use among young adults and long-term associations with marijuana use and problems. *Journal of Studies on Alcohol and Drugs, 77*, 881-888. doi:10.15288/jsad.2016.77.881.

Patton, G. C., Coffey, C., Lynskey, M. T., Reid, S., Hemphill, S., Carlin, J. B. & Hall, W. (2007). Trajectories of adolescent alcohol and cannabis use into young adulthood. *Addiction, 102*, 607–615. doi:10.1111/j.1360-0443.2006.01728.x.

Payton, J. W., Wardlaw, D. M., Graczyk, P. A., Bloodworth, M. R., Tompsett, C. J. & Weissberg, R. P. (2000). Social and emotional learning: A framework for promoting mental health and reducing risk behavior in children and youth. *Journal of School Health, 70,* 179-185. doi:10.1111/j.1746-1561.2000.tb06468.x.

Ramaekers, J. G., Theunissen, E. L., de Brouwer, M., Toennes, S. W., Moeller, M. R. & Kauert, G. (2011). Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. *Psychopharmacology, 214*, 391–401. doi:10.1007/s00213-010-2042-1.

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.

Socidrogalcohol. (2017). *Estudio sociológico cualitativo sobre el consumo de alcohol y cannabis entre adolescentes y jóvenes*. Retrieved at http://www.socidrogalcohol.org/phocadownload/Publicaciones/manuales-guias/estudiosociologico_cannabis_alcohol_def.pdf.

Villalbí, J. R., Suelves, J. M., Saltó, E. & Cabezas, C. (2011). Valoración de las encuestas a adolescentes sobre consumo de tabaco, alcohol y cannabis en España. *Adicciones, 23*, 11–16.

Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., … Baler, R. (2016). Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. *JAMA Psychiatry, 73*, 292-297. doi:10.1001/jamapsychiatry.2015.3278.

Walther, L., Gantner, A., Heinz, A. & Majić, T. (2016). Evidence-based treatment options in cannabis dependency. *Deutsches Arzteblatt International, 113*, 653–659. doi:10.3238/arztebl.2016.0653.

Witkiewitz, K., Bowen, S., Harrop, E. N., Douglas, H., Enkema, M. & Sedgwick, C. (2014). Mindfulness-based treatment to prevent addictive behavior relapse: Theoretical models and hypothesized mechanisms of change. *Substance Use and Misuse, 49*, 513–524. doi:10.3109/10826084.2014.891845.

World Health Organization. (2016). *The health and social effects of nonmedical cannabis use. WHO*. Geneva: World Health Organization. Retrieved at http://who.int/substance_abuse/publications/msbcannabis.pdf?ua=1.

World Medical Association Declaration of Helsinki. (2013). Ethical principles for medical research involving human

subjects. *The Journal of the American Medical Association, 20,* 2191–2194.

Yildiz, A., Vieta, E., Leucht, S. & Baldessarini, R. J. (2011). Efficacy of antimanic treatments: Meta-analysis of randomized, controlled trials. *Neuropsychopharmacology, 36,* 375–389. doi:10.1038/npp.2010.192.

Epidemiology of acute poisoning by substances of abuse in the Emergency Department. Descriptive study in District IV of Asturias

Epidemiología de las intoxicaciones agudas por sustancias de abuso en Urgencias. Estudio descriptivo en el área IV de Asturias

Ana Fernández-Ibáñez*, Rodrigo Ugalde-Herrá**, José Ángel Rodriguez-Getino*, Juan Bautista Garcia-Casas*, Jorge Cipriano Diaz-Suarez*.

* Faculty of Medicine. University of Oviedo, Oviedo. Spain.
** Hospital Universitario Central de Asturias, Oviedo. Spain.

Abstract

The incidence of acute poisonings has increased in recent years and constitutes approximately 2% of the services provided by the Emergency Department currently.

The objective of this study is to describe the frequency and characteristics of the intoxications treated at the Central University Hospital of Asturias during 2015 from biochemical-analytical, epidemiological and medical-legal perspectives. We conducted a retrospective study and a descriptive analysis of the clinical and sociodemographic variables included in the acute intoxication (AI) protocol at the national level. This hospital treated 2,478 cases of acute poisoning, representing 2.3% of the emergencies treated and corresponding to an incidence of 764 cases/100,000 inhabitants/year with an age ranging from under 1 year to over 80 years. The average age of the patients was 43.6 (*SD* = 16.6) years. Of these patients, 59.4% were males with an average age of 44 (*SD* = 16.8) years, and women represented 43.1% with an average age of 42.8 (*SD* = 16.5) years. These intoxications have a frequency of 47.2% during the weekend, while 37.4% occur between June and September. Acute voluntary intoxication is the most frequent intentionality, corresponding to 83.2% of the cases. We must point out that the medical records register 16.8% of the cases as suicide attempts. Ethanol and benzodiazepines are the most commonly-used toxics. These intoxications are treated in the Emergency Department without requiring hospitalization and have a very low mortality rate.

Keywords: Acute intoxication; Epidemiology; Toxicology; Suicide attempt; Alcohol intoxication; Drug overdose.

Resumen

La incidencia de las intoxicaciones agudas ha aumentado en los últimos años, y actualmente constituye aproximadamente el 2% de las atenciones sanitarias llevadas a cabo por los Servicios de Urgencias.

El objetivo de este estudio es describir la frecuencia y características de las intoxicaciones atendidas en el Hospital Universitario Central de Asturias durante el año 2015 desde la perspectiva bioquímica-analítica, epidemiológica y médico-legal. Se realizó un estudio retrospectivo y un análisis descriptivo de las variables clínicas y sociodemográficas incluidas en el protocolo de intoxicación aguda a nivel nacional. Este hospital atendió 2478 casos de intoxicaciones agudas representando el 2,3% de las urgencias atendidas y que corresponde a una incidencia de 764 casos/100000 habitantes/año con un rango de edad de menores de 1 año a mayores de 80 años. La edad media de los pacientes atendidos fue de 43,6 (*DE* = 16,6) años. El 59,4% de los pacientes eran varones con una edad media de 44 (*DE* = 16,8) años, las mujeres representaban el 43,1% y su edad media era de 42,8 (*DE* = 16,5) años. El 47,2% de estas intoxicaciones ocurren durante el fin de semana y el 37,4% se dan entre junio y septiembre. La intencionalidad más frecuente es la intoxicación aguda voluntaria correspondiente al 83,2% de los casos. Cabe destacar que el 16,8% de los casos están referenciados en su historia clínica como intentos de suicidio. Los tóxicos más empleados son el etanol y las benzodiacepinas. Estas intoxicaciones son resueltas en el Servicio de Urgencias sin requerir ingreso hospitalario y poseen una tasa de mortalidad muy baja.

Palabras clave: Intoxicación aguda; Epidemiología; Toxicología; Intento suicidio; Intoxicación medicamentosa; Intoxicación alcohólica; Intoxicación por drogas abuso.

Received: September 2018; Accepted: June 2019.

Send correspondence to:
Ana Fernández Ibáñez. Faculty of Medicine. University of Oviedo. Av. Julián Clavería, s/n. 33006 Oviedo, Asturias.
E-mail: anafi16@hotmail.com.

Introduction

Intoxications are as ancient as humankind, and have since early days been present in the daily lives of people conditioned by their lifestyles, jobs, and leisure and recreational activities. Currently, the acquisition of these new toxic substances usually has a direct relationship with greater access to consumer goods (da Silva Moreira et al., 2010). Technology also fosters the emergence of toxic, synthetic, illegal substances of increasing purity that enable generating and promoting pathological consumption in society. In recent decades, an increase in the number of acute intoxications (AI) in Spain constitutes a potentially serious health problem (de Miguel-Bouzas et al., 2012).

These AI not only have medical implications in requiring health assistance, but also a series of economic, sociocultural, demographic, psychological and legal problems. Therefore, resolving them becomes increasingly complex and the social problem entails large-scale repercussions (Caballero & Dorado, 1980; de la Fuente et al., 2006).

In this study on intoxications, it is important to know which toxics are involved, together with their specific clinical characteristics and antidotes or treatments (Caballero, Dorado & Alonso, 1981). These premises may serve as the basis for prevention programs and professional training and to provide both Hospital and Primary Care services with diagnostic and therapeutic supports for correctly implementing their assistance-related functions (Pastó Cardona, Martorell Puigserver, Mercadal Orfila, Machí Ribes & Jódar Massanès, 2007).

As we have mentioned above, AI represent a widespread social phenomenon themselves, given that the behaviour of toxic substance abusers causes diverse problems for the general population. Therefore, studies are necessary to define their epidemiology (Caballero, Gutiérrez & Dorado, 1987).

The design and methodology of epidemiological studies on AI published in the 80s and 90s worldwide were vastly different. As a result, it was practically impossible to compare their results or perform an evolutionary analysis (Camí, Frati & Martín, 1980; Duce Tello et al., 1998).

This trend has changed over recent decades. Multicentre studies have been implemented, including SEMESTOX and HISPATOX, two national studies carried out between 2003-2008, with the participation of the hospital Emergency Departments of different Autonomous Communities. This generated a global epidemiological vision of this pathology on a countrywide scale (Burillo-Putze et al., 2003; Burillo-Putze et al., 2008).

In addition to the characteristics and incidence of AI, it is also interesting to detect their evolution over time. To this end, some health departments have implemented a time series of epidemiological surveillance of AI (VEIA), updated regularly for validity purposes (Caballero Vallés et al., 2008; Dorado et al., 1992; Dorado, Martín, Sabugal & Caballero, 1996).

Most of the studies reviewed are from hospital Emergency Departments which is where these patients receive health assistance and treatment initially, although the first studies on AI within the hospital setting were carried out in Intensive Care units using treatment records (Amigo-Tadín, Nogué-Xarau & Miró-Andreu, 2010; Duce Tello et al., 1998; Henderson, Wright & Pond, 1993; Medina, Fuentes, Suárez, Arranz & Ochoa, 2008).

Shifting our focus to a more local scale, the Principality of Asturias has published a few isolated articles (Barraca de Ramos et al., 1991; González-Fernández & Alonso-Fernández, 2009; Rodríguez Getino & Hinojal Fonseca, 1994) that helped to reveal this Community's trend in terms of intoxications a few years ago, wherefore our goal is to study and compare updated results to the extent possible.

It is useful to explain that in AI, there usually exists an almost linear relationship between exposure to a substance, the analysis values detected in the biological samples and the emergence of symptoms and signs of illness (Borrell, et al., 2001; Carpintero Escudero et al., 2000).

The purpose of this study is to detect the frequency of AI treated in the Emergency Department of a tertiary hospital in Spain to determine their analytical and socioepidemiological characteristics and medical-legal repercussions.

Methods and materials

This descriptive retrospective study was performed in the Medical Laboratory of the Central University Hospital of Asturias, a tertiary centre that is a benchmark in this autonomous region, with 1,039 hospital beds and providing coverage to the 324,218 inhabitants of Health District IV.

This study data is based on a review of the results of the analyses carried out at the Medical Laboratory with the laboratory software (GestLab) between January 1 and December 31, 2015 to identify those patients whose analytical values of ethanol or substances of abuse exceeded the reference limit for AI. This diagnosis encompasses exposure to the toxic, together with the patient's clinical symptoms and/or analytical confirmation through a toxicology study (quantification of ethanol in blood and/or detection of substances in urine). Emergency Department medical staff request these analyses when doctors, at their discretion, consider complimentary tests necessary.

The reference limits are defined specifically for each substance. Ethanol is determined via an automated enzymatic technique, yielding a quantitative result that considers AI as of 10 mg/dL, although the initial clinical symptoms are noticeable with 40-50 mg/dL. Substances of abuse are those drugs that have a qualitative analysis only: a dichotomous positive or negative result is possible with a lateral flow immunochromatographic assay. A positive result means that the specific cut-off point for a given substance has been exceeded. In other words, the drug's concentration surpasses that value (Table 1).

Table 1. *Cut-off values of the substances of abuse detected in the screening.*

Substance of abuse	Cut-off values
Amphetamine (AMP)	1000 ng/mL
Methamphetamine (MET)	1000 ng/mL
Barbiturate (BAR)	300 ng/mL
Methadone (MTD)	300 ng/mL
Cocaine (COC)	300 ng/mL
Ecstasy (MDMA)	500 ng/mL
Tricyclic antidepressants (TAC)	1000 ng/mL
Benzodiazepines (BZO)	300 ng/mL
Cannabis (THC)	50 ng/mL
Opioides (MOP)	300 ng/mL

Note. *Cut-off is the drug concentration value, above which the result is positive and when detection in the urine is possible with the corresponding analysis, in this case lateral flow immunochromatographic assay.

We performed a case-by-case review of the electronic medical records of the selected patients and completed a sheet to anonymize each record with an ad hoc code number (completely unrelated with the patient's medical record and identification) that included the study variables according to the patients' personal characteristics, intentionality, duration of abuse, substance used, therapeutic measures implemented and the medical-legal repercussions of the results. The Ethics Committee of the Principality of Asturias approved the study and the researcher, who also implemented the review, adhered to all of the mandatory confidentiality-related obligations.

AI in the Emergency Department was classified into two different groups, depending on the intentionality reported in the patient's medical records: voluntary AI, in which the patient voluntarily consumed alcohol or drugs in pursuit of psychoactive effects, and suicide attempts, in which the patient consumed the substance with the intention of committing suicide.

The IBM SPSS Statistics v21 package was used for the statistical analysis. The variables studied were described with the corresponding statistics, depending on variable type. The mean and standard deviation were used for quantitative variables and the proportion of the total for categorical variables.

Results

The cases were considered when the results of the analysis samples exceeded the defined reference limit. During that year, 4,586 cases of AI were treated, of which 2,478 received assistance at the Emergency Department, representing 2.3% of all of the hospital's emergencies in 2015. The remaining 2,108 cases correspond to AI treated and analysed as part of regular inpatient and outpatient assistance. Of these 2,478 cases treated in the Emergency Department, 5.3% (n = 131) correspond to patients that required medical assistance on two or more occasions during the same period. The incidence of intoxications attended to in the Emergency Department in relation to the total population of District IV is 764 cases/100,000 inhabitants/year with an age ranging from under 1 year to over 80 years. The mean age of the patients that received assistance was 43.6 (*SD* = 16.6) years. Of these patients, 59.4% were male (n = 1,411) with a mean age of 44 (*SD* = 16.8) years, while females (n = 1,067) represented 43.1% with a mean age of 42.8 (*SD* = 16. 5) years (Figure 1).

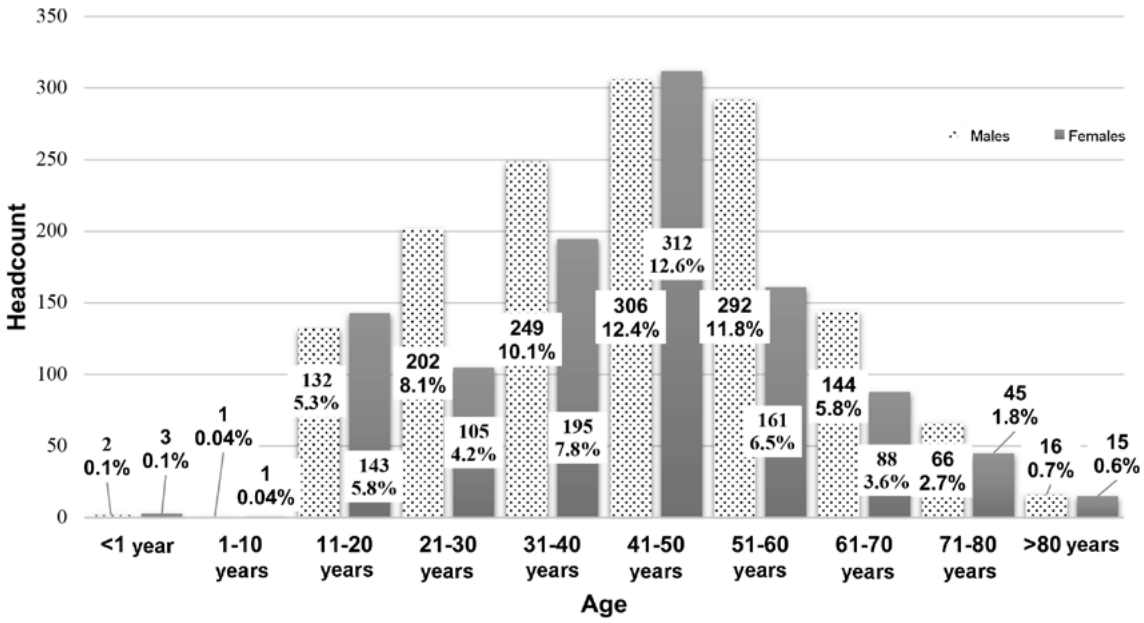
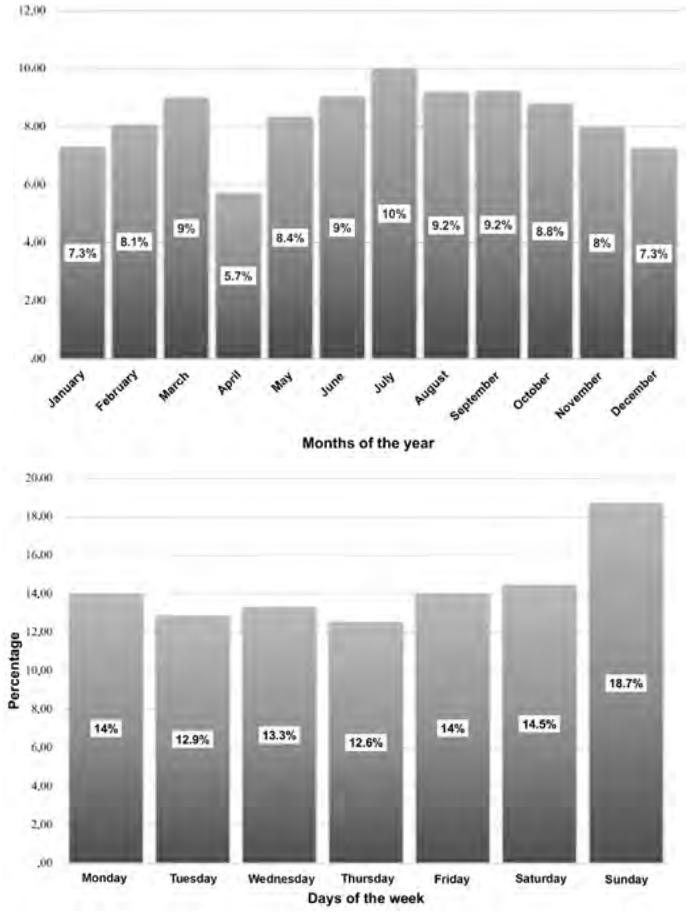


Figure 1. Distribution of AI by age and gender.



Figures 2A and 2B. Distribution of AI by Emergency Department admission date.

