IMPACT FACTOR 2014
1.154

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

2015 | Vol. 27 | n.3

FUNDED BY:

adicciones

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

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 • Permanent paper according to stardard 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) & SCIENCE CITATION INDEX EXPANDED (SCIE).TOBACCO AND HEALTH ABSTRACTS (NISC), TOXIBASE

impact factor 2014: 1.154

editorial

originals / originales

review / revisión

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 2015

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

Drugs, Substance Use Disorder and Driving: Intervention of Health Professionals in the Treatment of Addictions

Drogas, Trastorno por Uso de Sustancias y Conducción: La intervención de los profesionales que trabajan en adicciones

Francisco Javier Álvarez*, Juan Carlos González-Luque**, María Seguí-Gómez**

*Pharmacology, Faculty of Medicine, Valladolid, Spain. **Directorate General for Traffic, Madrid, Spain.

Without a doubt, driving with the presence of drugs in the body is a real problem associated with a higher risk of being involved in road traffic collisions. Thus, intervention aimed at preventing drug driving is a top priority (Álvarez & González-Luque, 2010; DRUID, 2012; Schulze et al., 2012).

In this article, we use the concept *injuries due to road traffic collisions* and not the inadequate term, *traffic accidents*. Most injuries resulting from road traffic collisions are preventable (Álvarez, 2005; Redelmeier & McLellan, 2013), hence the aim of this article: making professionals aware of the fact that these injuries are avoidable, particularly professionals who treat patients for any Substance Use Disorder (SUD), and that they can and should intervene in the prevention of injuries due to road traffic collisions. Like the slogan of the 2004 World Health Day: "Road safety is no accident" (Álvarez, 2005).

When focusing on drugs and road safety, no doubt the most dangerous culprit is alcohol. Based on the results of the European DRUID project (DRUID, 2012; Schulze et al., 2012), intervention in the field of road safety and drugs other than alcohol cannot be carried out if it implies reducing the amount of alcohol-related interventions (Romano, Torres-Saavedra, Voas, & Lacey, 2014). For all professionals who work in the field of addictions, intervention related to alcohol, drugs and driving should be carried out integrally, and under no circumstances should alcohol be left out.

About the Terminology: Driving with the Presence of Drugs

This article includes the term *driving with the presence of drugs in the body*, which means there are quantifiable amounts of drugs in the driver´s organism, avoiding the term *driving under the effect or influence of drugs*. Some countries practice a *zero tolerance* policy, that is, any amount of drugs detected in the driver´s body is a punishable offence, whereas in other cases, a certain concentration level is established, a cut-off point, and any amount of drugs detected above that level is a driving offence. In other cases, *impairment* is the focus, in which the driver's display of evidence of impairment (driving under the influence or effect of drugs)— detected through the use of various field sobriety tests (coordination tests, etc.) (Álvarez & González-Luque, 2014)— is forbidden, and therefore punishable by law.

Received: March 2015; Accepted: June 2015

Address for correspondence:
F. Javier Álvarez, Farmacología, Facultad de Medicina, Universidad de Valladolid, C/ Ramón y Cajal, 7, 47005 Valladolid, España.
E-mail: alvarez@med.uva.es

Driving with the Presence of Drugs: Is it a Real Problem?

Previous studies have shown that driving with the presence of drugs is a frequent occurrence (Barlés, Escario, & Galbé, 2014; EMCDDA, 2007; Verstraete & Legrand, 2014), and the results should be analysed taking into account the different populations of drivers included in the study (general population, offenders, injured or killed drivers).

The European DRUID project (DRUID, 2012; Schulze et al., 2012) has provided data for Europe, obtained from random roadside testing: in 8.43% (range: 1.34-15.01%) of the drivers, the presence of alcohol/drugs/certain medications was confirmed, with large differences between countries: Italy (15.01%) and Spain (14.85%) were the countries in which drivers testing positive for these substances were most frequently found. At the European level, without taking into account the association between substances, the most frequently detected drug was alcohol, followed by cannabis (THC) (1.32%) and cocaine (0.42%). The highest prevalence of drivers testing positive for cannabis and cocaine was observed in Spaniards. Furthermore, it is important to highlight that, of all the countries participating in the study, Spain had the highest percentage (7.63%) of drivers with the presence of any of these drugs.

According to a recent study (Fierro, González-Luque, Seguí-Gomez, & Álvarez, 2015) performed using representative samples of vehicle drivers in Spain in 2008/9 and 2013, a decrease was observed in the frequency of drivers with the presence of alcohol (4.92%; 95% CI [4.18, 5.66] in 2008/9, and 3.41% [2.27, 4.07] in 2013) and drugs (6.93% [6.07, 7.80] in 2008/9, and 4.87% [4.09, 5.65] in 2013). The decrease in positive cases for drugs is, to a great measure, due to a decrease in the positive cases for cannabis. The routine use of roadside drug controls may have been a contributing factor in this respect.

Drugs and the Risk of Road Traffic Collisions

Currently, preventive interventions should be developed on the basis of scientific evidence. For this purpose, one of the priorities of the European DRUID projects was to analyse the risk involved in drug driving (serious injuries or deaths) (DRUID, 2012; Schulze et al., 2012).

Four risk levels were established to interpret the results:

Slight increase in risk (RR=1-3): Risk associated with driving with a blood alcohol concentration between 0.1 and <0.5 g/L, and with the presence of cannabis.

Medium increase in risk (RR=2-10): Driving with a blood alcohol concentration between 0.5 g/L and < 0.8 g/L, or with the presence of cocaine, illegal and medicinal opiates, benzodiazepines, and Z-hypnotics (without mixing one drug group with another).

High increase in risk (RR=5-30): Driving with a blood alcohol concentration between 0.8 and <1.2 g/L, as well as the presence of amphetamines and a mixture of different drugs.

Extremely high increase in risk (RR=20-200): Driving with a blood alcohol concentration ≥ 1.2 g/L, and with the simultaneous presence of alcohol and drugs.

The data showed that driving with the presence of alcohol (blood alcohol concentration ≥0.8 g/L) in combination with other drugs or multi-drug consumption (alcohol + drugs or an association of drugs) correlates with a higher risk of road traffic collisions.

Most of the available information is about cannabis, which could be used to establish a relationship between concentration and risk (Asbridge, Hayden, & Cartwright, 2012; Laumon et al., 2006; Verstraete & Legrand, 2014). Recently, Elvik (2013) and Verstraete & Legrand (2014) have updated the available information related to alcohol, drugs and certain types of medicines and risk of road traffic collisions.

Driving with the presence of Drugs: Legal Issues

In most countries, driving with the presence of drugs is an offence (EMCDDA, 2015). In the case of Spain, it is regulated as an offense in the administrative area, as well as a crime under criminal law, although both sanctions cannot occur simultaneously. The model differentiates between "presence" and the abstract danger referred to in administrative laws (zero tolerance criterion) and "influence" (impairment criterion) and the specific danger stipulated by the Penal Code (Álvarez & González-Luque, 2014).

Recently, Spanish legislation has introduced relevant changes (Ley 6/2014) involving:

- The prohibition of driving with the presence of drugs in the body, in other words, the "zero tolerance" principle in the matter of drugs and driving.
- Consideration of the Saliva Test, using an authorized device as the preferred way to detect the presence of drugs in the person's body *in situ* and as the chosen means of post-analysis confirmation.
- The fine for driving with the presence of drugs in the person's body, or for refusing to undergo the detection tests, is established at €1,000, along with the loss of 6 driver's licence points.

Roadside Tests for the Detection of Drugs: Saliva versus Blood

Until the present, and due to great extent to the legal and practical issues of taking blood samples, performing roadside tests to detect the presence of drugs in drivers was unusual. Currently, however, it is possible to detect the presence of drugs in saliva samples, or more specifically

"oral fluid," through non-invasive methods. These systems are already available and are being used on a routine basis. Although there are some limitations, especially in relation to sensitivity, specificity, and cut-off values (Verstraete, 2005), drug detection through oral fluid is reliable when the roadside test is linked to a subsequent laboratory confirmation analysis, as in the case of Spanish legal regulations.

Different devices are used for roadside testing; currently, in the case of Spain, the Dräger DrugTest® 5000, DrugWipe®, and Alere™ DDS®2 Mobile Test System are being employed. With these devices, various types of substances can be detected: cannabis, opiates, cocaine, amphetamines and their analogues, benzodiazepines, etc. These devices detect the active substance in the person's oral fluid, confirming the recent use of the drug.

Project DRUID established a core list of detectable substances (27) and their cut-off values for the confirmatory tests and quantification with chromatography, with the principle aim of using them in epidemiological studies. The available information about substance concentration equivalence in blood and saliva (oral fluid) is limited, and the information from the Project DRUID is currently used as a reference (DRUID, 2012; Schulze et al., 2012). Recently, equivalences of blood and oral fluid have been proposed for 12 key substances (Gjerde, Langel, Favretto, & Verstraete, 2014).

The practice of performing drug tests on drivers' oral fluid is already being adopted in developed countries.

What Can Health Professionals Do?

So far, in this article, we have only referred to drivers in general as well as driving with the presence of drugs. However, professionals who treat addictions attend to patients with SUD (Substance Use Disorder). Why is driving important for these professionals and relevant to their clinical practice? Why should they intervene actively?

1. Do Our SUD Patients Drive?

Previous studies (Álvarez, Gómez-Talegón, & Marcos, 2010) have indicated that SUD patients frequently drive, and data from the multi-centre Spanish study, PROTEUS (Roncero et al., 2013) have confirmed that: a significant percentage (52%) of opiate dependent patients (in treatment) drive. Ninety-four percent of those patients were being treated, with average doses of 60 mg/day of methadone. At this level of dosage, methadone interferes—or could potentially interfere—with driving. The patients who drove were found to have fewer legal problems, which could be explained by the fact that driving may be a part of the "normalization" process for the patient and, in some cases, indispensable for professional activity. Therefore, it is important to ensure these patients can drive safely.

2. SUD Patients, Neuropsychological Deficits and Driving Ability

Regular drug use is associated with deficits in various neuropsychological domains or areas. Furthermore, SUD patients frequently present medical comorbidity and psychiatric comorbidity. Finally, SUD patients receive specific treatment for their addiction, commonly including adjunctive psychopharmacological treatment, which could interfere with psychomotor performance and adequate driving fitness.

Within the global treatment/re-integration process of SUD patients, the following three aspects should be taken into account: (a) the disease itself, the addiction, and the neuropsychological deficits; (b) comorbidity; and (c) the pharmacological treatment (Baldaccino et al., 2012; Lorea et al., 2011; Lundqvist, 2005; Soler, Balcells, & Gual, 2014).

European legislation (CD 439/1991/EEC) and Spanish legislation (Real Decreto 818/2009) establish the minimum requirements when assessing driving fitness. In the case of Spain, testing driving fitness is carried out at the Medical Driver Test Centres (in Spanish, Centros de Reconocimiento de Conductores, hereafter, CRC). Being diagnosed with SUD does not in itself indicate a deterioration of driving fitness. In any case, evaluation of drivers with SUD must be performed individually in the above-mentioned centres along with a necessary medical report about the patient.

The assessment of driving fitness and reports to the CRC are problematic in clinical practice. Sometimes, the health professional must present a report about the patient to the CRC, either at the request of the patient, the CRC itself, or the authorities. The role of the health professional treating these patients does not include determining whether or not the patient can drive, but rather reporting the patient's clinical status. The patient's analysis must include: diagnosis, patient's treatment adherence, dates of remissions or relapses, suicide risk and behaviour, length of time in a stable condition, and possible side-effects of the medication involved, and whether or not the patient consumes other types of drugs (for example, results of urine analyses, etc.) (Álvarez & González-Luque, 2014).

Another issue related to, yet independent from, the above-mentioned aspect of assessing driving fitness is the medical advice that must be offered to the patient at every visit to the doctor, in particular, whether or not the patient should drive, or whether the patient should limit his/her driving activity, all based on the patient's clinical state. These aspects will be analysed in greater detail in section 6.

3. Do SUD Patients Run a Higher Risk of Road Traffic Collisions?

Drivers with certain psychiatric pathologies present a higher risk of road traffic collisions than healthy drivers. In a meta-analysis (Vaa, 2003) in which the risk of traffic collisions was analysed in relation to the medical and

neuropsychiatric disorders outlined by the European Directive CD 91/439/EEC, having a mental disorder was one of the conditions with the highest risk of suffering a road traffic collision (RR= 1.72, 95% CI [1.48, 1.99]), along with alcohol abuse or dependency (RR = 2.00, 95% CI [1.89, 2.12]) and drug abuse or dependency (RR = 1.58, 95%, CI [1.45, 1.73]).

On the other hand, many studies (Álvarez, Gómez-Talegón, & Marcos, 2010; Gomes et al., 2013) have shown that patients with SUD have more accidents in general, not only road traffic collisions, and that the road traffic collisions contribute to a higher mortality rate in this group of patients, even if the accidents are not the main cause of death (Degenhardt el al., 2014).

4. Prescription Drugs for SUD Patients and Driving

The use of pharmaceuticals to treat underlying pathologies (SUD) and medical and psychiatric comorbidity leads to frequent use of prescription drugs in these patients, as mentioned above.

Of the medicines authorized in the treatment of addictions, bupropion, varenicline, naltrexone, buprenorphine, and methadone include the pictogram warning of driving-impairing medicines in Spain (Fierro, Gómez-Talegón, & Álvarez, 2013), whereas nicotine, acamprosate, carbamide, disulfiram, or nalmefene do not include such a pictogram (AEMPS, 2015; Álvarez & González-Luque, 2014). However, the summary of product characteristics and patient information leaflets include information about the effect of these medications on driving (Ravera et al., 2012).

Although the pictogram's purpose is only to inform, one should pay attention to the fact that it is present and always make the patient aware of this, especially when the majority of SUD patients are undergoing treatment with psychotropic drugs: of the 198 active substances authorized in group N in Spain, 180 include a pictogram concerning medicines and driving on the package (AEMPS, 2015; Álvarez & González-Luque, 2014).

Recently, patients in maintenance programs with an opioid agonist (methadone and buprenorphine) and who drive vehicles have been the focus of attention (Strand, Fjeld, Arnestad & Morland, 2013; Soyka, 2014). Both medicines can affect a person's ability to drive safely, and this information is provided in the summary of product characteristics, patient information leaflets, and also shown in the driving-impairing medicines pictogram on the medicine package in the case of Spain. Buprenorphine has been shown to have some advantages (Roncero et al., 2013), for example, the deterioration of the psychomotor performance of opiate dependent SUD patients is lower than for methadone (Rapeli, Fabritius, Kalska & Alho, 2011; 2012).

The key factors are the pathology, the neuropsychological deficits and the medical and psychiatric comorbidity. Medication is an added factor: it could interfere negatively at the beginning of treatment, but as the patients improve their clinical situation, the effect may be positive. Special attention should be paid to prescription drugs for these particular patients and the possibility of drug interactions that could consequently increase the sedative effects on the central nervous system, anticholinergic effects, and effects on vision. The consumption of alcohol and other drugs should also be avoided (Álvarez & González-Luque, 2014).

Furthermore, health professionals should inform their patients, especially in the area of addictions, about which medications (opiates, benzodiazepines, etc.) could screen positive in roadside drug testing.

5. Treatment Reduces the Rate of Traffic Accidents in SUD Patients

There is increasing evidence that treatment programs for SUD patients help to reduce their involvement in road traffic collisions (Darke, Kelly, & Ross, 2004; Gómez-Talegón & Álvarez, 2006).

A Norwegian study (Bukten et al., 2013) spanning 9 years, in which data was collected before, during and after treatment on collisions and road traffic infractions specific to patients being treated with substitute opiates, observed that these particular patients reduced road traffic collisions and infractions by 40%.

6. Drugs, Addictions, and Driving: Information and Advice Given to Patients with SUD

We now present the key points, in our opinion, concerning information and medical/healthcare advice for patients with SUD.

- Based on scientific evidence about SUD patients and driving (change in behaviour at the wheel and road rage; Benavidez, Flores, Fierro, & Álvarez, 2013), frequent involvement in road traffic collisions and other types of injuries (Álvarez, Gómez-Talegón, & Marcos, 2010; Coghlan & Macdonald, 2010; Darke, Kelly, & Ross, 2004; Macdonald et al., 2004), and a higher risk of road traffic collisions (Schulze et al., 2012; Verstraete & Legrand, 2014)), patients should be fully informed that if they drive with the presence of drugs, they are choosing high risk behaviour not only for themselves but for other people on the road (Álvarez & González-Luque, 2010; 2014).
- Patients should be informed that illnesses, comorbidity, etc., and the side- effects of medication can influence their ability to drive safely. In this regard, studies have supported the fact that doctors' advice to patients who are potentially unfit to drive helps reduce traffic collisions (Redelmeier et al., 2012).
- Prescribing medication that interferes less with psychomotor performance is a top priority. It is also impor-

tant to avoid and prevent pharmacodynamic interactions that intensify sedative side-effects, anticholinergic side-effects and vision impairment. To this end, the patient should also be informed that he/she should not consume alcohol and/or drugs, not only to avoid driving with the presence of drugs, but also to avoid possible interactions with the different medications.

- Patients should be informed that treatment not only improves their pathological processes but is also associated with less frequent involvement in road traffic collisions.
- Furthermore, patients must be informed that the devices currently used in roadside testing detect the presence of drugs and certain medicines (opiates, benzodiazepines, etc.) in saliva, and, in the case of positive detection, the individual will be penalized. In Spain, a future regulation to avoid the sanction is foreseen if the patient is undergoing medical treatment and fulfils certain criteria.

An important aspect is the advice or recommendation of whether or not to drive: no doubt, the most critical moments are at the start of the treatment. Patients should be told not to drive, or to limit driving as much as possible (only short journeys, frequent rests, etc.). This recommendation should be updated at every visit at the beginning of the treatment, according to the clinical evolution of each patient. Adequate information will allow the patient to be aware of the risk both to him/herself and to other road users.

Another aspect is whether or not the patient is fit to drive (see point 2). This should be evaluated by the competent organism, in the case of Spain, by the CRC. In any case, this does not mean that, as health professionals, we should not inform the patient with SUD when necessary and recommend not driving or performing other activities that may pose a risk.

A triptych including some aspects that SUD patients should know about drugs and driving has been created (Álvarez & González-Luque, 2014).

Conclusion

Operating a vehicle is a good prognostic factor for the social integration of an SUD patient, and interventions should be developed for their implementation, favouring and encouraging these patients to drive safely under medical-psychological supervision. Health professionals should be actively involved, informing their patients and giving them advice (Redelmeier & Tien, 2014) as well as choosing the correct medication to prescribe.

Conflict of Interest

The authors confirm that there is no conflict of interest.

Funding

This work (F. Javier Álvarez) was supported by the Instituto de Salud Carlos III (Health Institute Carlos III), Ministerio de Economía y Competitividad (Ministry of Economy of Competitiveness), and Red de Trastornos Adictivos (Network of Addictive Disorders) grant number RD12/0028/0012.

References

AEMPS (2015). Medicamentos y conducción. Retrieved at http://www.aemps.gob.es/industria/etiquetado/conduccion/home.htm

Álvarez, F. J. (2005). La prevención de las lesiones derivadas de las colisiones de tráfico. *Semergen – Medicina de Familia, 31,* 151-153. doi:10.1016/S1138-3593(05)72904-X.

Álvarez, F. J., Gómez-Talegón, T., & Marcos, A. (2010). Accident rates for drug-dependent patients in treatment for substance dependence: a pilot trial. *Traffic Injury Prevention, 11,* 460-465. doi:10.1080/15389588.2010.492844.

Álvarez, F. J. & González-Luque, J. C. (2010). Illicit drugs and driving. *Medicina Clinica (Barc), 135,* 549-551. doi:10.1016/j.medcli.2009.05.033.

Álvarez, F. J. & González-Luque, J. C. (2014). Drogas, adicciones y aptitud para conducir. 3ª Ed. Valladolid: Universidad de Valladolid. Retrieved at http://www.drogasyconduccion.com/otros.php?seccion=3

Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *British Medical Journal, 344,* -e536. doi:10.1136/bmj.e536

Baldacchino, A., Balfour, D. J., Passetti, F., Humphris, G., & Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 36,* 2056-2068. doi:10.1016/j.neubiorev.2012.06.006

Barlés Arizon, M.J., Escario, J.J., & Galbé Sánchez-Ventura, J. (2014). Predictors of driving under the influence of alcohol among Spanish adolescents. *Adicciones, 26,* 96-105.

Benavidez, D. C., Flores, A. M., Fierro, I., & Álvarez, F. J. (2013). Road rage among drug dependent patients. *Accident Analysis & Prevention, 50,* 848-853. doi:10.1016/j.aap.2012.07.010.

Bukten, A., Herskedal, A., Skurtveit, S., Bramness, J. G., & Clausen, T. (2013). Driving under the influence (DUI) among patients in opioid maintenance treatment (OMT): a registry-based national cohort study. *Addiction, 108,* 1954-1961. doi:10.1111/add.12275.

Coghlan, M. & Macdonald, S. (2010). The role of substance use and psychosocial characteristics in explaining unintentional injuries. *Accident Analysis & Prevention, 42,* 476-479. doi:10.1016/j.aap.2009.09.010

Council Directive 91/439/EEC of 29 July 1991 on driving licences. Official Journal, 1991; L 237: 0001-0024. Retrieved at http://eur-lex.europa.eu/legal-content/ES/TXT/?uri=CELEX:31991L0439

Darke, S., Kelly, E., & Ross, J. (2004). Drug driving among injecting drug users in Sydney, Australia: Prevalence, risk factors and risk perceptions. Addiction, 99, 175-185. doi:10.1046/j.1360-0443.2003.00604.x

Degenhart, L., Larney, S., Randall, D., Burns, L., & Hall, W. (2014). Causes of death in a cohort treated for opioid dependence between 1985 and 2005. *Addiction, 109,* 90-99. doi:10.1111/add.12337

DRUID (2012). Final Report: Work performed, main results and recommendations. Revisión 2.0. Cologne: BAST. Retrieved at http://www.druid-project.eu/Druid/EN/Dissemination/downloads_and_links/Final_Report.html?nn=613800

Elvik, R. (2013). Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis & Prevention, 60,* 254-267. doi:10.1016/j.aap.2012.06.017.

EMCDDA (2015). Legal approaches to drugs and driving. Retrieved at http://www.emcdda.europa.eu/html.cfm/index19034EN.html.

EMCDDA (2007). Drugs and Driving. Luxembourg: Office for Official Publications of the European Communities, 2007. Retrieved at http://www.drugsandalcohol.ie/6368/1/EMCDDA_Selected_issue_2007_Driving.pdf

Fierro, I., Gómez-Talegón, T., & Álvarez, F.J. (2013). The Spanish pictogram on medicines and driving: The population's comprehension of and attitudes towards its use on medication packaging. *Accident Analysis & Prevention, 50,* 1056-1061. doi: 10.1016/j.aap.2012.08.009.

Fierro, I, González-Luque, J.C., Seguí-Gómez, M., & Álvarez, F.J. (2015). Alcohol and drug use by Spanish drivers: Comparison of two cross-sectional road-side surveys (2008-9/2013). *International Journal of Drug Policy, 26,* 794-797, doi:10.1016/j.drugpo.2015.04.021.

Gjerde, H., Langel K., Favretto, D., & Verstraete, A.G. (2014). Estimation of equivalent cutoff thresholds in blood and oral fluid for drug prevalence studies. *Journal of Analytical Toxicology, 38,* 92-98. doi:10.1093/jat/bkt122.

Gomes, T., Redelmeier, D. A., Juurlink, D. N., Dhalla, I. A., Camacho, X., & Mamdani M. M. (2013). Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Internal Medicine, 173,* 196-201. doi:10.1001/2013.jamainternmed.733

Gómez-Talegón, M. T. & Álvarez, F. J. (2006). Road traffic accidents among alcohol-dependent patients: the effect of treatment. *Accident Analysis & Prevention, 38,* 201-217. doi:10.1016/j.aap.2005.09.006

Laumon, B., Gadegbeku, B., Martin, J. L., Biecheler, M. B., & SAM Group (2006). Cannabis intoxication and fatal road crashes in France: population based case-control study. *British Medical Journal, 332,* 1298. doi:10.1136/bmj.332.7553.1298

Ley 6/2014, de 7 de abril, por la que se modifica el texto articulado de la Ley sobre Tráfico, Circulación de Vehículos a Motor y Seguridad Vial, aprobado por el Real Decreto Legislativo 339/1990, de 2 de marzo. Retieved at http://www.boe.es/diario_boe/txt.php?id=BOE-A-2014-3715

Lorea, I., Fernández-Montalvo, J., Tirapu-Ustárroz, J., Landa, N., & López-Goñi, J. J. (2010). Neuropsychological performance in cocaine addiction: a critical review. *Revista de Neurología, 51,* 412-426.

Lundqvist, T. (2005). Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacology Biochemistry & Behavior, 81,* 319-330. doi:10.1016/j.pbb.2005.02.017

Macdonald, S., Mann, R. E., Chipman, M., & Anglin-Bodrug, K. (2004). Collisions and traffic violations of alcohol, cannabis and cocaine abuse clients before and after treatment. *Accident Analysis and Prevention, 36,* 795-800. doi:10.1016/j.aap.2003.07.004

Ravera, S., Monteiro, S., de Gier J. J., van der Linden, T., Gómez-Talegón, T., Álvarez, F. J., & the DRUID Project WP4 Partner (2012). A European approach to categorising medicines for fitness to drive: Outcomes of the DRUID project. *British Journal of Clinical Pharmacology, 74,* 920-931. doi:10.1111/j.1365-2125.2012.04279.x.

Rapeli, P., Fabritius, C., Kalska, H., & Alho, H. (2011). Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates. *BMC Clinical Pharmacology, 21,* 11-13. doi:10.1186/1472-6904-11-13.

Rapeli, P., Fabritius, C., Kalska, H., & Alho, H. (2012). Do drug treatment variables predict cognitive performance in multidrug-treated opioid-dependent patients? A regression analysis study. *Substance Abuse Treatment, Prevention, and Policy, 2,* 7-45. doi:10.1186/1747-597X-7-45.

Real Decreto 818/2009, de 8 de mayo, por el que se aprueba el Reglamento General de Conductores. Retrieved at http://www.boe.es/boe/dias/2009/06/08/pdfs/BOE-A-2009-9481.pdf

Redelmeier, D. A., Yarnell, C. J., Thiruchelvam, D., Tibshirani, R. J. (2012). Physicians' warnings for unfit drivers and the risk of trauma from road crashes. *The New England Journal of Medicine, 367,* 1228-1236. doi:10.1056/NEJMsa1114310

Redelmeier, D. A. & McLellan, B. A. (2013). Modern Medicine Is Neglecting Road Traffic Crashes. *PLoS Medicine, 10,* e1001463. doi:10.1371/journal.pmed.1001463

Redelmeier, D. A. & Tien, H. C. (2014). Medical interventions to reduce motor vehicle collisions. *Canadian Medical Association Journal, 186,* 118-124. doi:10.1503/cmaj.122001.

Romano, E., Torres-Saavedra, P., Voas, R. B., & Lacey, J. H. (2014). Drugs and alcohol: their relative crash risk. *Journal of Studies on Alcohol and Drugs, 75,* 56-64.

Roncero, C., Álvarez, J., Barral, C., Gómez-Baeza, S., Gonzalvo, B., Rodríguez-Cintas, L.,… Casas M (2013). Driving and legal status of Spanish opioid-dependent patients. Substance *Abuse Treatment, Prevention, and Policy, 8,* 19. doi:10.1186/1747-597X-8-19.

Schulze, H., Schumacher, l. M., Urmeew, R., Auerbach, K., Álvarez, F. J., Bernhoft, I. M.,… Zlender B. (2012). Driving under the influence of drugs, alcohol and medicines in Europe — findings from the DRUID project. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Publications Office of the European Union, Luxembourg. doi:10.2810/74023. Retrieved at http://www.emcdda.europa.eu/attachements.cfm/att_192773_EN_TDXA12006ENN.pdf

Soler González, C., Balcells Oliveró, M., & Gual Solé, A. (2014). Alcohol related brain damage. State of the art and a call for action. *Adicciones, 26,* 199-207.

Soyka, M. (2014). Opioids and Traffic Safety – focus on Buprenorphine. *Pharmacopsychiatry, 47,* 7-17. doi:10.1055/s-0033-1358707

Strand, M. C., Fjeld, B., Arnestad, M., & Morland, J. (2013). Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. *Traffic Injury Prevention, 14,* 26-38. doi:10.1080/15389588.2012.689451.

Vaa, T. (2003). Impairments, diseases, age and their relative risks of accident involvement: Results from meta-analysis. Oslo: Institute of Transport.

Verstraete, A. G. (2005). Oral fluid testing for driving under the influence of drugs: history, recent progress and remaining challenges. *European Journal of Forensic Sciences, 50,* 143-150. doi:10.1016/j.forsciint.2004.11.023

Verstraete, A. G. & Legrand, S. A. (2014). Drug use, impaired driving and traffic accidents. 2nd Ed. EMCDDA Insights 16. Luxembourg: Office for Official Publications of the European Communities. Retrieved at http://www.emcdda.europa.eu/attachements.cfm/att_229259_EN_TDXD14016ENN.pdf

A group intervention to reduce intimate partner violence among female drug users. Results from a randomized controlled pilot trial in a community substance abuse center

Intervención grupal para reducir la violencia de género entre consumidoras de drogas. Resultados de un estudio piloto en un centro comunitario de tratamiento de adicciones

Judit Tirado-Muñoz*, Gail Gilchrist*,***, Eva Lligoña**, Louisa Gilbert****, Marta Torrens *,**

*Addiction Research Group, IMIM-Institut Hospital del Mar d'Investigacions Mèdiques; Universitat Autónoma de Barcelona, Barcelona, Spain
** Institute of Neuropsychiatry and Addictions, Parc de Salut Mar, Barcelona, Spain
*** National Addiction Centre, Institute of Psychiatry, King's College, London, UK
**** Social Intervention Group, Columbia University, New York, NY, USA

Abstract

Background: A greater proportion of drug dependent women are victims of intimate partner violence (IPV) than women in the general population; however, few interventions have been developed to reduce IPV among drug dependent women. *Methods:* An adapted version of the *Women's Wellness Treatment*, to address IPV and depressive symptoms, was piloted in a randomized controlled trial conducted in outpatient treatment program in Barcelona, Spain among 14 women receiving outpatient treatment for a drug use disorder who screened positive for IPV in the previous month. Participants were randomly assigned to receive the 10 session cognitive behavioral therapy (IPaViT-CBT) group intervention or treatment as usual. The frequency of IPV, depressive symptoms, substance use, quality of life and health status were assessed at baseline and 1, 3 and 12 months post intervention. Intention to treat analysis was performed. *Results:* Moderate effects for the intervention were found in reducing psychological maltreatment, increasing assertiveness of IPV and reducing aggressiveness in the partner relationship, and in reducing the frequency of drinking up to 3 months post intervention. The intervention did not significantly reduce the likelihood of any IPV, depressive symptoms, quality of life or self-reported health status, up to 12-months post intervention.
Conclusion: This pilot trial suggests some initial support for the 10-session CBT group intervention among IPV victims who received treatment for drug use. Study findings indicate that it is feasible to deliver the intervention in a community substance abuse center. An adequately powered trial is required to replicate these results.
Keywords: intimate partner violence; substance abuse; females; cognitive behavioral therapy; group intervention; randomized controlled trial.

Resumen

Antecedentes: Las mujeres usuarias de drogas son víctimas de violencia de género en mayor proporción que las mujeres en población general; sin embargo, pocas intervenciones se han desarrollado para reducir la violencia de género entre mujeres usuarias de drogas. *Métodos:* Una versión adaptada de la intervención *"Women's Wellness Treatment"* para reducir violencia de género y síntomas depresivos, ha sido evaluada mediante un ensayo clínico piloto en un centro de tratamiento ambulatorio en Barcelona, España. Catorce mujeres que recibían tratamiento ambulatorio para un trastorno por consumo de sustancias y que declararon ser víctimas de violencia en el mes anterior fueron incluidas en el ensayo clínico. Las participantes fueron asignados al azar para recibir 10 sesiones grupales de terapia cognitivo-conductual (IPaViT-CBT) o tratamiento habitual. La frecuencia de violencia, síntomas depresivos, consumo de sustancias, calidad de vida y estado de salud fueron evaluados al inicio del estudio y 1, 3 y 12 meses después de la intervención. Se realizó análisis por intención de tratar. *Resultados:* Se encontraron efectos moderados de la intervención en la reducción de maltrato psicológico, aumento de la asertividad y la reducción de la agresividad en la relación de pareja, y reducción en la frecuencia de consumo de alcohol hasta 3 meses después de la intervención. La intervención no redujo significativamente la probabilidad de ser víctima de cualquier tipo de violencia de género, los síntomas depresivos, calidad de vida o el estado de salud auto-referido, hasta 12 meses después de la intervención. *Conclusiones:* Los resultados de este estudio piloto indican que es factible realizar una intervención de 10 sesiones grupales de TCC entre las víctimas de violencia de género que reciben tratamiento por uso de sustancias en un centro comunitario de tratamiento de adicciones. Se requiere un ensayo clínico más robusto para replicar estos resultados.
Palabras clave: violencia de género; abuso de substancias, mujeres, terapia cognitivo-conductual, intervención grupal, ensayo aleatorizado controlado.

Received: July 2014; Accepted: December 2014

Send correspondence to:
Marta Torrens MD, PhD. Addiction Unit. Institute of Neuropsychiatry and Addictions, Parc de Salut Mar, Passeig Marítim, 25-29, 08003 Barcelona, Spain. E-mail: mtorrens@parcdesalutmar.cat

Intimate partner violence (IPV) is a growing public health concern. The World Health Organisation (WHO) estimate that one-third of women globally have been victims of IPV at least once in their lifetime (World Health Organization, 2013). Rates of physical and sexual IPV victimization are even higher among women with a substance use disorder (SUD) (Cohen & Hien, 2006; El-Bassel, Gilbert, Witte, Wu, & Chang, 2011; El-Bassel, Gilbert, Wu, Go, & Hill, 2005; Miller, Downs, & Testa, 1993) ranging from 40-70% among women in substance abuse treatment programs (Gilbert et al., 2006; Gilchrist, Blazquez, & Torrens, 2011; Wagner et al., 2009). IPV victimization is strongly associated with mental health problems (Campbell, 2002; Howard et al., 2010; Trevillion, Oram, Feder, & Howard, 2012), with recent evidence confirming that around 20% of women who experienced IPV in the past year, developing a new onset psychiatric disorder (Okuda et al., 2011). The high rate of IPV among female substance users has adverse consequences on physical, mental and reproductive health. Among female drug users, IPV is associated with mental health problems including depression (Connelly, Hazen, Baker-Ericzen, Landsverk, & Horwitz, 2013; Gilchrist, Blazquez, & Torrens, 2012; Illangasekare, Burke, McDonnell, & Gielen, 2013), borderline personality disorder (Gilchrist, Blazquez, & Torrens, 2012) and Post-Traumatic Stress Disorder (PTSD) (Cohen, Field, Campbell, & Hien, 2013; Kaysen et al., 2007; Najavits, Sonn, Walsh, & Weiss, 2004; Peters, Khondkaryan, & Sullivan, 2012). Those drug dependent women with depression are more than twice as likely to experience IPV (OR= 2.42), and over three times as likely (OR= 3.05) for those drug dependent women with a borderline personality disorder (Gilchrist, Blazquez, & Torrens, 2012). Women who met criteria for PTSD and SUD, were more than twice as likely to experience IPV (OR= 2.7) (Cohen, Field, Campbell, & Hien, 2013). A recent general population study in Chile found that the prevalence of being a victim of assault, aggression or sexual violence was greater among men and women with higher monthly alcohol consumption or who binge drink (six or more drinks on one occasion at least once in the month) compared to those who did not report these consumption patterns (Castillo-Carniglia, Pizarro, Luengo, & Soto-Brandt, 2014). In addition, IPV results in increasing or maintaining substance abuse (El-Bassel, Gilbert, Wu, Go, & Hill, 2005; McKinney, Caetano, Rodriguez, & Okoro, 2010; Testa, Livingston, & Hoffman, 2007) and more physical ill health and health care utilization (Liebschutz, Mulvey, & Samet, 1997). Drug dependent women who experience IPV may engage in risky sex and drug taking practices, potentially due to the negative influence of the perpetrator (Wagner et al., 2009) which may put them at increased risk for bloodborne viruses, sexually acquired infections and unwanted pregnancy (Bourgois, Prince, & Moss, 2004; Campbell et al., 2008; El-Bassel, Gilbert, Witte, Wu, & Chang, 2011; Singer, 1996). As such, interventions need to consider female drug users' relationships with their partners (Hearn, O'Sullivan, El-Bassel, & Gilbert, 2005) and address all aspects of their lives including substance use disorders, psychiatric comorbidity and sexual and injecting risk behaviours. Previous systematic reviews identified interventions addressing trauma and substance abuse simultaneously (Najavits, 2009) and SUD among women survivors of IPV (Fowler & Faulkner, 2011). A more recent systematic review of RCT interventions to reduce IPV among women (Tirado-Muñoz, Gilchrist, Farré, Hegarty, & Torrens, 2014), identified only one RCT intervention targeted at female drug abusers where the outcome assessed was IPV, the Women's Wellness Treatment (WWT) (Gilbert et al., 2006). Other interventions addressing substance use, PTSD symptoms and IPV were identified such us ATRIUM (Addiction and trauma recovery integration model) (Miller & Guidry, 2001), TREM (Trauma Recovery and Empowerment Model) (Harris, 1998). Seeking Safety (SS: A treatment manual for PTSD and Substance Abuse) (Najavits, 2002) and TRIAD (more focused on teaching interpersonal skills) (Fearday, Clark, & Edington, 2001). Seeking Safety is clearly the most studied PTSD-SUDs intervention. Finally, WWT was the intervention which most focused on the purpose of this research in terms of primary outcome and intensity of intervention.

The purpose of this pilot trial was (1) to adapt the WWT manualized group intervention to address IPV and depressive symptoms among females receiving drug treatment; (2) to conduct a pilot randomized controlled trial to assess the feasibility and initial efficacy of the CBT intervention on reducing IPV compared to treatment as usual at 1,3 and 12 months post intervention.

Methods

Study design and sample description

The clinical trial was conducted from March 2011 to June 2012 at an outpatient community drug treatment centre in Barcelona (Spain). Ethical approved was granted by the Institute's Human Research Ethics Committee of IMIM-Institut Hospital del Mar d'Investigacions Mèdiques; Parc de Salut Mar de Barcelona.

Participants were recruited from the waiting rooms of two outpatient drug treatment centres in Barcelona. Potential participants were approached by the researcher in the waiting room who discussed the objectives of the study, and gave them an information leaflet. If they agreed to participate, they were screened to determine whether they met the study's inclusion criteria. Female drug abusers were eligible for the study if they a) were aged 18 or older; b) were currently receiving substance abuse treatment in a outpatient drug treatment center; c) were currently in a relationship with a male partner and d) reported IPV in the past month using an adapted version of the Composite Abuse Scale (Hegarty, Sheehan, & Sconfeld, 1999) and the Psychological Maltreatment of Women Inventory (Tolman, 1999) e) could

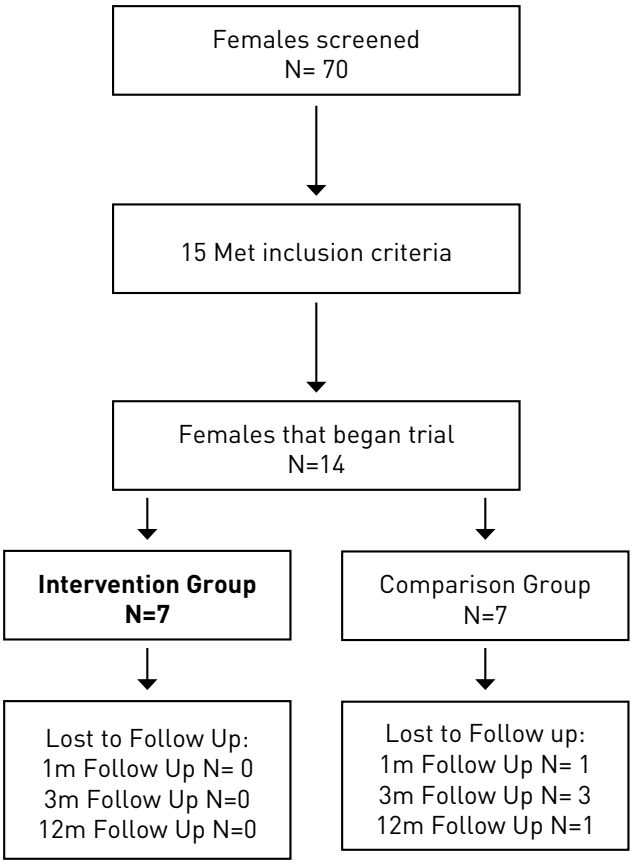


Figure 1. Study Flowchart

communicate in Spanish. Seventy female drug abusers were screened, 15 were eligible to participate and 14 agreed to participate. None of the participants received financial incentive to respond the follow-up assessments. Of the 14 participants who began the trial following randomisation, three were lost to follow up - one moved away from Barcelona, one was receiving inpatient treatment, and one was incarcerated (Figure 1).

Intervention: Process of adaptation

A systematic review of RCT interventions to reduce IPV among females (Tirado-Muñoz, Gilchrist, Farré, Hegarty, & Torrens, 2014), identified only one RCT intervention targeted at female substance users, the Women's Wellness Treatment (WWT) (Gilbert et al., 2006). With the authors' consent, the WWT intervention was translated into Spanish and adapted to meet the needs of female drug abusers and the drug abuse treatment system in Spain. The original WWT intervention had 11 2-hour group sessions plus 1 individual session, aimed to promote relationship safety and to reduce drug use. Based on previous experience of delivering group interventions and retaining participants in Spain, we decided to reduce the number of sessions from 12 to 10 and address negative mood given the high prevalence of depression among women in drug treatment (Torrens, Gilchrist, & Domingo-Salvany, 2011). Therefore, a new session on addressing negative mood was included, which was adapted with the authors' permission from the Behavioural Therapy for Depression in Drug Dependence (BTDD) Manual (Carpenter, Aharonovich, Smith, Iguchi, & Nunes, 2006). This session presented and discussed the model of depression and highlights the importance of life satisfaction, through encouraging women to introduce pleasant activities into their lives, and assists them to develop a pleasant activities list. Women in the trial were offered the chance to participate (free of charge) in classes of their choice at a local community centre (e.g., yoga, dance, cooking, computing etc.) in an attempt to facilitate pleasant activities and in turn reduce negative mood. Due to the high prevalence of hepatitis C among females who inject drugs (Gilchrist, Blazquez, & Torrens, 2011) we adapted the original session on HIV to also include education on hepatitis C transmission.

The adaptation phase was undertaken by the research team in Spain, in consultation with the original authors of both manualized therapies (Carpenter, Aharonovich, Smith, Iguchi, & Nunes, 2006; Gilbert et al., 2006). The final intervention *"IPaViT-CBT"* (Intimate Partner Violence Therapy-Cognitive Behavioral Therapy) consisted of 10 weekly 2 hour group sessions. The following 10 sessions were administered in a group format:

- Session 1 Preparing for the journey: Enhancing motivation for wellness
- Session 2 Building relationship safety (group session)
- Session 3 Identifying triggers for drug use and relationship conflict
- Session 4 Healing from psychological IPV
- Session 5 Dealing with physical IPV: reconstructing anger
- Session 6 Recovering from trauma: Identifying PTSD triggers
- Session 7 Managing negative mood
- Session 8 Setting sexual boundaries: Negotiation skills
- Session 9 Avoiding dangerous sexual liaisons: Identifying triggers for HIV/ HCV risk and Identifying strategies for reducing HIV/ HCV risk.
- Session 10 On the road to recovery and safety: Celebrating successes.

The format of the intervention across sessions consisted of a sequence of 5 steps. Each session started with: (1) an inspirational opening (quote from a female artist or writer) which served to inspire and motivate participants in their recovery, and tied into the context of the session; (2) a recovery and relationship check-in was completed for each participant thereafter to detect and discuss any incident occurring between sessions related to participants' drug use or relationship conflicts, identifying triggers that would help women generate safety plans and provides new skills to reduce IPV; (3) raising awareness, through discussion, about the relationship between drug-related behaviours and different forms of IPV; (4) skills building and group discussion; and (5) a check-in of the participants' outstanding needs/

problems and how to address these. At the end of each session, participants were encouraged to practice 'homework' exercises between sessions (e.g. positive self talk, behavioural activation). The final intervention "*IPaViT-CBT*" was a manualized small-group, cognitive behavioural intervention, designed to reduce IPV and improve depressive symptoms in female drug users. A formal cultural adaptation and translation of WWT to adapt the intervention content activities to the target population was conducted taking into account the following aspects: 1) language: some concepts or words that could not be literally translated were replaced in order to make more sense to participants; and 2) resources: Some exercises, quotes and resources information were replaced to be more culturally meaningful to the target population.

Intervention conditions

The 14 participants were randomly assigned to receive either the experimental or control condition. Participants were assigned a random number generated using SPSS from 1-14. Numbers 1 to 7 were assigned to (a) the treatment condition (10 session *IPaViT-CBT* group intervention) and numbers 8 to 14 were assigned to (b) control condition. Due to the nature of the study, blinding of the participants was not feasible. Assessors were not blinded to the study condition. A pre-experimental evaluation was not conducted; the researcher (JT) was responsible for collecting baseline and follow-up data from participants in both the intervention and control conditions.

Women randomized to the intervention condition received 10 2-hour sessions over 5 weeks. The intervention was delivered in outpatient drug treatment settings by a clinical psychologist. The professional providing the *IPaViT-CBT* intervention in the experimental condition was a clinical psychologist (ELL) with over 30 years' experience working with drug users, including the delivery of CBT in groups. The intervention was manualized, therefore, instructions were contained in the manual. However, JT met with the clinical psychologist to discuss the delivery of the manualized therapy before each session was delivered. A researcher (JT) attended each session to check the fidelity of the intervention delivered against the manual. To increase participation, participants in the treatment group received text reminders 24 hours before each session, a financial incentive for attending each session and had their travel costs reimbursed as the integrated intervention was in addition to their treatment as usual for their drug use. Participants assigned to the intervention group continued to receive all treatment as usual services. The control and intervention groups did not receive any financial incentives, text reminders (sms) or reimbursement of travel costs to attend treatment as usual at the community drugs treatment center.

The control condition received treatment as usual provided by the outpatient drug treatment centre. Treatment as usual consisted of fortnightly monitoring of their substance use and psychiatric comorbidity by relevant professionals (psychiatrists, psychologists, and social workers) and monitoring medication if it was prescribed. Treatment as usual included motivational interviewing, relapse prevention and counselling. While addressing IPV was not part of usual treatment, if participants in the control group disclosed IPV during a routine visit with a professional, the usual referral/treatment pathways were followed to ensure the participant was not in immediate danger. At recruitment potential participants were informed that they would be randomized to receive either the integrated intervention or to treatment as usual, and that if the intervention significantly reduced IPV, those randomized to the control group would be offered the intervention in the future. This was explained to participants prior to their consenting to be randomized.

Different therapists delivered the control and intervention conditions. Women in both the intervention and control groups received treatment as usual for their drug use.

Outcome measures

All participants completed a one to one interviewer-administered assessment at baseline in a private room of the centres involved in the study. Follow up interviews were completed in a private room or by telephone if the participant was unable to attend in person.

Sociodemographics variables

Data on age, education, employment status, marital status, health status and partner characteristics were collected.

Intimate partner violence

Two instruments were used to measure IPV - the Composite Abuse Scale (CAS) (Hegarty, Sheehan, & Sconfeld, 1999) and the Psychological Maltreatment of Women Inventory (PMWI) (Tolman, 1999). In addition, the Spouse Specific Assertion/Aggression Scale (SSAAS) (O'Leary & Curley, 1986) assessed assertiveness and aggression in intimate relationships.

Any IPV in the past month and 12 months was assessed using the 30-item CAS to identify the type of abuse experienced (severe combined (sexual and physical abuse); physical abuse only; physical abuse and emotional abuse and/or harassment; emotional abuse and/or harassment). Good internal reliability (Cronbach's alpha > 0.85) was found for these 4 factors and the corrected item-total correlations were high (> 0.5) (Hegarty, Bush, & Sheehan, 2005). Each item requires a response to the frequency of occurrence in the previous 12 months: "never", "only once", "several times", "monthly", "weekly" or "daily'. An accepted cut-off score of ≥7 was used to indicate any IPV.

The Psychological Maltreatment of Women Inventory (PMWI) measured psychological abuse in the past month and 12 months (Tolman, 1989). The PMWI has 58 items

that assess the frequency of emotional/verbal abuse and dominance/isolation from 1 "never" to 5 "very frequently". The dominance/isolation subscale includes "items related to rigid observance of traditional sex roles, demands for subservience, and isolation from resources" and the emotional/verbal abuse subscale includes "withholding emotional resources, behaviour that could degrades women and verbal abuse". The PMWI was also shown to have good reliability and validity in a sample of primarily white and African American women (Cronbach's alpha = 0.88) (Tolman, 1999)

Abusive relationships show lower levels of spouse-specific assertion in comparison with non-abusive relationships (O'Leary & Curley, 1986). SSAAS measured the degree of similarity or difference that the respondent felt towards each of 29 statements about assertiveness and aggression in their relationship, ranging from; -3 (extremely unlike me) to +3 (extremely like me).

The CAS, PMWI and SASS were not available in Spanish. Therefore, these instruments were forward translated from English to Spanish by a native Spanish speaker familiar with the research area, and these Spanish versions were back translated to English by a native English speaker. These back translated English versions were sent to the original authors of each instrument for approval. The Spanish version of the CAS, PMWI and SASS were thereafter, approved by the original authors.

Depression

The Spanish version of the Beck Depression Inventory (BDI-II) assessed depressive symptoms in the last week (Bonicatto, Dew, & Soria, 1998). BDI-II (Beck, Steer, & Garbin, 1988) has 21 items that measure the severity of depression where each answer is scored 0 (absence of symptoms) to 3 (more presence of symptoms). The BDI-II has a high internal reliability (Cronbach's alpha = 0.88) (Bonicatto, Dew, & Soria, 1998). Participants with depression (Score of 19-63, indicating moderate to severe depression) were referred to a psychologist/psychiatrist at the outpatient drug treatment centre.

Quality of Life and Health Status

Quality of life and health perception were measured by a visual analogue scale ranking form 0 (lowest quality of life/ health) to 100 (highest quality of life/ health). Good (0.87) test re-test reliability correlation has been reported (Boer et al., 2004)

Substance use

Finally, the frequency and amount of alcohol, heroin, cocaine, cannabis and benzodiazepine use in the past week were recorded using a substance use consumption table designed by the Spanish research team based on the Time Line Follow-back (Sobell & Sobell, 1992). The test-retest reliability ranges from r = +0.79 to +0.98 (Sobell, Maisto, Sobell, & Cooper, 1979).

All instruments were re-administered by the researcher 1, 3, and 12 months post intervention. IPV in the past month was assessed using the CAS and PMWI at all follow up points. Any IPV in the past 12 months was also assessed using the CAS at 12 month follow up. Depressive symptoms in the last week were assessed using the BDI at all follow up points.