As to the diverse age groups, the ages between 41- 60 years represent 43.2% (n = 1,070) of Emergency Department patients. The most frequent age group of females was 31-50 years, representing 47.4% (n = 506), whereas the most frequent age group of males was 41- 60 years (42.3%; n = 597), with the same proportion in terms of total AI treated in the Emergency Department.

Intoxications by substances of abuse treated in the Emergency Department have a frequency of 47.2% (n = 1,170) on weekends: Friday-Sunday and 37.4% (n = 929) occur in summer: June-September (Figures 2A, 2B).

The most frequent intentionality of patients in terms of substances of abuse treated in the Emergency Department (n = 2,478) is voluntary AI (n = 2,061), corresponding to 83.2% of the cases. We must highlight the presence of 16.8% (n = 417) referenced as suicide attempts via AI with drugs, mainly benzodiazepines or other means, like hanging or lesions caused by knife wounds.

A background of psychiatric pathology (as per the DSM-V classification of 2013, including all behaviours and noticeable clinical symptoms) was present in 52.8% (n = 1,309) of all cases treated in the Emergency Department. The main pathologies were addiction disorders and substance use (n = 297; 22.7%), anxiety disorders (n = 228; 17.4%) and depression (n = 213; 16.2%).

Three groups are differentiated according to the positive toxicology analyses results of patients with presumed AI, treated in the Emergency Department. Of these, 34.6% (n = 856) had ethanol in blood, 52.4% (n = 1.298) had a qualitative screening of substances of abuse in urine, and 13% (n = 324) presented AI with ethanol and substances of abuse in urine.

When performing a joint analysis of the first and third group (n = 1,180), the most frequent range of qualitative ethanol values exceeded 100 mg/dL (n = 910), corresponding to patients with signs and symptoms of a depressed central nervous system. We must mention that in cases of drug-ethanol combinations, ethanol concentration is used as the reference value, based on the assumption of a positive screening.

Furthermore, we must highlight that 33.7% (n = 836) of all intoxicated patients treated in the Emergency Department had positive values in the qualitative screening of benzodiazepines in urine.

When analysing the toxics used in AI according to intentionality, 53.5% (n = 223) of the patients who visit the Emergency Department as a result of suicide attempts presented AI with benzodiazepines. To the contrary, 39.6% (n = 816) of the voluntary intoxications (n = 2,061) detected the use of ethanol (Table 2).

The concomitant clinical symptoms reported in the medical records of intoxicated patients treated in the Emergency Department were: 34.3% (n = 208) traumatology-related injuries (lesions, fractures, head trauma, contusions), which despite not directly resulting of intoxications seem to be associated with these, given the accidents and falls these patients frequently suffer. Of the cases, 27.4% (n = 166) showed neurological clinical symptoms (dizziness, unsteadiness of gait, decreased level of consciousness). There was a lower frequency of cardiology-related (palpitations, fainting) and digestion-related symptoms (nausea, vomiting).

The Emergency Department treated 38% of the AIs (n = 942), and the patients were discharged a few hours after their arrival or kept under observation. Of these, 19.7% (n = 489) required hospitalisation and 16.1% (n = 399) required follow-up by the Mental Health Centre on the grounds of this acute episode, due neither to psychiatric comorbidities nor addiction disorders. One male died during our study (mortality rate of 0.1%) as a result of a suicide attempt by intoxication with substances of abuse. This male, addicted to several drugs (user of several types of narcotics, substances or drugs) and with a history of psychiatric pathology was brought to the Emergency Department in a mobile ICU from prison, hardly conscious and with septic shock of unknown aetiology. The patient was hospitalised in the ICU, where he passed away.

Therapeutic measures were used in 4.8% of the intoxications treated in the Emergency Department (n = 120), with 68.3% of the patients (n = 82) requiring treatment

Table 2. *Individual and combined toxics detected in the different AI types treated in the Emergency Department.*

Substance of abuse	Suicide attempt	Voluntary intoxication	Total
Ethanol	40 (9.6%)	816 (39.6%)	856 (34.5%)
Amphetamines (screening)	1 (0.2%)	0 (0%)	1 (0.1%)
Tricyclic antidepressants (screening)	3 (0.7%)	10 (0.5%)	13 (0.5%)
Barbiturates (screening)	0 (0%)	3 (0.2%)	3 (0.1%)
Benzodiazepines (screening)	223 (53.4%)	613 (29.7%)	836 (33.7%)
Cannabis (screening)	7 (1.7%)	89 (4.3%)	96 (3.8%)
Cocaine (screening)	4 (1%)	12 (0.6%)	16 (0.6%)
Methadone (screening)	0 (0%)	5 (0.2%)	5 (0.2%)
Opioids (screening)	1 (0.2%)	9 (0.4%)	10 (0.4%)
Methamphetamines (screening)	0 (0%)	1 (0.1%)	1 (0.1%)
Prescribed drug + illegal drug	35 (8.4%)	132 (6.4%)	167 (6.7%)
Prescribed drug + several drugs	10 (2.4%)	51 (2.5%)	61 (2.5%)
Several prescribed drugs	15 (3.6%)	41 (2%)	56 (2.3%)
Several prescribed drugs + illegal drug	1 (0.2%)	10 (0.5%)	11 (0.4%)
Several prescribed drugs + several drugs	2 (0.5%)	2 (0.1%)	4 (0.2%)
Several drugs	1 (0.2%)	17 (0.8%)	18 (0.7%)
Alcohol + prescribed drug	57 (13.7%)	116 (5.6%)	173 (7%)
Alcohol + several prescribed drugs	2 (0.5%)	1 (1%)	3 (0.1%)
Alcohol + illegal drug	5 (1.2%)	64 (3.1%)	69 (2.8%)
Alcohol + several drugs	0 (0%)	15 (0.7%)	15 (0.6%)
Alcohol + prescribed drug + illegal drug	8 (1.9%)	39 (1.9%)	47 (1.9%)
Alcohol + prescribed drug + several drugs	2 (0.5%)	15 (0.7%)	17 (0.7%)
Total	417	2061	2478

with drugs. Flumazenil was used in 41 cases of AI caused by benzodiazepines, Naloxone in eight intoxications with opioids, a combination of Flumazenil and Naloxone in 19 patients with several drug addictions, and Thiamine (Vitamin B1) with Pyridoxine (Vitamin B6) in 14 alcohol poisonings. In 31.7% of the cases (n = 38), a gastric lavage with activated charcoal with/without perfusion of Flumazenil was also necessary (Figure 3).

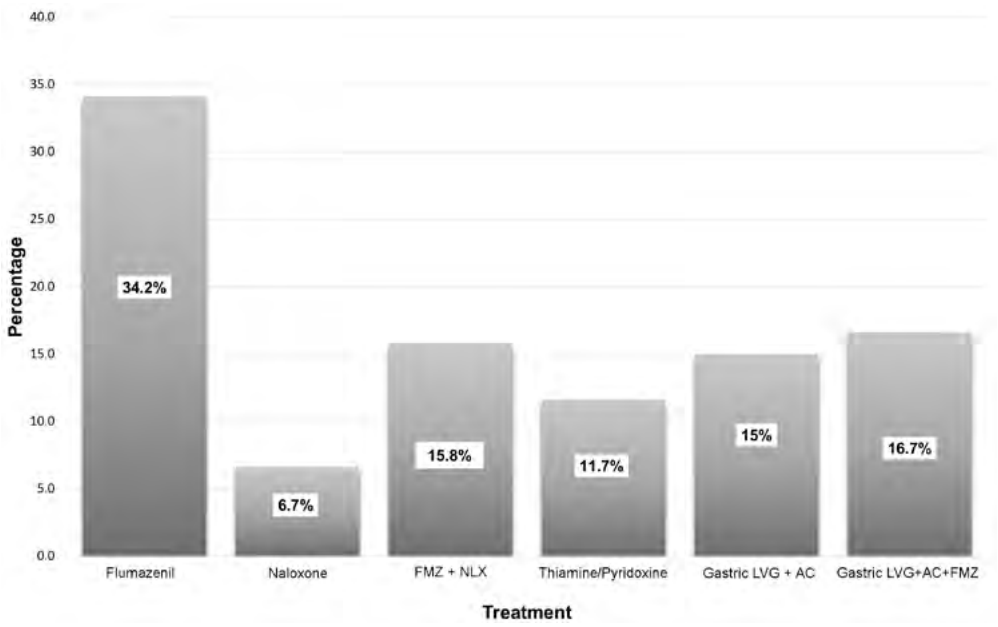


Figure 3. Treatment used in the Emergency Department by resolution of the AI.

Only 0.8% (n = 19) of these positive toxicology results for different intoxications due to substance abuse are subsequently used as samples in judicial processes, therefore having medical-legal implications.

Discussion

The results of our study detect 2,478 intoxications by substances of abuse, mainly ethanol and benzodiazepines, treated in the Emergency Department. In sociodemographic terms, the former corresponds to males with ages between 41-60 years and the latter to women in their 30s or 40s. In terms of medical-legal repercussions of AI, only 0.8% of the positive toxicology results were required for judicial proceedings.

The Central University Hospital of Asturias is the benchmark centre of the Autonomous Community and provides healthcare to a population of 324,218 inhabitants, distributed across 20 councils of District IV, including Oviedo. These figures usually increase due to the approximately 3,000 patients from other districts, wherefore some intoxications that do not require emergency hospital treatment are referred to Primary Care Facilities.

The incidence of AI of this study, 764 cases/100,000 inhabitants/year, considerably exceeds the figures published previously in similar studies implemented in Spain. This result is coherent with the observed increase of AI over recent decades (Caballero, Dorado, Brusint, Jerez & Medina, 1999; Caballero Vallés et al., 2004; Dorado et al., 1992 & Dorado et al., 1996).

The 44-year mean age of the intoxicated patients was quite higher than that obtained by other authors (Fernández-Egido, García-Herrero, Romero-García & Marquina-Santos, 2008; García-Baró et al., 2005), suggesting that perhaps increasingly older individuals are habitual consumers of toxics.

We must point out that 2.9% of the AI with ethanol occurred in adolescents (ages 14-15 years), a figure quite lower to the 8.2% corresponding to the alcohol use level in Spain for the same age range (Bousoño et al., 2019), coherent with some authors' claim of a direct relationship between users' habitual consumption of toxic substances and higher availability of economic resources (Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018).

The distribution of AI by gender confirms predominant use by males, in our study corresponding to 59.4%, as occurs in most studies published in Spain and abroad alike (Clemente Rodríguez et al., 2010; da Silva Moreira et al., 2010; Fernández et al., 2003; Ferrer et al., 2005).

There is a major increase of voluntary AI on weekends (Friday-Sunday), corresponding to 47.2%, and 37.4% during summer vacation (mainly June-September) possibly as a result of an increase in recreational activities. Many authors highlight an association between the use of substances of abuse and leisure time (Burillo-Putze et al., 2003; Echarte et al., 2005).

The percentage of suicide attempts (16.8%) is similar to other published studies, and mainly corresponds to drug-related AI involving benzodiazepines (Lambert, Manel, Bellou & el Kouch, 1997; Riquelme Rodríguez, Burillo-Putze, Jiménez Sosa & Hardisson De La Torre, 2001). Compared with the rest of Spain, this Autonomous Community has a high suicide rate (National Statistics Institute, 2016), but with the methods of hanging and jumping from heights (Iglesias García & Álvarez Riesgo, 1999). Published medical studies (Borrell et al., 2001; Fernández González, Sáiz Martínez, González G-Portilla, González Seijo & Bobes García, 2000; Jimenez-Trevino et al., 2012) show that suicide attempts (n = 417) are more frequent in women (n = 252; 60%) between the ages of 41-50 years (n = 135; 32.2%). The Principality of Asturias has designed a protocol for detecting and addressing cases of persons at risk of suicide as a preventive measure (Ministry of Health and Health Services of the Principality of Asturias, 2018).

In our study, 47.6% of the cases of intoxication involved ethanol, whether alone or combined with other drugs. Over the last 20 years, ethanol has always been considered the toxic involved in most AIs (de las Cuevas, Sanz, de la Fuente, Cabrera & Mateos, 1999; García del Pozo et al., 2004). The second substance was benzodiazepines, a medication that despite requiring a medical prescription is quite accessible by the population, present in isolation in 33.7% of the AIs (Bugarin, Galego, Gude, García & Galban, 2000; Carpintero Escudero et al., 2000; Fernández, Sertral, Bermejo & Tabernero, 2005).

At the Emergency Department, some of these patients (n = 606) presented a concomitant injury, many times accidental and other times intentional, including traumatic brain injury (TBI) with/without lesions and post-traumatic headaches (n = 208; 34.3%) and neurological pathology (n = 166; 27.4%) which do not differ from those found in other similar studies with the Spanish population (Medina et al., 2008; Pascual Catalán, Fuentes Solsona, Castellano Arroyo, Ferrer Dufol & López Lancis, 1992; Pinillos, Grijalba & Alfaro, 2003).

Improvements in techniques for analytical determination of drugs has fostered an increase in complementary examinations of patients and the obtention of more reliable results than in the past. Of our patients, 34.6% had their blood analysed for ethanol, 52.4% underwent a qualitative screening of substances in urine, and 13% experienced both. With these facts, we must mention that the quantitative results via the automated enzymatic technique analyses exceeding 100 mg/dL (36.7%) were most frequently detected in patients with AI with ethanol who showed clinical signs and symptoms of a depressed central nervous system, like lethargy and delayed reflexes (Aragón, Miquel, Correa & Sanchis-Segura, 2002; Bajo Bajo et al., 1999).

Therapeutic measures were used in 4.8% of the intoxications treated (n = 120). Treatment with drugs was necessary for 68.3% of the patients. Flumazenil was used in 41 cases of AI with benzodiazepines, Naloxone in eight intoxications with opioids, a combination of Flumazenil and Naloxone in 19 patients with several drug addictions, and Thiamine (Vitamin B1) with Pyridoxine (Vitamin B6) in 14 alcohol poisonings. In 31.7% of the cases (n = 38), a gastric lavage with activated charcoal with/without perfusion of Flumazenil was also necessary, following current recommendations (Benson et al., 2013; Burillo-Putze et al., 2003; Chyka et al., 2005).

The most frequent end actions of the Emergency Department (n = 2,478) were home-based observation/discharge (n = 942; 38%), hospitalisation (n = 489; 19.7%) whether in the ICU or not depending on the aetiology of the AI and, finally, follow-up by the Mental Health Centre (n = 399; 16.1%) given that 52.8% of the patients treated (n = 1309) had a prior background of psychiatric pathology. There was only one case of exitus as a result of intoxication with several substances. The percentage of hospitalisation is lower than that observed in other studies (Hermida, Fernández, Ferrer, Bermejo & Tabernero, 2003).

As regards the judicial-legal complications applicable in cases of AI, 19 cases were associated with crimes against road safety stipulated in Act 6/2014 dated 7 April, of which 84.2% (n = 16) had a blood alcohol concentration above 0.5g/L, entailing fines of €500 and the reduction of 4 points from the driver's license.

Conclusions

The incidence rate of our study is higher than that published previously, according to the last 20-year trend. The percentage of intoxicated males who are taken to the Emergency Department for treatment is approximately 60%, similar to the figure of previous studies.

Likewise, the tendency of AI to occur on weekends and during summer vacation (June-September) is the same in our study. The number of suicide attempts, corresponding to 16.8% of the patients taken to the Emergency Department for urgent treatment, is similar to previous findings. The most-frequently used toxic is ethanol, in line with the trend of recent decades, followed by benzodiazepines, despite requiring a medical prescription. The quantitative results of the toxicology analyses implemented as complementary tests showed that 36.7% of the intoxications with ethanol had values in the blood exceeding 100 mg/dL, with symptoms of a depressed central nervous system.

Patients mostly had accidental head trauma of the head and neck, followed by neurological pathology. Of the patients, 54.1% were treated in the Emergency Department and discharged with either home-based observation/discharge or follow-up at the Mental Health Centre, without requiring hospitalisation. The mortality of 0.1% was quite lower than that of recent publications.

Ethical issues

Legislation in effect on clinical research as established in the Declaration of Helsinki, the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of the European Council, and the Universal Declaration of Human Rights of the UNESCO, were all taken into account during this study. Likewise, our study complied with the requirements set forth in Spanish Act 14/2007 of July, on Biomedical Research, the protection of personal data and bioethics, and other related legislative requirements. The study was approved by the Clinical Research Ethics Committee of the Central University Hospital of Asturias (HUCA).

Acknowledgements

The authors wish to thank the Emergency Department of the Hospital Universitario Central de Asturias collaborator in this study.

Conflict of interests

The authors declare the inexistence of conflicts of interest.

References

Act 6/2014, dated 7 April, modifying the articulated text of the Act on Traffic, Motor Vehicle Circulation and Road Safety (Ley sobre Tráfico, Circulación de Vehículos a Motor y Seguridad Vial), approved by Legislative Royal Decree 339/1990, dated 2 March. *Boletín Oficial del Estado (BOE), 85, de 8 de abril de 2014,* 29508-29528.

Amigo-Tadín, M., Nogué-Xarau, S. & Miró-Andreu, O. (2010). Presentación clínica, actitud terapéutica y evolución de las intoxicaciones agudas tratadas con carbón activado: ¿existen diferencias entre hombres y mujeres? *Enfermería Clínica, 20,* 273-279. doi:10.1016/j.enfcli.2010.06.003.

Aragón, C., Miquel, M., Correa, M. & Sanchis-Segura, C. (2002). Alcohol y metabolismo humano. *Adicciones, 14 (Suppl. 1),* 23-42. doi:10.20882/adicciones.541.

Bajo Bajo, A., Santos Pérez, M. E., Sanz Ortega, F., Zapico Álvarez, N., Okatsu, K. T., García Pérez, A. & Borrás Beato, R. (1999). Estudio epidemiológico sobre intoxicaciones agudas y dotación de botiquines de antídotos. *Anales de Medicina Interna, 16,* 285-289.

Barraca de Ramos, R., Alonso Calo, L., Del Busto Prado, F., Ibarra Peláez, A., Menéndez Fernández, J. & Álvarez García, A. J. (1991). Aproximación epidemiológica a las intoxicaciones agudas en Asturias. *Revista de Sanidad e Higiene Pública, 65,* 53-60.

Benson, B. E., Hoppu, K., Troutman, W. G., Bedry, R., Erdman, A., Höjer, J.,… European Association of Poisons Centers and Clinical Toxicologists. (2013). Position paper update: gastric lavage for gastrointestinal decontamination. *Clinical Toxicology, 51,* 140-146. doi:10.3109/15563650.2013.770154.

Borrell, C., Pasarin, M. I., Cirera, E., Klutke, P., Pipitone, E. & Plasència, A. (2001). Trends in young adult mortality in three european cities: Barcelona, Bologne and Munich, 1986-1995. *Journal of Epidemiology and Community Health, 55*, 577-582. doi:10.1136/jech.55.8.577.

Bousoño, M., Al-Halabí, S., Burón, P., Garrido, M., Díaz-Mesa, E. M., Galván, G.,… Bobes, J. (2019). Predictive factors of alcohol consumption in adolescents: data from 1-year follow-up prospective study. *Adicciones, 31,* 52-63. doi:10.20882/adicciones.998.