Fidelity

Participants in the intervention arm of the trial completed an evaluation form at the end of each of the 10 group sessions to determine whether the content and information gained in each session met the objectives of each session with responses ranging from 1 (strongly disagree) to 5 (totally agree). Furthermore, 3 questions were asked at the end of each session about: 1) how comfortable the participant felt during the session, ranging from 1 (very uncomfortable) to 5 (very comfortable); 2) the skill/ability of the therapist, ranging from 1 (excellent) to 5 (poor) and 3) their satisfaction with the session, ranging from 1 (not at all satisfied) to 5 (very satisfied).

Analysis

Categorical variables were calculated as frequencies and percentages, and continuous variables as means and standard deviations. Intention to treat analyses was conducted to avoid loss to follow-up using baseline scores or last follow up scores. Fisher's exact tests were used to compare differences in outcomes between groups for categorical variables, and Mann–Whitney tests were used to compare differences in outcomes between groups for continuous variables. Pre-post differences between baseline and follow ups were calculated. It was not possible to control for baseline outcome indicators due to the small sample size. For the purpose of this study, a 5% or lower p-value is considered statistically significant. We hypothesized that participants who received the WWT would be more likely to reduce IPV and depression symptoms compared to TAU participants. Differential attrition by treatment group was found. All those lost to follow up were allocated to the control condition. Intention to treat analysis was conducted.

Results

Attendance and Retention

Participation in the group intervention was variable (average 5 sessions attended, range 0-9 sessions).

Sociodemographics

The sociodemographic characteristics of the participants are shown in table 1. The mean age of 14 substance abusers women was 40 years (SD = 8.8). At baseline the majority of participants were unemployed or receiving a disability pen-

Table 1
Sociodemographic Characteristics of Participants (n=14)

Variables	Intervention (n=7)	Comparison (n=7)
Age Total	40 (8.81)	
Mean (SD)	42.0 (5.56)	39.8 (11.61)
Living with		
Alone	1	1
Partner	5	6
Employment		
Employed	2	1
Unemployed	2	2
Disability benefit/other	0	2
Housewife	1	2
Heterosexual	7	7
Injecting		
Never	5	7
More than once a week	2	0
Sex trading		
Never	4	5
Yes in the past	2	2
Yes in the last month	1	0
Length of current relationship		
6- 12 months	3	2
13-60 months	1	2
+ 5 years	3	3
Current partner		
Problems with alcohol	5	5
Problems with drugs	1	2
Health status		
HIV +	2	0
HCV +	1	2

sion or benefit. Only 2 women had injected drugs in their lifetime and were allocated to the intervention group. In both groups, women had been previously involved in prostitution during their lifetime. The length of their current intimate relationships was variable however; most participants reported that their current male partner had problems with alcohol. Regarding baseline outcome variables, the intervention and control groups were comparable on almost all characteristics with the exception of self-perceived health status and responses in SSAAS scale. At baseline, all 14 participants reported any IPV (cut-off score of ≥7) but those allocated to the intervention group described slightly more psychological maltreatment than those allocated to the control group. Baseline differences in the outcomes variables could not be statistically controlled due to the small sample size.

IPV outcomes

Composite Abuse Scale (CAS). Table 2 presents the percentage of participants at each follow up point by treatment condition who reported experiencing any incident of IPV. We present data for those participants who remained in a relationship with their partners. All women reported any IPV (CAS score equal or more than seven) at baseline. In the intervention group, participants reported a 60% decrease in experiencing any IPV (physical, emotional or harassment) from baseline to 1-month (n= 2 women reported IPV) and 3-month (n=2 women reported IPV) post intervention and an 80% decrease at 12 months post intervention, only one women reported IPV in the previous month. In the control group, the percentage of participants who reported any IPV also decreased but to a lesser extent, from 100% at baseline to 71% at 1 and 83% at 3 months post intervention, decreasing at 12 months post intervention to 60% of participants reporting experiencing any IPV.

No statistical significance was found between groups, despite this, the intervention group showed a tendency for greater reductions in IPV victimization at all follow up points post intervention when compared to the control group. However, the sample size may not have been large enough to detect differences.

Psychological Maltreatment of Women Inventory (PMWI). Psychological maltreatment and assertiveness scores are reported in table 2. Again, we present data only for those women who remained in a relationship with their partner. The isolation/dominance subscale of the PMWI reduced from baseline (Mean: 17.20; SD: 6.14) to 12 months post intervention (Mean: 12.00; SD: 5.61) for those allocated to the intervention group. For those participants randomized to the control group, the mean isolation/dominance subscale score also reduced from baseline (Mean: 13.85; SD: 5.39) to 12 months post intervention (Mean: 8.60; SD: 2.07). Significance differences were found between groups at 1 (p=0.048) and 3-months (p=0.030) follow up. The mean score on the emotional/verbal subscale of the PMWI reduced from baseline (Mean: 21.40; SD: 8.64) to 12 months post intervention (Mean: 11.60; SD: 1.67) for those allocated to the intervention group. The mean emotional/verbal subscale score also reduced for participants in the control group from baseline (Mean: 18.28; SD: 5.49) to 12 months post intervention (Mean: 12.80; SD: 4.76). No statistical differences between groups were found.

Spouse Specific Assertion/Aggression Scale (SSAAS). In the intervention group, the mean aggression scores reduced from baseline (Mean: -8.40; SD: 6.10) to 12 months post intervention (Mean: -12.60; SD: 5.12). For participants randomized to the control group, the mean aggression scores increased from baseline (Mean: -6.42; SD: 13.62) to 12 months post intervention (Mean: -3.60; SD: 14.80). Those participants receiving the intervention showed greater decreases in aggressiveness during the relationship than those receiving treatment as usual. A statistical difference was found between groups at 1-month (p= 0.030) post intervention. In the intervention group, the mean assertiveness score increased from baseline (Mean: -3.80; SD: 16.39) to 12 months post intervention (Mean: 17.00; SD: 15.41) in the expected direction. For participants randomized to the control group, the mean assertiveness mean score also increased from baseline (Mean: 7.71; SD: 21.76) to 12 months post intervention (Mean: 16.60; SD: 7.14). All participants showed increases in assertiveness during the follow up points. A sig-

Table 2
Mean study instrument Scores for both groups (IPV, Assertiveness)

Outcome			Baseline N=14	1 month FU N=12	3 months FU N=11	12 months FU N=10	p-value 1 m	p- value 3 m	p- value 12 m
Women abused Nº (%) CAS ≥ 7		**Intervention**	7 (100)	2 (40)	2(40)	1(20)	0.558	0.242	0.524
		Comparison	7 (100)	5 (71)	5 (83)	3 (60)			
Psychological Maltreatment of Women Inventory (PMWI) M (SD)	Isolation/ Dominance	**Intervention**	17.20 (6.14)	8.80 (1.64)	8.20 (0.83)	12.00 (5.61)	**0.048**	**0.030**	0.690
		Comparison	13.85 (5.39)	11.71 (3.81)	12.33 (3.50)	8.60 (2.07)			
	Emotional/ Verbal	**Intervention**	21.40 (8.64)	11.00 (2.00)	10.60 (1.34)	11.60 (1.67)	0.073	0.126	0.421
		Comparison	18.28 (5.49)	14.85 (4.59)	17.16 (2.31)	12.80 (4.76)			
Spouse Assertiveness Scale (SSAAS) M (SD)	Aggressiveness	**Intervention**	-8.40 (6.10)	-18.80 (7.32)	-16.80 (7.19)	-12.60 (5.12)	**0.030**	0.056	0.841
		Comparison	-6.42 (13.62)	-1.00 (12.21)	1.40 (9.44)	-3.60 (14.80)			
	Assertiveness	Intervention	-3.80 (16.39)	26.40 (12.44)	31.40 (14.62)	17.00 (15.41)	**0.017**	0.056	0.151
		Comparison	7.71 (21.76)	15.33 (11.97)	19.20 (9.65)	16.00 (7.14)			

*Note. For the PMWI and SSAAS the baseline means are frequencies for the past year, the other time periods are mean frequency for the past month.

nificance difference was found between groups at 1-months post intervention (p= 0.017).

Depression

Depressive symptom outcomes are reported in table 3. Mean BDI scores in the intervention group reduced from baseline (Mean: 22.42; SD: 8.34) to 12 months post intervention (Mean: 14.57; SD: 8.96). In comparison, mean BDI scores also reduced in the control group from baseline (Mean: 23.42; SD: 12.73) to 1 month post intervention (Mean: 17.00; SD: 10.36), and continued decreasing at 12 post intervention (Mean: 12.28; SD: 9.60). No significance difference was found between groups.

Health status and Quality of life

Self-perceived health status and quality of life are reported in table 3. In the intervention group, mean self-perceived health status scores reduced from baseline (Mean: 61.42; SD: 22.45) to 1-month post intervention (Mean: 48.71; SD: 33.78), but increased at 3 (Mean: 76.42; SD: 15.73) and 12-months post intervention (Mean: 62.85; SD: 23.42) compared to baseline. In the control group, the mean scores remained stable across all follow up periods (Baseline mean: 49.01; SD: 21.07) to 12 months post intervention (Mean: 48.57; SD: 25.44). Women randomized to the intervention group reported better self-perceived health status than women in the control group, but not statistical differences were founded between groups.

Quality of life increased for participants randomized to the intervention group at all follow up points, with the exception of 1 month post intervention, from baseline (Mean: 40.71; SD: 23.52), to 3 months post intervention (Mean: 55.71; SD: 17.18) and to 12 month post intervention (Mean: 59.28; SD: 20.08). The mean score for participants in the control group also increased from baseline (Mean: 42.42; SD: 18.06) to 12 month post intervention (Mean: 54.28; SD: 19.02) but to a lesser extent than for the comparison group. No statistical differences were found between groups for this outcome.

Substance Use

The mean number of days of alcohol consumption reduced from baseline (Mean: 22.28; SD: 40.35) to 1-month post intervention (Mean: 6.42; SD: 12.83) for participants in the intervention group. The mean number of days of alcohol consumption increased for participants allocated to the control group from baseline (Mean: 6.28; SD: 13.79) to one month post intervention (Mean: 10.0; SD: 17.29). A significant difference was found between groups in the alcohol use self-reported (p= 0.035). No significant difference was found between groups in the number of days of alcohol consumption at the other follow up time points. For other substances, no significance differences were found.

Table 3
Mean study instrument Scores for both groups (Depression, Health Status and Quality of life)

Outcome		Baseline	1 month FU	3 months FU	12 months FU	p-value 1 m	p- value 3 m	p- value 12 m
Depression BDI M (SD)	**Intervention**	22.42 (8.34)	14.42 (8.16)	11.28 (5.18)	14.57 (8.96)	0.535	0.535	0.620
	Comparison	23.42 (12.73)	17.00 (10.36)	15.28 (10.95)	12.28 (9.60)			
Health Status M (SD)	**Intervention**	61.42 (22.45)	48.71 (33.78)	76.42 (15.73)	62.85 (23.42)	0.209	0.165	0.805
	Comparison	49.01 (21.07)	55.71 (13.04)	55.00 (23.80)	48.57 (25.44)			
Quality of Life M (SD)	**Intervention**	40.71 (23.52)	29.78 (27.27)	55.71 (17.18)	59.28 (20.08)	0.209	1	0.620
	Comparison	42.42 (18.06)	49.00 (12.79)	52.85 (19.11)	54.28 (19.02)			

Evaluation of the sessions

An assessment of the quality of the session was completed by participants at the end of each session. Participants reported that the content knowledge acquired during the sessions was high, with a mean score of 4.5 (SD: 0.50) - the maximum score possible was 5. In relation to feeling comfortable during sessions, 83% of participants reported feeling "very comfortable" during the sessions, 90% considered the therapist's performance was "excellent" and 80% evaluated sessions overall, as "excellent".

Discussion

Although women drug users report high rates of IPV, and depressive symptoms, few studies have tested the effectiveness of CBT interventions to reduce IPV victimization among this population. Some of these studies had short follow ups (Gilbert et al., 2006) that do not allow assessing whether benefits are maintained in long-term. To our knowledge, this feasibility and pilot trial is the first study to assess outcomes for female IPV victims attending substance abuse treatment, 12 months post intervention. This pilot randomized control trial shows encouraging results in terms of feasibility and initial effectiveness of the intervention studied. Twelve months post intervention, participants who received the intervention and remained with their partners showed reductions in the frequency of psychological violence received and improvements in their relationships showing increased assertiveness and reduced aggressiveness in their communication with their partner. A trend for greater reductions in physical IPV has also been detected. Participants randomized to the control group also showed reductions in IPV (physical and psychological). This could be due to the fact that they also received treatment for their drug use which may have resulted in improvements in their partner relationships and therefore improved outcomes, although improvements were less in this group than in the intervention group. Despite this, significant differences were found between groups for psychological abuse. The *IPaViT-CBT* intervention was more effective than treatment as usual in improving psychological maltreatment such as isolation/dominance at 1 and 3-months post intervention but this was not maintained longer term (12 month follow-up). Also statistical significance was found between groups in assertiveness and aggressiveness in the relationship at 1 month post intervention. These findings suggest that women receiving the *IPaViT-CBT* intervention were more likely to report less psychological abuse and improve their relationships than those in the treatment as usual group at all follow-ups. That may be because the CBT intervention aimed to provide women with the necessary skills to re-evaluate their relationships and this in turn changed the dynamic of psychological abuse. Our findings are consistent with other studies in terms of effectiveness in reducing IPV (Gilbert et al., 2006; Cohen, Field, Campbell, & Hien, 2013). A recent trial of CBT counseling compared to treatment as usual in primary care reported decreases in depressive symptoms among female IPV victims (Hegarty et al., 2013). We did not find that the *IPaViT-CBT* intervention favored the reduction of depressive symptoms compared to usual treatment in female drug users. Participants in both groups showed a reduction in self-reported depressive symptoms and showed an improvement in self-reported quality of life. It is possible therefore, that a single session addressing negative mood was insufficient to address complex depression comorbidity among female drug users. Future trials may need to enhance the intervention to address depressive symptoms. The *IPaViT-CBT* intervention showed a high fidelity and good attendance as well as high participation and retention rates, suggesting that this type of intervention is feasible to implement in community drug treatment centers to address IPV victimization. Moreover, study findings suggest very good ac-

ceptability among participants who indicated a high level of satisfaction with the intervention and their group therapist. Participants also believed they had gained new knowledge.

Around fifteen of women assessed were eligible to participate in that they were victims of IPV in the past month and remained in a relationship with their partner. Future studies may consider lengthening this time period to facilitate recruitment. The main limitation of this study is the small sample size, the interpretation of the findings need to be undertaken with caution. The findings from the current trial can be used to inform the parameters of a future definitive trial of the intervention. One limitation is that outcome data were self-reported. Another limitation was the variable participation of women at the group sessions, despite financial incentives, text reminders (sms) and reimbursement of travel costs. The administration of contingencies based on the principles of operant conditioning, such as the use of vouchers as incentives (Higgins et al., 1994) has been particularly effective in improving the monitoring of treatment and its results among this population (Higgins, Alessi, & Dantona, 2002). As literature has demonstrated, these strategies can be used and seem to be effective. Despite this fact, these variables should be controlled in future RCTs as they have proven influence in outcomes consistently through literature on the topic. Unfortunately, baseline differences were identified after randomization. Baseline differences in the outcomes variables could not be statistically controlled due to the small sample size. Observed baseline differences in alcohol consumption may be impacting on the evolution. However, all participants received treatment for the alcohol use disorder, and the alcohol problem and its evolution were monitored from the community center in both groups.

A future adequately powered trial is required to replicate these results and to draw firm conclusions about the effectiveness of the intervention compared to usual care. The cost effectiveness of the intervention compared to usual care should also be considered in future trials.

Conclusions

The findings from the feasibility and pilot trial suggests some initial support for the 10 session CBT group intervention among IPV victims who received treatment for drug use. This manualized small-group, *IPaViT-CBT* intervention designed to reduce IPV and improve depressive symptoms provides an opportunity when making decisions about how to address IPV victimization among female drug users. An adequately powered trial is required to replicate these results.

Acknowledgements

This work was supported by grants: RD12/0028/009 from Fondo de Investigaciones Sanitarias, Instituto Carlos III-FEDER and a co-operation agreement between "Departament de Salut" and "Parc de Salut Mar de Barcelona" to develop and implement a group intervention to reduce intimate partner violence among female drug users. All authors contributed equally to this work. All authors critically reviewed the manuscript and were involved in the interpretation of data.

Conflicts of interest

All authors declare that they have no conflicts of interest.

References

Beck, A. T., Steer, R. A., & Garbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*, 77-100.

Boer, A. G., Lanschot, J. J., Stalmeier, P. F., Sandick, J. W., Hulscher, J. B., Haes, J. C., & Sprangers, M. A. (2004). Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Quality of Life Research, 13*, 311-320.

Bonicatto, S., Dew, A. M., & Soria, J. J. (1998). Analysis of the psychometric properties of the Spanish version of the Beck Depression Inventory in Argentina. *Psychiatry Research, 79*, 277-285.

Bourgois, P., Prince, B., & Moss, A. (2004). The everyday violence of hepatitis C among young women who inject drugs in San Francisco. *Human Organization, 63*, 253-264.

Campbell, J. C. (2002). Health consequences of intimate partner violence. *Lancet, 359*, 1331-1336. doi: 10.1016/s0140-6736(02)08336-8

Campbell, J. C., Baty, M. L., Ghandour, R. M., Stockman, J. K., Francisco, L., & Wagman, J. (2008). The intersection of intimate partner violence against women and HIV/AIDS: A review. *International Journal of Injury Control and Safety Promotion, 15*, 221-231. doi: 10.1080/17457300802423224

Carpenter, K. M., Aharonovich, E., Smith, J. L., Iguchi, M. Y., & Nunes, E. V. (2006). Behavior therapy for depression in drug dependence (BTDD): Results of a stage Ia therapy development pilot. *The American Journal of Drug and Alcohol Abuse, 32*, 541-548. doi: 10.1080/00952990600919450

Castillo-Camiglia, A., Pizarro, E., Luengo, D., & Soto-Brandt, G. (2014). Consumo de alcohol y autoinforme de eventos violentos en Chile. *Adicciones, 26*, 46-53.

Cohen, L. R., Field, C., Campbell, A. N., & Hien, D. A. (2013). Intimate partner violence outcomes in women with PTSD and substance use: A secondary analysis of NIDA Clinical Trials Network "Women and Trauma" Multi-site Study. *Addictive Behaviors, 38*, 2325-2332. doi: 10.1016/j.addbeh.2013.03.006

Cohen, L. R. & Hien, D. A. (2006). Treatment outcomes for women with substance abuse and PTSD who have ex-

perienced complex trauma. *Psychiatric Services, 57*, 100-106. doi: 10.1176/appi.ps.57.1.100

Connelly, C. D., Hazen, A. L., Baker-Ericzen, M. J., Landsverk, J., & Horwitz, S. M. (2013). Is screening for depression in the perinatal period enough? The co-occurrence of depression, substance abuse, and intimate partner violence in culturally diverse pregnant women. *Journal of Women's Health (Larchmt), 22*, 844-852. doi: 10.1089/jwh.2012.4121

El-Bassel, N., Gilbert, L., Witte, S., Wu, E., & Chang, M. (2011). Intimate partner violence and HIV among drug-involved women: contexts linking these two epidemics–challenges and implications for prevention and treatment. *Substance Use & Misuse, 46*, 295-306. doi: 10.3109/10826084.2011.523296

El-Bassel, N., Gilbert, L., Wu, E., Go, H., & Hill, J. (2005). Relationship between drug abuse and intimate partner violence: a longitudinal study among women receiving methadone. *American Journal of Public Health, 95*, 465-470. doi: 10.2105/ajph.2003.023200

Fearday, F., Clark, C., & Edington, M. (Eds.) (2001). *Triad Women's Project Group Facilitator Manual and Workbook.* Tampa, FL: Louis de la Porte Florida Mental Health Institute, University of South Florida.

Fowler, D. N. & Faulkner, M. (2011). Interventions targeting substance abuse among women survivors of intimate partner abuse: a meta-analysis. *Journal of Substance Abuse Treatment, 41*, 386-98. doi: 10.1016/j.jsat.2011.06.001.

Gilbert, L., El-Bassel, N., Manuel, J., Wu, E., Go, H., Golder, S., . . . Sanders, G. (2006). An integrated relapse prevention and relationship safety intervention for women on methadone: testing short-term effects on intimate partner violence and substance use. *Violence and Victims, 21*, 657-672. Gilchrist, G., Blazquez, A., & Torrens, M. (2011). Psychiatric, behavioural and social risk factors for HIV infection among female drug users. *AIDS and Behavior, 15*, 1834-1843. doi: 10.1007/s10461-011-9991-1

Gilchrist, G., Blazquez, A., & Torrens, M. (2012). Exploring the relationship between intimate partner violence, childhood abuse and psychiatric disorders among female drug users. *Advances in Dual Diagnosis, 5*, 46-58.

Harris, M. & Community Connections Trauma Work Group (Eds.) (1998). *Trauma Recovery and Empowerment: A Clinician's guide for working with women in groups.* New York: Community Connections, Inc.

Hearn, K. D., O'Sullivan, L. F., El-Bassel, N., & Gilbert, L. (2005). Intimate partner violence and monogamy among women in methadone treatment. *AIDS and Behavior, 9*, 177-186. doi: 10.1007/s10461-005-3899-6

Hegarty, K., Bush, R., & Sheehan, M. (2005). The composite abuse scale: further development and assessment of reliability and validity of a multidimensional partner abuse measure in clinical settings. *Violence and Victims, 20*, 529-547. Hegarty, K., O'Doherty, L., Taft, A., Chondros, P., Brown, S., Valpied, J., . . . Gunn, J. (2013). Screening and counselling in the primary care setting for women who have experienced intimate partner violence (WEAVE): a cluster randomised controlled trial. *Lancet, 382*, 249-258. doi: 10.1016/s0140-6736(13)60052-5

Hegarty, K., Sheehan, M., & Schonfeld, C. (1999). A Multidimensional Definition of Partner Abuse: Development and Preliminary Validation of the Composite Abuse Scale. *Journal of Family Violence, 14*, 399-415.

Higgins, S. T., Alessi, S. M., & Dantona, R. L. (2002). Voucher-based incentives. A substance abuse treatment innovation. *Addictive Behaviors, 27*, 887-910.

Higgins, S. T., Budney, A. J., Bickel, W. K., Foerg, F. E., Donham, R., & Badger, G. J. (1994). Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Archives of General Psychiatry, 51*, 568-576.

Howard, L. M., Trevillion, K., Khalifeh, H., Woodall, A., Agnew-Davies, R., & Feder, G. (2010). Domestic violence and severe psychiatric disorders: prevalence and interventions. *Psychological Medicine, 40*, 881-893. doi: 10.1017/s0033291709991589

Illangasekare, S. L., Burke, J. G., McDonnell, K. A., & Gielen, A. C. (2013). The impact of intimate partner violence, substance use, and HIV on depressive symptoms among abused low-income urban women. *Journal of Interpersonal Violence, 28*, 2831-2848. doi: 10.1177/0886260513488682

Kaysen, D., Dillworth, T. M., Simpson, T., Waldrop, A., Larimer, M. E., & Resick, P. A. (2007). Domestic violence and alcohol use: trauma-related symptoms and motives for drinking. *Addictive Behaviors, 32*, 1272-1283. doi: 10.1016/j.addbeh.2006.09.007

Liebschutz, J. M., Mulvey, K. P., & Samet, J. H. (1997). Victimization among substance-abusing women. Worse health outcomes. *Archives of Internal Medicine, 157*, 1093-1097.

McKinney, C. M., Caetano, R., Rodriguez, L. A., & Okoro, N. (2010). Does alcohol involvement increase the severity of intimate partner violence? *Alcoholism, Clinical and Experimental Research, 34*, 655-658. doi: 10.1111/j.1530-0277.2009.01134.x

Miller, D. & Guidry, L. (Eds.) (2001). *Addictions and Trauma Recovery: Healing the Body, Mind, and Spirit.* New York: W.W. Norton and Co.

Miller, B. A., Downs, W. R., & Testa, M. (1993). Interrelationships between victimization experiences and women's alcohol use. *Journal of Studies on Alcohol. Supplement, 11*, 109-117.

Najavits, L. M. (2009). Psychotherapies for trauma and substance abuse in women: review and policy implications. *Trauma, Violence & Abuse*, 10, 290-8. doi: 10.1177/1524838009334455.

Najavits, L. M. (Ed.) (2002). *Seeking Safety: A Treatment Manual for PTSD and Substance Abuse.* Nueva York: Guildford Press.

Najavits, L. M., Sonn, J., Walsh, M., & Weiss, R. D. (2004). Domestic violence in women with PTSD and substance abuse. *Addictive Behaviors, 29*, 707-715. doi: 10.1016/j.addbeh.2004.01.003

O'Leary, K. D., & Curley, A.D. (1986). Assertion and family violence: Correlates of Spouse Abuse. *Journal of Marital and Family Therapy, 12*, 281- 289.

Okuda, M., Olfson, M., Hasin, D., Grant, B. F., Lin, K. H., & Blanco, C. (2011). Mental health of victims of intimate partner violence: results from a national epidemiologic survey. *Psychiatric Services, 62*, 959-962. doi: 10.1176/appi.ps.62.8.959

Peters, E. N., Khondkaryan, E., & Sullivan, T. P. (2012). Associations between expectancies of alcohol and drug use, severity of partner violence, and posttraumatic stress among women. *Journal of Interpersonal Violence, 27*, 2108-2127. doi: 10.1177/0886260511432151

Singer, M. (1996). A dose of drugs, a touch of violence, a case of AIDS: Conceptualizing the SAVA syndemic. *Free Inquiry in Creative Sociology, 24*, 99–110.

Sobell, L. S. & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported ethanol consumption. *Measuring Alcohol Consumption: Psychological and Biological Methods*, 41–72.

Sobell, L. C., Maisto, S. A., Sobell, M. B., & Cooper, A. M. (1979). Reliability of alcohol abusers' self-reports of drinking behavior. *Behaviour Research and Therapy*, 17, 157-160.

Testa, M., Livingston, J. A., & Hoffman, J. H. (2007). Does sexual victimization predict subsequent alcohol consumption? A prospective study among a community sample of women. *Addictive Behaviors, 32*, 2926-2939. doi: 10.1016/j.addbeh.2007.05.017

Tirado-Muñoz, J., Gilchrist, G., Farré, M., Hegarty, K., & Torrens, M. (2014). The efficacy of cognitive behavioural therapy and advocacy interventions for women who have experienced intimate partner violence: A systematic review and meta-analysis. *Annals of Medicine, 11*, 1-20. doi:10.3109/07853890.2014.941918

Tolman, R.M. (1989). The development of a measure of psychological maltreatment of women by their male partners. *Violence and Victims*, *4*, 159-177.

Tolman, R. M. (1999). The validation of the Psychological Maltreatment of Women Inventory. *Violence and Victims, 14*, 25-37.

Torrens, M., Gilchrist, G., & Domingo-Salvany, A. (2011). Psychiatric comorbidity in illicit drug users: substance-induced versus independent disorders. *Drug and Alcohol Dependence, 113*, 147-156. doi: 10.1016/j.drugalcdep.2010.07.013

Trevillion, K., Oram, S., Feder, G., & Howard, L. M. (2012). Experiences of domestic violence and mental disorders: a systematic review and meta-analysis. *PLoS One, 7*, e51740. doi: 10.1371/journal.pone.0051740

Wagner, K. D., Hudson, S. M., Latka, M. H., Strathdee, S. A., Thiede, H., Mackesy-Amiti, M. E., & Garfein, R. S. (2009). The effect of intimate partner violence on receptive syringe sharing among young female injection drug users: an analysis of mediation effects. *AIDS and Behavior, 13*, 217-224. doi: 10.1007/s10461-007-9309-5

World Health Organization. (2013). *Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines*. Retrieved from http://apps.who.int/iris/bitstream/10665/85240/1/9789241548595_eng.pdf?ua=1.

Management of opioid-dependent patients: comparison of the cost associated with use of buprenorphine/naloxone or methadone, and their interactions with concomitant treatments for infectious or psychiatric comorbidities

Manejo de pacientes dependientes de opiáceos: Comparación del coste asociado al uso de buprenorfina/naloxona o metadona, y sus interacciones con tratamientos concomitantes para comorbilidades infecciosas o psiquiátricas

Carlos Roncero*, Raquel Domínguez-Hernández**, Tomás Díaz***, José Manuel Fernández****, Rafael Forcada*****, José Manuel Martínez******, Pedro Seijo*******, Antonio Terán********, Itziar Oyagüez**

* CAS Drogodependencias Vall Hebron. Hospital Universitario Vall d'Hebron-ASPB. CIBERSAM. Departamento de Psiquiatría. Universidad Autónoma de Barcelona, Barcelona. ** Pharmacoeconomics & Outcomes Research Iberia. Madrid. ***Unidad de Tratamiento de Toxicomanías de Oviedo (UTT). Unidad de Desintoxicación Hospitalaria (UDH). Servicios de Salud Mental Área IV del Principado de Asturias. ****Unidad Asistencial de Drogodependencias de Riveira, La Coruña. *****Unidad de Conductas Adictivas de Moncada, Valencia. ******Centro de Tratamiento Ambulatorio de las Adicciones de Cádiz, Diputación de Cádiz. *******Centro de Tratamiento Ambulatorio de las Adicciones de Villamartín, Diputación de Cádiz. ********Centro de Atención a Drogodependencias "San Juan de Dios", Palencia.

Abstract

The objective was to estimate the annual interaction management cost of agonist opioid treatment (AOT) for opioid-dependent (OD) patients with buprenorphine-naloxone (Suboxone®) (B/N) or methadone associated with concomitant treatments for infectious (HIV) or psychiatric comorbidities. A costs analysis model was developed to calculate the associated cost of AOT and interaction management. The AOT cost included pharmaceutical costs, drug preparation, distribution and dispensing, based on intake regimen (healthcare center or take-home) and type and frequency of dispensing (healthcare center or pharmacy), and medical visits. The cost of methadone also included single-dose bottles, monthly costs of custody at pharmacy, urine toxicology drug screenings and nursing visits. Potential interactions between AOT and concomitant treatments (antivirals, antibacterials/antifungals, antipsychotics, anxiolytics, antidepressant and anticonvulsants), were identified to determine the additional use of healthcare resources for each interaction management. The annual cost per patient of AOT was €1,525.97 for B/N and €1,467.29 for methadone. The average annual cost per patient of interaction management was €257.07 (infectious comorbidities), €114.03 (psychiatric comorbidities) and €185.55 (double comorbidity) with methadone and €7.90 with B/N in psychiatric comorbidities. Total annual costs of B/N were €1,525.97, €1,533.87 and €1,533.87 compared to €1,724.35, €1,581.32 and €1,652.84 for methadone per patient with infectious, psychiatric or double comorbidity respectively.

Compared to methadone, the total cost per patient with OD was lower with B/N (€47.45-€198.38 per year). This is due to the differences in interaction management costs associated with the concomitant treatment of infectious and/or psychiatric comorbidities.

Key Words: costs analysis, buprenorphine-naloxone, methadone, comorbidities, opioid dependence.

Resumen

El objetivo fue estimar en pacientes con dependencia a opiáceos (DO), el coste anual del manejo de interacciones del tratamiento sustitutivo con buprenorfina/naloxona (Suboxone®) (B/N) o metadona, asociado con tratamientos concomitantes por comorbilidades infecciosas (VIH) o psiquiátricas. Se realizó un análisis de costes (€, 2013), del tratamiento sustitutivo y del manejo de interacciones. El coste del tratamiento de B/N incluyó costes farmacológicos, elaboración, distribución y dispensación, en función del régimen de administración (centro asistencial o domiciliaria) y del tipo y frecuencia de dispensación (centro asistencial o farmacia), y visitas al especialista para prescripción. El coste de tratamiento con metadona incluyó, además, frascos monodosis, coste de custodia en farmacia, determinación en orina y visitas a enfermería. Se identificaron las interacciones para determinar los recursos sanitarios adicionales consumidos por la administración conjunta del tratamiento sustitutivo y concomitante (antirretrovirales, bactericidas/antifúngicos, antipsicóticos, ansiolíticos, antidepresivos y anticonvulsivos). El coste anual/paciente estimado del tratamiento sustitutivo fue de 1.525,97€ (B/N) y 1.467,29€ (metadona). El coste promedio anual/paciente estimado del manejo de interacciones fue de 257,07€ (infecciosas), 114,03€ (psiquiátricas) y 185,55€ (ambas) con metadona, y de 7,90€ con B/N por comorbilidades psiquiátricas. El coste total anual/paciente estimado de B/N fue 1.525,97€, 1.533,87€ y 1.533,87€ comparado con 1.724,35€, 1.581,32€ y 1.652,84€ de metadona, en pacientes que presentan comorbilidad infecciosa, psiquiátrica o ambas, respectivamente. Comparado con metadona, el coste total por paciente con DO de B/N fue menor (47,45€-198,38€ anuales) derivado de la diferencia del coste por manejo de interacciones del tratamiento concomitante de las comorbilidades infecciosas y/o psiquiátricas.

Palabras clave: análisis de costes, dependencia de opiáceos, buprenorfina/naloxona, metadona, comorbilidades.

Received: October 2014; Accepted: February 2015

Send correspondence to:
Carlos Roncero, MD PhD. Servicio de psiquiatría, Hospital Universitario Vall d'Hebron. Passeig Vall d´Hebron, 119-129, 08035 Barcelona, España.
Correo electrónico: croncero@vhebron.net.

Addiction to opioids such as heroin can pose significant medical, social and economic problems for both the individual and society (Canadian Agency for Drugs and Technologies in Health, 2013). Different therapies are currently in use to combat opioid dependence, with methadone and buprenorphine-naloxone (Suboxone®) (B/N) being the most widespread therapeutic alternatives in agonist opioid treatments in Spain. In 2011, 76,263 people aged 15 to 64 were treated in opioid replacement programs, of which 97.29% were attended to in programs administering methadone while 2.71% used B/N (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2011).

Methadone is the most widely used opioid agonist in the treatment of heroin addiction, and is dispensed in health care centers. In pill form and taken sublingually, B/N has proven to be an effective treatment for heroin addicts and can be used by outpatients, thus making life easier for them (Sittambalam, Vij, & Ferguson, 2014).

Patients usually remain in maintenance treatment for long periods (Roncero et al., 2011), the average duration being 26 months (Observatorio Vasco de Drogodependencias, 2004). This period is typically divided into three phases: induction, maintenance and dose reduction. The induction phase lasts three days, during which time the opioid previously consumed by the patient is substituted and the dosage is adjusted based on the clinical response of the patient. In the maintenance phase, which lasts for months and even years, a dosage is established to prevent withdrawal symptoms. The dose reduction phase is implemented when the patient reaches and maintains clinical stability over time, and is typically initiated after a year of treatment (Terán, 2010).

Patients with opioid dependence (OD) present high clinical comorbidity, most commonly with infectious diseases and psychiatric disorders. The most frequent infectious comorbidities are those related to the human immunodeficiency virus (HIV), the hepatitis C virus (HCV) and co-infections of both HCV/HIV with a prevalence between 21%-53%, 47%-73% and 14% respectively (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014). Based on the classification of psychiatric disorders in accordance with DSM-IV-TR axes I and II (American Psychiatric Association, 2000), the prevalence of psychiatric comorbidity is between 25%-78% (Pereiro, Pino, Flórez, Arrojo, & Becoña, 2013; Roncero et al., 2011; Sanvisens et al., 2014). The majority of these patients receive concomitant treatment for their different illnesses, with 30.6% being treated for infectious disease and 21.6% for psychiatric disorders (Roncero et al., 2011). Patients frequently receive such treatment since the presence of some mental disorders is associated with a greater likelihood of engaging in behaviour with risks of contracting infectious diseases (Cervera, Valderrama, Bolinches, Salazar, & Martínez, 1998).

The administration of opioid replacement treatment together with other pharmaceutical drugs can lead to side effects (Haro, 2012) as well as pharmacological interactions (pharmacogenetic or pharmacodynamic) which can bring about modifications in plasma concentrations or affect the efficacy and safety of the drugs involved (Sociodrogoalcohol, 2010). To prevent possible withdrawal symptoms or overdose caused by such interaction, it is necessary to adjust dosage and patient monitoring (Puche, Faus, Soler, & Blasco, 2000). This can provoke an increase in the use of health resources with a resulting rise in the costs of treating the illness. Not many economic assessments have been published regarding rehabilitation programs. While the majority focus on the costs of drugs and care incurred by methadone maintenance programs (Cobacho, López, & Ramos, 2011; Del Pozo, Soldevilla, Murga, & Antoñanzas, 2012; Puigdollersa, Cotsa, Brugal, Torralba, & Domingo-Salvany, 2003) only a very few investigate B/N programs (Martínez-Raga, González-Saiz, Pascual, Casado, & Sabater, 2010; Martínez-Raga et al., 2012). Today it is essential that all costs associated with or complementary to the different treatments received by the patients are taken into account with the aim of seeking out those which are most effective and efficient (Bernal-Delgado, Campillo-Artero, & García-Armesto, 2014; López-Bastida et al., 2010). Nevertheless, it is difficult to calculate such costs given the variations between the different care centers which can attend to these patients, the manner in which the opioid pharmaceutical is prescribed and dispensed, the monitoring of patients depending on the type of center in the different communities and because of the variability associated with how comorbidity is managed. Despite the widespread presence of medical comorbidity and dual pathology in opioid dependents on opioid maintenance programs (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014; Szerman et al., 2014), and studies assessing the interactions occurring due to concomitant medication, there is no information available about the additional costs produced by managing the pharmacological interactions in everyday clinical practice with this type of patient.

The present analysis attempts to estimate and compare the annual costs of replacement therapy with B/N or methadone in OD patients, together with the costs of dealing with the potential interactions caused by the co-administration of the opiate drug with the medication for infectious and psychiatric comorbidity, and study if there are significant differences between both treatments.

Method

Study design

A cost analysis was designed based on a decision-making tree representing clinical practice (Figure 1) to calculate the annual cost of replacement treatment in OD patients and the cost of managing interactions caused by the co-administration of drugs in patients with at least one infectious and/or psychiatric comorbidity.

The analysis was carried out with Microsoft Excel® 2010 and included all costs of the replacement treatment with the alternatives in question (B/N and methadone) as well as the costs associated with the presence of infectious and psychiatric comorbidity.

The identification of health resources was carried out through a questionnaire sent to a panel of experts (PE) consisting of a group of seven clinicians expert in the care of OD patients from different parts of Spain. The questionnaire included data obtained from the literature on therapeutic management and physical and psychiatric comorbidity, and questions about information not found in the bibliography but necessary for this study. The results of the questionnaires were unified and filtered so that the PE was able to reach a consensus on the clinical management of OD patients undergoing replacement treatment and associated comorbidities in clinical practice in different health centers throughout Spain.

The analysis was carried out from a Spanish National Health System (SNHS) perspective, following national and international recommendations for this type of study (López-Bastida et al., 2010; Prieto et al., 2004). The time horizon was one year and for this reason no discount was applied.

The results were expressed as average cost per patient.

Resources and costs

The total estimated cost per patient for each of the alternatives included the cost of the replacement treatment on the one hand, which included the cost of the drug, preparation, distribution and dispensing, and the cost of managing the interactions on the other, taking into account the consumption of additional healthcare resources (increase or decrease in the opioid drug, psychiatrist or medical visits, electrocardiograms, blood and urine toxicology screening, and single-dose bottles for dispensing methadone) associated with this issue in everyday clinical practice.

Replacement therapy. The dosage used to estimate the cost of drugs involved in replacement therapy included the daily average doses in the induction and maintenance phases, i.e. 10mg for 3 days and 8 mg for 362 days for B/N and 50.45 mg for 14 days and 61.52 mg for 351 days for methadone (Roncero et al., 2011). To calculate the cost of B/N, the retail price (RP+VAT) was used (Consejo General de Colegios Oficiales de Farmacéuticos, 2013). The cost of drugs finally included in the analysis was that incurred by the financing body (the Spanish National Health System). The estimated annual drugs cost of B/N incurred by the financing body (€1,461.43) took into account the employment situation of the OD patients (Roncero et al., 2011), as well as the distribution of income levels across three groups (<€18,000, €18,000-€100,000, >€100,000) (Instituto Nacional de Estadística, 2013), the co-payment percentage for each type of patient and the maximum monthly contribution (Real Decreto-ley 16/2012) (Table 1).

Methadone is a pharmaceutical drug which is centrally produced and then distributed under security to the different autonomous communities, which are responsible for distributing them to the dispensing centers and authorized pharmacies (Cobacho et al., 2011). In the present study, the costs associated with the preparation (€378.57), distribution (€258.31) and purchase of methadone (wholesale price per kg) were obtained from the literature (Martínez-Raga et al., 2012), and were updated to 2013 by applying the rate of change in the Consumer Price Index of the Spanish Statistical Office (Instituto Nacional de Estadística, 2011).

Regarding dispensing, two groups of patients were differentiated in terms of how the dose was administered

Table 1
Number of patients by employment situation and income.

GROUP	RETIRED			WORKING			UNEMPLOYED
Income	<18,000	18,000-100,000	>100,000	<18,000	18,000-100,000	>100,000	------
Roncero et al., 2013		21.00%			24.50%		52,00%
Co-payment (%)	10%	10%	60%	40%	50%	60%	0
Maximum monthly contribution per patient	8.14€	12.18€	61.08€	N/A	N/A	N/A	N/A
Patients by income (%)	84.16%	15.57%	0.18%	58.19%	40.97%	0.84%	100.00%

Note. N/A: not applicable

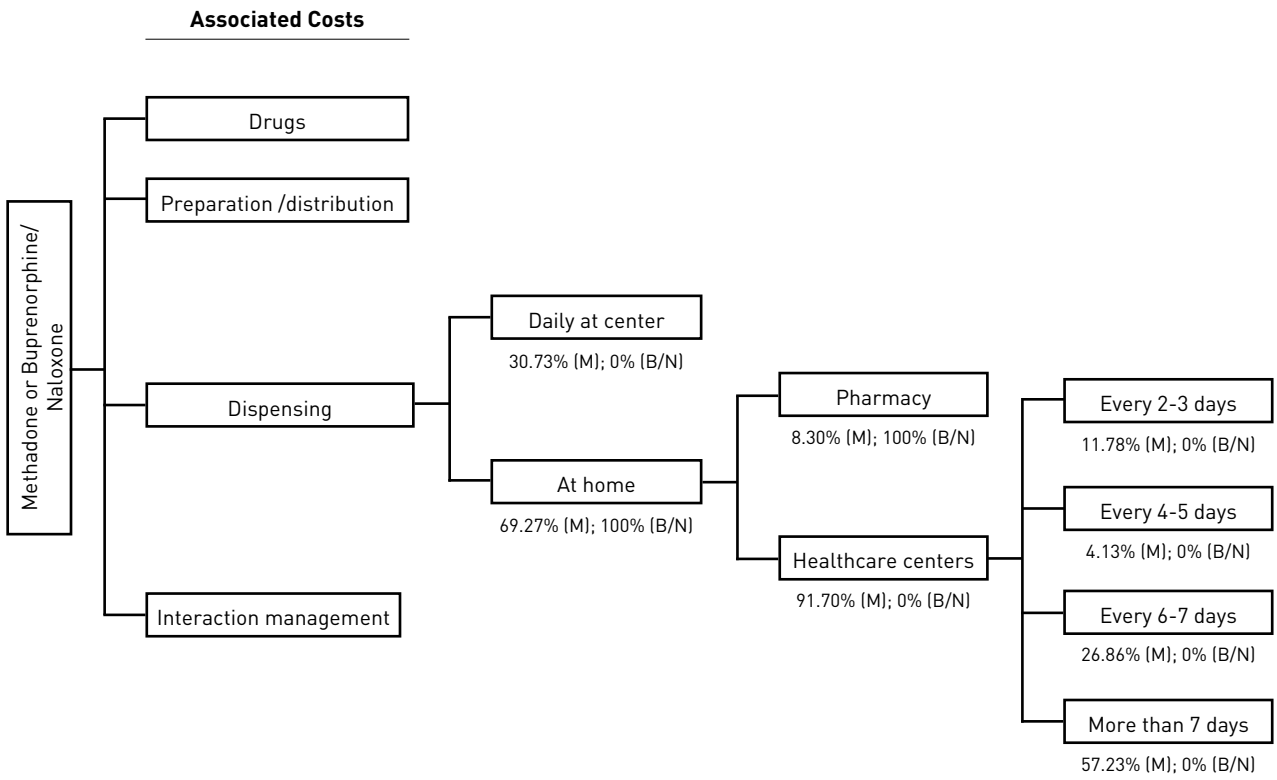


Figure 1. Study design. Patient distribution.

and dispensed. For methadone, the dose was administered daily at the healthcare center or at home. For those patients on a take-home regimen, the drug was dispensed at the healthcare center every 2-3 days, 4-5 days, 6-7 days or more than 7 days, or through the pharmacy. The distribution of patients assigned to each group was taken from an observational study carried out in Spain (Roncero et al., 2011) (Figure 1).

The resources calculated per patient were: 5 minutes of nurse time when dispensed at the health center or custody at pharmacy if dispensed there, and a single-dose bottle per day. In addition, a 50% increase in bottles was calculated for fast-metabolising patients (10%) for whom the bottle is divided into several doses (Instituto de Adicciones Madrid, 2008). Reuse of the single-dose bottle was not considered in the calculations. Quarterly urine toxicology screening was included. A medical appointment every 6 weeks for the prescription was included in both treatments.

Interaction management. When different drugs are taken together, the possible pharmacological interactions require closer control of the patient (Bruce, Moody, Altice, Gourevitch, & Friedland, 2013). For this reason, additional costs associated with the use of resources for managing the interactions caused by the co-administration of drugs were analyzed. The pharmacological treatment groups included were antivirals, antibacterials/antifungals, antipsychotics, anxiolytics, antidepressant and anticonvulsants (McCance-Katz, Sullivan, & Nallani, 2010; McCance-Katz, 2012). Based on the information found in the literature (Amariles, Giraldo, & Faus, 2007; Bruce, Altice, Gourevitch, & Friedland, 2006; Gallego, Barreio, & López-Ibor, 2012; McCance-Katz et al. 2010; McCance-Katz, 2012; Pérez, Jornet, & Bonet, 2002; Puche et al., 2000; Serrano, 2011) and provided by the panel of experts, the drugs from each group to be included in the study due to their potential interaction with B/N or methadone and their use in everyday clinical practice were identified. At the same time, in order to estimate the costs of an average patient, the panel of experts, estimated the disaggregated additional consumption of healthcare resources generated by the interaction, and the frequency and percentage of patients using each resource for each of the treatment options. In the case of B/N, the drugs examined for their interaction potential and for the variation from the norm generated in patient management were citalopram and escitalopram (Table 2). The interaction between drugs included as concomitant medication and their dosage variations were not examined. The costs of using drugs which are not normally administered due to the seriousness of the interaction were also not analyzed. The increase in dose of the opioid was included when occasioned by the clinical manifestation of withdrawal symptoms. A rise in the number of specialist

Table 2
Resources consumed by interaction management, by methadone therapy group.

Drug	Action	Dose (mg/day)		Frequency (annual)		Patients (%)	
		Methadone	B/N[a]	Methadone	B/N[a]	Methadone	B/N[a]
citalopram/escitalopram	Psychiatric visits			2	2	100	100
	Electrocardiogram			1	1	100	100
		Methadone		**Methadone**		**Methadone**	
efavirenz, lopinavir and nevirapine	Dose increase	24.61		351		100	
	Psychiatric visits			2			
	Nursing visits			7			
	Blood toxicology screening			2			
	Electrocardiogram			1			
	Bottles			365			
indinavir	Dose reduction	6.15		351		100	
	Psychiatric visits			1		100	
rilpivirine	Psychiatric visits			2		100	
	Electrocardiogram			1		100	
rifampicine	Dose increase	61.52		351		100	
	Psychiatric visits			4		100	
	Nursing visits			16		100	
	Blood toxicology screening			2		5	
	Electrocardiogram			1		100	
	Bottles			365		75	
amitriptyline, clomipramine and doxepina	Nursing visits			1		100	
	Electrocardiogram			1		100	
diazepam, alprazolam, clonazepam, lorazepam, midazolam, triazolam, zolpidem and zopiclone	Psychiatric visits			2		100	
carbamazepine	Dose increase	24.61		351		100	
	Psychiatric visits			2		100	
	Nursing visits			7		100	
	Blood toxicology screening			2		5	
	Electrocardiogram			1		50	
	Bottles			365		5	
ziprasidone and pimozide	Psychiatric visits			2		100	
	Electrocardiogram			1		100	

Note. [a]Buprenorfina/Naloxona

and medical visits was associated with greater monitoring and a variation in the treatment regimen. Blood toxicology screening was associated with methadone doses above 100 mg per day, with antiretroviral treatments, and medication liable to interfere with methadone metabolism (Instituto de Adicciones Madrid, 2008). Electrocardiograms were linked to drugs which can cause prolongation of the QT-interval, and the increase in the number of bottles was linked to those drugs which increased methadone metabolism and caused dose fractionation. To determine total infectious or psychiatric comorbidity costs, an average of the cost of drugs with interaction potential in each comorbidity was calculated.

In order to estimate the monthly frequency of each resource, an average month length of 30.4 days was applied. All costs included in the analysis were direct healthcare costs in 2013 and quoted in Euros (Table 3).

Table 3
Unit costs of drugs and healthcare resources (€, 2013).

	Unit cost
Drug	
Methadone	0.0006€/kg (Wholesale)
Buprenorphine/naloxona (Suboxone®)	0.50€/mg (Retail+VAT)
Healthcare resources	
Specialist visits	46.22€[a]
Medical visits (cost per minute)	0.34€[a]
Custody of methadone per patient	69€/mes[b]
Bottle for dispensing	0.45€[c]
Urine toxicology screening	12.03[a]
Electrocardiogram	33.90€[a]
Test of plasma levels	115.04€[a]

Note. [a]e-Health Database. [b]Agreement between Comunidad de Madrid and the Professional Association of Pharmacists in Madrid (COFM), [c]Panel of experts.

Sensitivity analysis

To determine the stability of the results, univariate sensitivity analyses (SA) were carried out with the highest uncertainty values of the analysis. The variables included were minutes of nurse time, from 4 to 6 minutes, and the cost of single-dose bottles within a ±20% range.

Results

Replacement therapy with B/N generated an annual per-patient cost of €1,525.97, of which 75.77% corresponded to pharmaceutical costs and 24.23% to dispensing. The annual cost of methadone treatment was €1,467.29, with the pharmaceutical cost making up 0.86%, preparation and distribution 43.41% and dispensing 55.73% (Table 4).

Table 4
Total annual cost of therapy with B/N or methadone per patient with infectious or psychiatric comorbidity (€, 2013).

Cost type	B/N (Suboxone®)	Methadone
Replacement therapy	1,525.97€	1,467.29€
Drugs	1,156.25€	12.58€
Preparation and distribution	0.00€	636.98€
Dispensing	369.72€	817.73€
Interaction management		
Infectious	0.00€	257.07€
Psychiatric	7.90€	114.03€
Both	7.90€	185.55€
TOTAL ANNUAL PER PATIENT		
Infectious Comorbidity	1,525.97€	1,724.35€
Psychiatric Comorbidity	1,533.87€	1,581.32€
Both Comorbidities	1,533.87€	1,652.84€

The annual per-patient costs of interaction management for infectious and psychiatric comorbidity for methadone were €257.07 and €114.03 respectively. B/N generated costs of €7.90, associated solely with the average costs incurred in the interaction management of psychiatric comorbidity. To avoid duplication of resources, the cost of a patient with both comorbidities was calculated by taking an average of the two: €185.55 (methadone) and €7.90 (B/N).