Bugarin, R., Galego, P., Gude, F., García, A. & Galban, C. (2000). Estudio de intoxicaciones etílicas agudas en un servicio de urgencias. *Anales de Medicina Interna, 17,* 588-591.

Burillo-Putze, G., Munne, P., Dueñas, A., Pinillos, M. A., Naveiro, J. M., Cobo, J.,… the Clinical Toxicology Working Group, Spanish Society of Emergency Medicine (SEMESTOX). (2003). National multicentre study of acute intoxication in emergency departments of Spain. *European Journal of Emergency Medicine, 10,* 101-104. doi: 10.1097/00063110-200306000-00006.

Burillo-Putze, G., Munné Mas, P., Dueñas Laita, A., Trujillo Martín, M. M., Jiménez Sosa, A., Adrián Martín, M. J.,… Investigadores del Estudio HISPATOX. (2008). Intoxicaciones agudas: perfil epidemiológico y clínico, y análisis de las técnicas de descontaminación digestiva utilizadas en los servicios de urgencias españoles en el año 2006 – Estudio HISPATOX-. *Emergencias, 20,* 15-26.

Caballero, P. J. & Dorado, M. S. (1980). Factores epidemiológicos de la intoxicación. *Medicine, 59,* 3691-3699.

Caballero, P. J., Dorado, M. S. & Alonso, F. (1981). Intoxicación aguda: Estudio de 673 casos. *Medicina Clínica, 77,* 139-145.

Caballero, P. J., Dorado, M. S., Brusint, B., Jerez, B. & Medina, M. (1999). Vigilancia epidemiológica de la intoxicación aguda 1997 (Estudio de 1.140 casos del área sur de la Comunidad de Madrid). *Revista Clínica Española, 199,* 424-430.

Caballero, P. J., Gutiérrez, F. & Dorado, M. S. (1987). Epidemiología de la intoxicaron aguda: Estudio comparativo 1979-1985 en el área sur de la Comunidad Autónoma de Madrid. *Revista Clínica Española, 181,* 334-339.

Caballero Vallés, P. J., Dorado Pombo, S., Díaz Brasero, A., García Gil, M. E., Yubero Salgado, L., Torres Pacho, N.,… Cantero Bengoechea, J. (2008). Vigilancia epidemiológica de la intoxicación aguda en el área sur de la Comunidad de Madrid: estudio VEIA 2004. *Anales de Medicina Interna, 25*, 262-268. doi:10.4321/S0212-71992008000600003.

Camí, J., Frati, M. & Martín, M. L. (1980). Intoxicación aguda en Barcelona. Epidemiología y consideraciones sobre su terapéutica. *Medicina Clínica, 75,* 287-291.

Carpintero Escudero, J. M., Ochoa Gómez, F. J., Ruiz Aspiazu, J. I., Bragado Blas, L., Palacios Marín, G., Ramalle-Gómara, E.,… Grupo de Toxicología de SEMES-La Rioja (2000). Prevalencia de las intoxicaciones agudas en Urgencias de La Rioja. *Emergencias, 12,* 92-97.

Chyka, P. A., Seger, D., Krenzelok, E. P., Vale, J.A., American Academy of Clinical Toxicology & European Association of Poisons Centres and Clinical Toxicologists. (2005). Position paper: Single-dose activated charcoal. *Clinical Toxicology, 43,* 61-87.

Clemente Rodríguez, C., Echarte Pazos, J. L., Aguirre Tejedo, A., Puente Palacios, I., Iglesias Lepine, M. L. & Supervía Caparrós, A. (2010). Diferencias entre hombres y mujeres en las características de las intoxicaciones. *Emergencias, 22,* 435-440.

da Silva Moreira, C., Rezende Barbosa, N., Alves Vieira, R. C. P., Carvalho, M. R., Marangon, P. B., Carneiro Santos, P. L. & Teixeira Júnior, M. L. (2010). Análise retrospectiva das intoxicações admitidas no hospital universitario da UFJF no período 2000-2004. *Ciencia & Saúde Coletiva, 15,* 879-888. doi:10.1590/S1413-81232010000300003.

de la Fuente, L., Brugal, M. T., Domingo-Salvany, A., Bravo, M. J., Neira-León, M. & Barrio, G. (2006). Más de treinta años de drogas ilegales en España: una amarga historia con algunos consejos para el futuro. *Revista Española de Salud Pública, 80,* 505-520.

de las Cuevas, C., Sanz, E. J., de la Fuente, J., Cabrera, C. & Mateos, A. (1999). Prescribed daily doses and risk factors associated with the use of benzodiazepines in primary care. *Pharmacoepidemiology and Drug Safety, 8,* 207-216. doi:10.1002/(SICI)1099-1557(199905/06)8:3<207::AID-PDS421>3.0.CO;2-1.

de Miguel-Bouzas, J. C., Castro-Tubío, E., Bermejo-Barrera, A. M., Fernández-Gómez, P., Estévez-Núñez, J. C. & Tabernero-Duque, M. J. (2012). Estudio epidemiológico de las intoxicaciones agudas atendidas en un hospital gallego entre 2005 y 2008. *Adicciones, 24,* 239-246. doi:10.20882/adicciones.95.

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

Dorado, M. S., Álvarez, R., Caballero, P. J., Medina, J., Casanova, C. & Granado, J. A. (1992). Epidemiología de la intoxicación aguda: Estudio de 815 casos habidos en 1990 en el área sur de la Comunidad de Madrid. *Revista Clínica Española, 191,* 131-136.

Dorado, M. S., Martín, J., Sabugal, G. & Caballero, P. J. (1996). Epidemiología de la intoxicación aguda: estudio de 613 casos habidos en 1994 en el área sur de la Comunidad de Madrid. *Revista Clínica Española, 196,* 150-156.

Duce Tello, S., López Martínez, E., Navas Serrano, V., Piqueras Villaidea, M., Jara Peñacoba, M., Servián Carroquino, R.,… Abril García, A. (1998). Intoxicaciones medicamentosas voluntarias atendidas en un Servicio de Urgencias. *Emergencias, 10,* 225-233.

Echarte, J. L., Iglesias, M. L., Hernández, E., García, L., Orriols, M., Villar, J.,… Skaf, E. (2005). Registro de las intoxicaciones agudas en un Servicio de Urgencias hospitalario. *Revista de Toxicología, 22,* 116.

Fernández, P., Ortega, M., Bermejo, A. M., Tabernero, M. J., López-Rivadulla, M. & Concheiro, M. E. (2003). Intoxicaciones agudas en Santiago de Compostela en un período de cuatro años. *Revista de Toxicología, 20,* 216-220.

Fernández, P., Sertral, R., Bermejo, A. M. & Tabernero, M. J. (2005). Intoxicaciones agudas por psicofármacos y drogas de abuso en Pontevedra durante el año 2001. *Revista de Toxicología, 22,* 37-40.

Fernández-Egido, C., García-Herrero, G., Romero-García, R. & Marquina-Santos, A. J. (2008). Intoxicaciones agudas en las urgencias extrahospitalarias. *Emergencias, 20,* 328-331.

Fernández González, C., Sáiz Martínez, P. A., González G-Portilla, M. P., González Seijo, J. C. & Bobes García, J. (2000). Tentativa suicida versus intención suicida: un estudio de las características diferenciales. *Actas Españolas de Psiquiatría, 28,* 224-230.

Ferrer, A., Royo, R., Rivas, M., Menao, S., Moreno, M. & Civeira, E. (2005). Perfil de las intoxicaciones agudas en el Servicio de Urgencias del Hospital Clínico de Zaragoza. *Toxicología, 22,* 121.

García-Baró, M., Lasarte-Turumbay, L., Prieto-Ferrer, M., Montiel, J. A., Lloret, J. & Marruecos, L. (2005). Intoxicaciones agudas del adulto. Epidemiología en un Servicio de Urgencias. *Toxicología, 22,* 119-120.

García del Pozo, J., de Abajo Iglesias, F. J., Carvajal García-Pando, A., Montero Corominas, D., Madurga Sanz, M. & García del Pozo, V. (2004). Utilización de ansiolíticos e hipnóticos en España (1995-2002). *Revista Española de Salud Pública, 78,* 379-387.

González-Fernández, D. & Alonso-Fernández, M. (2009). Intoxicaciones agudas en un Servicio de Urgencias. Estudio descriptivo en el Área Sanitaria III de Asturias. *Revista de Toxicología, 26,* 122-127.

Henderson, A., Wright, M. & Pond, S. M. (1993). Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Medical Journal of Australia, 158,* 28-30.

Hermida, I., Fernández, P., Ferrer, A., Bermejo, A. M. & Tabernero, M. J. (2003). Perfil psicosocial de pacientes ingresados por intoxicación aguda voluntaria. *Revista de Toxicología, 20,* 33-37.

Iglesias García, C. & Álvarez Riesgo, J. A. (1999). Un estudio del suicidio en Asturias: incremento de la frecuencia en las dos últimas décadas. *Actas Españolas de Psiquiatría, 27,* 217-222.

Jimenez-Trevino, L., Saiz, P. A., Corcoran, P., Garcia-Portilla, M. P., Buron, P., Garrido, M.,… Bobes, J. (2012). The incidence of hospital-treated attempted suicide in Oviedo, Spain. *Crisis, 33,* 46-53. doi:10.1027/0227-5910/a000094.

Lambert, H., Manel, J., Bellou, A. & el Kouch, S. (1997). Morbidity and mortality from acute drug poisoning in France. *La Revue du Practicien, 47,* 716-720.

Medina, L., Fuentes, M. E., Suárez, J. P., Arranz, M. I. & Ochoa, E. (2008). Epidemiología de las intoxicaciones medicamentosas durante un año en el Hospital Universitario Ramón y Cajal. *Revista Clínica Española, 208,* 432-436. doi:10.1157/13127603.

Ministry of Health and Health Services of the Principality of Asturias. (2018). *Protocolo de detección y manejo de caso en personas con riesgo de suicidio.* Asturias: Unidad de Coordinación del Programa Marco de Salud Mental - SESPA. Retrieved at https://www.astursalud.es/documents/31867/225127/PROTOCOLO+SUICIDIO+def.pdf/48775c44-b688-961e-be16-f81511d4eba2.

National Statistics Institute. (2016). Estadística del suicidio en España 2015. Retrieved at http://www.ine.es/jaxi/tabla.do?type=pcaxis&path=/t15/p417/a2014/l0/&file=06004.px.

Pascual Catalán, A., Fuentes Solsona, F., Castellano Arroyo, M., Ferrer Dufol, A. & López Lancis, A. (1992). Estudio epidemiológico de las intoxicaciones agudas en la población de Zaragoza. *Anales de Medicina Interna, 9,* 381-385.

Pastó Cardona, L., Martorell Puigserver, C., Mercadal Orfila, G., Machí Ribes, J. J. & Jódar Massanès, R. (2007). Intoxicaciones agudas en el servicio de urgencias de un hospital universitario de nivel III: cambios producidos en los últimos 10 años. *Revista de Toxicología, 24,* 36-41.

Pinillos, M. A., Grijalba, A. & Alfaro, J. (2003). Situación de las intoxicaciones en Navarra. *Anales del Sistema Sanitario de Navarra, 26 (Supl. 1),* 7-19.

Riquelme Rodríguez, A., Burillo-Putze, G., Jiménez Sosa, A. & Hardisson De La Torre, A. (2001). Epidemiología global de la intoxicación aguda en un área de salud. *Atención Primaria, 28,* 506-509.

Rodríguez Getino, J. A. & Hinojal Fonseca, R. (1994). Intoxicaciones agudas: estudio epidemiológico retrospectivo en un Área Asturiana (1985-1989). *Revista de Toxicología, 11,* 99-104.

Alcohol use and risk factors for self-harm behavior in Spanish adolescents

Consumo de alcohol y factores de riesgo de conductas autolesivas en adolescentes españoles

Matilde Bousoño*, Susana Al-Halabí**,***,****, Patricia Burón*,****, Marlen Garrido*, Eva Mª Díaz-Mesa*,****, Gonzalo Galván*****, Leticia García-Álvarez**,****,******, Ángela Velasco*,***, Julia Rodríguez-Revuelta*,****,******,*******, Camilla Wasserman********,*********, Vladimir Carli********, Christina Hoven*********, Marco Sarchiapone*********, Danuta Wasserman*******, Manuel Bousoño*,***,****, Mª Paz García-Portilla*,***,****,******,*******, Celso Iglesias*,***,****,******,*******, Pilar Alejandra Sáiz*,***,****,******,*******, Julio Bobes*,***,****,******,*******.

* Área de Psiquiatría. Universidad de Oviedo. ** Departamento de Psicología. Universidad de Oviedo. *** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). **** Instituto de Neurociencias del Principado de Asturias (INEUROPA). ***** Universidad Cooperativa de Colombia. Colombia. ****** Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). ******* Servicio de Salud del Principado de Asturias (SESPA). ******** National Centre for Suicide Research and Prevention of Mental Ill-Health, Karolinska Institutet, Stockholm. Sweden. ********* Division of Child and Adolescent Psychiatry and Department of Psychiatry, New York State Psychiatric Institute. Columbia University, New York. USA. Department of Epidemiology, Mailman School of Public Health. Columbia University, New York. USA. ********** Department of Medicine and Health Science. University of Molise, Campobasso. Italy. National Institute for Health, Migration and Poverty, Rome. Italy.

Abstract

Self-harm behaviors in children and adolescents constitute an important public health problem with prevalence figures in the clinical population between 40 and 80%. The objectives of the study were to analyze and compare the Spanish sub-samples of two studies, SEYLE and WE-STAY to determine prevalence, self-harm patterns and factors associated with self-harm behaviors, notably the use of alcohol or drugs. The questionnaires used in both studies were the Global School Health Survey (GSHS), the Beck Depression Inventory (BDI-II), the Strengths and Difficulties Questionnaire (SDQ). The self-harm behaviors were evaluated with a modified 6-item version of s the Deliberate Self-Harm Inventory (DSHI). The independence of the study's categorical variables was assessed using the Chi-square test. The change in the relative risk of self-harm between the SEYLE study and WE-STAY was evaluated through the odds ratio (OR) calculation. Two different logistic regression models were calculated in order to establish the factors associated with self-harm behaviors in each study. In the present study, the rates of DSH vary according to study and sex, ranging from 0.58% to 2.08%, and different patterns of self-harm are evidenced by sex, with males self-injuring more frequently by self-inflicted blows and burns, while young women more often cut themselves. The presence of depressive symptoms and alcohol use were the factors most strongly associated with an increased risk of DSH.

Key Words: Self-harm behaviors; Adolescents; Depression; Alcohol consumption; SEYLE; WE-STAY.

Resumen

Las conductas autolesivas en niños y adolescentes constituyen un importante problema de salud pública con cifras de prevalencia en la población clínica entre el 40 y 80%. Los objetivos del estudio son analizar y comparar las submuestras españolas de dos trabajos, SEYLE y WE-STAY, para conocer la prevalencia, los patrones de autolesión y los factores asociados a las conductas autolesivas, en particular el consumo de alcohol o drogas. Los cuestionarios utilizados en ambos estudios fueron la Encuesta Global de Salud Escolar (GSHS), el Inventario de Depresión de Beck (BDI-II), el Cuestionario de Fortalezas y Dificultades (SDQ). Los comportamientos autolesivos fueron evaluados con una versión modificada de 6 ítems basada en el Inventario de Autolesiones Deliberadas (DSHI). La independencia de las variables categóricas del estudio se evaluó mediante la prueba Ji-Cuadrado. El cambio en el riesgo relativo de autolesión entre el estudio SEYLE y WE-STAY, se evaluó a través del cálculo de odds ratio (OR). Se calcularon dos modelos de regresión logística diferentes con el fin de establecer los factores asociados con comportamientos autolesivos en cada estudio. En el presente estudio las tasas de DSH varían en función del estudio y del sexo en un rango entre 0,58% y 2,08%, presentando patrones de autolesiones diferentes según el sexo, los hombres se autolesionaron más frecuentemente mediante golpes autoinfligidos y quemaduras, mientras que las mujeres se hicieron más frecuentemente cortes. La presencia de síntomas depresivos y el consumo de alcohol fueron los factores asociados de forma más robusta a un mayor riesgo de DSH.

Palabras clave: Conductas autolesivas; Adolescentes; Depresión; Consumo de alcohol; SEYLE; WE-STAY.

Received: September 2018; Accepted: November 2018.

Send correspondence to: Julio Bobes García.
Área de Psiquiatría. Facultad de Medicina. Julián Clavería 6- 3º, 33006, Oviedo.
E-mail: bobes@uniovi.es.

Adolescence is a period during which risky behaviors appear that have been linked both to characteristics of the brain maturation process and to social and cultural factors typical of this life stage (McCormick, Qu & Telzer, 2017; Somerville, Hare & Casey, 2011). Among the most frequent risky practices found in adolescents are self-injurious behaviors (Kaess, Fischer-Waldschmidt, Resch & Koenig, 2017).

Self-injury is the act of deliberately hurting oneself by causing a physical wound, placing oneself in situations of risk or being negligent in self-care (Bifulco et al., 2014). "Non-suicidal self-injury" (NSSI) has been proposed as one of the "DSM-5 diagnostic categories that require further study", and is defined as intentionally self-inflicted harm to the surface of the body without conscious suicidal intent and with purposes not socially sanctioned; it includes behaviors such as cutting, burning, biting, or scratching the skin (American Psychiatric Association, 2013; Zetterqvist, 2015). "Deliberate self-harm" (DSH) is a similar concept in which the existence or not of suicidal intentionality is not taken into account (Pattison & Kahan, 1983), and which can be direct (cutting or hitting) and indirect, or self-destructive behavior (drinking alcohol, smoking, etc.) (Nock, 2010).

Self-harm behaviors in children and adolescents represent an important public health problem, with annual incidence rates in children and adolescents of between 12.3 and 37.4 per 10000 (Morgan et al., 2017). Establishing prevalence figures for self-harm in the general population is difficult due to the scarcity of data, but the evaluation of studies available in different countries leads to the conclusion that it is a frequent phenomenon in adolescents and young adults in the general population (13% to 42%) and even more frequent in clinical populations (40% to 80%) (Lenkiewicz, Racicka & Bryńska, 2017). Prevalence does not vary depending on cultural factors, socioeconomic status or area of residence (Lenkiewicz, Racicka & Bryńska, 2017; Muehlenkamp, Claes, Havertape & Plener, 2012).