The annual total costs per OD patient in replacement treatment with infectious or psychiatric comorbidity or both were €1,525.97, €1,533.87 and €1,533.87 respectively for B/N and €1,724.35, €1,581.32 and €1,625.84 for methadone (Figure 2).

The SAs showed that variations in minutes of nurse time spent on dispensing the drug, or in the cost of the single-dose bottle of ±20%, can generate savings of €6.90-€242.54.

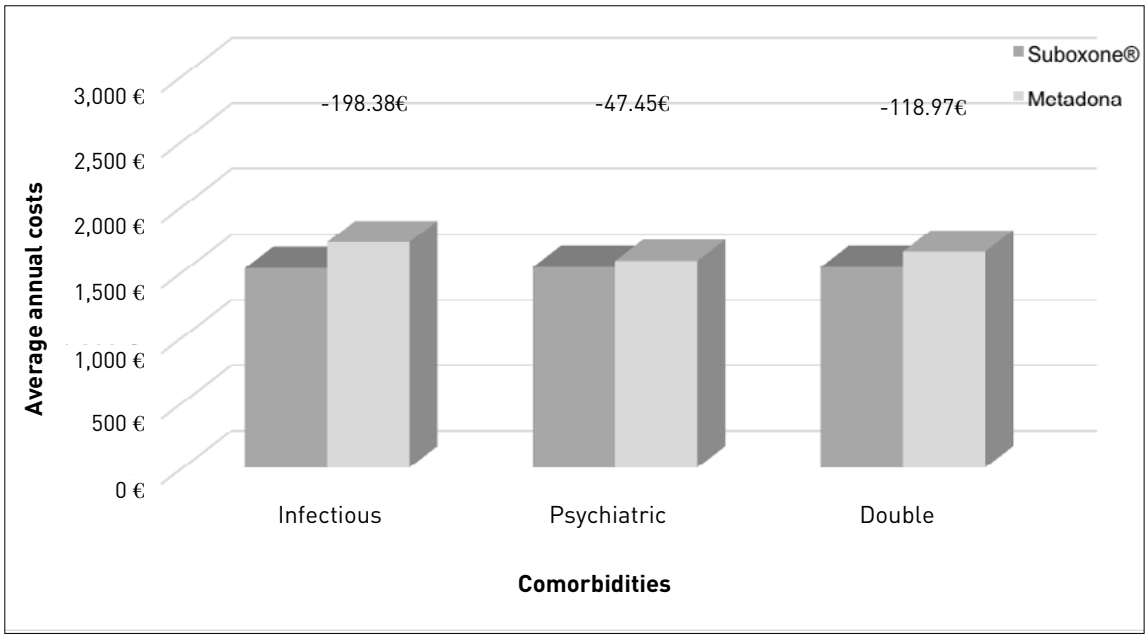


Figure 2. Results per patient.

Discussion

The study of medical or psychiatric comorbidity in OD patients is important for several reasons. Its frequent occurrence (González-Saiz et al., 2011; Pereiro et al., 2013; Roncero et al., 2011) means that different aspects of patients' lives, such as driving, can be affected (Roncero et al., 2013). Furthermore, pharmacological interactions caused by the co-administration of other drugs, especially antiretrovirals, with methadone and buprenorfina can have clinical consequences which necessitate closer patient monitoring (Bruce et al., 2013) and generate a change in total treatment cost, as demonstrated by this study.

Today it is necessary to implement strategic plans to optimize existing resources dedicated to patients with addictions (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2013) and dual patients (Arias et al., 2013; Roncero et al., 2014; Szerman et al., 2014), and to carry out more studies which evaluate the direct and indirect costs of the pathology to the healthcare system. For these reasons, apart from analyzing the direct costs of B/N and methadone treatment, it is important to account for the costs generated by the co-administration of drugs which can cause changes in the monitoring of patients leading to increases in the consumption of resources and thus a rise in costs.

This study calculates treatment and interaction costs for both therapies. Results are quoted in terms of total cost per OD patient in replacement treatment with infectious and psychiatric morbidity. This information can be useful in decision making if we are interested in making better use of healthcare resources dedicated to replacement therapy programs.

Studies published in Spain of the costs involved in opioid replacement therapies are few and far between. Almost all of them focus on the costs of RTPs with methadone and only a few compare these with B/N (Martínez-Raga et al., 2010; Martínez-Raga et al., 2012). The results of a recent study comparing the budgetary impact of introducing B/N as a treatment for OD as opposed to methadone showed that B/N carried an additional cost of €9 (in 2007) per patient. Costs included in the study were medication, logistics, dispensing, medical and social services staff and toxicology tests (Martínez-Raga et al., 2010). On updating the study in 2012, the use of B/N was found to have an additional per-patient cost of €10.58 in the first year, €6.58 in the second and €7.34 in the third (costs in 2010) (Martínez-Raga et al., 2012).

Although there are numerous studies of the interaction caused by the use of opioids alongside other medication, the authors believe that the present study is the first to analyze the costs of comorbidity in OD patients in clinical practice in Spain or other countries. For this reason, it was not possible to compare our results with those of other studies.

It is important to point out that psychiatric comorbidity management is rather variable and depends on both the characteristics of each patient as well as on the psychotherapeutic measures employed simultaneously, which means that the analysis of all the costs associated with the comorbidity can be complex. At the same time, this type of patient can be attended to in a variety of settings, such as healthcare centers, official opioid prescription centers, primary healthcare, and regional HIV programs (Roncero et al., 2011). Prescription and dis-

pensing of the drug and monitoring of the patient takes on different forms depending on the center and the autonomous community (Torrens, Fonseca, Castillo, & Domingo-Salvany, 2013). This makes it difficult to determine the cost of resources per OD patient exactly, which in turn accounts for the diversity of results in previous studies. In the present study, the costs associated with both the therapy and interaction management represent the average use of resources of a standard OD patient. This may not be representative of clinical practice and could have an influence on the results.

Although the pharmaceutical cost of B/N in this analysis was higher than that of methadone, when taking into account the preparation, distribution and dispensing costs the difference is significantly reduced. Nevertheless, it must be pointed out that there are a number of costs associated with methadone maintenance programs (depreciation of equipment, glass crushers, security staff at the centers, mobile units) which were not considered in this study (Cobacho et al., 2011; Del Pozo et al., 2012; Pellín, Gimeno, Barril, Climent, & Vilanova, 2000; Puigdollersa et al., 2003). The inclusion of these variable costs could raise the cost of methadone treatment, which would alter the difference between the two strategies analyzed.

There are a number of limitations to be taken into account in this study. The most important is the lack of scientific evidence regarding the interaction of B/N with other medication. For this reason, the same interactions as for buprenorphine alone are considered here. The list of pharmaceuticals which interact with methadone or buprenorphine is longer, but in this study only those most frequently used in clinical practice are taken into account. It can be pointed out that buprenorphine is associated with fewer pharmacological interactions than methadone (McCance-Katz, 2012; Terán, 2010), thereby reducing management costs.

The analysis did not account for the possible interactions among the drugs included as concomitant medication, nor the costs associated with them, since these were not the goal of the study. Also excluded were the costs of drugs which are contraindicated as well as those for HCV, given that the most frequently used (interferon and ribavirin) do not interact at all with opioids (Panel de expertos de Gesida, 2010). The administration of methadone in beveled tablet form, as carried out in some autonomous communities, was also excluded because it is not standard clinical practice in Spain and there is a lack of available data.

A variation of ±20% was assumed in the SA parameters (minutes of nurse time and single-dose bottles) because no more data were available for analysis.

In costs analyses comparing more than one alternative therapy, it is important that as well as the pharmaceutical costs, the patient management costs of clinical practice are also assessed.

One study comparing the total cost of OD patients treated with and without B/N concluded that although the medication costs of B/N were higher, when considering the costs associated with the care of these patients, the total costs of B/N therapy was lower than for those not treated (Kharitonova, Aballéa, Clay, Ruby, & Azh, 2014).

The present study has shown that the choice of B/N or methadone has economic implications when treating patients with infectious and psychiatric comorbidities. B/N is associated with fewer pharmaceutical interactions, which means that there is no increase in the consumption of resources caused by interaction management and therefore no increase in cost. Given the frequent presence of these comorbidities in OD patients (González-Saiz et al., 2011; Roncero et al., 2011; Sanvisens et al., 2014; Szerman et al., 2014), the choice of one or the other drug can generate substantial savings for the national health system.

Finally, the results of this analysis indicate that, compared to methadone, the total cost per OD patient was lower with B/N due to the difference in interaction management costs regarding concomitant treatments of infectious and/or psychiatric comorbidities.

Acknowledgments

The study was designed by Pharmacoeconomics, & Outcomes Research Iberia, a consulting company specialized in Economic Analysis of Healthcare Interventions which received non-conditional funding from Reckitt Benckiser Pharmaceuticals to carry out the analysis. Carlos Roncero, Tomás Díaz, José Manuel Fernández, Rafael Forcada, José Manuel Martínez, Pedro Seijo and Antonio Terán hereby declare that they have received non-conditional funding from Reckitt Benckiser Pharmaceuticals for their participation in validating clinical practice in Spain.

Conflict of interests

Carlos Roncero has received fees for taking part as a speaker in the educational activities of Janssen-Cilag, Bristol-Mayers Squibb, Ferrer-Brainfarma, Pfizer, Reckitt Benckiser Pharmaceuticals, Lundbeck, Otsuka, Servier, Lilly, Shire, GSK, Rovi. He has also received payment for participating in meetings with Janssen-Cilag, Lilly, and Shire. He has developed the PROTEUS project with the support of a grant from Reckitt Benckiser Pharmaceuticals.

Tomás Díaz has taken part as a speaker in the educational activities of Pfizer, Reckitt Benckiser Pharmaceuticals, and Janssen-Cilag.

José Manuel Forcada has not received fees from other entities.

Rafael Forcada has taken part as a speaker in the educational activities of Janssen-Cilag, and Bristol-Mayers Squibb.

José Manuel Martínez has taken part as a speaker in the educational activities of Reckitt Benckiser Pharmaceuticals, Janssen-Cilag, Bioclever 2005 SL, Pfizer, Brainpharma, and Laboratorios Estévez.

Pedro Seijo has taken part as a speaker in the educational activities of Reckitt Benckinser Pharmaceuticals, Janssen-Cilag, Pfizer, Otsuka and Astrazeneca.

Antonio Terán has received fees for speaking in educational activities of Janssen-Cilag, Pfizer, Lundbeck, Otsuka, Lilly, Shire, and Reckitt Benckiser Pharmaceuticals, and for participating in meetings of Janssen-Cilag, Lilly, and Shire.

None of the authors report other relevant affiliations or have economic interests in any organization or entity with an economic interest in or in conflict with the subject or materials discussed in the manuscript, other than those described.

References

Amariles, P., Giraldo, N. A., & Faus, M. J. (2007). Interacciones medicamentosas en pacientes infectados con el VIH: aproximación para establecer y evaluar su relevancia clínica. *Farmacia Hospitalaria*, *31*, 283-302.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. Fourth Edition, Text Revision. Washington, D.C.: American Psychiatric Association.

Arias, F., Szerman, N., Vega, P., Mesias, B., Basurte, I., Morant, C.,… Babín. F. (2013). Estudio Madrid sobre prevalencia y características de los pacientes con patología dual en tratamiento en las redes de salud mental y de atención al drogodependiente. *Adicciones, 25,* 118-127.

Bernal-Delgado, E., Campillo-Artero, C., & García-Armesto, S. (2014). Oferta sanitaria y crisis: financiamos los bienes y servicios según su valor o caemos en la insolvencia. Informe SESPAS 2014. *Gaceta Sanitaria*, *28*, 69-74. doi:10.1016/j.gaceta.2014.02.004.

Bruce, R. D., Altice, F. L., Gourevitch, M. N., & Friedland, G. H. (2006). Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *Journal of Acquired Immune Deficiency Syndromes*, *41,* 563-572.

Bruce, R. D., Moody, D. E., Altice, F.L., Gourevitch, M. N., & Friedland, G. H. (2013). A review of pharmacological interactions between HIV or hepatitis C virus medications and opioid agonist therapy: implications and management for clinical practice. *Expert Review of Clinical Pharmacology*, *6*, 249-269. doi:10.1586/ecp.13.18.

Canadian Agency for Drugs and Technologies in Health. (2013). *Rapid Response Reports. Suboxone® versus Methadone for the Treatment of Opioid Dependence: A Review of the Clinical and Cost-effectiveness*. Recuperado de http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0064785/

Cervera, G., Valderrama, J. C., Bolinches, F., Salazar, A., & Martinez, J. (1998). Variables related to risk taking behavior for HIV transmission among drug-dependent patients. *Actas Luso Española de Neurología Psiquiatría y Ciencias Afines*, *26*, 155-164.

Cobacho, M. B., López, A., & Ramos, J. M. (2011). *Análisis de costes del programa de mantenimiento de metadona en la comunidad de Murcia*. Informe para la Formación e Investigación Sanitaria de la Región de Murcia. Retrieved from http://www.e-drogas.es/

Consejo General de Colegios Oficiales de Farmacéuticos. (2013). *Catálogo de Medicamentos*. Bot Plus. Madrid. Retrieved from https://botplusweb.portalfarma.com/.

Del Pozo, J., Soldevilla, D., Murga, J. A., & Antoñanzas, F. (2012). Análisis de costes del programa de metadona de en la comunidad autónoma de la Rioja. *Revista Española de Salud Pública*, *86*, 543-549.

Gallego, L., Barreio, P., & López-Ibor, J. J. (2012). Psychopharmacological treatments in HIV patients under antiretroviral therapy. *AIDS Reviews*, *14*, 101-11.

González-Saiz, F., Lozano, O. M., Martín, J., Bilbao, I., Ballesta, R., & Gutierrez, J. (2011). Comorbilidad psiquiátrica en una muestra de pacientes con dependencia de opiáceos tratados con buprenorfina sublingual en régimen de comunidad terapéutica. *Revista de Psiquiatría y Salud Mental (Barcelona)*, *4*, 81-87. doi:10.1016/j.rpsm.2011.01.003.

Haro, G. (2012). New clinical implications of opiate maintenance treatments. *International Journal of High Risk Behaviours & Addiction*, *1*, 88-89. doi:10.5812/ijhrba.6532.

Instituto de Adicciones Madrid. (2008). *Protocolo de Metadona.* Madrid: Madrid Salud Retrieved from http://www.madridsalud.es/adicciones/ProtocolosSanitariosAdicciones2015.pdf

Instituto Nacional de Estadística. (2011). *Cálculo de variaciones del Índice de Precios de Consumo (sistema IPC base 2011)***.** Retrieved from http://www.ine.es/varipc/

Kharitonova, E., Aballéa, S., Clay, E., Ruby J., & Azh, V. (2014, mayo). *Comparison of healthcare resource use and costs in prescription opioid-dependent patients treated with Buprenorphine/Naloxone and patients without pharmacological treatment: retrospective analysis of insurance claims in the US Public Healthcare System*. Póster presentado en 11th EUROPAD conference, Glasgow, Reino Unido.

López-Bastida J., Oliva, J., Antoñanzas, F., García-Altés, A., Gisbert, R., Mar. J., & Puig-Junoy J. (2010). Propuesta de guía para la evaluación económica aplicada a las tecnologías Sanitarias. *Gaceta Sanitaria*, *24*, 154-170. doi:10.1016/j.gaceta.2009.07.011.

Martínez-Raga J., González-Saiz F., Pascual C., Casado M. A., & Sabater F. J. (2010). Suboxone (buprenorphine/naloxone) as an agonist opioid treatment in Spain: a budgetary impact analysis. *European Addiction Research*, *16*, 31-42. doi:10.1159/000259614.

Martínez-Raga, J., González-Saiz, F., Oñate, J., Oyagüez, I., Sabater, E., & Casado, M. A. (2012). Budgetary impact analysis of buprenorphe-naloxone combination (Suboxone®) in Spain. *Health Economics Review*, *2*, 3. doi:10.1186/2191-1991-2-3.

McCance-Katz, E.F., Sullivan, L. E., & Nallani, S. (2010). Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. The *American Journal on Addictions*, *19*, 4-16. doi:10.1111/j.1521-0391.2009.00005.x.

McCance-Katz, E. F. (2012). *Drug-Drug interactions in opioids therapy*. (7th ed.). Recuperado de http://www.opioiddruginteractions.com/

Ministerio de Sanidad, Servicios Sociales e Igualdad. (2011). *Plan Nacional sobre Drogas: Memoria 2011*. Recuperado de http://www.pnsd.msssi.gob.es/Categoria2/publica/pdf/memo2011.pdf

Ministerio de Sanidad, Servicios Sociales e Igualdad. (2013). *Plan de Acción sobre Drogas 2013-2016*. Recuperado de http://www.pnsd.msssi.gob.es/Categoria2/publica/pdf/PLAN_ACCION_SOBRE_DROGAS2013_2016.pdf

Observatorio Vasco de Drogodependencias. (2004). *Perfil del Drogodependiente que no responde a los programas de mantenimiento con metadona*. País Vasco: GABIA. Recuperado de http://www.osakidetza.euskadi.net/

Panel de Experto de Gesida, Secretaría del Plan Nacional sobre el Sida (SPNS) y Asociación Española para el estudio del Hígado (AEEH). (2010). Recomendaciones de Gesida/PNS/AEEH sobre tratamiento y manejo del paciente adulto coinfectado por VIH y virus de las hepatitis A, B y C. *Enfermedades Infecciosas y Microbiología Clínica*, *28*, 31e1-31e31.

Pellín, M. C., Gimeno, C., Barril, J., Climent, J. M., & Vilanova, E. (2000). Estudio de costes de un tratamiento de mantenimiento con metadona de bajo nivel de prestaciones. *Medicina Clínica*, *114*, 171-173.

Pereiro, C., Pino, C., Flórez, G., Arrojo, M., & Becoña, E. (2013). Psychiatric comorbidity in patients from the addictive disorders assistance units of Galicia: The COPSIAD study. *PLoS One*, *8*, e66451. doi:10.1371/journal.pone.0066451.

Pérez, J. C., Jornet, S., & Bonet, A. (2002). Interacciones farmacocinéticas entre metadona y antirretrovirales en pacientes infectados por el virus de la inmunodeficiencia humana. *Medicina Clínica (Barcelona)*, *119*, 224-229.

Prieto, L., Sacristán, J. A., Pinto, J. L., Badia, X., Antoñanzas, F.,, & del Llano, J. (2004). Análisis de costes y resultados en la evaluación económica de las intervenciones sanitarias. *Medicina Clínica (Barcelona)*, *122*, 423-429.

Puche, E., Faus, M., Soler, E., & Blasco, J. (2000). Optimización de los programas de mantenimiento con metadona a través del conocimiento de sus interacciones farmacológicas. *Trastornos Adictivos*, *2*, 163-171.

Puigdollersa, E., Cotsa, F., Brugal, M. T. Torralba, L., & Domingo-Salvany, A. (2003). Programas de mantenimiento de metadona con servicios auxiliares: un estudio de coste-efectividad. *Gaceta Sanitaria*, *17*, 123-130.

Real Decreto-ley 16/2012, de 20 de abril, *de medidas urgentes para garantizar la sostenibilidad del Sistema Nacional de Salud y mejorar la calidad y seguridad de sus prestaciones*. BOE, Boletín Oficial del Estado Nº 98, 24 de abril de 2012. Retrieved from http://www.boe.es/boe/dias/2012/04/24/pdfs/BOE-A-2012-5403.pdf

Roncero, C., Fuste, G., Barral, C., Rodriguez-Cintas, L., Martinez-Luna, N., Eiroa-Orosa, F. J., & Casas, M. (2011). Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study. *Heroin Addiction And Related Clinical Problems*, *13*, 5-16.

Roncero, C., Álvarez, J., Barral, C., Gómez-Baeza, S., Gonzalvo, B., Rodriguez-Cintas, L.,… Casas, M. (2013). Driving and legal status of Spanish opioid-dependent patients. *Substance Abuse Treatment Prevention And Policy*, *8*, 19. doi:10.1186/1747-597X-8-19.

Roncero, C., Vega, P., Martínez-Raga, J., Barral, C., Basurte-Villamor, I., Rodriguez-Cintas, L.,… Szerman, N. (2014). Professionals' perceptions about healthcare resources for co-occuring disorders in Spain. *International Journal of Mental Health Systems*, *8*, 35. doi:10.1186/1752-4458-8-35.

Sanvisens, A., Rivas, I., Faure, E., Muñoz, T., Rubio, M., Fuster, D.,… Muga, R. (2014) Características de los pacientes adictos a la heroína admitidos en un programa de tratamiento con metadona. *Medicina Clínica (Barcelona)*, *142*, 53-8. doi:10.1016/j.medcli.2012.10.023.

Serrano, J. I. (2011). Interacciones farmacológicas de los nuevos antirretrovirales. *Farmacia Hospitalaria*, *35*, 36-43. doi:10.1016/j.farma.2010.01.018.

Sittambalam, C. D., Vij, R., & Ferguson, R. P. (2014). Buprenorphine Outpatient Outcomes Project: can Suboxone® be a viable outpatient option for heroin

addiction?. *Journal Community Hospital Internal Medicine Perspectives, 4*. doi:10.3402/jchimp.v4.22902.

Sociodrogoalcohol. (2010). *Guía para el tratamiento de la adicción a opiáceos con buprenorfina/naloxona*. Guías Clínicas Sociodrogoalcohol basadas en la Evidencia Clínica. Barcelona: Sociodrogoalcohol.

Szerman, N., Vega, P., Grau-López, L., Barral, C., Basurte-Villamor, I., Mesias, B.,… Roncero, C. (2014). Dual Diagnosis Resource Needs in Spain: A National Survey of Professionals. *Journal of Dual Diagnosis*, *10*, 84-90. doi:10.1080/15504263.2014.906195.

Terán, A. (2010). Experiencia clínica en el manejo de buprenorfina/naloxona. *Revista Española de Sanidad Penitenciaria*, *12*, 40-47.

Torrens, M., Fonseca, F., Castillo, C., & Domingo-Salvany, A. (2013). Methadone maintenance treatment in Spain: the success of a harm reduction approach. *Bull World Health Organ*, *91*, 136-141. doi:10.2471/BLT.12.111054.

Alcohol consumption in college students from the pharmacy faculty

Evaluación del consumo de riesgo de alcohol en estudiantes universitarios de la Facultad de Farmacia

Laia Miquel*,**,***, Miquel Rodamilans****, Rosa Giménez****, Trinitat Cambras****, Anna Maria Canudas****, Antoni Gual*,**,***

*Grup de recerca en Addiccions Clínic, Unitat de conductes addictives. Hospital Clínic Universitari de Barcelona, Institut Clínic de Neurociencies, España. **IDIBAPS. ***Red de Trastornos Adictivos (RTA), RETICS. ****Grupo de Trabajo Colaborativo Casos Clínicos Transversales de la Facultad de Farmacia (CCT-FARMA), Universidad de Barcelona, España.

Resumen

Alcohol consumption is highly prevalent in university students. Early detection in future health professionals is important: their consumption might not only influence their own health but may determine how they deal with the implementation of preventive strategies in the future.

The aim of this paper is to detect the prevalence of risky alcohol consumption in first- and last-degree year students and to compare their drinking patterns.

Risky drinking in pharmacy students (n=434) was assessed and measured with the AUDIT questionnaire (Alcohol Use Disorders Identification Test). A comparative analysis between college students from the first and fifth years of the degree in pharmacy, and that of a group of professors was carried to see differences in their alcohol intake patterns.

Risky drinking was detected in 31.3% of students. The highest prevalence of risky drinkers, and the total score of the AUDIT test was found in students in their first academic year. Students in the first academic level taking morning classes had a two-fold risk of risky drinking (OR=1.9 (IC 95%1.1-3.1)) compared with students in the fifth level. The frequency of alcohol consumption increases with the academic level, whereas the number of alcohol beverages per drinking occasion falls.

Risky drinking is high during the first year of university. As alcohol consumption might decrease with age, it is important to design preventive strategies that will strengthen this tendency.

Keywords: AUDIT questionnaire, screening, alcohol, hazardous drinking, college students.

Abstract

El consumo de alcohol es muy prevalente entre los estudiantes universitarios. La detección precoz en futuros profesionales sanitarios es muy importante puesto que puede incidir no solo en su salud, sino también en su enfoque en futuras acciones preventivas como profesionales de la salud.

Detectar la prevalencia del consumo de riesgo de alcohol en estudiantes de farmacia y en el profesorado y comparar el patrón de consumo entre estos grupos, y según el curso académico.

Se realiza un cribado del consumo de alcohol mediante el cuestionario AUDIT (Alcohol Use Disorders Identification Test) a estudiantes universitarios de farmacia (n=434) en el marco de un proyecto de innovación docente. Se realiza un análisis comparativo entre los estudiantes de primero y quinto curso, y el profesorado.

El 31,3% de los estudiantes fueron identificados como bebedores de riesgo. La mayor prevalencia de consumidores de riesgo y las mayores puntuaciones totales se observaron en los alumnos de primer curso. Los estudiantes de primero de turno de mañana presentaron un riesgo de 1,9 (IC 95%1,1-3,1) comparado con los de quinto. La frecuencia de consumo de alcohol se incrementa con el curso académico, mientras que el número de consumiciones por día de consumo se reduce.

Durante el primer año en la Facultad los estudiantes presentan una elevada prevalencia de consumo de riesgo. Puesto que con la edad se observa una tendencia decreciente en dichos consumos, es importante diseñar intervenciones preventivas que la favorezcan.

Palabras clave: AUDIT cuestionario, cribado, alcohol, consumo de riesgo, estudiantes universitarios.

Received: November 2014; Accepted: March 2015

Send correspondence to:
Laia Miquel de Montagut. Unidad de Conductas Adictivas, Hospital Clínico de Barcelona. Departamento de Psiquiatría. Instituto Clínico de Neurociencias. IDIBAPS. C/ Villarroel, 170, 08036 Barcelona. E-mail: MIQUEL@clinic.cat.