The effect of sex on self-injurious behaviors is controversial; some studies show a higher frequency in women (female:male ratios up to 6.5:1), while others find no differences between the sexes (Bresin & Schoenleber, 2015; Sornberger, Heath, Toste & McLouth, 2012; Whitlock et al., 2011). Some studies have linked gender and self-harm taking into account other associated factors such as: parental alcohol use, which is associated with a higher risk of self-harm in men; or the degree of urbanicity, as shown by a higher prevalence of non-suicidal self-harm in women in rural areas, which is not matched in urban zones (Pisinger, Hawton & Tolstrup, 2018; Yang & Feldman, 2017). One factor which does appear to have a clear link to self-injurious behavior is age, with the phenomenon usually starting to manifest itself between 12 and 14 years, and its frequency diminishing with increasing age (Cipriano, Cella & Cotrufo, 2017; Hawton & Harriss, 2008; Lenkiewicz, Racicka & Bryńska 2017). Links have also been found between self-harm and psychopathology. The presence of externalizing psychopathology in adolescents (related to manifestations of aggression, lack of attention, disobedience and criminal behavior) is associated with more non-suicidal self-harm, and adolescents who are subjected to life situations which generate frustration or existential emptiness present more suicidal behavior (Blasco-Fontecilla, 2018; Meszaros, Horvath & Balazs, 2017).

Recently, two multicenter studies, SEYLE (Wasserman et al., 2010) and WE-STAY (Strittmatter et al., 2015) have carried out in-depth research into self-injurious and suicidal behaviors among adolescents in several European countries, including Spain. In the present study, the Spanish subsamples of the aforementioned studies are analyzed in order to determine the prevalence of self-injurious behaviors, the types of self-harm and the associated risk factors. In addition, we compared the data of both studies based on the hypothesis that, due to their temporal proximity and their methodological similarities, they should yield similar results.

Method

The present study analyzes the Spanish sub-samples data of two studies carried out in the European area: *Saving and Empowering Young Lives in Europe* (SEYLE) implemented between 2009 and 2010, and *Working in Europe to Stop Truancy Among Youth* (WE-STAY) from 2011-2012. The procedures used in the SEYLE and WE-STAY studies have been the subject of specific publications (Carli et al., 2014; Strittmatter et al., 2015; Wasserman et al., 2010).

Participants

The Spanish sub-sample of the SEYLE study is composed of 1026 adolescents, with a mean age (MA) of 14.52 years and a standard deviation (SD) of 0.70 years; 51.66% of the sample were males. Participants were recruited in 12 state schools randomly selected from those in the Autonomous Community of the Principality of Asturias, taking into account the inclusion and exclusion criteria of the SEYLE project (Bousoño et al., 2017; Wasserman et al., 2010). The Spanish sub-sample of the WE-STAY study comprises 1409 adolescents, with an MA of 15.16 years (SD = 1.23 years), of which 48.83% were males. They were recruited in 26 state schools in the Principality of Asturias. The two studies did not involve the same schools.

Procedure

In compliance with the rules governing research with young people, and prior to the start of both studies, the authorization of the juvenile prosecutor was obtained, as was the approval of the Clinical Research Ethics Committee of the Principality of Asturias. In both cases, the local

school authorities gave permission to access the selected schools, and students agreed to participate and granted informed consent, as required. A structured self-report questionnaire was completed by the participants and the collected data were anonymized. The assessment was conducted during school hours and covered a wide range of demographic, psychological and social factors.

Assessment methods

For the assessment of substance use, the Global School-based Student Health Survey questionnaire, GSHS (World Health Organization, 2015), was used, with the following cut-off points: the criterion for "alcohol use" was considered to be the intake of any amount of alcohol two or more times a week, for "drug use", having used illicit drugs at least three times in his/her life, and for "smoking", to smoke more than ten cigarettes a day (Bousoño et al., 2019).

To evaluate the "depressive symptoms", Beck's inventory (BDI-II) was used (Beck, Steer, Ball & Ranieri, 1996), in which a score equal to or higher than 20 represented "risk of depression". For the present study, we have used a modified version, the BDI-II, eliminating the item "loss of libido" since it was considered an unsuitable question for the population under scrutiny. The omission of this question does not affect the reliability or validity of the instrument (Byrne, Stewart & Lee, 2004).

To assess psychopathology, the Capacity and Difficulties Questionnaire (SDQ) (Goodman, Meltzer & Bailey, 2003) was used, which assesses emotional symptoms, behavior problems, hyperactivity/inattention, relationship problems between peers and prosocial behavior. The established cut points were: a score equal to or greater than 7 for emotional symptoms, a score equal to or greater than 5 for "behavioral problems" and a score equal to or greater than 7 for "hyperactivity". In the case of "problems with peers", the cut-off point was set at a score of equal to or greater than 6, while the "lack of prosocial behavior" was defined by a score of equal to or less than 4 (Carli et al., 2014).

DSH was assessed using a modified six-item version (Brunner et al., 2014) of the Deliberate Self-Harm Inventory (DSHI) (Gratz, 2001) which measures different forms of self-injurious behavior, with a cut-off point for students reporting these behaviors three times or more in the last year (Carli et al., 2014). The six questions (Q1, Q2 ...) comprising the questionnaire are: Q1: During the last year, have you ever intentionally cut your wrists, arms or other parts of your body, or punctured your skin with sharp objects like needles, pins, pin buttons, staples (do not include tattoos, ear or other piercings, or syringe needles for drug use)?; Q2: During the last year, have you ever intentionally burned yourself with a cigarette, a lighter or a match?; Q3: During the last year, have you ever cut your skin intentionally to carve words, drawings, designs or other markings, or have you scratched yourself so much that you bled or scarred yourself?; Q4: During the last year, have you ever intentionally prevented wounds from healing or have you bitten so hard that you have punctured your skin?; Q5: During the last year, have you ever banged your head or another part of your body causing a bruise?; Q6 During the last year, have you ever intentionally hurt yourself so badly in any of the aforementioned ways that you had to be hospitalized or was it severe enough to receive medical treatment?

Statistical analysis

In order to verify the independence of the categorical variables of the study, the Chi-square test was applied. In addition, two logistic regression models were also calculated, one for the SEYLE study and another for WE-STAY, in which the dependent variable was the risk of self-harm and the independent variables were age, sex, SDQ emotional symptoms, SDQ behavioral problems, SDQ hyperactivity, SDQ problems with peers, SDQ lack of prosocial behavior, BDI-II smoking, alcohol and drug use.

Results

Subjects meeting the criteria for deliberate self-injurious behavior (Total DSHI ≥ 3) made up 1.56% (n = 16) of the SEYLE Spanish sub-sample, compared to 0.92% (n = 13) in the WE-STAY study ($X^2 = 2.046$, gl = 1, $p < 0.153$).

Analyzing DSH by sex yielded no prevalence differences among females across the two studies [1.01% (n = 5) vs. 1.26% (n = 9), respectively; $X^2 = 0.149$, gl = 1, p = 0.699], whereas male prevalence did produce a statistically significant difference [2.08% (n = 11) vs. 0.58% (n = 4), respectively; $X^2 = 5.494$, gl = 1, p = 0.019]. It should be noted that when both studies are analyzed separately, no differences are found in the prevalence of self-injurious behaviors between young men and women in either of the two studies (SEYLE: 2.08 vs. 1.01%, $X^2 = 1.902$, gl = 1, p = 0.168; WE-STAY: 0.58% vs. 1.26%, $X^2 = 1.713$, gl = 1, $p < 0.191$).

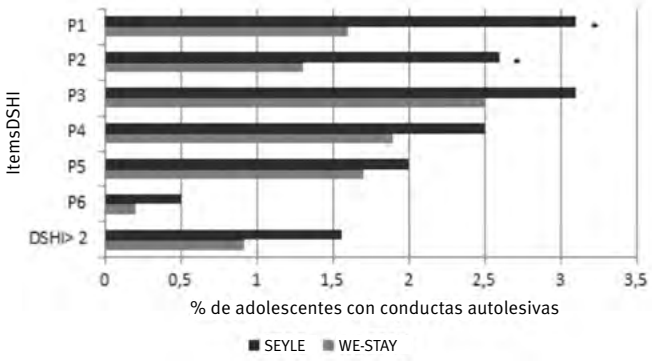
Table 1 shows the item-by-item results of the DSHI questionnaire in each study by sex. As can be seen, the frequency of young men exceeding the cut-off point in the SEYLE study (3 times or more in the last year) in items 2 (self-inflicted burns) and 5 (blows/bruises) is significantly higher to that of young women. Conversely, in the WE-STAY study, females exceed the cut-off point (3 times or more in the last year) in items 1 (cuts or use of sharp piercing objects) and 3 (carving words, drawings, etc.) with a frequency significantly higher than that of men.

A comparison of the results of both studies yields a significantly higher percentage in the SEYLE study of responses exceeding the cutoff point (3 times or more in the last year) in the first two questionnaire items (cuts or use of sharp objects, and self-inflicted burns) (Q1: 3.12 vs. 1.56%, $X^2 = 6.642$, gl = 1, p = 0.010; Q2: 2.63% vs. 1.28%, $X^2 = 6.001$, gl = 1, $p < 0.014$) (Figure 1).

Table 1. *Comparison of types of self-harm between the SEYLE and WE-STAY studies, according to individual scores on the different DSHI questionnaire items, disaggregated by sex.*

		Total n (%)	Males n (%)	Females n (%)	X^2 (gl)	p
Q1	SEYLE	32 (3.12%)	14 (2.64%)	18 (3.63%)	0.827 (1)	0.363
	WE-STAY	25 (1.77%)	6 (0.87%)	16 (2.23%)	4.156 (1)	0.041
Q2	SEYLE	27 (2.63%)	19 (3.58%)	8 (1.61%)	3.889 (1)	0.049
	WE-STAY	28 (1.99%)	11 (1.59%)	7 (0.98%)	1.101 (1)	0.294
Q3	SEYLE	32 (3.12%)	17 (3.21%)	15 (3.02%)	0.029 (1)	0.866
	WE-STAY	35 (2.48%)	8 (1.15%)	27 (3.77%)	9.689 (1)	0.002
Q4	SEYLE	26 (2.53%)	15 (2.83%)	11 (2.22%)	0.389 (1)	0.533
	WE-STAY	27 (1.92%)	11 (1.59%)	16 (2.23%)	0.721 (1)	0.396
Q5	SEYLE	21 (2.05%)	17 (3.21%)	4 (0.81%)	7.368 (1)	0.007
	WE-STAY	17 (1.21%)	8 (1.15%)	9 (1.26%)	0.022(1)	0.883
Q6	SEYLE	5 (0.49%)	4 (0.75%)	1 (0.20%)	1.616 (1)	0.204
	WE-STAY	3 (0.21%)	1 (0.14%)	2 (0.28%)	0.289 (1)	0.591
DSHI≥ 3	SEYLE	16 (1.56%)	11 (2.08%)	5 (1.01%)	1.902 (1)	0.168
	WE-STAY	13 (0.92%)	4 (0.58%)	9 (1.26%)	1.713 (1)	0.191

Note. DSHI= Deliberate Self-Harm Inventory.



Note. *p ≤ 0.050; DSHI= Deliberate Self-Harm Inventory.

Figure 1. Comparison of the type of self-injury between the SEYLE and WE-STAY studies, according to individual DSHI questionnaire item scores.

In Figure 2 (A and B), the item-by-item distribution of positive responses is shown in each study by sex. As can be seen in Figure 2A, males participating in the SEYLE study present a significantly higher percentage of positive responses for all items except 4 and 6 (Q1: 2.64 vs. 0.87%, X2 = 5.803, gl = 1, p = 0.016; Q2: 3.58% vs. 1.59%, X2 = 4.915, gl = 1, p = 0.027; Q3: 3.21% vs. 1.15%, X2 = 6.226, gl = 1, p = 0.013; Q5: 3.21% vs. 1.15%, X2 = 6.226, gl = 1, p = 0.013). Similarly, there is a higher percentage of young men with a DSHI score of ≥ 3 in SEYLE than in WE-STAY (2.08 vs. 0.58%, X2 = 5.494, gl = 1, p = 0.019). In contrast, no differences were observed among young women (Figure 2B) in the percentage of positive responses in any of the items, nor in the percentage of females with a DSHI score of ≥ 3, which is similar in both studies.

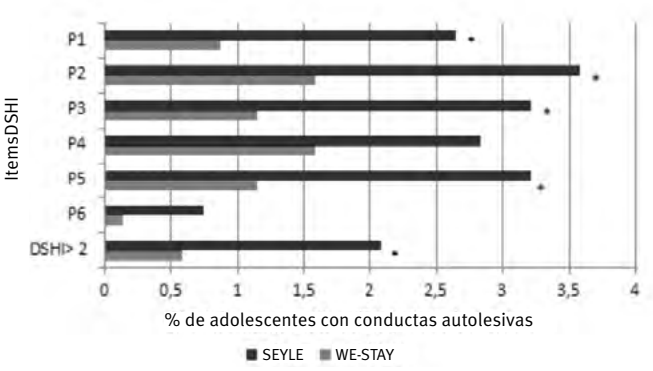


Figure 2A: Males

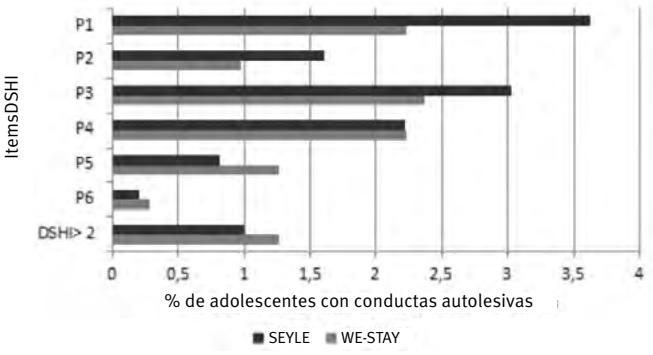


Figure 2B: Females

Note. *p ≤ 0,050; DSHI= Deliberate Self-Harm Inventory.

Figure 2. Type of self-harm observed in the SEYLE and WE-STAY studies, according to individual DSHI questionnaire item scores, disaggregated by sex.

In order to determine the factors associated with self harming, two independent logistic regression analyses were carried out (one for each study), in order to try to replicate (or not) the results in two independent samples. In both cases, age and sex were used as control variables.

As can be seen in Table 2, the factors associated with self-injurious behaviors in the SEYLE study (after controlling for age and sex), were the presence of hyperactivity/inattention (SDQ score hyperactivity/inattention ≥ 7) (OR = 2.367, CI 95% = 1.389-4.033; p = .002), peer relationship problems (SDQ peer relationship score ≥ 6) (OR = 3.096, CI 95% = 1.230-7.797; p = .024), presence of depression (BDI-II score ≥ 20) (OR = 4.046, CI 95% = 2.321-7.050; p < .001), alcohol use (≥ twice/week) (OR = 2.362, CI 95% = 1.240-4.499; p = .012), illicit drugs (≥ 3 times/lifetime) (OR = 2.843, CI 95% = 1.360-5.944; p = .007), and smoking (> 10 cigarettes/day) (OR = 3.464, CI 95% = 1.632-7.353; p = .002).

However, Table 3 shows that in WE-STAY only three factors are associated with self-injurious behaviors, namely the lack of pro-social behavior (pro-social SDQ score ≤ 4) (OR = 2809, CI 95% = 1199-6581; p = 027), the presence of depression (BDI-II score ≥ 20) (OR = 6357, CI 95% = 3613-11183; p < 001) and alcohol use (≥ twice/week) (OR = 2353, CI 95% = 1259-4399; p = 010).

Table 2. *Factors associated with self-injurious behaviors in the Spanish sample of the SEYLE study.*

Variable	B	SE	Wald	df	p	OR	CI 95%
Emotional symptoms (SDQ)	0.312	0.31	1.006	1	0.736	1.151	0.509-2.603
Behavior problems (SDQ)	0.265	0.38	0.486	1	0.328	1.495	0.676-3.302
Hyperactivity (SDQ)	0.450	0.28	2.620	1	0.002	2.367	1.389-4.033
Peer problems (SDQ)	0.715	0.26	7.447	1	0.024	3.096	1.230-7.797
Lack of prosocial behavior (SDQ)	1.140	0.44	6.743	1	0.306	1.727	0.626-4.769
Depression (BDI-II)	1.812	0.29	39.861	1	‹ 0.001	4.056	2.321-7.050
Smoking	0.218	0.56	0.154	1	0.002	3.464	1.632-7.353
Alcohol use	0.751	0.32	5.474	1	0.012	2.362	1.240-4.499
Drug use	-0.210	0.4	0.261	1	0.007	2.843	1.360-5.944
Constant	-4.190	0.24	294.741	1	0.009		

Note. SDQ= Strengths and Difficulties Questionnaire; BDI-II= Beck Depression Inventory; SE=Standard error; df= Degrees of freedom; OR= Odds ratio; CI= Confidence interval.

Table 3. *Factors associated with self-injurious behaviors in the Spanish sample of the WE-STAY study.*

Variable	B	SE	Wald	df	p	OR	CI 95%
Emotional symptoms (SDQ)	0.141	0.42	0.115	1	0.320	1.375	0.739-2.560
Behavior problems (SDQ)	0.401	0.41	0.980	1	0.454	1.330	0.639-2.764
Hyperactivity (SDQ)	0.862	0.27	10.043	1	0.088	1.614	0.929-2.771
Peer problems (SDQ)	1.130	0.47	5.756	1	0.180	1.776	0.791-3.987
Lack of prosocial behavior (SDQ)	0.547	0.52	1.115	1	0.027	2.809	1.199-6.582
Depression (BDI-II)	1.398	0.28	24.403	1	‹ 0.001	6.357	3.613-11.183
Smoking	1.242	0.38	10.461	1	0.593	1.354	0.457-4.017
Alcohol use	0.859	0.33	6.817	1	0.010	2.353	1.259-4.399
Drug use	1.045	0.38	7.724	1	0.637	0.828	0.375-1.829
Constant	-3.39	0.19	322.288	1	0.213		

Note. SDQ= Strengths and Difficulties Questionnaire; BDI-II= Beck Depression Inventory; SE=Standard error; df= Degrees of freedom; OR= Odds ratio; CI= Confidence interval.

Discussion

The present study analyzed the DSH, its characteristics and the risk factors associated with them in the groups of Spanish adolescents included in two European multicenter studies (SEYLE and WE-STAY).

The DSH prevalence rates of 1.56% and 0.92% found in these samples are at the lower end of the scale of rates evidenced in samples from the other European countries participating in the SEYLE and WE-STAY studies; the lowest rate (1.9%) was found in Romania, while Germany presented the highest rate (10.4%).

Prevalence rates varied according to the population groups analyzed. Statistically significant differences were found in the comparison of males across both studies (the prevalence of DSH among young men in the SEYLE study was 3.5 times higher than in the WE-STAY group). Previous studies have also found wide differences in prevalence figures for self-injurious behaviors, ranging from 3% (Taliaferro & Muehlenkamp, 2015) to 11.5% (Madge et al., 2008), with the differences being explained, fundamentally, by the heterogeneity of the concept of self-injurious behavior employed and by differences in the methods used for the detection of cases (Hargus, Hawton & Rodham, 2009; Silverman, Berman, Sanddal, O'Carroll & Joiner, 2007). The studies compared here also showed variations in rates of prevalence, despite being carried out at similar times, with samples of similar characteristics and with similar evaluation methods; thus, it is likely that, in addition to conceptual and methodological differences, there are other circumstances that influence the variability of the prevalence of self-injurious behaviors, such as the scarcity of the phenomenon studied, which leads to small variations in the absolute number of affected people resulting in large changes in rates.