In recent years, the consumption of alcohol among young people has grown, especially in the form of binge drinking and visits to emergency rooms owing to alcoholic intoxication have become more frequent, especially among women ("Observatorio Español de la droga y las toxicomanías," Spanish Drug Observatory, 2011). University students, especially, are a population at risk (Karam, Kypri, & Salamoun, 2007) and this is a good moment to introduce preventive strategies.

Approximately between 20% and 60% of the university population show risky consumption patterns (Arrieta, 2009; Montaño, Morales, Gómez, Maldonado, & Gantiva, 2011; Pengpid, Peltzer, van der Heever, & Skaal, 2013). The high consumption of alcoholic beverages among young people has been associated with high mortality and accident rates and unsafe behavior such as drink-driving or engaging in unprotected sexual relationships, as well as family problems (Barlés, Escario, Galbé, 2014; Arrieta, 2009; Hingson, Heeren, Winter, & Wechsler, 2005). Some of the risk factors related with excessive consumption of alcohol are: being male, impulsivity, having easy access to money, living alone or initiating consumption at an early age (Cortés, Giménez, Motos, & Cadaveirea, 2014; Montaño et al., 2011; Mota et al., 2010; Restrepo, Agudelo, Giraldo, & Sánchez, 2011; Wicki, Kuntsche, & Gmel, 2010). There have been many studies that have addressed this problem in university students. The majority of these studies focus on sociological aspects (Bani et al., 2013; Wicki et al., 2010; Young and de Klerk, 2008) and associated risk factors (Vinader-Caerols, Monleaon, and Parra, 2014; Ansari, Stock, and Mills, 2013; Caamaño-Isorna, Corral, Parada, and Cadaveira, 2008; DeMartini and Carey, 2012; Karam et al., 2007). There is, however, little information on the changes in consumption patterns depending on the academic year the students are in or of the differences between students and professors. There have been no follow-up studies over the length of the five-year degree program nor has there been any evaluation of the early intervention programs during the same. In addition, the data concerning the prevalence of risky consumption are somewhat heterogeneous owing to the different measurement tools used and the definitions employed by the different authors.

Awareness and prevention of alcohol consumption among the adult population is especially relevant. At the current time, there are tools for the screening of risky alcohol consumption which are easily applied and, as well, therapeutic interventions are available, both presential (brief presential intervention, Pengpid et al., 2013) or online (Khadjesari, Murray, Hewitt, Hartley, & Godfrey, 2011), which have proven to be efficacious in the reduction of risky consumption (Seigers & Carey, 2011; Toumbourou et al., 2007). Interventions aimed at future healthcare professionals are especially important given that they not only have repercussions on these people but also on the population in general. The university period, which is considered to be especially risky, is a good time for early intervention. In this sense, the Collaborative Working Group on Cross-sectional Clinical Studies of the Faculty of Pharmacy of the University of Barcelona (CCT-FARMA) decided to develop a cross-sectional clinical study on risky alcohol consumption over the five-year Pharmacy Degree course. The idea was to help students evaluate their own risks in terms of excessive alcohol consumption and provide them with the tools to recognize and identify risky behaviors in groups close to them which would allow them to carry out brief interventions in their future professional practice (Giménez et al., 2013; Rodamilans et al., 2012).

The objective of this study is to have an overall view of the alcohol consumption patterns of the students in the Faculty of Pharmacy at the University of Barcelona by means of determining the prevalence of risky consumption in first-year and fifth-year students prior to the development of the CCT-FARMA project. At the same time, the risk of participating professors in the Working Group is evaluated, with the aim of testing the levels of awareness of the same when addressing a clinical study of risky consumption.

As well as this, it aims to compare the differences in consumption patterns between the first-year and the fifth-year students, and the professors, after obtaining alcohol consumption data cross-sectionally at the moment in which the teaching project is initiated.

Method

Design

In the 2011-2012 academic year, the alcohol consumption patterns of the first-year and fifth-year students, and also those of the professors, were assessed cross-sectionally.

Study population

Those selected to participate were individuals who were studying pharmacy at the University of Barcelona (UB). Data were collected from first-year students (morning timetable and afternoon timetable), fifth-year students and professors. Of the 434 students enrolled in the first year, 67.1% of them responded to anonymous questionnaires; of the 325 fifth-year students, 34.2% participated and of a total of 46 professors involved in the educational project, 84.8% responded.

Procedure

In 2012 the CCT-FARMA innovative teaching project was begun, in which this cross-sectional study was introduced, starting with the first-year students. This clinical study is addressed from the different points of view provided by the subjects in the Pharmacy Degree (Rodamilans et al., 2012). In order to evaluate the efficacy of the CCT-FARMA, academic quantification mechanisms (knowledge, skills, integration and interpretation capacity) and health mechanisms, such as the evaluation of the risk of alcohol consumption (AUDIT test) were established. The survey was introduced unannounced; during class time, the students were asked

to respond voluntarily and anonymously to the Alcohol Use Disorders Identification Test (AUDIT). The professors responded to the test on the same day and at the same time.

The preliminary results presented form part of the new teaching project (CCT-FARMA), one of whose objectives is to evaluate, at the end of the Pharmacy Degree, and by means of the AUDIT test, whether the development of this clinical study has modified alcohol consumption compared to the initial evaluation carried out in 2012.

Data collection tools

As a screening tool for risky alcohol consumption among the university population the full version of the Alcohol Use Disorders Identification Test (AUDIT) was used. This standardized tool, developed by the World Health Organization, consists of ten questions about the quantity, the frequency and the consequences of alcohol consumption. The test is validated in both Spanish and Catalan and its reliability level is also good (Cronbach Alpha= 0.89) (Contel Guillamón, Gual Solé, and Colom Farran, 1999) for university students (Fleming, Barry, and MacDonald, 1991). The screening test has shown that it has a good level of sensitivity and specificity, not only for detecting harmful and risky consumption but also for disorders brought on by alcohol consumption. Using 8 as a cut-off point, the test has a sensitivity and specificity of 90% and 61% (Barry and Fleming, 1993). According to the study carried out by Contel et al., (1991) in the male group, if we use 9 as a cut-off point, the sensitivity of AUDIT is 90% and its specificity is 81.5%. And in the female group (cut-off point 6) its sensitivity is 33.3% and its specificity is 91.6%.

Statistical analysis

A descriptive analysis was carried out, of the sociodemographic data (gender and age) of the entire sample, and by groups studied (first-year, morning timetable students, first-yea, afternoon timetable students, fifth-year students and faculty). The variables that correspond to each question on the AUDIT were analyzed as quantitative and categorical variables. The distribution type of the AUDIT quantitative variable was verified by means of the Kolmogorov-Smirnov normality test. As it did not follow a normal distribution, non-parametric tests (Kruskal-Walis) were used to compare the total AUDIT score according to the group evaluated, and in addition ANCOVA ranging was used to adjust for gender and age. In order to carry out the 2 to 2 analysis between each group, the non-parametric U-de Mann-Whitney test was used. In order to detect the risky consumption groups it was decided to categorize the overall AUDIT score into a binary variable using 9 or higher as the cut-off point for males and 6 or higher as that for females (Pérula de Torres et al., 2005; Rubio Valladolid, Bermejo Vicedo, Caballero Sánchez-Serrano, and Santo-Domingo Carrasco, 1998). In order to analyze the categorical variables the chi-square test was used and ANOVA was used for the quantitative variables. The multiple post-hoc comparisons were made by means of Bonferroni. It is considered statistically significant when $p \leq 0.05$. Pearson correlation analysis was carried out in order to determine the correlation between the age and the academic level ($r=0.73$, $p<0.001$). In order to analyze the relationship between the presence of risky consumption and the year the student was in, a logistical regression analysis was done, using gender and age as co-variables.

Results

A total of 440 persons participated in the test. Complete data of gender and age of 434 persons were obtained. Of the total of responders, 286 were enrolled in the first year at university in the Faculty of Pharmacy (204 in the morning timetable and 82 in the afternoon timetable), 111 in the fifth year, and 37 were professors. Some 75.8% of the total sample taking part in the study were female, which corresponds to the normal distribution of students in this faculty. No significant differences in the distribution of genders according to the academic year were observed, and neither were any observed among the profes-

Table 1
Description of risky consumption in terms of the year of the degree the student is in

	FYMT (204)	FYAT (82)	Fifth-year (111)	Professors (37)	Total (434)		
	n (%)	n (%)	n (%)	n (%)	N (%)	χ^2/F	p-value
Gender (Female)	148 (72,5)	62 (75,6)	93 (83,8)	26 (70,3)	329 (75,8)	5,7	0,13
Age (mean (SD))	18,5 (1,1)[a, b]	19,8 (4,0)[c]	24,2 (3,9)[d]	50,9 (7,3)	22,96 (9,5)	935,2	<0,001
AUDIT Total (mean (SD))	6,3 (5,3)	5,3 (3,9)	4,6 (4,1)	2,6 (1,3)	5,35 (4,7)		<0,001
Risky consumption	82 (40,2)	25 (30,5)	29 (26,1)	0	136 (31,3)	26,3	<0,001
Males (%)	26 (46,4)	5 (25,0)	6 (33,3)		37 (35,2)	1,0	0,32
Females (%)	56 (37,8)	20 (32,3)	23 (24,7)		99 (30,1)		

Note. FYMT: First-year, morning timetable; FYAT: First-year, afternoon timetable; a FYMT vs FYAT p=0,039; b FYMT vs Fifth-year and vs Professors p<0,001; c FYAT vs Fifth-year vs Professors p<0,001; d Fifth-year vs Professors p<0,001

sors. The average age of the whole sample was of 23.0 (DE 9.5), with the differences between the average ages of each group studied being statistically significant (Table 1).

Relationship between alcohol consumption patterns and the year the student was in

Some 31.3% of the students showed signs of risky consumption. The greater proportion of risky drinkers was observed among the first-year, morning-timetable students. 40.2% of the first-year, morning-timetable students showed risky consumption, followed by those in the afternoon timetable (30.5%) and the fifth-year students (26.1%). Among the professors, no risky consumers were detected (Table 1). After adjusting the results for the gender variable, it was observed that the first-year, morning-timetable students had an almost two-fold probability of risky consumption compared with the fifth-year students (OR=1.9 IC95% 1.1-3.1) (Table 2). If we adjust the data by age, the differences between the year of the degree the student is in lose statistical significance because as age increases, the risk of risky consumption diminishes (OR=0.84 IC95% 0.72-0.98) (Table 2).

Figures 1 and 2 show the frequency and amount of alcohol consumption of the different groups studied. The data show the presence of significant differences between the groups both in relation to the frequency of consumption (χ^2= 33.2; p<0,001) as in the number of alcoholic drinks taken on a normal day (χ^2= 68.4; p<0,001). In general, the most habitual frequency of alcohol consumption of the entire sample was of between two and four times a month (54.8%), followed by monthly consumption (22.4%). Only 6.2% had not drunk at all over the last year. The professors were the group that drank with most frequency (43.2%: more than twice a week) followed by the fifth-year students (21.6%) and the first-year, morning-timetable students (11.3%) (Figure 1). The majority of first-year students (59.8% of the morning timetable and 63.4% of the afternoon timetable) and fifth-year students (45.0%) drank between two and four times a month (Figure 1).

Table 2

A. Relationship between the year the student is in and alcohol consumption risk after adjusting for gender

		95% I.C.	
	OR	**Min**	**Max**
FYMT vs FYAT	1.5	0.9	2.6
FYMT vs fifth-year	1.9	1.1	3.1
FYAT vs fifth-year	1.2	0.6	2.3
Gender	1.3	0.8	2.0

Note. FYMT: First-year, morning timetable; FYAT: First-year, afternoon timetable

B. Relationship between the year the student is in and alcohol consumption risk after adjusting for gender and age

		95% I.C.	
	OR	**Min**	**Max**
FYMT vs FYAT	1.3	0.8	2.3
FYMT vs fifth-year	0.7	0.3	1.7
FYAT vs fifth-year	0.5	0.2	1.4
Gender	1.4	0.9	2.3
Age	0.8	0.7	0.98

Note.FYMT: First-year, morning timetable; FYAT: First-year, afternoon timetable

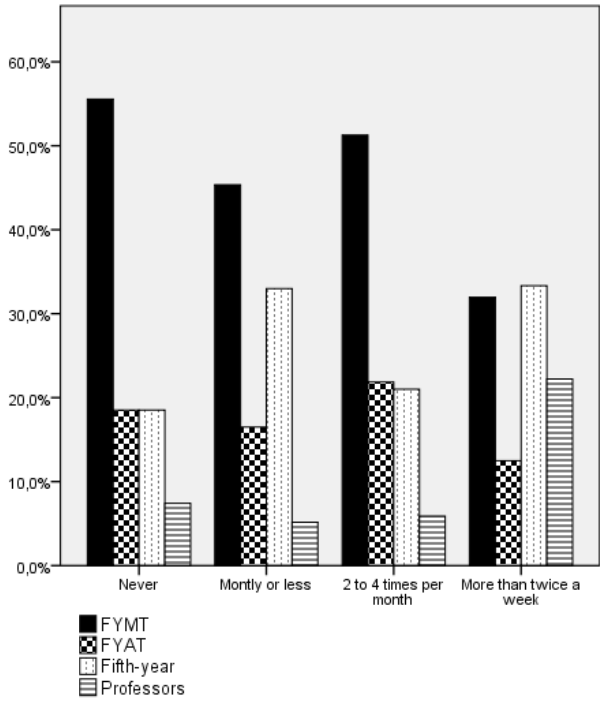


Figure 1. How often do you have a drink containing alcohol?

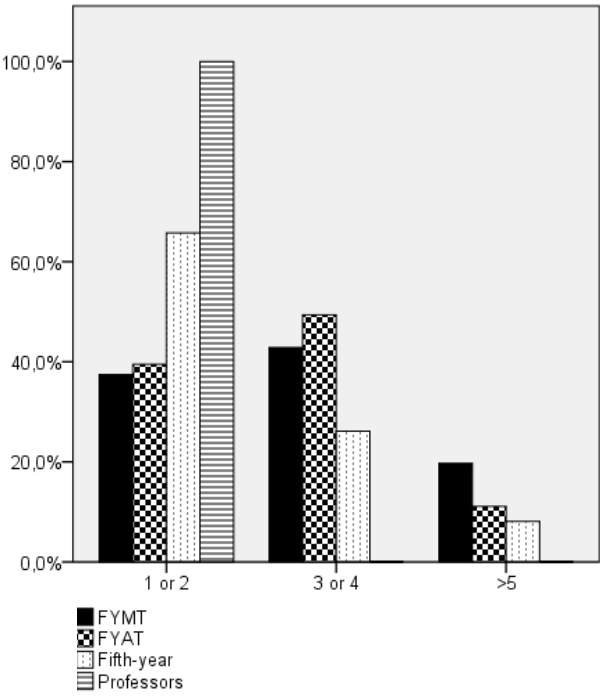


Figure 2. How many drinks containing alcohol do you have on a typical day when you are drinking

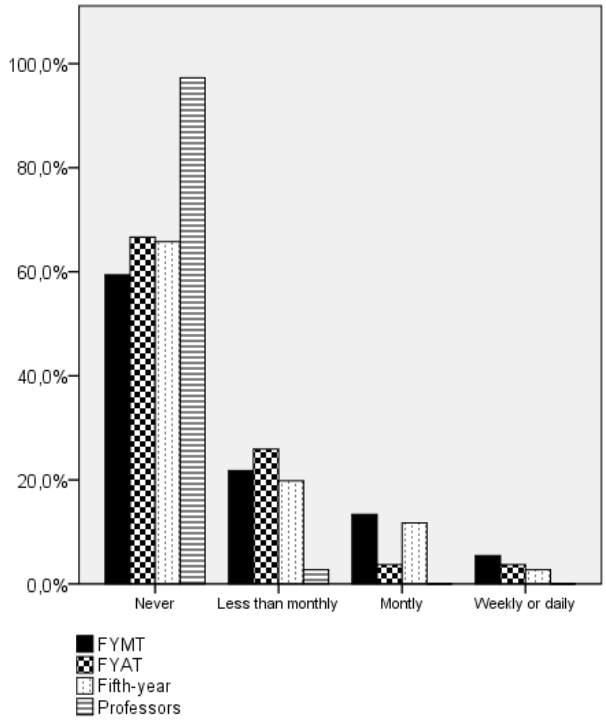
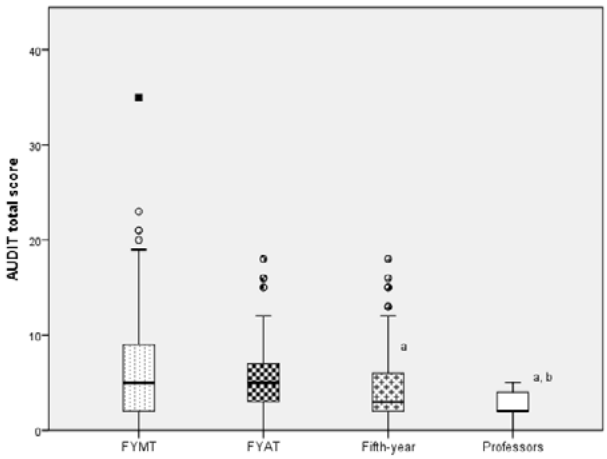


Figure 3. How often do you have 6 or more drinks on one occasion?



[a]: Significant differences with the first-year, morning timetable
[b]: Significant differences with the first-year, afternoon timetable

Figure 4. Total AUDIT questionnaire score according to the year the student is in (including professors)

In the case of the professors, the amount drunk on each occasion on which consumption took place follows a tendency that is diametrically opposed to the frequency of the consumption. Thus, although they consume alcohol with greater frequency (42.3% more than twice a week) (Figure 1) the amount of alcohol consumed on each occasion is low (one or two drinks on each occasion) (Figure 2). In the case of the students, it can be observed how the amount of alcohol consumed decreases as each academic year passes. Thus, the majority of students who consume more than five drinks on each occasion are concentrated in the morning-timetable, first-year group (19.7%) followed by the afternoon-timetable students (11.1%) and the fifth-year students (8.1%) (Figure 2). In this sense, it can also be observed that the morning-timetable, first-year group were those who had six or more alcoholic drinks with greater frequency (Figure 3). The majority of students in this year, when they have more than six drinks on one occasion, do so monthly (35.2%) and 5.4% of them consume greater quantities weekly or more frequently.

Comparison between the total AUDIT score and the year the student was in

Statistically significant differences were observed on comparing the total score of the four groups studied ($p<0.001$) (Figure 4, Table 1). After adjusting for age and gender, the relationship between the total AUDIT score and the academic level lost statistical significance ($F=1,138$; $p= 0.334$). The professors showed a total mean score that was significantly inferior to that of the first-year students (a mean difference with the morning-timetable students of 3.7 points; $p<0.001$; mean difference with the afternoon-timetable students of 2.7 points, $p<0.001$). Statistically significant differences were also observed between responders from the morning-timetable, first-year group and the fifth-year students ($p=0.003$), with the obtained mean of the first-year students being greater (mean difference= 1.7 points).

Discussion

The first results from the evaluation study of the efficacy of the CCT-FARMA project that show screened results of risky consumption among the Faculty of Pharmacy population of the University of Barcelona (31.3%), indicate that an important percentage of the students could benefit from an intervention with the aim of reducing consumption among the students and thus raising awareness among future healthcare workers of the risks of consuming alcohol. To sum up, risky consumption and the total AUDIT score are reduced as students pass from one year of their degree to the next in such a way that the morning-timetable, first-year students show a greater level of risky consumption and average total AUDIT score compared with those of the last year. The consumption patterns between the students and the faculty member are polar opposites. The students have a greater tendency to consume high quantities of alcohol in an episodic manner while the professors drink smaller quantities with greater frequency.

The prevalence of risky drinking in the university sample (31.3%) is considerably higher than that described for the general population (10%), but is similar to that of other university populations in other countries (Ansari et al., 2013; Caamaño-Isorna et al., 2008; Pengpid et al., 2013; Reavley, Jorm, McCann, and Lubman, 2011; Young and de Klerk, 2008).

Although the percentage of males with risky consumption was slightly higher than that of females, these differences were not significant, unlike what has been observed in other studies (Ansari et al., 2013; DeMartini and Carey, 2012; Reavley et al., 2011). In this sense it is worth highlighting that unlike in other research, we took into account different cut-off points for males and females. According to Wicki M et al. (2010), though, these gender differences are maintained even when different hazardous consumption cut-off points are used for males and females.

The university student group that has most at-risk drinkers is that of the morning-timetable, first-year students (42%), followed by the afternoon-timetable students (30.5%) and the fifth-year students (26.1%). Although our results coincide with those of other authors (Ansari et al., 2013; Sebena, Orosova, Mikolajczyk, and van Dijk, 2011) there is a certain controversy regarding the relationship between age and risk of alcohol consumption. While some studies have observed an increase in risk at higher ages or later in the degree program, other studies do not observe any such relationship or, what is more frequent, that this relationship is negative (Sebena et al., 2011; Wicki et al., 2010). No significant differences are detected between the morning-timetable first-year students and those enrolled in the afternoon timetable, possibly because these students are of similar ages, although it is not known whether there are other differentiating factors that may intervene, such as, for example, whether there any differences in their reasons being enrolled in one timetable or the other. Our data suggests that the differences between students in one year of their degree and another are because of age differences. Unlike what appears to be the case in other countries, hazardous consumption among professors appears to be non-existent (Reavley et al., 2011). The results obtained from the AUDIT test at the beginning of this project (2012) show us that there is a reduction of risk between the first year of a degree program and the fifth. The time spent at the Faculty, therefore, would seem to be a good opportunity to strengthen this tendency towards a reduction of the risk that occurs between first-year and fifth-year students by means of interventions aimed at increasing awareness and sensitivity.

The consumption pattern of the pharmacy students is the opposite to that of the professors of the same faculty. Student consumption is more sporadic (they mainly consume between two and four times a month) and they consume greater quantities of alcohol per occasion (more than three drinks), while the professors consume between one and two alcoholic drinks with a frequency greater than twice a week (43.2%). This pattern coincides with that of other studies (Reavley et al., 2011; Slutske, 2005).

One of the principal problems of university students is alcohol consumption in the form of binge drinking (compulsive consumption), which has been widely described by various authors (Ansari et al., 2013; Jim McCambridge et al., 2013). Between 34.2 and 40.6% of pharmacy students had, at some time in the year previous to the study consumed more than six alcoholic drinks on one single day, coinciding with the Spanish population data (EDADES 2011). In Spain, a drop in this type of consumption can be observed with age, with the highest prevalence of binge drinking being between the ages of 20 and 24 (EDADES 2011), coinciding with the university years. In some European studies, the percentage of excessive consumers (of five drinks or more) is around 60 to 70% (Ansari et al., 2013; Dantzer, Wardle, Fuller, Pampalone, and Steptoe, 2006). Students binge drink with greater frequency than professors, as occurs in other countries (Reavley et al., 2011). However, compared with the study carried out by Reavley et al., 2011 in which it is stated in objective terms that 21% of the teaching staff had more than six drinks a month or more, those in our sample did not indicate having more than six drinks with a frequency that was greater than monthly.

One of the principal limitations of this study, we should highlight, is that the data related to alcohol consumption are obtained from declared data, which although reliable in clinical populations, in general population could be skewed, despite the respondents answering anonymously. No sociodemographic data, which could act as a risk factor, were collected and nor were aspects of a sociocultural type taken into account, which could skew the results. In addition, it should be borne in mind that the results of this study were obtained from a sample of university students and staff and cannot, therefore, be extrapolated to other, non-university populations.

The developing of the clinical study of hazardous alcohol consumption from the perspective of the different subjects studied in the pharmacy degree means a teaching strategy with an integrative objective. To that end, the clinical study of hazardous alcohol consumption was designed via a fictitious character, Sam, who was clinically validated by the Addictive Behaviors Unit, and adjusted to real cases. Later, the participating subjects were coordinated. This character's pathology evolves over the five years of the Pharmacy Degree, and allows the students, in a certain way, to follow his life. To raise student awareness and to make them consider that hazardous alcohol consumption is not far removed from their environment, the evaluation of the students' own risky consumption is used.

Preventive campaigns aimed at this target population may be highly beneficial given the important social factor and the norms that this population go by (Wicki et al., 2010). Intervening in the at-risk university population could bring important benefits, not only in terms of their academic results, given that they are the students who are least motivated to perform well academically (Ansari et al., 2013), but also in terms of avoiding risky sexual behaviors and accidents. Given that brief interventions (including virtual ones) in this population are effective (Bewick et al., 2013; Jim McCambridge et al., 2013; Pengpid et al., 2013; Seigers & Carey, 2011),

it is important to be able to detect hazardous consumption early, with the aim of changing consumption patterns in a population that is so vulnerable to its effects. Without any doubt, new preventive developments must make extensive use of the new forms of communication (J McCambridge, Bendtsen, Bendtsen, & Nilsen, 2012).

Acknowledgements

Proyecto de innovación docente (2011PID-UB/19 y 2012PID/UB/157) Universitat de Barcelona. Proyecto RD12/0028/0016, integrado en el Plan Nacional de I+D+I y cofinanciado por el ISCII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER).

Conflict of interests

Dr. Antoni Gual has received financial support from Lundbeck, DyA Pharma and TEVA as well as honorariums from Lundbeck, DyA Pharma and Abbivie during the study which have no relation with the work presented.

Dr. Laia Miquel has received honorariums from Lundbeck which have no relation with this work.

The remaining authors do not present any conflict of interests regarding the study.

References

Ansari, W. El, Stock, C., & Mills, C. (2013). Is Alcohol Consumption Associated with Poor Academic Achievement in University Students? *International Journal of Preventive Medicine*, *4*, 1175–1188.

Arrieta, K. (2009). Consumo patológico de alcohol entre los estudiantes de la Universidad de Cartagena. *Revista de Salud Pública*, *11*, 878–886.

Bani, R., Hameed, R., Szymanowski, S., Greenwood, P., Kribs-Zaleta, C., & Mubayi, A. (2013). Influence of environmental factors on college alcohol drinking patterns. *Mathematical Bioscience and Engineering*, *10*, 1281–1300.

Barlés Arizon, M. J., Escario, J. J., & Galbé Sáncehz-Ventura, J. (2014). Predictors of driving under the inluence of alcohol among Spanish adolescents. *Adicciones, 26,* 96-405.

Barry, K. L. & Fleming, M.F. (1993). The Alcohol Use disorders Identification Test (AUDIT) and the SMAST-13: predictive validity in a rural primary care sample. *Alcohol and Alcoholism, 28,* 33-42.

Bewick, B. M., West, R. M., Barkham, M., Mulhern, B., Marlow, R., Traviss, G., & Hill, A. J. (2013). The effectiveness of a Web-based personalized feedback and social norms alcohol intervention on United Kingdom university students: randomized controlled trial. *Journal of Medical Internet Research*, *15*, e137. doi:10.2196/jmir.2581.

Caamaño-Isorna, F., Corral, M., Parada, M., & Cadaveira, F. (2008). Factors associated with risky consumption and heavy episodic drinking among Spanish university students. *Journal of Studies on Alcohol and Drugs*, *69*, 308–312.

Contel Guillamón, M., Gual Solé, A. & Colom Farran, J. (1999). Test para la identificación de transtornos por uso de alcohol (AUDIT): Traducción y validación del AUDIT al catalán y castellano. *Adicciones*, *11*, 337–347.

Cortés, M., Giménez, J. A., Motos, P., & Cadaveira, S . (2014). The importance of expectations in the relationship between impulsivity and binge drinking among university students. *Adicciones*, *26*, 134–145.

Dantzer, C., Wardle, J., Fuller, R., Pampalone, S. Z., & Steptoe, A. (2006). International Study of Heavy Drinking: Attitudes and Sociodemographic Factors in University Students. *Journal of American College Health*, *55, 83-89.* doi:10.3200/JACH.55.2.83-90.

DeMartini, K. S., & Carey, K. B. (2012). Optimizing the Use of the AUDIT for Alcohol Screening in College Students. *Psychological Assessment, 24, 954-963.* doi:10.1037/a0028519.

Encuesta sobre alcohol y drogas en población general en España (EDADES 2011) – 2012. (n.d.). http://www.pnsd.msc.es/Categoria2/observa/pdf/EDADES2011.pdf.

Fleming, M. F., Barry, K. L., & MacDonald, R. (1991). The alcohol use disorders identification test (AUDIT) in a college sample. *The International Journal of the Addictions*, *26*, 1173–1185. doi:10.3109/10826089109062153

Giménez, R., Badia, J., Baldomà, L., Vázquez, I., Serra, D., Cambras, T., & Rodamilans, M. (2013). Incorporación de un caso clínico transversal en el grado de Farmacia. Valoración de la experiencia docente en la asignatura de Bioquímica. *FEM*, *16*, 1–68.

Hingson, R., Heeren, T., Winter, M., & Wechsler, H. (2005). Magnitude of alcohol-related mortality and morbidity among U.S. college students ages 18-24: changes from 1998 to 2001. *Annual Review of Public Health*, *26*, 259–279. doi:10.1146/annurev.publhealth.26.021304.144652.

Karam, E., Kypri, K., & Salamoun, M. (2007). Alcohol use among college students: an international perspective. *Current Opinion in Psychiatry*, *20*, 213–221. doi:10.1097/YCO.0b013e3280fa836c.

Khadjesari, Z., Murray, E., Hewitt, C., Hartley, S., & Godfrey, C. (2011). Can stand-alone computer-based interventions reduce alcohol consumption? A systematic review. *Addiction*, *106*, 267–282. doi:10.1111/j.1360-0443.2010.03214.x.

McCambridge, J., Bendtsen, M., Karlsson, N., White, I. R., Nilsen, P., & Bendtsen, P. (2013). Alcohol assessment and feedback by email for university students: main findings from a randomised controlled trial. *The British Journal of Psychiatry, 203,* 334-340. doi:10.1192/bjp.bp.113.128660.

McCambridge, J., Bendtsen, P., Bendtsen, M., & Nilsen, P. (2012). Alcohol email assessment and feedback study dismantling effectiveness for university students (AMADEUS-1): study protocol for a randomized controlled trial. *Trials*, *13*, 49.

Montaño, M., Morales, A., Gómez, M., Maldonado, A., & Gantiva, C. (2011). Consumo de alcohol en estudiantes universitarios. *Psicogente*, *14*, 27–35.

Mota, N., Álvarez-Gil, R., Corral, M., Rodríguez-Holguín, S., Parada, M., Crego, A.,… Cadaveira, F. (2010). Risky alcohol use and heavy episodic drinking among Spanish University students: a two-year follow-up. *Gaceta Sanitaria*, *24*, 372–377.

Observatorio Español de la droga y las toxicomanías. (2011). *Informe*. Retrieved from http://www.pnsd.msc.es/Categoria2/observa/pdf/oed2011.pdf.

Pengpid, S., Peltzer, K., van der Heever, H., & Skaal, L. (2013). Screening and brief interventions for hazardous and harmful alcohol use among university students in South Africa: results from a randomized controlled trial. *International Journal of Environmental Research and Public Health*, *10*, 2043–2057. doi:10.3390/ijerph10052043.

Pérula de Torres, L. A., Fernández-García, J. A., Arias-Vega, R., Muriel-Palomino, M., Márquez-Rebollo, E., & Ruiz-Moral, R. (2005). Validación del cuestionario AUDIT para la identificación del consumo de riesgo y de los trastornos por el uso de alcohol en mujeres. *Atención Primaria, 36,* 499-506. doi:10.1016/S0212-6567(05)70552-7.

Reavley, N. J., Jorm, A. F., McCann, T. V, & Lubman, D. I. (2011). Alcohol consumption in tertiary education students. *BMC Public Health*, *11*, 545. doi:10.1186/1471-2458-11-545.

Restrepo, L., Agudelo, A., Giraldo, M., & Sánchez, L. (2011). Factores de contexto asociados al consumo de alcohol en estudiantes universitarios. *Revista CES Salud Pública*, *2*, 136–147.

Rodamilans, M., Gómez-Catalán, J., Piqué, E., Llobet, J., Gual, A., Giménez, R.,… Campanera, J. (2012). Desarrollo de casos clínicos transversales: experiencia dinamizadora de la Unidad Docente de Toxicología de la Universidad de Barcelona. *Revista de Toxicolgía*, *29*, 141–146.

Rubio Valladolid, G., Bermejo Vicedo, J., Caballero Sánchez-Serrano, M. C., & Santo-Domingo Carrasco, J. (1998). Validación de la prueba para la identificación de trastornos por uso de alcohol (AUDIT) en atención primaria. *Revista Clínica Española*, *198*, 11–14.

Sebena, R., Orosova, O., Mikolajczyk, R. T., & van Dijk, J. P. (2011). Selected sociodemographic factors and related differences in patterns of alcohol use among university students in Slovakia. *BMC Public Health, 11,* 849. doi:10.1186/1471-2458-11-849.

Seigers, D. K. L., & Carey, K. B. (2011). Screening and brief interventions for alcohol use in college health centers: a review. *Journal of American College Health, 59*, 151–8. doi:10.1080/07448481.2010.502199.

Slutske, W. S. (2005). Alcohol use disorders among US college students and their non-college-attending peers. *Archives of General Psychiatry*, *62*, 321–327. doi:10.1016/S0084-3717(08)70186-7.

Toumbourou, J., Stockwell, T., Neighbors, C., Marlatt, G., Sturge, J., & Rehm, J. (2007). Interventions to reduce harm associated with adolescent substance use. *Lancet, 369,*1391-1401. doi:10.1016/S0140-6736(07)60369-9.

Vinader-Caerols, C., Monleon, S., & Parra, A. (2014). Psycological and psycholicial effects of a high dose of alcohol in young men and women. *Adicciones, 26*, 238-246.

Wicki, M., Kuntsche, E., & Gmel, G. (2010). Drinking at European universities? A review of students' alcohol use. *Addictive Behaviors, 35,* 913-924. doi:10.1016/j.addbeh.2010.06.015.

Young, C. & de Klerk, V. (2008). Patterns of alcohol usage on a South African university campus: The findings of two annual drinking surveys. *The African Journal of Drug and Alcohol Studies*, *7*, 101–112.

Online Gambling Advertising Regulations in Spain. A Study on the Protection of Minors

La regulación publicitaria de los juegos de azar online en España. Una reflexión sobre la protección del menor

Pilar Buil*, Maria José Solé Moratilla**, Pablo García Ruiz***

*Facultad de Ciencias de la Comunicación, Universitat Internacional de Catalunya, **Consell de l'Audiovisual de Catalunya, Barcelona, ***Departamento de Sociología, Universidad de Zaragoza

Abstract

This article examines the online gambling advertising regulations in Spain currently in effect to assess the actual protection of underage youth. In recent years, online gambling among youth has increased. Through advertising, online gambling companies incite and encourage an involvement that can be harmful for vulnerable audiences. Some studies have demonstrated that advertising influences youths' assessment of gambling by increasing its appeal. We demonstrate that the shortcomings of the legal framework in force results in effective vulnerability of minors. We claim that society should seek to implement a regulatory framework to protect children from the risk of developing an addiction.

Keywords: addiction, advertising, children, gambling, regulation.

Resumen

Este trabajo estudia la actual regulación que existe en materia de publicidad de los juegos de azar online en España, con el fin de valorar si consigue una protección real al menor. En los últimos años, se ha producido un aumento en el consumo de juegos de azar online por parte de los menores. A través de la publicidad, las empresas proveedoras de juegos de azar incitan y motivan a esta actividad. Debido a que el menor de edad es un público que por sus características de inmadurez, credulidad y facilidad de persuasión resulta especialmente vulnerable frente a la publicidad, y debido al riesgo de adicción que contiene esta práctica, se debe procurar un marco regulatorio que proteja al menor. Los resultados de este estudio demuestran que si bien por voluntad de la ley se limita la posibilidad de participar de los menores en los juegos de azar online, la publicidad está influyendo en su valoración, normalizando esta práctica y haciéndola atractiva. Asimismo muestran que el marco jurídico actual presenta carencias que permiten concluir que existe una efectiva desprotección del menor.

Palabras clave: adicción, publicidad, menores, juegos de azar, regulación.

Received: December 2014; Accepted: March 2015

Send correspondence to:
Dra. Pilar Buil. Facultad de Ciencias de la Comunicación, Universitat Internacional de Catalunya. Immaculada 22, 08017 Barcelona.
E-mail: pbuil@uic.es

Gambling is a type of game in which the possibility of winning or losing is subject to chance; in other words, it is not exclusively dependent on the player's skill. Its practice is widely extended amongst the Spanish population. In 2014, online gambling platforms registered an average of 130,000 new players per month. There were 356,000 active players in the fourth quarter of 2014, about 20% more than the previous year (Directorate General for the Regulation of Gambling, 2014). However, despite the existing social acceptance of gambling, this activity entails risk: in fact, some countries consider it a serious public health problem (McMullan & Miller, 2009; Messerlian, Derevensky & Gupta, 2004). According to Carbonell (2014), though children and adults play many types of games, only those that entail placing bets and in which, therefore, the possibility of winning or losing money exists, are potentially pathological. The DSM-5 classifies pathological gambling as a behavioural addiction of the non substance-related disorders, and is no longer included in the section on impulse control disorders, as it appeared in previous editions of the manual (APA, 2013). In this regard, the fact that gambling has become another form of entertainment amongst youth and is amongst this group's most popular activities, like practising sports, listening to music or watching movies (Wiebe & Falkowsky-Ham, 2003), reveals a distressing reality (Messerlian et al., 2004), given that adolescents are more vulnerable than adults to the negative consequences of gambling (Volberg, Gupta, Griffiths, Olason, & Delfabbro, 2010).

To date, no nationwide studies have been completed in Spain on the prevalence of pathological gambling, and only partial studies carried out in different Autonomous Communities and in countries of our region are available as a reference (Becoña, 2004; Carbonell, Montiel, & Salom, 2013; Griffiths, 2009). Several studies prove that the addiction to gambling develops early on (Arbinaga, 2000; Becoña & Gestal, 1996; Derevensky & Gupta, 2007) and that prevalence rates during adolescence are particularly high (Petry, 2006). In some countries, minors have higher pathological gambling rates than adults do (Granero et al., 2014; Wiebe & Falkowsky-Ham, 2003). Furthermore, some studies have not yet considered the current rates of online gambling, which has an even greater potential for increasing the prevalence rates of gambling-related problems, given its combination of the dual threat of high speed with convenient access to technology (Derevensky & Gupta, 2007).

Greater accessibility offered by the Internet is one of the characteristics accounting for the broad acceptance of online gambling. The familiarity with which minors surf the Internet increases their likelihood of playing, both during the week and on weekends. In addition, betting over the Internet is private and doable from anywhere. On another hand, compared with traditional games, online gambling usually offers extra prizes to welcome new players and a wide variety of temporary promotions. Likewise, players manifest a positive playing experience and greater physical comfort (Wood & Williams, 2011).

From a psychological perspective, the Internet is an alternate reality and permits a sensation of immersion and anonymity that many adolescents find psychologically gratifying (Griffiths, 2002). Gambling becomes, this way, an option minors can use to handle pressure during adolescence and to disconnect from the outside world (Millán, 2006). In fact, some studies demonstrate an existing relationship between regulation of emotions and impulsive conduct inherent to pathological gambling (Estévez, Herrero, Sarabia, & Jáuregui, 2014).

The reasons for which underage youth find online gambling so attractive include, especially, the possibility of winning, their parents' example, emotion and competition (Fröberg, 2006). Minors seeks instant gratification and immediate satisfaction, neither making any effort nor bearing frustration.

Though Spanish legislation prohibits gambling by minors, evidence that this segment of the population gambles exists (Becoña, Míguez, & Vázquez, 2001; Derevensky, Gupta, & Winters, 2003; Granero et al., 2014). Results demonstrate that adolescents participate in Internet-based gambling and, therefore, that there are more adolescents with potential problems associated with practising this activity (Arbinaga, 2000; Muñoz-Molina, 2008). In fact, the existence of a significant relationship between youth that use the Internet to gamble and the development of gambling-related problems has been demonstrated (Carbonell et al., 2013; Secades, Fernández-Hermida, Duch, Skärstrand, Becoña, & Talic, 2014).

Advertising promotes participation in gambling (Felsher, Derevensky, & Gupta, 2004). In Spain, online gambling companies invested €140 million in publicity and marketing in 2013 (Spanish Association of Digital Gaming, 2014). Ads intend to influence attitudes and to inform of possibilities for gambling, thereby directly increasing the availability of gambling (Sklar & Derevensky, 2010). To this effect, advertising –to the extent that it sparks the initiation of gambling– may entail a notable risk for minors impacted by these commercial messages and with ready access to online gambling platforms. Likewise, in the same way that advertising of alcoholic beverages is restricted to protect the health of persons (Azurmendi, 2001), this protection should be extended to gambling advertising.

In Spain, gambling advertising is regulated by Article 7 of Act 13/2011, dated 27 May, on Gambling Regulations, but are underage youth effectively protected? In seeking to answer this question, this study evaluates Spanish legislation in effect as regards advertising of online gambling in relation to minors. The fact that online gambling is increasing amongst youth and that advertising promotes this activity demands a review of current Spanish legislation to assess whether it effectively protects minors. To achieve this goal, we completed an interdisciplinary review of literature speci-

fically on gambling and of participation in this activity by underage youth. Likewise, we also include annual reports on gambling in Spain and more recent, specialised studies on the growth of the Internet-based gambling industry and the social costs associated with it. This review reveals a scarcity of available reports and studies with valid, reliable data. This scarcity is understandable, given that online gambling is a relatively recent activity and, especially, directly interviewing users under this age is precluded, given that legislation prohibits gambling by youth under the age of 18.

The impact of gambling advertising on minors

Gambling advertising is a factor that interacts together with others in the development of problem gambling (Binde, 2007). At the same time, unanimity does not exist as to whether the advertising message has an obvious impact for players with problems, triggering excessive gambling, or if it is just one of many possible environmental factors interacting with a large number of characteristics related with gambling behaviour (Binde, 2009).

In general, advertising mainly maintains and reinforces establishing gambling habits, beliefs and behaviours (Planzer & Wardle, 2011); it apparently acts as a trigger and keeps some disordered gamblers from stopping (Derevensky, Sklar, Gupta, & Messerlian, 2010; Felsher, Derevensky & Gupta, 2004). The idea of "a spirit of winning" extends to gambling advertising through words, signs, myths and symbols surrounding the world of gambling (McMullan & Miller, 2009). Advertising reflects gambling as a means of entertainment, like something we can do with friends, instead of as something through which we can win or lose money (Domínguez, 2007).

Minors can also remember gambling advertising and concern exists that some advertising messages may directly target youth. In fact, studies have demonstrated how gambling advertising directly targets minors (Sklar & Derevensky, 2010). In any case, even if the messages do not directly target them intentionally, minors desiring to transcend their age to adulthood (Delfabbro, Lahn, & Grabosky, 2005) may perceive gambling as a sophisticated, adult activity.

The content and tone of the ads try to connect with users with a lifestyle seeking entertainment, shortcuts for attaining success, and solutions for overcoming fear of the future. Advertising displays gambling as an activity that is a normal and pleasant form of entertainment. In this regard, references are made neither to the scarce and real possibilities of winning nor to potential losses (McMullan & Kervin, 2012). The only obstacle minors face for participating in this type of entertainment is the existing age limit.

As part of their advertising strategy, gambling companies use the sponsorship of sports to reach large audiences (Binde, 2009; Chico & Ruiz, 2013). Furthermore, this sponsorship associates gambling with a healthy habit: sports, thereby achieving a greater normalisation of gambling and reinforcing the notion that gambling is an acceptable form of entertainment (Lamont, Hing, & Gainsbury, 2011). In summary, the exposure obtained by gambling companies through sports sponsorship represents a direct risk for underage youth in a stage of development that makes them susceptible to influences. This risk is higher amongst young males (Monaghan, Derevensky, & Sklar, 2008). Therefore, bookmakers use sports to promote a potentially risky behaviour that may intensify the public health problem derived of gambling (Lamont et al., 2011).

Gambling advertising regulations in relation to minors in the Spanish legal framework

In Spain, Article 7 of Act 13/2011, dated 27 May, on Gambling Regulations (LRJ) regulates gambling advertising. This article defines the general principles that apply to advertising, sponsorship and promotion of gambling activities that are subject to statutory regulations. Online gambling advertising is bound to regulations based on the principles that inspired this Act which, as set forth in the Preamble, are those under the powers of the State as per Article 149 of the Constitution, particularly as regards the protection of minors. In addition, operators are obliged to inform certain groups, including minors and other vulnerable individuals, on the prohibition of gambling as set forth in Article 6.2 of the LRJ. This protection is set forth in Article 26 of Royal Decree 1613/2011

Table 1
Gambling Advertising Regulations

Act 13/2011 on Gambling Regulations (LRJ)	Article 6.2. Prohibition of gambling by minors, of which operators are obliged to inform.
	Article 7. Requirement of express authorisation for advertising. Obligation of informing on basic requirements for gambling. Regulations must define the conditions for: - sending advertisements using e-mail, - sponsorship, - insertion of printed advertisements, - television contests. These regulations have not yet been developed.
Royal Decree 1613/2011	Article 26. Obligations of operators as to the identification and verification of participant data.
Code of Conduct on Commercial Communication (Self-regulation)	Ethical standards based on principles of loyalty, veracity and social responsibility. Principles of responsible gambling in communications and self-promotions. Television broadcasting of advertising during non-children's programming.

listing the different obligations of operators as regards the identification and verification of participant data.

Table 1 summarises the regulations applicable to gambling advertising in Spain currently in force. Article 7 of the LRJ sets forth that the business license issued by the Directorate General for the Regulation of Gambling must expressly authorise gambling operators, advertising agencies and media wishing to participate in online gambling advertising. The LRJ also sets forth (Article 7.2) the statutory regulations defining the conditions for commercial communication, in particular: e-mailing of advertisements, inclusion of ads, sponsorships, insertion of printed advertisements on gambling, television contests and the obligations of informing on basic requirements for gambling, amongst others. These statutory regulations, essential for developing a legal framework on online gambling advertising, have not yet been drafted.

This same Act defines a system of responsibility specifically for online gambling that includes not only the corresponding gambling operator, but also includes other participating agents, like media, advertising agencies or Internet access providers, amongst others. The reason for this measure is that the operators of online gambling activities may reside outside of Spain, wherefore the only way to control that they have obtained the required business license is through the Spanish advertisers or media in which they insert advertising messages.

The LRJ establishes the possibility for the Directorate General for the Regulation of Gambling to sign co-regulation agreements, in particular concerning advertising. In 2012, the Directorate General for the Regulation of Gambling, the Deputy Directorate General for Contents of the Information Society, and the Association for the Self-regulation of Commercial Communication (Autocontrol)[1] signed an agreement to establish a code of conduct. Called the "Code of Conduct on Commercial Communication of Gambling Activities" (Autocontrol, 2012), its purpose is to protect consumers, especially underage youth and other vulnerable groups, as regards gambling advertising. This Code is applicable to all advertising, promotions, sponsorships and any other type of commercial communications disseminated in Spain, for any type of gambling activity subject to the regulations of the Act on Gambling Regulations, including the promotion of companies, brands and events, carried out by companies or entities adhered to the same.

By virtue of this agreement, the companies adhered to the Code may submit their advertising for gambling operators to prior review, through a previous confidential and binding consultation system known as *copy advice*. When Autocontrol issues the advertising message a positive report prior to its emission, it is interpreted that the advertiser has acted in good faith. Last year 529 consultations were processed. Of these, changes were suggest in 69 to avoid possible infractions and only 8 were considered non-recommendable (Spanish Association of Digital Gaming, 2014).

This Code establishes a series of ethical standards based on the principles of legality, loyalty, identification, veracity and social responsibility, amongst others. Moreover, for commercial communications and self-promotions, it sets forth some principles on responsible gambling that should be respected, such as the prohibition of advertising that incites addictive habits or that suggests that gambling is a means of escape and can resolve financial problems.

In the context of the protection of minors, commercial communications or self-promotions that insinuate that underage youth may participate or place bets, that use or include minors, that incite minors -whether directly or indirectly- to gamble, or that exploit a relationship based on their trust in parents, teachers or other persons, are prohibited. Furthermore, visual elements - whether visual, auditory, spoken or written - that target minors are not allowed, and when used, must contain a warning on the use of fiction in advertising messages; gambling may be presented neither as a sign of maturity or as the initiation into adulthood, nor as a gift that a child may give or receive.

As regards broadcasting times, commercial communications or self-promotions of gambling cannot be emitted during children's programming, in compliance with the Code on Self-regulation of Television Content and Children. As a result, advertising and self-promotion for playing roulette, baccarat, blackjack, poker, and all types of sports betting exchanges, may only be broadcast between the hours of 10 p.m. and 6 a.m., with the exception of regulations applicable to live broadcasting. This exception, unfortunately, contradicts all regulations for the protection of minors.

As regards advertising sponsorship in television, compliance is mandatory with the conditions set forth in the general law on Audiovisual Communication (Act 7/2010, dated 31 March) and in Article 12.e, Royal Decree 1624/2011, dated 14 November, approving the implementing regulations of the general law on Audiovisual Communication.

According to this legislation, surveillance by public administrations and the imposition of penalties are powers entrusted to the audiovisual authorities, which are responsible for ensuring compliance with codes. A Joint Committee - presided over by a representative of the Directorate General for the Regulation of Gambling - must be established for monitoring co-regulation agreements and unto which the self-regulation system is held accountable and periodically reports on its activity. The powers for taking procedural steps and imposing sanctions on audiovisual communication service providers correspond to the Directorate General for the Regulation of Gambling; in these cases, applicable sanctions are those set forth in the general law on Audiovisual Com-

1 In 1995, Spain's main advertisers, agencies and media established this non-profit organisation for self-regulation of commercial communication: true, legal, honest and loyal.

munication. In 2013, there were 16 out-of-court settlements for claims related to gambling advertising that Autocontrol processed at the request of the Association of Communication Users (Spanish Association of Digital Gaming, 2014).

Discussion

The purpose of this investigation was to analyse current legislation on gambling advertising to evaluate the extent to which it effectively protects minors from the risks associated with exposure to advertising that promotes participation in online gambling.

First, the study affirms that gambling advertising is a risk factor for underage youth. This variable influences addiction to gambling. Though it exerts lesser impact than other factors –in fact, the only factor that is associated with the development of gambling-related problems in adolescents unanimously acknowledged by the scientific community is the absence of strong parental bonding–, its messages influence the behaviour and perceptions of minors. In recent years, bookmakers have considerably increased their advertising. In fact, a majority of young people claim to have received gambling advertising, while a minority acknowledge having seen any content referring to responsible gambling.

Second, the study confirms that the Spanish legal framework acknowledges the influence of gambling advertising on minors. Specifically, gambling advertising, regulated by Act 13/2011 on Gambling Regulations, directly refers to the need for protecting minors. A Self-Regulation Code has been approved to protect minors and other vulnerable individuals: the Code of Conduct on Commercial Communication of Gambling Activities. This Code prohibits advertising messages that target minors. This study proves that this Code has significant deficiencies as regards fulfilling its goal involving the constitutional rights of underage youth. Specifically, the study verifies that no legal obligation exists for informing in advertising of the possible risks derived of gambling. Though principle 6.2 of the Code sets forth the obligation of including a message on social responsibility or the fight against addiction, the guidelines for implementing this obligation have not been addressed. Likewise, as regards informational and warning messages set forth in Article 8 of Act 13/2011, dated 27 May, on Gambling Regulations as concerns the protection of consumers and responsible gambling policies, a same set of standards for all operators has not been established. In addition, the fact that the gambling industry is the party defining these rules raises doubts as to their effectiveness, given that economic interests may impede the goal of protecting individuals.