The rates of self-injury observed in the Spanish samples of the SEYLE and WE-STAY studies are lower than those observed in other Spanish samples. A study with 1,171 secondary school students (518 boys and 653 girls) aged between 12 and 16 from state and private schools in Barcelona and surrounding areas (Kirchner, Ferrer, Forns & Zanini, 2011) found a prevalence of 11.4% of DSH in the previous year. This study used a different evaluation method, the Youth Self Report (YSR) scale (Achenbach, 1991), and of the positive responses to the item that investigated

self-injurious behaviors, 2.9% answered "completely true" and 8.5% "possibly true". Another recent study, conducted with a large sample of 1664 adolescents (average age = 16.12 years) in the Autonomous Community of La Rioja found that 4.1% had attempted to take their own lives in the previous year (Fonseca-Pedrero et al., 2018), although the survey did not assess self-injurious behaviors. Another Spanish study provides figures of 21.7% for lifetime deliberate self-harm, although the data are not comparable because it is a clinical sample (adolescents seen in psychiatric outpatient clinics in a general hospital) (Díaz de Neira et al., 2015).

As with data from previous studies, the analysis of prevalence rates in the SEYLE and WE-STAY studies disaggregated by sex does not provide clear results that could conclusively establish the influence of sex on DSH. However, different patterns of self-injury between the sexes were found: in one of the studies, males self-injured more frequently through self-inflicted blows and burns, while females more often cut or scratched themselves. It seems that the male pattern (blows, burns) has characteristics of immediate tension-releasing impulse, while the female one is a more complex behavior, less impulsive, more compulsive and in which, in addition to the pain, what is sought is to leave marks that denote a distinct identity or personality, in the manner of tattoos or piercings, that is, with an identity-related meaning.

The risk factors linked to the presence of DSH differed in the two studies analyzed, which is consistent with the fact that self-harm risk factors demonstrate very low specificity and low predictive value (Barrigón & Baca-García, 2018). The following risk factors appeared as significantly associated with DSH in only one of the studies: hyperactivity, problems with peers, smoking, drug use and lack of prosocial behavior. Risk factors associated with DSH in both studies were the presence of depressive symptoms and alcohol use.

Thus, the presence of depressive symptoms and alcohol use emerge the factors most associated with DSH. A depressive state of mind has been shown to be a factor associated with self-harm behaviors in most studies conducted with adolescents (Dougherty et al., 2009; Fliege, Lee, Grimm & Klapp, 2009; Hawton, Rodham, Evans & Weatherall, 2002; Lowenstein, 2005; Portzky & van Heeringen, 2007; Skegg, 2005; Stewart, Baiden & Theall-Honey, 2014; Swahn et al., 2012; Vajani, Annest, Crosby, Alexander & Millet, 2007; Valencia-Agudo, Burcher, Ezpeleta & Kramer, 2018). It should be noted that the effect of depressive symptoms is complex and depends not only directly on their presence but also on their intensity, the coexistence with other associated psychopathological symptoms and the sex of the person involved (Lundh, Wångby-Lundh & Bjärehed, 2011).

Regarding the use of alcohol and drugs, with the exception of some studies which do not find a relationship between self-injurious behaviors and these variables (Madge et al., 2008), their direct influence on self-harm behaviors has been robustly established (Balázs, Győri, Horváth, Mészáros & Szentiványi, 2018; Fulwiler, Forbes, Santangelo & Folstein, 1997; Heerde et al., 2015; Ilomäki, Räsänen, Viilo, Hakko & STUDY-70 Workgroup, 2007; Vargas-Martínez et al., 2018).

In terms of the other factors associated with DSH, the data in the literature are less clear. Prosocial behavior is a complex behavior resulting from the interaction between intrapsychic and environmental aspects. It is likely that the search for a link between personality traits and suicidal behavior, which was not a focus of this study, would provide more conclusive data of association with self-injury than the study of behavioral manifestations such as prosocial behavior (Villar et al., 2018) or other behavioral variables, such as the lack of relationships with colleagues, a variable for which the literature also provides diverging data (Kaminski et al., 2010; Ruchkin, Sukhodolsky, Vermeiren, Koposov & Schwab-Stone, 2006).

Hyperactivity is similar, yielding a significant but weak association with suicidal behavior only in the SEYLE study. Previous studies have found a relationship between hyperactivity as a disorder and self-injurious behaviors (Balázs et al., 2018; Bentley, Cassiello-Robbins, Vittorio, Sauer-Zavala & Barlow, 2015; Meszaros et al., 2017). It has also been postulated that the relationship of hyperactivity with self-harm could be indirect through common factors such as impulsivity, as indicated by the results of different studies, which also show that the association would be different depending on sex (Hinshaw et al., 2012; Huang et al., 2017; Kashden, Fremouw, Callahan & Franzen, 1993; Meza, Owens & Hinshaw, 2016). The characteristics of the present study do not allow the nature of the influence of hyperactivity or impulsivity on self-injurious behaviors to be defined.

Finally, drug use and smoking were shown to be factors significantly associated with self-injurious behaviors in the SEYLE study but not in WE-STAY. The case of smoking deserves special consideration since social changes related to smoking took place during the period of time between the two studies: a price increase, the implementation of prevention and awareness programs aimed at the young population, and the enactment of laws to restrict smoking (Law 42/2010, December 30, 2010). Other earlier studies have also found a link between smoking and self-injurious behavior (Huang et al., 2017; Madge et al., 2011; Romero, Rodríguez, Villar & Gómez-Fraguela, 2017). The hypothesis that the measures taken in Spain to restrict smoking could have modified the prevalence of DSH in young people is attractive but would need an analysis of longer time series for confirmation.

The present study presents a series of limitations, among them the fact that it is an analysis of retrospective data which was collected by self-report, that the populations, albeit similar, are not totally comparable, and that the

populations are not representative of Spanish adolescents, which prevents generalization to population prevalence. Moreover, differences in the data between two studies with similar methodology and population could raise doubts about the reliability of the results. However, it is also worth highlighting the main strengths of this study, which include the fact that the results analyzed are from two methodologically similar studies with large and homogeneous samples, and the methodological soundness guaranteed by the international projects of which they form a part.

In conclusion, the analysis of two studies on self-injurious behaviors in adolescents, carried out with a similar methodology and in populations with comparable sociodemographic characteristics in close temporal proximity shows that DSH rates vary depending on study and sex and range from 0.58% to 2.08%, that men self-harm more frequently by self-inflicted blows and burns, while women more frequently cut and scratch themselves, and that the presence of depressive symptoms and alcohol use are the factors most strongly associated with an increased risk of DSH; both would be the priority factors on which preventive and intervention campaigns should focus.

Acknowledgements

The SEYLE and WE-STAY projects have been financed by the European Union through the Seventh Framework Program (FP7), through grant agreements number HEALTH-F2.2009-223091 and HEALTH-2010e241542, respectively. The authors would like to thank all the researchers and staff who collaborated on both projects.

Conflict of interests

The authors declare that there is no conflict of interest.

Bibliography

Achenbach, T. M. (1991). Manual for the Youth Self-Report and 1991 Profile. Burlington, VT: University of Vermont Department of Psychiatry.

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

Balázs, J., Győri, D., Horváth, L. O., Mészáros, G. & Szentiványi, D. (2018). Attention-deficit hyperactivity disorder and nonsuicidal self-injury in a clinical sample of adolescents: the role of comorbidities and gender. *BMC Psychiatry*, *18*, 34. doi:10.1186/s12888-018-1620-3.

Barrigón, M. L. & Baca-García, E. (2018). Retos actuales en la investigación en suicidio. *Revista de Psiquiatría y Salud Mental*, *11*, 1-3. doi:10.1016/j.rpsm.2017.10.001.

Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. (1996). Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*, 588-597. doi:10.1207/s15327752jpa6703_13.

Bentley, K. H., Cassiello-Robbins, C. F., Vittorio, L., Sauer-Zavala, S. & Barlow, D. H. (2015). The association between nonsuicidal self-injury and the emotional disorders: A meta-analytic review. *Clinical Psychology Review*, *37*, 72-88. doi:10.1016/j.cpr.2015.02.006.

Bifulco, A., Schimmenti, A., Moran, P., Jacobs, C., Bunn, A. & Rusu, A. C. (2014). Problem parental care and teenage deliberate self-harm in young community adults. *Bulletin of the Menninger Clinic*, *78*, 95-114. doi:10.1521/bumc.2014.78.2.95.

Blasco-Fontecilla, H. (2018). Postmodernity, addictive societies, cannabis and suicidal behaviour: Towards a brave new world? *Adicciones*, *30*, 3-8. doi:10.20882/adicciones.1104.

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.

Bousoño, M., Al-Halabí, S., Burón, P., Garrido, M., Díaz-Mesa, E. M., Galván, G., … Bobes, J. (2019). Predictive factors of alcohol consumption in adolescents: data from 1-year follow-up prospective study. *Adicciones, 31*, 52-63. doi:10.20882/adicciones.998.

Bresin, K. & Schoenleber, M. (2015). Gender differences in the prevalence of nonsuicidal self-injury: A meta-analysis. *Clinical Psychology Review*, *38*, 55-64. doi:10.1016/j.cpr.2015.02.009.

Brunner, R., Kaess, M., Parzer, P., Fischer, G., Carli, V., Hoven, C. W., … Wasserman, D. (2014). Life-time prevalence and psychosocial correlates of adolescent direct self-injurious behavior: a comparative study of findings in 11 European countries. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*, 337-348. doi:10.1111/jcpp.12166.

Byrne, B. M., Stewart, S. M. & Lee, P. W. (2004). Validating the beck depression inventory-II for Hong Kong community adolescents. *International Journal of Testing, 4*, 199-216. doi:10.1207/s15327574ijt0403_1.

Carli, V., Hoven, C.W., Wasserman, C., Chiesa, F., Guffanti, G., Sarchiapone, M., … Wasserman D. (2014). A newly identified group of adolescents at "invisible" risk for psychopathology and suicidal behavior: findings from the SEYLE study. *World Psychiatry, 13,* 78-86. doi:10.1002/wps.20088.

Cipriano, A., Cella, S. & Cotrufo, P. (2017). Nonsuicidal self-injury: A systematic review. *Frontiers in Psychology, 8,* 1946. doi:10.3389/fpsyg.2017.01946.

Díaz de Neira, M., García-Nieto, R., de León-Martinez, V., Pérez Fominaya, M., Baca-García, E. & Carballo, J. J. (2015). Prevalence and functions of self-injurious thoughts and behaviors in a sample of Spanish adolescents

assessed in mental health outpatient departments. *Revista de Psiquiatria y Salud Mental*, *8*, 137-145. doi:10.1016/j.rpsm.2013.09.003.

Dougherty, D. M., Mathias, C. W., Marsh-Richard, D. M., Prevette, K. N., Dawes, M. A., Hatzis, E. S., … Nouvion, S. O. (2009). Impulsivity and clinical symptoms among adolescents with non-suicidal self-injury with or without attempted suicide. *Psychiatry Research*, *169*, 22-27. doi:10.1016/j.psychres.2008.06.011.

Fliege, H., Lee, J.R., Grimm, A. & Klapp, B. F. (2009). Risk factors and correlates of deliberate self-harm behavior: a systematic review. *Journal of Psychosomatic Research*, *66*, 477-493. doi:10.1016/j.jpsychores.2008.10.013.

Fonseca-Pedrero, E., Inchausti, F., Pérez-Gutiérrez, L., Aritio Solana, R., Ortuño-Sierra, J., Sánchez-García, M. Á., … Pérez de Albéniz Iturriaga, A. (2018). Ideación suicida en una muestra representativa de adolescentes españoles. *Revista de Psiquiatría y Salud Mental*, *11*, 76-85. doi:10.1016/j.rpsm.2017.07.004.

Fulwiler, C., Forbes, C., Santangelo, S. L. & Folstein, M. (1997). Self-mutilation and suicide attempt: distinguishing features in prisoners. *The Journal of the American Academy of Psychiatry and the Law*, *25*, 69-77.

Goodman, R., Meltzer, H. & Bailey, V. (2003). The Strengths and Difficulties Questionnaire: a pilot study on the validity of the self-report version. *International Review of Psychiatry*, *15*, 173-177. doi:10.1080/0954026021000046137.

Gratz, K. L. (2001). Measurement of Deliberate Self-Harm: Preliminary Data on the Deliberate Self-Harm Inventory. *Journal of Psychopathology and Behavioral Assessment*, *23*, 253-263. doi:10.1023/A:1012779403943.

Hargus, E., Hawton, K. & Rodham, K. (2009). Distinguishing between subgroups of adolescents who self-harm. *Suicide & Life-Threatening Behavior*, *39*, 518-537. doi:10.1521/suli.2009.39.5.518.

Hawton, K. & Harriss, L. (2008). Deliberate self-harm by under-15-year-olds: characteristics, trends and outcome. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49*, 441-448. doi:10.1111/j.1469-7610.2007.01852.x.

Hawton, K., Rodham, K., Evans, E. & Weatherall, R. (2002). Deliberate self-harm in adolescents: self-report survey in schools in England. *British Medical Journal*, *325*, 1207-1211.

Heerde, J. A., Toumbourou, J. W., Hemphill, S. A., Herrenkohl, T. I., Patton, G. C. & Catalano, R. F. (2015). Incidence and Course of Adolescent Deliberate Self-Harm in Victoria, Australia, and Washington State. *Journal of Adolescent Health*, *57*, 537-544. doi:10.1016/j.jadohealth.2015.07.017.

Hinshaw, S. P., Owens, E. B., Zalecki, C., Huggins, S. P., Montenegro-Nevado, A. J., Schrodek, E. & Swanson, E. N. (2012). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *Journal of Consulting and Clinical Psychology*, *80*, 1041-1051. doi:10.1037/a0029451.

Huang, Y.H., Liu, H.-C., Tsai, F.-J., Sun, F.-J., Huang, K.-Y., Chiu, Y.-C., … Liu, S.-I. (2017). Correlation of impulsivity with self-harm and suicidal attempt: a community study of adolescents in Taiwan. *BMJ Open*, *7*, e017949. doi:10.1136/bmjopen-2017-017949.

Ilomäki, E., Räsänen, P., Viilo, K., Hakko, H. & STUDY-70 Workgroup. (2007). Suicidal behavior among adolescents with conduct disorder–the role of alcohol dependence. *Psychiatry Research*, *150*, 305-311. doi:10.1016/j.psychres.2006.02.011.

Kaess, M., Fischer-Waldschmidt, G., Resch, F. & Koenig, J. (2017). Health related quality of life and psychopathological distress in risk taking and self-harming adolescents with full-syndrome, subthreshold and without borderline personality disorder: rethinking the clinical cut-off? *Borderline Personality Disorder and Emotion Dysregulation*, *4*, 7. doi:10.1186/s40479-017-0058-4.

Kaminski, J. W., Puddy, R. W., Hall, D. M., Cashman, S. Y., Crosby, A. E. & Ortega, L. A. G. (2010). The relative influence of different domains of social connectedness on self-directed violence in adolescence. *Journal of Youth and Adolescence*, *39*, 460-473. doi:10.1007/s10964-009-9472-2.

Kashden, J., Fremouw, W. J., Callahan, T. S. & Franzen, M. D. (1993). Impulsivity in suicidal and nonsuicidal adolescents. *Journal of Abnormal Child Psychology*, *21*, 339-353.

Kirchner, T., Ferrer, L., Forns, M. & Zanini, D. (2011). Self-harm behavior and suicidal ideation among high school students. Gender differences and relationship with coping strategies. *Actas Españolas de Psiquiatría*, *39*, 226-235.

Lenkiewicz, K., Racicka, E. & Bryńska, A. (2017). Self-injury - placement in mental disorders classifications, risk factors and primary mechanisms. Review of the literature. *Psychiatria Polska*, *51*, 323-334. doi:10.12740/PP/62655.

Lowenstein, L. F. (2005). Youths who intentionally practise self-harm. Review of the recent research 2001-2004. *International Journal of Adolescent Medicine and Health*, *17*, 225-230.

Lundh, L.G., Wångby-Lundh, M. & Bjärehed, J. (2011). Deliberate self-harm and psychological problems in young adolescents: evidence of a bidirectional relationship in girls. *Scandinavian Journal of Psychology*, *52*, 476-483. doi:10.1111/j.1467-9450.2011.00894.x.

Madge, N., Hawton, K., McMahon, E. M., Corcoran, P., De Leo, D., de Wilde, E. J., … Arensman, E. (2011). Psychological characteristics, stressful life events and deliberate self-harm: findings from the Child & Adolescent Self-harm in Europe (CASE) Study. *European Child & Adolescent Psychiatry*, *20*, 499-508. doi:10.1007/s00787-011-0210-4.

Madge, N., Hewitt, A., Hawton, K., de Wilde, E. J., Corcoran, P., Fekete, S., … Ystgaard, M. (2008). Deliberate self-harm within an international community sample of young people: comparative findings from the Child &

Adolescent Self-harm in Europe (CASE) Study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49*, 667-677. doi:.10.1111/j.1469-7610.2008.01879.x.

McCormick, E. M., Qu, Y. & Telzer, E. H. (2017). Activation in context: Differential conclusions drawn from cross-sectional and longitudinal analyses of adolescents' cognitive control-related neural activity. *Frontiers in Human Neuroscience*, *11*, 141. doi:10.3389/fnhum.2017.00141.

Meszaros, G., Horvath, L. O. & Balazs, J. (2017). Self-injury and externalizing pathology: a systematic literature review. *BMC Psychiatry*, *17*, 160. doi:10.1186/s12888-017-1326-y.

Meza, J. I., Owens, E. B. & Hinshaw, S. P. (2016). Response inhibition, peer preference and victimization, and self-harm: Longitudinal associations in young adult women with and without ADHD. *Journal of Abnormal Child Psychology*, *44*, 323-334. doi:10.1007/s10802-015-0036-5.

Morgan, C., Webb, R. T., Carr, M. J., Kontopantelis, E., Green, J., Chew-Graham, C. A., … Ashcroft, D. M. (2017). Incidence, clinical management, and mortality risk following self-harm among children and adolescents: cohort study in primary care. *British Medical Journal*, *359*, j4351. doi:10.1136/bmj.j4351.

Muehlenkamp, J. J., Claes, L., Havertape, L. & Plener, P. L. (2012). International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. *Child and Adolescent Psychiatry and Mental Health*, *6*, 10. doi:10.1186/1753-2000-6-10.

Nock, M. K. (2010). Self-injury. *Annual Review of Clinical Psychology*, *6*, 339-363. doi:10.1146/annurev.clinpsy.121208.131258.

Pattison, E. M. & Kahan, J. (1983). The deliberate self-harm syndrome. *The American Journal of Psychiatry*, *140*, 867-872. doi:10.1176/ajp.140.7.867.

Pisinger, V. S. C., Hawton, K. & Tolstrup, J. S. (2018). Self-injury and suicide behavior among young people with perceived parental alcohol problems in Denmark: a school-based survey. *European Child & Adolescent Psychiatry*, *27*, 201-208. doi:10.1007/s00787-017-1031-x.

Portzky, G. & van Heeringen, K. (2007). Deliberate self-harm in adolescents. *Current Opinion in Psychiatry*, *20*, 337-342. doi:10.1097/YCO.0b013e3281c49ff1.

Romero, E., Rodríguez, C., Villar, P. & Gómez-Fraguela, X. A. (2017). Intervention on early-onset conduct problems as indicated prevention for substance use: A seven-year follow up. *Adicciones*, *29*, 150-162. doi:10.20882/adicciones.722.

Ruchkin, V., Sukhodolsky, D. G., Vermeiren, R., Koposov, R. A. & Schwab-Stone, M. (2006). Depressive symptoms and associated psychopathology in urban adolescents: A cross-cultural study of three countries. *Journal of Nervous and Mental Disease*, *194*, 106-113. doi:10.1097/01.nmd.0000198142.26754.18.

Silverman, M. M., Berman, A. L., Sanddal, N. D., O'Carroll, P. W. & Joiner, T. E. (2007). Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 2: Suicide-related ideations, communications, and behaviors. *Suicide & Life-Threatening Behavior*, *37*, 264-277. doi:10.1521/suli.2007.37.3.264.

Skegg, K. (2005). Self-harm. *Lancet*, *366*, 1471-1483. doi:10.1016/S0140-6736(05)67600-3.

Somerville, L. H., Hare, T. & Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of Cognitive Neuroscience*, *23*, 2123-2134. doi:10.1162/jocn.2010.21572.

Sornberger, M. J., Heath, N. L., Toste, J. R. & McLouth, R. (2012). Nonsuicidal self-injury and gender: patterns of prevalence, methods, and locations among adolescents. *Suicide & Life-Threatening Behavior*, *42*, 266-278. doi:10.1111/j.1943-278X.2012.0088.x.

Stewart, S. L., Baiden, P. & Theall-Honey, L. (2014). Examining non-suicidal self-injury among adolescents with mental health needs, in Ontario, Canada. *Archives of Suicide Research*, *18*, 392-409. doi:10.1080/13811118.2013.824838.

Strittmatter, E., Kaess, M., Parzer, P., Fischer, G., Carli, V., Hoven, C.W., … Wasserman D. (2015). Pathological Internet use among adolescents: Comparing gamers and non-gamers. *Psychiatry Research*, *228*, 128-135. doi:10.1016/j.psychres.2015.04.029.

Swahn, M. H., Ali, B., Bossarte, R. M., Van Dulmen, M., Crosby, A., Jones, A. C. & Schinka, K. C. (2012). Self-harm and suicide attempts among high-risk, urban youth in the U.S.: shared and unique risk and protective factors. *International Journal of Environmental Research and Public Health*, *9*, 178-191. doi:10.3390/ijerph9010178.

Taliaferro, L. A. & Muehlenkamp, J. J. (2015). Risk factors associated with self-injurious behavior among a national sample of undergraduate college students. *Journal of American College Health*, *63*, 40-48. doi:10.1080/07448481.2014.953166.

Vajani, M., Annest, J. L., Crosby, A. E., Alexander, J. D. & Millet, L. M. (2007). Nonfatal and fatal self-harm injuries among children aged 10-14 years–United States and Oregon, 2001-2003. *Suicide & Life-Threatening Behavior*, *37*, 493-506. doi:10.1521/suli.2007.37.5.493.

Valencia-Agudo, F., Burcher, G. C., Ezpeleta, L. & Kramer, T. (2018). Nonsuicidal self-injury in community adolescents: A systematic review of prospective predictors, mediators and moderators. *Journal of Adolescence*, *65*, 25-38. doi:10.1016/j.adolescence.2018.02.012.

Vargas-Martínez, A. M., Trapero-Bertran, M., Gil-García, E. & Lima-Serrano, M. (2018). Impact of the Binge Drinking (BD) in Adolescence. Are we doing it right? *Adicciones*, *30*, 152-154. doi:10.20882/adicciones.1033.

Villar, F., Letemendia, E. E., Blasco, T., Toribio, T. P., Verge, M., Grifoll, M. del M. V., … Tejedor, C. C. (2018).

Análisis dimensional de la personalidad del adolescente con conducta suicida. *Actas Españolas de Psiquiatría*, *46*, 104-111.

Wasserman, D., Carli, V., Wasserman, C., Apter, A., Balazs, J., Bobes, J., … Hoven, C. W. (2010). Saving and Empowering Young Lives in Europe (SEYLE): A randomized controlled trial. *BMC Public Health*, *10*, 192. doi:10.1186/1471-2458-10-192.

Whitlock, J., Muehlenkamp, J., Purington, A., Eckenrode, J., Barreira, P., Baral Abrams, G., … Knox, K. (2011). Nonsuicidal self-injury in a college population: general trends and sex differences. *Journal of American College Health*, *59*, 691-698. doi:10.1080/07448481.2010.529626.

World Health Organization. (2015). Global School-Based Student Health Survey. Retrieved at http://www.who.int/chp/gshs/GSHS_Questionnaire_Core_2009_Spanish.pdf.

Yang, X. & Feldman, M. W. (2017). A reversed gender pattern? A meta-analysis of gender differences in the prevalence of non-suicidal self-injurious behaviour among Chinese adolescents. *BMC Public Health*, *18*, 66. doi:10.1186/s12889-017-4614-z.

Zetterqvist, M. (2015). The DSM-5 diagnosis of nonsuicidal self-injury disorder: a review of the empirical literature. *Child and Adolescent Psychiatry and Mental Health*, *9*, 31. doi:10.1186/s13034-015-0062-7.

Relationship of problematic cannabis use among youth in Spain with perceived risk, environmental factors and sociodemographic factors

Relación del consumo problemático de cannabis en la población joven de España con el riesgo percibido, los factores ambientales y los factores sociodemográficos

Jorge Arias-de la Torre*,**,***, Francisco José Eiroa-Orosa****, Antonio J. Molina**, Esther Colell*****, Verónica Dávila-Batista**,***, Fernando Moreno-Montero****, Noemí Robles******, Jose M. Valderas*******, Vicente-Martín**,***.

* Institute of Psychiatry, Psychology and Neurosciences (IoPPN). King's College London, London. UK.
** Instituto de Biomedicina (IBIOMED). Universidad de León, León. España.
*** Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid. España.
**** Departamento de Psicología Clínica y Psicobiología, Facultad de Psicología. Universidad de Barcelona, Barcelona. España.
***** Consorcio Sanitario de Barcelona, Barcelona. España.
****** eHealth Center. Universitat Oberta de Catalunya, Barcelona. España.
******* Health Services and Policy Research Group. University of Exeter Medical School, Exeter. UK.

Abstract

The relationship of problematic cannabis consumption with perceived risk, socioenvironmental and sociodemographic factors among youth in Spain is not well known. The aims of this study are: 1) to describe the patterns of cannabis consumption (problematic and non-problematic) in Spanish youth, and 2) to explore whether problematic cannabis consumption is related to perceived risk, environmental factors and individual sociodemographic characteristics. A cross-sectional design based on data from the 2015/16 Spanish Household Survey on Alcohol and Drugs (EDADES) was performed. Individuals between 15 and 35 years old having used cannabis during the last year with a complete Cannabis Abuse Screening Test (CAST) were included (N = 1,674). Problematic consumption (CAST >= 7) was considered as dependent variable. Perceived risk, environmental factors (availability of the substance and exposure to consumption situations) and sociodemographic factors were taken as independent variables. Descriptive analyses of consumption patterns were performed and univariable and multivariable Poisson regression models were done. All analyses were stratified by gender. Problematic cannabis consumption was more frequent among men (38.9 %) than among women (23.2 %). While among men, problematic use was related to environmental factors and educational level, among women it was associated with perceived risk and unemployment. Problematic cannabis consumption among Spanish youth is associated with

Resumen

La relación entre el consumo problemático de cannabis, el riesgo percibido y los factores socioambientales y sociodemográficos no es clara actualmente. Los objetivos del estudio son: describir los patrones de consumo de cannabis (problemático y no problemático) en la población joven de España y explorar como el consumo problemático se relaciona con el riesgo percibido, y los factores ambientales y sociodemográficos. Se llevó a cabo un diseño transversal basado en datos de la edición de 2015/2016 de la Encuesta Domiciliaria sobre Alcohol y Drogas (EDADES). La encuesta incluyó participantes de entre 15 y 35 años que habían consumido cannabis en al menos una ocasión durante el último año y que completaron el *Cannabis Abuse Screening Test* (CAST) (N = 1674). Se consideró el consumo problemático (CAST >= 7) como variable dependiente. Como variables independientes se consideraron el riesgo percibido, los factores ambientales (disponibilidad de la sustancia y exposición a situaciones de consumo) y los factores sociodemográficos. Se llevaron a cabo análisis descriptivos de los patrones de consumo y se realizaron modelos univariables y multivariables de Poisson. Todos los análisis se estratificaron por género. El consumo problemático fue más frecuente en hombres (38,9 %) que en mujeres (23,2 %). Mientras en hombres el consumo problemático se relacionó con factores ambientales y nivel educativo, en mujeres se asoció con riesgo percibido y desempleo.

Received: October 2018; Accepted: January 2020.

Send correspondence to:
Department of Psychological Medicine, Division of Academic Psychiatry, Institute of Psychiatry, Psychology and Neuroscience (IoPPN). King's College London, De Crespigny Park, London SE5 8AF. Tel. +44 754309727.
E-mail: Jorge.arias_de_la_torre@kcl.ac.uk.

different types of gender-related factors. Due to its representativeness at the population level and the validity of the measures, these results might have important implications on the development of prevention strategies targeted at problematic cannabis consumption.
Key words: Cannabis; Sociodemographic factors; Environmental factors; Perceived risk; Survey studies.

Dada la representatividad de los datos y la validez de las medidas, estos resultados podrían tener importantes implicaciones para el desarrollo de medidas preventivas contra el consumo problemático de cannabis.
Palabras clave: Cannabis; Factores sociodemográficos; Factores ambientales; Riesgo percibido; Estudios de encuestas.

Nowadays cannabis is one of the most consumed recreational drugs among the young population and one of the most burdensome worldwide (United Nations Office on Drugs and Crime, 2016). It has been estimated that around 17.2 million young European adults between 15 and 34 years old (about 14.1% of this segment of the population) have used cannabis at least once during the previous year, and around 9.8 million of those between 15 and 24 years old, 17.4% of this population group (European Monitoring Centre for Drugs and Drug Addiction, 2017). In this context of high prevalence of use, it is essential to determine which factors could lead to the development of a problematic pattern of consumption among sporadic users. It has been shown that problems associated with cannabis use are highly dependent on consumption patterns (Silins et al., 2014), with problematic use being consistently associated with severe and chronic health illnesses as well as with negative psychosocial consequences.

Several studies have been carried out to try to determine which factors are related to problematic cannabis consumption (Colell, Sánchez-Niubò, Delclos, Benavides & Domingo-Salvany, 2015; Kokkevi, Richardson, Florescu, Kuzman & Stergar, 2007; Observatorio Español de las Drogas y las Toxicomanías, 2016; Redonnet, Chollet, Fombonne, Bowes & Melchior, 2012). Gender and age differences have been consistently found, with a higher problematic consumption in male and younger populations (Arias-De la Torre et al., 2019; Rial et al., 2019). However, this literature usually focuses on specific population groups, such as students or specific work environments, and on specific determinants such as socio-economic and/or personality factors.

Regarding other variables related to problematic cannabis use, several studies have pointed out a strong relationship with risk perception (Grevenstein, Nagy & Kroeninger-Jungaberle, 2015; Kirst, Mecredy, Borland & Chaiton, 2014; Salloum, Krauss, Agrawal, Bierut & Grucza, 2018). However, many of these studies were carried out within general population samples, including both substance users and non-users. Carrying out separate studies may contribute to improving our understanding about how perceived risk could lead to the development of a problematic pattern of consumption. In addition, other variables that have been pointed out as being influential over cannabis problematic use are factors from the environment in which the individual lives, as the availability of the substance, the social exposure to consumption, and the socio-economic correlates (Kirst et al., 2014; Parnes, Smith & Conner, 2018). Knowing how environmental factors are related to problematic use could be helpful to propose more effective and efficient preventive strategies adapted to the context in which they will be implemented. Nevertheless, there is a lack of knowledge on the relationship between this type of variables and problematic use. Regarding socio-economic correlates, several studies have indicated that both employment status and educational level might be related to cannabis consumption in the young population (Colell et al., 2015; Teixidó-Compañó et al., 2018). Consequently, bearing in mind these variables when studying cannabis use may contribute to a better understanding of the different patterns of consumption.

Therefore, the aims of the present study are: (1) to describe the patterns of cannabis consumption (problematic and non-problematic) in the Spanish young population, and (2) to test whether problematic cannabis consumption is related to perceived risk, environmental and socio-demographic factors.

Material and methods

Design and study population

A cross-sectional design based on data from the 2015/2016 edition of the Spanish Household Survey on Alcohol and Drugs (EDADES) (Observatorio Español de las Drogas y las Toxicomanías, 2016) was carried out. EDADES is a representative survey of the Spanish population aged 15 to 64 years old. The sample was selected using a three-stage clustered sampling method without replacement, obtaining a response rate of 50.5%. The survey questionnaire contains information on cannabis consumption and its patterns, as well as environmental and socio-demographic variables.

As study population, individuals aged less than 36 years that have used cannabis at least once during the year prior to the interview and that completed the *Cannabis Abuse Screening Test* (CAST) were selected (n=1,674). Individuals without information on educational level (n=2; 0.1%), employment status (n=51; 3.1%), perceived risk regarding regular use (n=10; 0.6%), perception on the availability

of the substance (n=29; 1.7%) and/or social exposure to situations of consumption (n=11; 0.7%) were excluded. Finally, a total sample of 1,579 individuals was considered for the analyses.

Study variables

The dependent variable of the present study was problematic cannabis use evaluated through the CAST. This questionnaire, is a valid and reliable screening tool to detect a problematic pattern of cannabis use (Cuenca-Royo et al., 2012). This questionnaire is composed of 6 Likert-type items regarding the frequency of 5 different events within the 12 months prior to its administration: non-recreational smoking (2 items), memory problems related to consumption (1 item), preoccupation of parents or friends about consumption (1 item), unsuccessful attempts to quit (1 item) and other possible problems related to consumption. The items are scored on a 5-point Likert scale from 0 ("never"), to 4 ("very often"). A total score is obtained by adding each item of the scale, ranging from 0 to 24. The cut-off point for problem cannabis use was fixed at 7 or higher (AUC=0.83) as proposed by a Spanish population validation study (Cuenca-Royo et al., 2012).

As explanatory variables, perceived risk, environmental (availability of the substance and exposure to consumption situations) and socio-demographic factors were selected. Perceived Risk was assessed by using a Likert-type item with a four-point response scale from 1 ("any problems"), to 4 ("many problems") regarding to the consequences of use of cannabis one or more times a week. Availability of the substance was evaluated through a Likert-type item with a 4-point response scale from 1 ("practically impossible"), to 4 ("very easy") regarding the difficulty to obtain the substance within 24 hours. Due to the low number of individuals in the levels of the variable "practically impossible" and "difficult", these categories were collapsed into "difficult". Exposure to consumption situations was assessed using a Likert-type item with a four-point response scale from 1 ("usually") to 4 ("never") about how often people were found smoking cannabis in their nearby environment. Additionally, the following socio-demographic factors were considered: gender, age as a dichotomous variable (from 16 to 25 years and from 26 to 35 years), educational level (university studies, secondary/high school and primary/no education) and employment status (working, unemployed and studying).

Statistical analyses

A descriptive analysis of the distribution of problematic cannabis use across the explanatory factors by gender was done. Differences were evaluated using Chi-square and Fisher F exact tests. Subsequently, bivariable and multivariable level Poisson regression models were used to test the association between explanatory factors and the dependent variable. From these models, crude Risk Ratio (RR), adjusted Risk Ratio (aRR) and their 95% Confidence Intervals (95%CI) were obtained. All multivariable models were adjusted for all the explanatory variables. The goodness of fit of multivariable models was assessed using a Chi Square test. Besides, the absence of multi-collinearity and the absence of interactions between variables were verified. The *p* values for the global statistical significance for each variable were obtained from Wald tests. All models were stratified by gender based on the theoretical framework proposed by previous studies (Arias-De la Torre et al., 2019; Colell et al., 2015; Kirst et al., 2014; Redonnet et al., 2012), and were carried out considering the weights derived from the complex sample design. All analyses were carried out using the statistical software Stata v.14 (StataCorp, 2015).

Results

Table 1 shows the characteristics of the studied sample and the patterns of cannabis consumption by gender. It can be observed that problematic cannabis consumption is more frequent in men (38.9%) than in women (23.2%). Among men, statistically significant differences in the patterns of consumption in all explanatory variables excluding age were found. However, among women, these differences were found in perceived risk, educational level and employment status.

In addition, Table 2 shows the relationship between problematic cannabis consumption and all explanatory variables. After adjustment, the availability of the substance, the exposure to consumption situations and the educational level were significantly related to problematic consumption ($p<.05$) among men. In contrast, among women only the perceived risk was associated with this pattern of consumption. In addition, and considering the specific categories for each of the variables included, a higher risk of problematic consumption was shown in men usually exposed to consumption situations (aRR: 1.42; 95CI%: 1.02-1.98 taking "never exposed" as reference category) and among those with educational level primary or illiterate (aRR: 1.68; 95CI%: 1.22-2.30 taking university studies as reference category). Among women, a higher risk of problematic consumption was exhibited among those that do not perceive "any problems" related to the consumption (aRR: 1.96; 95%CI: 1.01-3.80 taking "many problems" as reference category) and among those unemployed (aOR: 1.95; 95%CI: 1.27-2.98 taking working as reference category).

Discussion

The results show that, nowadays, the prevalence of problem cannabis use among the young population of Spain is high, particularly among men. Additionally, while among

Table 1. *Characteristics of the studied sample and differences in patterns of cannabis consumption in Spanish young population by gender. Spanish Household Survey on Alcohol and Drugs 2015/2016.*

	Men (N = 1,117)					Women (N = 462)				
	Non-Problematic users (n = 683; 61.1%)		Problematic users (n = 434; 38.9%)			Non-Problematic users (n = 355; 76.8%)		Problematic users (n = 107; 23.2%)		
	n	%	n	%	p value	n	%	n	%	p value
Perceived risk					‹ .001					.008
Many problems	107	15.7	57	13.1		56	17.8	10	9.4	
Some problems	179	26.2	74	17.1		101	28.5	25	23.4	
Few problems	253	37.0	163	37.6		127	35.8	34	31.8	
Any problems	144	21.1	140	32.3		71	20.0	38	35.5	
Availability (within 24 hours)					‹ .001					.271
Difficult	49	7.2	21	4.8		23	6.5	5	4.7	
Relatively easy	182	26.7	69	15.9		103	29.0	24	22.4	
Very easy	452	66.2	344	79.3		229	64.5	78	72.9	
Exposure to situations					‹ .001					.438
Never	92	13.5	34	7.8		37	10.4	9	8.4	
Rarely	125	18.3	57	13.1		60	16.9	12	11.2	
Frequently	249	36.5	157	36.2		130	36.6	44	41.1	
Usually	217	31.8	186	42.9		128	36.1	42	39.3	
Educational level					‹ .001					,022
University studies	95	13.9	45	10.4		83	23.4	14	13.1	
Secondary or high school	525	76.9	301	69.6		251	70.7	81	75.7	
Primary or illiterate	63	9.2	87	20.1		21	5.9	12	11.2	
Working					‹ .001					.010
Employment status	309	45.2	194	44.7		173	48.7	45	42.1	
Unemployed	166	24.3	150	34.6		59	16.6	32	29.9	
Student	208	30.5	90	20.7		123	34.7	30	28.0	
Age					.086					.670
16-25 years old	304	44.5	216	49.8		151	42.5	48	44.9	
26-35 years old	379	55.5	218	50.2		204	57.5	59	55.1	

Note. n: total sample analysed; %: percentage by column; 95% CI: 95% Confidence Interval.
p value: Chi square and Fisher exact tests. Non-problematic users: CAST ‹7; problematic users CAST ›=7.

men problematic use seems to be related to environmental factors and educational level, among women problem cannabis use might be associated with perceived risk and unemployment. Focusing on factors related to problematic consumption, it should be highlighted that problematic use prevalence is higher among men than in women, and for men, external and contextual factors seem to be closely related to this pattern of use. Among women, however, internal and personal factors seem to be particularly relevant. These results are consistent with those obtained by some previous studies (Bonar et al., 2017; Foster, Jeffries, Zvolensky & Buckner, 2016; Haug, Núñez, Becker, Gmel & Schaub, 2014; Kirst et al., 2014), and could be partially explained by gender differences in stress coping strategies among youngsters. While in countries with traditional family values such as Spain young men are expected to have an externally focused coping style and might be more driven by impulse and opportunity, young women are expected to have an internally focused coping style and might adjust their attitudes more to behavioural experiences (Casajuana Kögel et al., 2021; Foster et al., 2016; García-Sánchez et al., 2016). Therefore, as was suggested by previous research (Casajuana Kögel et al., 2021; Haug et al., 2014; Kokkevi et al., 2007; López-Pelayo, Miquel De Montagut, Casajuana Kögel & Balcells Oliveró, 2018), providing adaptive stress management strategies (focused on external factors in men, and on internal factors in women) might be an effective approach to face the problematic cannabis consumption. Nevertheless, to explore the possible bi-directional influence between the explanatory variables and problem cannabis use, it might be particularly relevant to establish specific preventive measures focused on the cause of problematic use, as is the case of unemployment among women though, as previous longitudinal research has suggested, the direction of this relationship is unclear (Popovici & French, 2014).

Table 2. *Relationship between problematic cannabis consumption with perceived risk, availability of the substance, exposure to consumption situations and socio-demographic factors in Spanish young population. Bivariable and multivariable analysis. Spanish Household Survey on Alcohol and Drugs 2015/2016.*

	Men				Women			
	RR (95% CI)	**p**	**aRR (95% CI)**	**p**	**RR (95% CI)**	**p**	**aRR (95% CI)**	**p**
Perceived risk		.006		.067		.007		.022
Many problems	1.00		1,00		1.00		1,00	
Some problems	0.66 (0.48-0.91)		0.67 (0.49-0.91)		1.17 (0.56-2.45)		1.21 (0.59-2.46)	
Few problems	0.94 (0.73-1.22)		0.91 (0.71-1.18)		1.28 (0.63-2.60)		1.31 (0.65-2.64)	
Any problems	1.21 (0.94-1.56)		1.06 (0.82-1.36)		2.27 (1.15-4.50)		1.96 (1.01-3.80)	
Availability (within 24 hours)		.001		.008				
Difficult	1.00		1.00		1.00	.629	1.00	.897
Relatively easy	1.03 (0.62-1.02)		1.04 (0.63-1.69)		0.63 (0.26-1.65)		0.65 (0.30-1.41)	
Very easy	1.57 (0.98-2.50)		1.41 (0.90-2.21)		0.92 (0.39-2.18)		0.81 (0.41-1.60)	
Exposure to situations		.001		.023		.091		.245
Never	1.00		1.00		1.00		1.00	
Rarely	1.05 (0.70-1.58)		1.11 (0.75-1.64)		0.66 (0.26-1.65)		0.67 (0.27-1.64)	
Frequently	1.24 (0.87-1.76)		1.21 (0.86-1.71)		1.39 (0.65-2.97)		1.24 (0.59-2.63)	
Usually	1.56 (1.11-2.20)		1.42 (1.02-1.98)		1.36 (0.63-2.94)		1.07 (0.51-2.22)	
Educational level		‹ .001		‹ .001		.114		.203
University studies	1.00		1.00		1.00		1.00	
Secondary or high school	1.17 (0.87-1.56)		1.14 (0.86-1.52)		1.47 (0.80-2.68)		1.38 (0.75-2.52)	
Primary or illiterate	1.91 (1.39-2.61)		1.68 (1.22-2.30)		1.79 (0.81-3.95)		1.48 (0.65-3.38)	
Employment status		.049		.165		.557		.536
Working	1.00		1.00		1.00		1.00	
Unemployed	1.19 (0.99-1.43)		1.09 (0.91-1.31)		2.21 (1.45-3.36)		1.95 (1.27-2.98)	
Student	0.75 (0.59-0.95)		0.79 (0.61-1.01)		1.10 (0.68-1.76)		1.09 (0.65-1.83)	
Age		.128		.222		.764		.545
16-25 years old	1.00		1.00		1.00		1.00	
26-35 years old	0.88 (0.74-1.04)		0.97 (0.81-1.15)		0.94 (0.64-1.38)		0.91 (0.61-1.35)	

Note. RR: crude Risk Ratio. aRR: adjusted Risk Ratio. 95% CI: 95% Confidence Interval. p: p value from Wald test. Multivariable models were adjusted for all the main explanatory variables and socio-demographic factors. All analyses were carried out considering the weights derived from the complex sample design. All multivariable models had a p-value›0.05 in the Chi Square goodness of fit test.

Regarding the directionality of the relationships between variables it should be noted that, as was shown in previous research, the relationship found between risk perception and problem use might be bi-directional (Salloum et al., 2018). The results from this study confirms the principle that "attitude follows behaviour". In this sense, longitudinal associations between cannabis use and risk perception could be reciprocal in nature, with a stronger association between cannabis use and lower subsequent risk perception. Further research in the Spanish population with longitudinal data, might be valuable to have a better understanding of this relationship in the Spanish context.

Regarding the employed methods, it should be noted that our study is one of the biggest carried out in Europe aimed at assessing problem cannabis use. Furthermore, a representative sample at country level and a valid and reliable tool designed specifically for this purpose were used. Previous studies do not commonly use representative samples and valid and reliable tools to determine the consumption patterns. The combination of this type of samples with the use of tools with adequate metric properties, such as the CAST questionnaire (Cuenca-Royo et al., 2012), might provide more accurate estimations of problematic use, and additionally may help improve the accuracy when determining the specific factors related to the different patterns.

Several limitations of the study need to be discussed. Firstly, its cross-sectional design precludes determining the causal direction of the relationship between problematic use and the explanatory factors. Nevertheless, this design could be adequate for identifying possible factors related to the pattern of consumption. Secondly, it should be noted that CAST's sensitivity and specificity are not optimal. Despite this, the CAST questionnaire has shown adequate metric properties (Cuenca-Royo et al., 2012). Additionally, it is the first time that this tool has been included in the EDADES

survey. Consequently, our results may serve as a baseline for a valid and reliable assessment of problematic cannabis use and its related factors. Finally, there are limitations inherent to the self-reported nature of the information (i.e., some people may be reluctant to answer certain questions related to drug use). Nevertheless, as the questionnaire was anonymous, answers can be considered as *a priori* unbiased. Besides, the sample response rate was 50.5%, with the representativeness at population level having been guaranteed (Observatorio Español de las Drogas y las Toxicomanías, 2016). Therefore, we consider that the studied population is adequate to develop the proposed aims.

In conclusion, our study shows that problem cannabis use among the Spanish youth is high, particularly among men, and might be related to different types of factors according to gender. Additionally, these results may serve as a starting point for further research within and outside Europe and, furthermore, they may help to identify factors associated with the development of problematic patterns of cannabis consumption.

Acknowledgements

We acknowledge to CIBERESP the funding received for this study.

Role of funding source

This study was funded by CIBER Epidemiology and Public Health (CIBERESP) as part of the aid for short internships granted to Jorge Arias-De la Torre in 2017 and 2018.

Conflict of interest: authors declare that they have no competing interestsatic with respect to the research, authorship, and/or publication of this article.

References

Arias-De la Torre, J., Fernández-Villa, T., Molina, A. J., Amezcua-Prieto, C., Mateos, R., Cancela, J. M., … Martín, V. (2019). Drug use, family support and related factors in university students. A cross-sectional study based on the uniHcos Project data. *Gaceta Sanitaria*, *33*, 141-147. doi:10.1016/j.gaceta.2017.10.019.

Bonar, E. E., Goldstick, J. E., Collins, R. L., Cranford, J. A., Cunningham, R. M., Chermack, S. T., … Walton, M. A. (2017). Daily associations between cannabis motives and consumption in emerging adults. *Drug and Alcohol Dependence*, *178*, 136-142. doi:10.1016/j.drugalcdep.2017.05.006.

Casajuana Kögel, C., López-Pelayo, H., Oliveras, C., Colom, J., Gual, A. & Balcells-Oliveró, M. M. (2021). The relationship between motivations for cannabis consumption and problematic use. *Adicciones*, *33*, 31-41. doi:10.20882/adicciones.1221.

Colell, E., Sánchez-Niubò, A., Delclos, G. L., Benavides, F. G. & Domingo-Salvany, A. (2015). Economic crisis and changes in drug use in the Spanish economically active population. *Addiction*, *110*, 1129-1137. doi:10.1111/add.12923.

Cuenca-Royo, A. M., Sánchez-Niubó, A., Forero, C. G., Torrens, M., Suelves, J. M. & Domingo-Salvany, A. (2012). Psychometric properties of the CAST and SDS scales in young adult cannabis users. *Addictive Behaviors*, *37*, 709-715. doi:10.1016/j.addbeh.2012.02.012.

European Monitoring Centre for Drugs and Drug Addiction. (2017). *European Drug Report 2017: Trends and Developments*. Luxembourg: Publications Office of the European Union.

Foster, D. W., Jeffries, E. R., Zvolensky, M. J. & Buckner, J. D. (2016). The interactive influence of cannabis-related negative expectancies and coping motives on cannabis use behavior and problems. *Substance Use & Misuse*, *51*, 1504-1511. doi:10.1080/10826084.2016.1188947.

García-Sánchez, S., Matalí, J. L., Martín-Fernández, M., Pardo, M., Lleras, M., Castellano-Tejedor, C. & Haro, J. M. (2016). Internalizing and externalizing personality and subjective effects in a sample of adolescent cannabis users. *Adicciones*, *28*, 231-241. doi:10.20882/adicciones.887.

Grevenstein, D., Nagy, E. & Kroeninger-Jungaberle, H. (2015). Development of risk perception and substance use of tobacco, alcohol and cannabis among adolescents and emerging adults: evidence of directional influences. *Substance Use & Misuse*, *50*, 376-386. doi:10.3109/10826084.2014.984847.

Haug, S., Núñez, C. L., Becker, J., Gmel, G. & Schaub, M. P. (2014). Predictors of onset of cannabis and other drug use in male young adults: results from a longitudinal study. *BMC Public Health*, *14*, 1202. doi:10.1186/1471-2458-14-1202.

Kirst, M., Mecredy, G., Borland, T. & Chaiton, M. (2014). Predictors of substance use among young adults transitioning away from high school: A narrative review. *Substance Use & Misuse*, *49*, 1795-1807. doi:10.3109/10826084.2014.933240.

Kokkevi, A., Richardson, C., Florescu, S., Kuzman, M. & Stergar, E. (2007). Psychosocial correlates of substance use in adolescence: A cross-national study in six European countries. *Drug and Alcohol Dependence*, *86*, 67-74. doi:10.1016/j.drugalcdep.2006.05.018.

López Pelayo, H., Miquel De Montagut, L., Casajuana Kögel, C. & Balcells Oliveró, M. (2018). Post-truth Cannabis use: back to evidence-based medicine. *Adicciones*, *30*, 237-242. doi:10.20882/adicciones.1095.

Observatorio Español de las Drogas y las Toxicomanías. (2016). *Encuesta sobre alcohol y otras drogas en España 2015/2016*. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad.

Parnes, J. E., Smith, J. K. & Conner, B. T. (2018). Reefer madness or much ado about nothing? Cannabis legalization outcomes among young adults in the United States. *International Journal of Drug Policy*, *56*, 116-120. doi:10.1016/j.drugpo.2018.03.011.

Popovici, I. & French, M. T. (2014). Cannabis Use, Employment, and Income: Fixed-Effects Analysis of Panel Data. *The Journal of Behavioral Health Services & Research*, *41*, 185-202. doi:10.1007/s11414-013-9349-8.

Redonnet, B., Chollet, A., Fombonne, E., Bowes, L. & Melchior, M. (2012). Tobacco, alcohol, cannabis and other illegal drug use among young adults: The socioeconomic context. *Drug and Alcohol Dependence*, *121*, 231-239. doi:10.1016/j.drugalcdep.2011.09.002.

Rial, A., Burkhart, G., Isorna, M., Barreiro, C., Varela, J. & Golpe, S. (2019). Cannabis use among adolescents: Risk pattern, implications and possible explanatory variables. *Adicciones*, *31*, 64-77. doi:10.20882/adicciones.1212.

Salloum, N. C., Krauss, M. J., Agrawal, A., Bierut, L. J. & Grucza, R. A. (2018). A reciprocal effects analysis of cannabis use and perceptions of risk. *Addiction*, *113*, 1077-1085. doi:10.1111/add.14174.

Silins, E., Horwood, L. J., Patton, G. C., Fergusson, D. M., Olsson, C. A., Hutchinson, D. M.,… Mattick, R. P. (2014). Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry*, *1*, 286-293. doi:10.1016/S2215-0366(14)70307-4.

StataCorp. (2015). *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LLC.

Teixidó-Compañó, E., Espelt, A., Sordo, L., Bravo, M. J., Sarasa-Renedo, A., Indave, B. I.,… Brugal, M. T. (2018). Differences between men and women in substance use: the role of educational level and employment status. *Gaceta Sanitaria*, *32*, 41-47. doi:10.1016/j.gaceta.2016.12.017.

United Nations Office on Drugs and Crime. (2016). *World Drug Report 2016*. New York: United Nations publication, Sales No. E.16.XI.7.

Alcohol consumption, neurological symptoms and diagnostic challenges in a patient with a percutaneous endoscopic gastrostomy

Consumo de alcohol, síntomas neurológicos y retos diagnósticos en un paciente con una gastrostomía percutánea

Pablo Barrio*, Marzia Merlino**, Mercè Balcells-Oliveró*.

* Clínic Institute of Neurosciences, Department of Psychiatry, Addictive Disorders Unit. Hospital Clínic, Barcelona. Spain.
** Psychiatry Unit, Department of Biomedical and Dental Sciences and Morphofunctional Imaging. University of Messina, Messina. Italy.

Addiction is a highly complex phenomenon that involves manifestations in a wide a range of dimensions, such as psychological, behavioral, medical and socioeconomic. Many theories have tried to explain the extreme behaviors addiction imposes on afflicted individuals. However, we're still far from reaching a definite and global explanation capable of unifying all the aspects of addiction (Nutt, Lingford-Hughes, Erritzoe & Stokes, 2015; Pober, 2013).

Alcohol is only second to nicotine in the list of the most consumed substances worldwide. Here we present a case report that describes a complex behavioral phenomenon in an alcohol dependent patient, which indeed serves to illustrate some of the core features of addiction.

The patient was a 60 year-old male, who carried a feeding gastrostomy due to a oropharyngeal cancer that required a bucopharyngectomy and an hemiglossectomy, as well as a tracheostomy in 1999. The patient suffered also from a long standing alcohol use disorder.

In the beginning of 2005 the patient was admitted to the Emergency Room due to an acute episode with gait ataxia, a decrease in his level of alertness, dysarthria and bilateral nistagmus in all gaze directions. Several ancillary tests were performed (CT scan, blood analysis, EKG, EEG), with no anomalies found. The symptoms resolved in less than 24 hours. Two more admissions took place during 2005 with identical symptoms. As the previous one, it was self-limited and anciliarry tests found no relevant anomalies.

In 2006 the patient was admitted to the Neurology Ward in order to study what were deemed as recurrent encephalopatic episodes. Again, several ancillary tests (CNS MRI, EEG, supraaortic Eco-Doppler, lumbar puncture) retrieved no relevant findings.

A possible epileptic origin was attributed to the clinical presentation, therefore levetiracetam 1000 mg per day was started. It was subsequently changed to valproic acid, and finally in 2008 to carbamazepine 600 mg daily. Despite all that, he was admitted several times to the Emergency Department due to the same neurological symptoms between 2006 and 2009.

It was not until August 2009 that the final diagnosis was made. The patient had been injecting himself large amounts of alcoholic beverages through his gastrostomy, a fact that had gone unrecognized up until then. He started being visited in the Addiction Unit, and several treatments, both psychological and pharmacological have been delivered so far. However, the patient has only attained brief abstinence periods. He has also presented some complications, such as gastric hemorrhage after drinking while on disulfiram.

Some considerations seem important while reviewing this case. First, the unusual route of administration. Not only is the gastrostomy a very rare manner of ingesting alcoholic beverages, but also one that allows for high alcohol blood concentrations to be achieved. This fact was the origin of the neurological symptoms the patient presented with several times. Although other non-oral routes

Received: May 2019; Accepted: November 2019.

Send correspondence to:
Pablo Barrio. Unidad de Conductas Adictivas, Hospital Clínico de Barcelona. Calle Villarroel 170 08036 Barcelona, España.
E-mail: pbarrio@clinic.cat.

of alcohol ingestion have been described, it seems they are also highly infrequent (Stogner, Eassey, Baldwin & Miller, 2014).

Second, despite his medical records (alcohol dependence and bucopharyngeal cancer) which are clearly associated with current alcohol ingestion, the physical state of the patient made it seem reasonable not to consider alcohol in the differential diagnostic process, since he could not ingest any beverage. Moreover, some of the classical symptoms that allow for the recognition of alcohol intoxication, such as fetor, where absent. Taken all together, despite the simple, final solution to the puzzle, the diagnostic process was a clear challenge. Proof of that are the 4 years follow-up by the Neurology Department, the several pharmacological treatments received and the amount of ancillary tests performed.

Finally, this case serves well to illustrate the nature of addiction itself, where ingestion of the substance becomes overriding, no matter what the difficulties and the consequences are.

As a conclusion, we believe this case shows how alcohol, a frequently consumed substance in our society, must remain an important option when working on several differential diagnoses, especially those with neurological symptoms such as stupor, ataxia and nistagmus.

Conflict of interests

The authors declare no conflict of interests.

References

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D. & Stokes, P. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews Neuroscience*, *16*, 305–312. doi:10.1038/nrn3939.

Pober, J. M. (2013). Addiction is not a natural kind. *Frontiers in Psychiatry*, *4*, 123. doi:10.3389/fpsyt.2013.00123.

Stogner, J. M., Eassey, J. M., Baldwin, J. M. & Miller, B. L. (2014). Innovative alcohol use: Assessing the prevalence of alcohol without liquid and other non-oral routes of alcohol administration. *Drug and Alcohol Dependence*, *142*, 74–78. doi:10.1016/j.drugalcdep.2014.05.026.

Chatbots to stop smoking: is this the future?

Un chatbot *para dejar de fumar. ¿Será el futuro?*

Gonzalo Segrelles-Calvo*, Ana María de Granda-Beltrán**,
José Ignacio de Granda-Orive***.

* Servicio de Neumología, Hospital Rey Juan Carlos. Universidad Rey Juan Carlos, Móstoles. Spain.
** Servicio de Psiquiatría. Fundación Jiménez Díaz, Madrid. Spain.
*** Servicio de Neumología, Hospital Universitario 12 de Octubre. Universidad Complutense, Madrid. Spain

Information and communication technologies (ICTs) and their applications in different fields, including medicine, are part of our everyday lives. The use of ICTs (telemedicine, gamification and mobile applications) is moving the conventional healthcare model forward and has already been employed in helping to quit smoking and promoting healthy life changes (Segrelles-Calvo, Escribano-Gimeno, Llopis-Pastor, Pérez-Gallán & de Granda-Orive, 2018). The use of chatbots (CHB), originally defined as *a program which makes a certain type of natural language conversation between man and computer possible* (Weizenbaum, 1966), has recently been introduced in healthcare. The value of CHB in a health setting is given by a series of characteristics acting as technical enablers: an amazing combination of immediacy (rapid response) and asynchrony (notifications and reminders), rapid use (usability), anonymity (when interacting with the machine, patients may feel less embarrassed and show their feelings), authentication (they can safely protect themselves), personalization, scalability (they can target large audiences profitably), monitoring (understanding habits is a first step in promoting healthy behaviour), acquiring knowledge (making commitment to change easier through understanding), affect (combining personality and emotional aspects in dialogues can increase satisfaction and commitment), and behaviour (they may influence behaviour) (Pereira & Díaz, 2019).

CHB have already been applied in various medical fields. An example is the exploration by Vaidyam, Wisniewski, Halamka, Kashavan and Torous (2019) of the existing evidence regarding CHB in the field of psychiatry and its role in the screening, diagnosis, and treatment of mental illness. They found that CHB were particularly helpful in psycho-education and self-adherence, with CHB having a high satisfaction rate. Kretzschmar, Tyroll, Pavarini, Manzini and Singh (2019) showed us that CHB could have great potential in helping people with mental issues, and may be seen as less stigmatizing than consultation support. Between 2014 and 2018, Pereira et al. (2019) analyzed health-related use of CHB regarding behavioural changes and found that the most active areas of use were primarily in mental and physical well-being and nutritional and metabolic disorders, with affect and knowledge being the human competences most sought by CHB to achieve behaviour change.

Could CHB thus help to quit smoking? Current evidence is scarce, but that which is available can highlight its potential effectiveness, focusing on: 1) Helping smokers to make progress in their stages of change: Almusharraf (2019) ran a CHB which used the motivational interview

Received: March 2020; Accepted: March 2020.

Send correspondence to:
Dr. José Ignacio de Granda-Orive. C/Cavanilles 43, 7ºE, 28007 Madrid.
E-mail: igo01m@gmail.com.

to get the smoker to move to the decision to quit, noting that the CHB really helped these subjects in their decision to advance the stage of change. 2) Helping smokers to quit: Simon, Krishnan-Sarin and Huang (2019) indicated the usefulness of CHB in promoting smoking cessation in adolescents/young people with low income. An interesting experience was reported by Folly, Riedo, Felder, Falomir-Pichastor and Desrichard (2016) who developed the program for the first version of *J'arrete de fumer* which sought to group *Facebook* communities of those willing to quit smoking on the same day. After six months, 13.5% of a total of 7,008 participants had stopped smoking. 3) Helping smokers to long-term abstinence: Dubosson, Schaer, Savioz and Schumacher (2017) developed a CHB (with motivating comments, information, and the ability to relate to users) to help them go beyond the relapse peak presented by these authors in earlier studies, observing that the CHB helped smokers to cope with craving and thus maintain abstinence over time. Perski, Crane, Beard and Brown (2019) aimed to compare whether a version of the *Smoke Free* app with a supportive CHB allowed for increased commitment and abstinence in the short term compared to the app without the CHB. The authors found that the CHB version of the app did increase commitment, leading to higher withdrawal rates, albeit with low follow-up rates.

Regarding the possible risks and limitations of CHB, Kretzschmar et al. (2019) noted that their capacity to recreate human interaction and offer individualized treatment may currently be limited, and the authors even wondered whether CHB could actually harm patients – such harm is generally invisible if not specifically tracked, which adds ethical concerns to the discussion. The authors indicate possible solutions to these risks and limitations: CHB must respect privacy and ensure user security, be evidence-based and be as transparent as possible.

We know that a clinical trial, called "Dejalo bot" is currently underway (https://clinicaltrials.gov/ct2/show/NCT03445507), developed by the tobacco addiction group of the Madrid Primary Healthcare Society (SOMAMFYC) and designed to demonstrate the effectiveness of a conversational CHB to help quit smoking. We are eager to hear the results.

Now is the time to build, develop, and demonstrate the potential of CHB, as it appears that they could now be useful and effective in helping people to quit smoking. The current evidence is scarce but hopeful.

Bibliography

Almusharraf, F. (2019). Motivating smokers to quit through a computer-based conversational system. Retrieved at https://tspace.library.utoronto.ca/bitstream/1807/94055/1/Almusharraf_Fahad_201903_MAS_thesis.pdf.

Dubosson, F., Schaer, R., Savioz, R. & Schumacher, M. (2017). Going beyond the relapse peak on social networks smoking cessation programs: Chatbot opportunities. *Swiss Medical Informatics*, *33*, 00397. doi:10.4414/smi.33.00397.

Folly, L., Riedo, G., Felder, M., Falomir-Pichastor, J. M. & Desrichard, O. (2016). Rapport de l'évaluation externe du programme « J'arrête de fumer » sur Facebook. Sur mandat du Fonds de Prévention du Tabagisme. Retrieved at http://www.obeeone.com/wp-content/uploads/2017/05/Rapport_JDF_BCLab-Re%CC%81sume%CC%81-nov.-2016.pdf.

Kretzschmar, K., Tyroll, H., Pavarini, G., Manzini, A. & Singh, I. (2019). NeurOx Young People's Advisory Group. *Biomedical Informatics Insights*, *11*, 1–9. doi:10.1177/1178222619829083.

Pereira, J. & Díaz, O. (2019). Using health chatbots for behavior change: A mapping study. *Journal of Medical System*, *43*, 135. doi:10.1007/s10916-019-1237-1.

Perski, O., Crane, D., Beard, E. & Brown, J. (2019). Does the addition of a supportive chatbot promote user engagement with a smoking cessation app? An experimental study. *Digit Health*, *5*, 1-13. doi:10.1177/2055207619880676.

Segrelles-Calvo, G., Escribano-Gimeno, I., Llopis-Pastor, E., Pérez-Gallán, M. & de Granda-Orive, J. I. (2018). Aplicaciones de las nuevas tecnologías en la deshabituación tabáquica: telemedicina y gamificación. *Prevención del Tabaquismo*, *20*, 129-140.

Simon, P., Krishnan-Sarin, S. & Huang, T. H. (2019). On using chatbots to promote smoking cessation among adolescents of low socioeconomic status. Retrieved at https://arxiv.org/pdf/1910.08814v1.pdf.

Vaidyam, A. N., Wisniewski, H., Halamka, J. D., Kashavan, M. S. & Torous, J.B. (2019). Chatbots and conversational agents in mental health: a review of the psychiatric landscape. *Canadian Journal of Psychiatry*, *64*, 456-464. doi:10.1177/0706743719828977.

Weizenbaum, J. (1966). ELIZA - a computer program for the study of natural language communication between man and machine. *Communications of the ACM*, *9*, 36-45. doi:10.1145/365153.365168.

Cannabis use and cyclic vomiting

Consumo de cannabis y vómitos cíclicos

Enriqueta Ochoa-Mangado*, Agustín Madoz-Gúrpide*.

* Psychiatry Department, Ramón y Cajal University Hospital. Ramón y Cajal Health Research Institute (IRYCIS). Department of Medicine and Medical Specializations, Faculty of Medicine. Alcalá University, Madrid. Spain.

Cannabis has traditionally been associated with antiemetic effects and used by some patients to control chemotherapy-induced vomiting. In 2004, however, cannabinoid hyperemesis or cyclic vomiting secondary to cannabis use was described (Allen, de Moore, Heddle & Twartz, 2004), and this has since been confirmed in a variety of studies (Contreras Narváez et al., 2016; Ochoa-Mangado, Madoz-Gúrpide, Jiménez Giménez & Salvador Vadillo, 2009; Simonetto, Oxentenko, Herman & Szostek, 2012).

Cannabinoid hyperemesis is defined as a condition characterized by the presence, in cannabis users, of cyclic episodes of nausea and uncontrolled vomiting. Such vomiting is relieved by compulsive bathing or showering in very hot water. Vomiting often occurs up to five times per hour, with cyclic episodes lasting from one to two days. Some cases are even more intense, however, both in frequency and duration. Vomiting is normally accompanied by other physical symptoms, such as polydipsia and diaphoresis, abdominal pain and weight loss. Although the condition may occur in early cannabis use, it manifests itself most commonly after several years. Cannabis abstinence, meanwhile, leads to cessation of vomiting.

The condition does not usually appear abruptly. Normally, sufferers describe early symptoms a few months previously, with morning episodes of nausea or vomiting on one or two days a week, causing reduced food intake for fear of vomiting and pain. The clinical picture is dose dependent, with greater intensity of vomiting due to increased cannabis use, and the type of vomiting and its relief with compulsive bathing in hot water is very typical. These baths are a learned behaviour that often do not appear in the initial episodes, but once sufferers become aware of their benefits they become compulsive (Allen et al., 2004; Ochoa-Mangado et al., 2009; Simonetto et al., 2012; Venkatesan, Hillard, Rein, Banerjje & Lisdahal, 2020).

The relevance of this condition becomes clear when the prevalence of cannabis use is taken into account. According to the EDADES survey, 35.2% of the population aged between 15 and 65 have used cannabis at least once in their lives; 9.1% did so in the previous month; and 1.2% use it daily (Observatorio Español de las Drogas y Adicciones (OEDA), 2018). This diagnosis must therefore be considered for any cannabis-using patient with repeated vomiting.

Patients suffering from this condition very frequently attend a variety of health services (ER, primary care, gastroenterology, etc.) and undergo numerous examinations, some potentially iatrogenic, which normally fail to find anything pathological.

Received: June 2020; Accepted: July 2020.

Corresponding author:
Enriqueta Ochoa. Servicio de Psiquiatría. Hospital Universitario Ramón y Cajal. Ctra Colmenar Km 9,100. 28034 Madrid.
E-mail: enriquetaochoam@gmail.com.

Differential diagnoses can be made with hyperemesis gravidarum, gastrointestinal disorders and those with metabolic causes, eating disorders, psychogenic vomiting and, of course, the symptoms of cannabis withdrawal. An important situation to consider is when cannabis is used precisely to mitigate the nausea and vomiting associated with other clinical conditions. Far from improving the situation, this will actually worsen the condition in some cases by causing cyclic hyperemesis.

Diagnostic suspicion of this condition is essential to guide diagnosis and treatment. Assessing the history and pattern of cannabis use should be part of the psychiatric interview. Compulsively taking multiple hot showers or baths can help in the differential diagnosis of unexplained vomiting, especially when use is heavy. The detection of cannabis in urinalysis can support the diagnosis, although it must be remembered that false positives may be caused by drugs which are widely used by these patients (ibuprofen, naproxen, pantoprazole, efavirenz), just as synthetic cannabinoids can cause false negatives (Glauser, 2019).

Emergency room treatment of hyperemesis requires the usual basic support measures and hydroelectrolytic balance restoration. In severe conditions, dehydration can lead to acute kidney failure. In such situations, capsaicin, haloperidol or benzodiazepines have been used with some success (Burillo-Putze & Llorens, 2017). Classic antiemetic drugs are not effective in any case.

The clinical management of cannabinoid hyperemesis syndrome requires continuous cannabis abstinence, and this involves acceptance by the patient of the relationship between cannabis and vomiting. The motivation to change will depend on the basis of this realisation since cannabis cessation is the only treatment (Sorensen, DeSanto, Borgelt, Phillips & Monte, 2017). In our still limited experience (Ochoa-Mangado et al., 2009), continuous cannabis abstinence eliminates cannabinoid hyperemesis symptoms. Relapses in use, however, lead to a recurrence of cyclic vomiting, which stops again on renewed cannabis abstinence.

The high frequency of cannabis use in our context and the severity that cyclic vomiting syndrome can reach, as well as the health and social costs involved, call for this diagnosis to be taken into account when patients report repeated vomiting with the characteristics described. Cannabis abstinence appears to be the only effective measure to correct the disorder. Further research is necessary to completely clarify the etiopathogenesis of the syndrome and to propose new therapeutic approaches.

Bibliography

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

Burillo-Putze, G. & Llorens, P. (2017). Perspectives in the treatment for cannabinoid hyperemesis syndrome. *Adicciones, 29,* 134-135. doi:10.20882/adicciones.875.

Contreras Narváez, C., Mola Gilbert, M., Batle de Santiago, E., Bigas Farreres, J., Giné Serven, E. & Cañeta Crespillo, J. (2016). Síndrome de hiperémesis cannabinoide. Reporte de seis nuevos casos clínicos y resumen de casos previos publicados. *Adicciones, 28,* 90-98.

Glauser, W. (2019). Nausea-inducing illness caused by cannabis still underdiagnosed. *CMAJ, 191,* E13167. doi:10.1503/cmaj.1095820.

Observatorio Español de las Drogas y Adicciones (OEDA). Encuesta sobre alcohol y otras drogas en España 2017 (EDADES). 2018.

Ochoa-Mangado, E., Madoz-Gúrpide, A., Jiménez Giménez, M. & Salvador Vadillo, E. (2009). Vómitos cíclicos secundarios al consumo de cannabis. *Gastroenterología y Hepatología, 32,* 406-409. doi:10.1016/j.gastrohep.2009.02.002.

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

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.

Venkatesan, T., Hillard, C. J., Rein, L., Banerjee, A. & Lisdahl, K. (2020). Patterns of cannabis use in patients with cyclic vomiting syndrome. *Clinical Gastroenterology and Hepatology, 18,* 1082-1090. doi:10.1016/j.cgh.2019.07.039.

Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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

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

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

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

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

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

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

PRESENTACIÓN DE LOS TRABAJOS

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

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

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

MIRANDO *al* FUTURO

PLAN TREVICTA®

DIARIO[1,2]
ORALES
RISPERIDONA/
PALIPERIDONA

MENSUAL[3]
XEPLION®
PALMITATO DE
PALIPERIDONA

4 AL AÑO[4]
TREVICTA®
PALMITATO DE
PALIPERIDONA

CP-146909-04-2020

Janssen Neuroscience

PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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

1. NOMBRE DEL MEDICAMENTO. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. CÓMPOSICION 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 equivaleptes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a la inyección trimestral de palmitato de paliperidona. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

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

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

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

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

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

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

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

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

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

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

Dosis omitidas

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

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

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

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

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

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

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

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

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

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

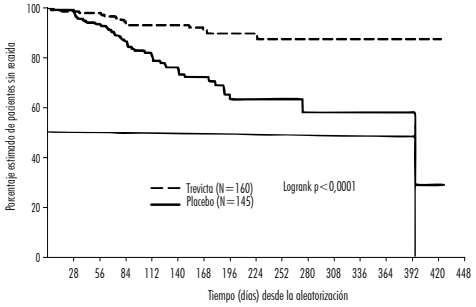


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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

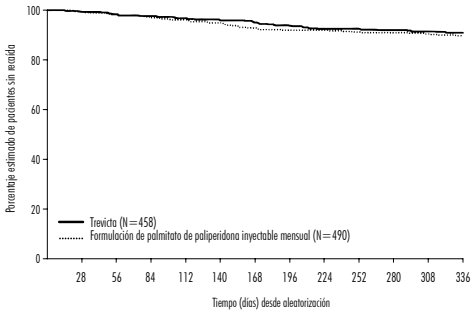


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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

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

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

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

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

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

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

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

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

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

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

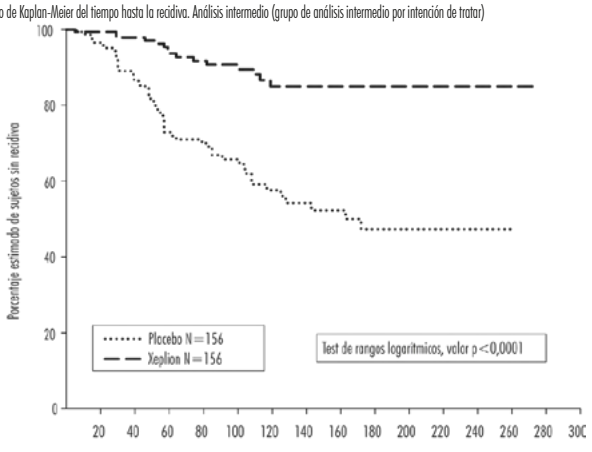
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CrCl=10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{∞}) de 1,5; 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACEUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada PVL: 168,18 €; PVP: 214,09 €; PVP (IVA): 222,65 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 218,62 €; PVP: 269,53 €; PVP (IVA): 280,31 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 269,10 €; PVP: 320,01 €; PVP (IVA): 332,81 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 403,64 €; PVP: 454,55 €; PVP (IVA): 472,73 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

MIRANDO *al* FUTURO

PLAN TREVICTA®

DIARIO[1,2] **ORALES** RISPERIDONA/ PALIPERIDONA

MENSUAL[3] **XEPLION®** PALMITATO DE PALIPERIDONA

4 AL AÑO[4] **TREVICTA®** PALMITATO DE PALIPERIDONA

CP-146909-04-2020

janssen Neuroscience

PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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