On another hand, the study reveals that, due to its nature as a code, companies are not obligated to comply with it, wherefore many remain beyond the scope of the control system. In that sense, as to the level of non-compliance, though the code prohibits the advertising of bingo during the special times for protecting minors, in reality this advertising occurs. The current gambling advertising code is not sufficiently effective.

Third, the study has verified that gambling companies recur to sponsorship of sports events as part of their advertising strategy, and this type of advertising contradicts legislation on the protection of minors. Likewise, the investigation has confirmed that the Code allows bookmakers to sponsor sports teams as well as for their advertising to appear on players' uniforms. This displays the brand, amongst other occasions, during the retransmission of games/matches or press conferences after the events, as well as in clips of these broadcasts and press conferences with athletes also aired during news coverage of sporting events, something specifically prohibited by legislation on news programmes (Articles 13 and 16 of R.D. 1624/2011). Moreover, the study affirms that this type of advertising is especially harmful to children, as it reinforces the notion that it is an acceptable and healthy form of entertainment (Lamont et al., 2011), while it disregards its potential for generating negative effects, especially amongst youth that are developing and defining their personal identity.

In conclusion, this study reveals that online gambling advertising may increase the risk of gambling amongst underage youth. Though gambling by minors is prohibited, evidence reveals that they gamble. The self-regulation code is not a sufficient resource for effectively protecting minors and other vulnerable individuals. For this reason, it is necessary to define regulations that address gaps in legislation and that effectively protect minors from gambling advertising. This way, we hope that the conclusions of this study will represent a contribution so that an activity that generates a public health problem will have an increasingly less negative impact on underage youth.

Conflict of interests

The authors declare the inexistence of conflicts of interest.

References

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

Arbinaga, F. (2000). Estudio descriptivo sobre el juego patológico en estudiantes: características sociodemográficas, consumo de drogas y depresión. *Adicciones, 12*, 493-505.

Asociación Española del Juego Digital. (2014). Informe anual del juego online en España. Retrieved from: http://www.jdigital.es/emailing/2014/docs/2014-Informe-Anual-Jdigital.pdf

Autocontrol. (2012). Código de conducta sobre comunicaciones comerciales de las actividades de juego. Retrieved from: http://www.autocontrol.es/pdfs/pdfs_codigos/cod_actividad_juego2013.pdf

Azurmendi, A. (2001). *El derecho de la comunicación*. Barcelona: Bosch.

Becoña, E. & Gestal C. (1996). El juego patológico en niños del 2º ciclo de E.G.B. *Psicothema, 8*, 13-23.

Becoña, E., Míguez, M. C., & Vázquez, F.L. (2001). El juego problema en los estudiantes de Enseñanza Secundaria. *Psicothema, 13*, 551-556.

Becoña, E. (2004). El juego patológico: prevalencia en España. *Salud y Drogas, 4*, 9-34.

Binde, P. (2007). Selling dreams—causing nightmares? On gambling advertising and problem gambling. *Journal of Gambling Issues, 20,* 167-192. doi:10.4309/jgi.2007.20.5

Binde, P. (2009). Exploring the impact of gambling advertising: An interview study of problem gamblers, *International Journal of Mental Health and Addiction, 7*, 541-554. doi:10.1007/s11469-008-9186-9

Carbonell, X. (2014). La adicción a los videojuegos en el DSM-5. *Adicciones, 26,* 91-95.

Carbonell, X., Montiel, I., & Salom, M. (2013). Jóvenes, nuevas tecnologías y juego de azar. In X. Carbonell & I. Montiel (Eds.), *El juego de azar online en los nativos digitales* (pp. 17-38). Valencia: Tirant Humanidades.

Chico, P. & Ruiz, M. (2013). Empresas de juego y el patrocinio de actividades con especial referencia a los incentivos fiscales. In A. Palomar & R. Baena (Eds.), *En torno al Juego de Azar* (pp. 409-459). Pamplona: Thomson Reuters-Aranzadi.

Delfabbro, P., Lahn, J., & Grabosky, P. (2005). Further evidence concerning the prevalence of adolescent gambling and problem gambling in Australia: A study of the ACT. *International Gambling Studies, 5*, 209-228. doi: 10.1080/14459790500303469

Derevensky, J. L., Gupta, R., & Winters, K. (2003). Prevalence rates of youth gambling problems: Are the current rates inflated? *Journal of Gambling Studies, 19,* 405-425. doi: 10.1023/A:1026379910094

Derevensky, J. L. & Gupta, R. (2007). Internet gambling amongst adolescents: A growing concern. *International Journal of Mental & Health Addiction, 5,* 93–101. doi:10.1007/s11469-007-9057-9

Derevensky, J. L., Sklar, A. Gupta, R., & Messerlian, C. (2010). An empirical study examining the impact of gambling advertisements on adolescent gambling attitudes and behaviours. *International Journal of Mental Health and Addiction, 8,* 21-34. doi:10.1007/s11469-009-9211-7

Dirección General de Ordenación del Juego. (2014). Informe Análisis Global del Mercado Nacional del Juego Online. Octubre-Diciembre 2014. Retrieved from: http://www.dgojuego.minhap.gob.es/es/art-cuartotrimestre-2014

Dirección General de Ordenación del Juego. (2013). Informe Observatorio de la protección al jugador online. Informe de resultados: Noviembre 2013. Retrieved from: http://www.ordenacionjuego.es/es/estudios-informes#observatorio

Domínguez, A. M. (2007). *Guía Clínica: Actuar en el juego patológico. Dirección General para las Drogodependencias y Adicciones.* Sevilla: Consejería para la Igualdad y Bienestar Social. Junta de Andalucía.

Estévez Gutiérrez, A., Herrero Fernández, D., Sarabia Gonzalvo, P., & Jáuregui Bilbao, P. (2014). El papel mediador de la regulación emocional entre el juego patológico, uso abusivo de Internet y videojuegos y la sintomatología disfuncional en jóvenes y adolescentes. *Adicciones, 26,* 282-290.

Felsher, J., R. Derevensky, J. L., & Gupta, R. (2004). Lottery playing amongst youth: Implications for prevention and social policy. *Journal of Gambling Studies, 20*, 127-154. doi:10.1023/B:JOGS.0000022306.72513.7c

Fröberg, F. (2006). *Gambling among young people, a knowledge review.* Stockholm: Swedish National Institute of Public Health.

Granero, R. Penelo, E., Stinchfield, R., Fernández-Aranda, F., Savidou, L. G., Fröberg, F., ... Jiménez, S. (2014). Is pathological gambling moderated by age? *Journal of Gambling Studies, 30*, 475-492. doi:10.1007/s10899-013-9369-6

Griffiths, M. (2002). *Gambling and gaming addictions in adolescence.* London: Blackwell.

Griffiths, M. D. (2009). Problem gambling in Europe: an Overview. International Gaming Research Unit. Nottingham Trent University. Retrieved from: http://www.nsgamingfoundation.org/uploads/Problem%20Gambling%20in%20Europe.pdf

Lamont, M., Hing, N., & Gainsbury, S. (2011). Gambling on sport sponsorship: A conceptual framework for research and regulatory review. *Sport Management Review, 14*, 247-257. doi:10.1016/j.smr.2011.04.004

McMullan, J.L. & Miller, D. (2009). Wins, winning and winners: The commercial advertising of lottery gambling, *Journal of Gambling Studies, 25*, 273–295. doi:10.1007/s10899-009-9120-5

McMullan, J.L. & Kervin, M. (2012). Selling Internet gambling: Advertising, newmedia and the content of poker promotion. *International Journal of Mental Health and Addiction, 10,* 622-645. doi:10.1007/s11469-011-9336-3

Messerlian, C., Derevensky, J., & Gupta, R. (2004). A public health perspective for youth gambling. *International Gambling Studies, 4,* 147-160. doi:10.1080/14459790412331296974

Millán, T. (2006). La digitalización de la realidad en las nuevas generaciones del siglo XXI. *Comunicar, 26*, 171-175.

Monaghan, S., Derevensky, J., & Sklar, A. (2008). Impact of gambling advertisements and marketing on children and adolescents: policy recommendations to minimise harm. *Journal of Gambling Issues, 22,* 252–274. doi: 10.4309/jgi.2008.22.7

Muñoz-Molina, Y. (2008). Meta-análisis sobre juego patológico (1997-2007). *Revista de Salud Pública, 10*, 150-159.

Petry, N.M. (2006). Internet gambling: An emerging concern in family practice medicine?. *Family Practice, 23*, 421-426. doi:10.1093/fampra/cm1005

Planzer, S. & Wardle, H. (2011). *The comparative effectiveness of regulatory approaches and the Impact of advertising on propensity for problem gambling*. London: Responsible Gambling Fund.

Secades Villa, R., Calafat, A., Fernández-Hermida, J.R., Duch, M., Skärstrand, E., Becoña, E., & Talic, S. (2014). Duration of Internet use and adverse psychosocial effects among European adolescents. *Adicciones, 26,* 247-253.

Sklar, A. & Derevensky J.L. (2010). Way to play: Analyzing ads for their appeal to underage youth. *Canadian Journal of Communication, 35*, 533-554.

Volberg, R., Gupta, R., Griffiths, M. D., Olason, D., & Delfabbro, P. (2010). An international perspective on youth gambling prevalence studies. *International Journal of Adolescent Medicine and Health, 22*, 3-38. doi:10.1515/IJAMH.2010.22.1.3

Wiebe, J. & Falkowsky-Ham, A. (2003). *Understanding the audience: The key to preventing youth gambling problems*. Toronto: Ontario Gambling Council.

Wood, R. T. & Williams, R. J. (2011). A comparative profile of the Internet gambler: Demographic characteristics, game-play patterns, and problem gambling status. *New Media & Society, 13,* 1123-1141. doi: 10.1177/1461444810397650

Polydrug use and its relationship with the familiar and social context amongst young college students

Policonsumo de drogas y su relación con el contexto familiar y social en jóvenes universitarios

Olga Hernández-Serrano*, Sílvia Font-Mayolas**, Maria Eugènia Gras**

*Escola Universitària de la Salut i l'Esport. Universitat de Girona, Girona
**Instituto de Investigación sobre Calidad de Vida. Universitat de Girona, Girona

Abstract

The prevalence of polydrug use continues to grow among Spanish college students. The European Observatory for Drugs and Addictions establishes three different types of polydrug use: Pattern A (consumers of alcohol and tobacco), Pattern B (consumers of cannabis plus alcohol and/or tobacco) and Pattern C (consumers of cannabis plus alcohol plus tobacco plus at least one other kind of illegal drug). The objectives are: 1) to study the frequency of substance consumption among a sample of young Spanish undergradudates studying health and sports science according to their sex; 2) to describe the patterns of polydrug use; 3) to study the relationship between the polydrug use of the participants and polydrug use within their closest environment (parents, sisters or brothers, best friend and partner). The sample was composed of 480 Spanish undergraduates (43.7% females) aged 18 to 36. The level of drug consumption of students and their closest reference persons was evaluated by means of a self-report measure. A total of 46% of the participants reported consumption of two or more substances; among them 29.4% corresponded to Pattern A, 50.7% to Pattern B and 16.7% to Pattern C, while 3.2% corresponded to other multiple consumption patterns (alcohol + cocaine; alcohol + cocaine + tobacco; alcohol + inhalants; amphetamines + hallucinogens + Spice). An important correlation was observed concerning polydrug use between participants and their closest reference persons: the more the reference person is a multiple consumer, the more the participant tends to consume. Polydrug use within the closest environment emerges as one of the key elements to be taken into account in further prevention programs.

Keywords: polydrug use, contextual factors, college students.

Resumen

El policonsumo de drogas es cada vez más prevalente entre los jóvenes españoles. El Observatorio Europeo de las Drogas y las Toxicomanías establece tres tipologías de policonsumo: Patrón A (consumidores de alcohol y tabaco), Patrón B (consumidores de cannabis junto con alcohol y/o tabaco) y Patrón C (consumidores de cannabis junto con alcohol y tabaco y al menos otra droga ilegal). Los objetivos son: 1) estudiar la frecuencia de consumo de drogas en una muestra de jóvenes universitarios españoles del ámbito de la salud y el deporte según el sexo; 2) describir los patrones de policonsumo; 3) estudiar la relación entre el policonsumo de los participantes y el policonsumo de las personas de su entorno próximo (padres, hermanos, pareja y mejor amigo). La muestra consta de 480 universitarios (43.7% chicas) entre 18 y 36 años. Se administró un autoinforme para evaluar el policonsumo de los participantes y de sus referentes más próximos. Un 46% de los participantes eran consumidores de dos o más sustancias, de los cuales un 29.4% correspondían al Patrón A, un 50.7% al Patrón B, un 16.7% al Patrón C y un 3.2% a otros patrones de policonsumo (alcohol + cocaína; alcohol + cocaína + tabaco; alcohol + inhalantes; anfetaminas + alucinógenos + Spice). Se observa una elevada concordancia entre el policonsumo de los participantes y el de sus referentes próximos, de modo que si el referente es policonsumidor es más probable que el participante también lo sea. El policonsumo de drogas en el entorno próximo de los jóvenes deviene uno de los elementos clave a tener en cuenta en futuras campañas preventivas.

Palabras clave: policonsumo de drogas, factores contextuales, estudiantes universitarios.

Received: September 2014; Accepted: February 2015

Send correspondence to:
Dra. Olga Hernández Serrano. Escola Universitària de la Salut i l'Esport (EUSES). Universitat de Girona (UdG). Departamento de Fisioterapia. Campus de Salt. Carrer Francesc Macià, 65 – 17190. Salt (Girona). España. E-mail: olga.hernandez@cadscrits.udg.edu/ ohernandez@euses.cat

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2011), polydrug use has become one of the most common patterns of substance consumption in Europe. This observatory classifies the main types of polydrug use among adolescents into Pattern A (consumers of alcohol and tobacco), Pattern B (consumers of cannabis plus alcohol and/or tobacco consumers) and Pattern C (consumers of cannabis plus alcohol plus tobacco plus at least one other kind of illegal drug). Among young adults between the ages of 15 and 34, the most widely used substances in all European countries are alcohol and tobacco, followed by cannabis. Despite the fact that the EMCDDA (2009a) does not classify types of polydrug use specifically among young people, a link has been found between frequent or excessive consumption of alcohol and a high probability of consuming cannabis or cocaine compared with the general population. At the same time, many cocaine users also consume cannabis. Nevertheless, the majority of cannabis users do not consume illicit drugs.

According to the Spanish Observatory on Drugs (Observatorio Español de la Droga y las Toxicomanías, 2011), the situation in Spain is similar to the rest of Europe, with alcohol, tobacco and cannabis being the most widely consumed substances in the population aged 15-64. During the last year, 49.3% of psychoactive substance users have admitted taking two or more drugs. Among the users of two substances, alcohol and tobacco are the most frequently consumed, while alcohol, tobacco and cannabis are the most widely used among consumers of three substances. Consumers of four or more drugs, however, mostly take alcohol, tobacco, cannabis, cocaine in powder form and ecstasy/designer drugs (OEDT, 2011). In this regard, and specifically among the university population, some studies have explored whether the consumption of one substance increases the likelihood of using other drugs, and have found positive correlations depending on the type of substance. Thus a link exists between the occasional consumption of ecstasy and the use of marihuana, and there is a greater likelihood that other substances such as cocaine, heroin, LSD or inhalants will be consumed by users of ecstasy than by users of marihuana (Wish, Fitzelle, O´Grady, Hsu, & Arria, 2006). Other studies find a strong association between tobacco and cannabis consumption: nine out of ten adolescents who have never smoked and only 1.5 of every ten smokers have never consumed cannabis (Font-Mayolas, Gras, & Planes, 2006). Similarly, a study of cocaine consumption found that young people who normally take cocaine are also mostly consumers of alcohol and cannabis (Patiño-Masó, Gras-Pérez, Font-Mayolas, & Baltasar-Bagué, 2013). Likewise, Tirado, Aguaded, & Marin (2009) show that polydrug use (low strength alcohol + tobacco) is the prime risk factor for the consumption of spirits among university students.

In demographic terms, recent years have seen research into the differences in polydrug use according to the sex and age of young consumers. Many of these studies suggest that men exhibit greater polydrug use than women (Substance Abuse and Mental Health Services Administration, 2009; Whitehorne-Smith et al., 2012). With regard to age, data on young adults confirm links with polydrug use (Ramo, Liu, & Prochaska, 2012). Polydrug consumption is moreover associated with serious issues such as low cognitive performance, physical problems, traffic accidents, injuries, infectious and sexually transmitted diseases, suicide, fighting and other violent behaviour, as well as the risk of developing into a pattern of permanent abuse of various substance (Connor, Gullo, White, & Kelly, 2014; EMCDDA, 2011, 2014; Halley, Forster, Wood, Baezconde-Garbanati, & Beth, 2014; Hughes et al., 2009; Mariño, Castro, & Torrado, 2012; Trenz et al., 2012).

Understanding the risk and protection factors linked to polydrug consumption is important for developing interventions aimed at preventing these problems. The review carried out by Stone, Becker, Huber, & Catalano (2012) of risk and prevention factors in young adults (18-26 years of age) deserves special attention in this connection. Following Hawkins, Catalano, & Miller (1992), they establish a classification of contextual factors (sex, ethnicity, biological indicators, pre- and postnatal indicators, socioeconomic status, educational level of parents, parental status, family history of substance use, psychopathological problems of parents, poor neighborhoods, social norms, laws and taxes, availability), interpersonal aspects (background of substance abuse, family relations, family management, external and internal attributions, drug consumption and expectations in adolescence, positive attitudes and expectations, life circumstances, status/level of employment, university attendance, peer group relationships, moral beliefs, participation in religion, educational factors, marital status or engagement, stressful events). The present study focuses on contextual factors and in particular on the substance consumption of members of the subject's closest circle as possible risk factors for polydrug use.

Based on Bandura and Walters' (1979) social learning theory, learning can be seen as the observation of other models of behavior or modelling, and this can for example lead young people to start consuming substances and increase their use. There is evidence showing links between the consumption of certain substances in families, among partners and friends, and the consumption behavior of undergraduates. Font-Mayolas & Planes (2000), for example, found that young smokers tended to have a father and/or a mother and/or friends who also smoked, while they did not discover differences among partners and siblings. However, most of this research is focused on the independent study of substances like alcohol, tobacco, marihuana and medicines (Becoña et al., 2012; Buu et al., 2009; Martín-Montañez et

al., 2011; Mason et al. 2009), and studies looking at the relationships between polydrug use and these contextual factors are few and far between. With regard to the polydrug use of friends, research findings support a positive link between the consumption of various substances and having friends who are multiple consumers. Varela, Salazar, Cáceres, & Tovar (2007), for example, identified a strong association between the consumption of marihuana, opiates, cocaine and ecstasy among Brazilian university students and maintaining friendships with other drug users in which consumption can increase. Other studies have found that using cannabis for the first time is strongly associated with being a member of a group of friends in which drugs are consumed (Vázquez & Becoña, 2000). In terms of finding out about the polydrug use of psychoactive substances, a large percentage of undergraduates assert that the most frequently used way is through a friend (Herrera et al., 2012; Riquelme et al., 2012; Veloza et al., 2012). It has recently been found that having three or four close friends who are substance users is a significant predictor of drug consumption issues when compared to those with friends who are not consumers (Halley et al., 2014). On the other hand, the findings regarding a possible link between the consumption of more than one substance and polydrug use of parents is not conclusive. Some authors claim that consumption of alcohol and tobacco of 12% of university students is linked to learning from a close family member such as father, mother or sibling, or through other relatives (Veloza et al., 2012). Other authors find, however, that having a parent who consumes drugs is not a relevant predictor of their children developing consumption problems during adolescence (Halley et al., 2014). In the case of partners, Veloza et al. (2012) identify a link in 13% of their sample between the polydrug use of alcohol and tobacco among undergraduates and having a boy/girlfriend who is a multi-consumer.

In general, the majority of studies on polydrug use focus on the adolescent population (Connell, Gilreath, Aklin, & Brex, 2010; Font-Mayolas et al., 2013; Martínez, Fuentes, García, & Madrid, 2013). Regarding university students, many studies deal with a single substance (for example Font-Mayolas et al., 2006), and those which focus on the consumption of various drugs analyze a limited number of substances (mostly tobacco, alcohol, cannabis, cocaine, ecstasy and medicines). In addition, data available on polydrug use include research in the social studies, humanities and health fields which were carried out in geographic and socio-cultural contexts different to the Spanish ones (Gómez, Herde, Laffee, Lobo, & Martín, 2007; Herrera et al., 2012; Prieto et al., 2012; Veloza et al., 2012; Whitehorne-Smith et al., 2012). Indeed, a variety of authors highlight the importance of studying university students in the health and also sports areas because they are considered a vulnerable population (Lores, Murcia, Gutiérrez, & Sicilia, 2003; Oliveira & Furegato, 2008; Urrego, 2002) with responsibilities for health, wellbeing and quality of life in society as a whole. Furthermore, a new feature of European markets is the growing availability of "new psychotropic substances" which are not regulated by international drug control treaties (EMCDDA, 2014). Substances like *Spice* (synthetic marihuana), which is included in the range of drugs covered by this study, is very popular among young people and the second most consumed illicit drug after marihuana (EMCDDA, 2009b). Therefore, we highlight the importance of understanding the issues involved in polydrug use bearing in mind the new generation of substances. The objectives of the present study, then, are: 1) to analyze the frequency of drug consumption in a sample of young Spanish undergraduates studying in the areas of health and sports according to sex; 2) to describe the patterns of polydrug use among these young people; 3) to study the association between the consumption of more than one substance and the polydrug use of people in the subjects' closest circle (parents or guardians, siblings, best friends, partners).

Method

Participants

The target population is students enrolled in Girona University (Escola Universitària de la Salut i l´Esport, EUSES) on its campus at Salt (Girona). A descriptive cross-sectional study of prevalence was carried out. Of a total of 804 enrolled students, 324 did not attend class on the day and time of data collection, so the participation percentage of 59.7% is not due to lack of interest on the part of the students. The sample is made up of all the students who were present at the moment of data collection, and of these 480 undergraduates 43.7% were women and 56.3% men, aged between 18 and 36 (M = 21.3; DT = 2.8), in their first (32.5%), second (29.3%) and third (38.2%) years of study respectively

Instruments

Sociodemographic questionnaire. Information about type of course, year, age, sex, occupation and academic performance was collected.

Information regarding polydrug use was collected through a self-report in which the following variables were assessed:

Subjects' frequency of consumption. This is made up of 9 items with multiple responses ("never", "occasionally", "once a week", "more than once a week", "daily") which assess how often these are taken: tobacco, alcohol, cannabis, cocaine, heroin, inhalation sprays, speed or amphetamines, hallucinogens and *Spice*.

Frequency of consumption of close circle. This is made up of 9 items with multiple responses ("never", "occasionally", "once a week", "more than once a week", "daily") which assess the beliefs of students about how often these

drugs (tobacco, alcohol, cannabis, cocaine, heroin, inhalation sprays, speed or amphetamines, hallucinogens and *Spice*) are consumed by father/guardian, mother/guardian, brother of sister, best friend, partner.

The internal consistency of the instrument as assessed by Cronbach's alpha is 0.81.

Procedure

Data collection was carried out among students In their first three years of Physiotherapy and Sports Science degrees. The present study was approved by the Research Committee of Girona University. Prior to data collection, we spoke to the school management in order to explain the characteristics of the investigation and ask for their cooperation. We then spoke to the corresponding teaching staff to set a date for the administration of the questionnaire. The self-report was administered by the research team at a specific time on a single day during the academic year 2013/14. We asked students to participate voluntarily, and guaranteed that their responses would be confidential and used solely for research purposes.

Results

Table 1 shows the consumption of substances by sex and frequency of consumption by substance. Tobacco is the substance most often consumed daily, followed by cannabis. Daily alcohol consumption is low among these participants, although those who report never drinking it are in a minority. Only one participant claims to take cocaine and hallucinogens daily and none report daily consumption of heroin, inhalation sprays, speed or amphetamines, and *Spice*.

Cannabis is the most widely used illegal drug, with three out of ten participants reporting consumption more or less frequently. Between 10 and 21 participants report occasional consumption of cocaine, speed/amphetamines, inhalation sprays or hallucinogens. Heroin and *Spice* are the least frequently consumed substances: only two men reported occasional use of heroin and a further two used *Spice* (one occasionally and the other more than once a week).

There were no statistically significant differences between men and women in terms of frequency of substance use (Tobacco: $\chi^2_{(4)} = 7.47$; $p = 0.11$; Alcohol: $\chi^2_{(4)} = 1.84$; $p = 0.77$; Cocaine: $\chi^2_{(3)} = 3.62$; $p = 0.31$; Heroin: $\chi^2_{(1)} = 1.56$; $p = 0.21$; Inhalants: $\chi^2_{(1)} = 0.37$; $p = 0.55$; Speed or amphetamines: $\chi^2_{(2)} = 2.27$; $p = 0.32$; Hallucinogens: $\chi^2_{(3)} = 1.62$; $p = 0.65$; *Spice*: $\chi^2_{(2)} = 1.56$; $p = 0.46$) except in the case of cannabis ($\chi^2_{(4)} = 14.07$; $p = 0.007$) where we found significantly more women than men who had never tried the drug ($z = -2.24$; $p = 0.025$) and more men than women report using it more often than once a week ($z = 2.58$; $p = 0.001$)

Forty-six percent of participants (45.7% of men and 46.4% of women) report using two or more substances, with no significant differences by sex ($z = 0.14$; $p = 0.88$). Among multiple consumers, 29.4% (20.3% of men and 41.2% of women) corresponded to Pattern A (alcohol and tobacco), 50.7% (53.7% of men and 46.4% of women) to Pattern B (cannabis and alcohol and/or tobacco), 16.7% (22% of men and 10.3% of women) to Pattern C (cannabis and alcohol and/or tobacco and at least one other illegal drug), and 3.2% (4.1% of men and 2.1% of women) to other atypical patterns of polydrug use. The proportion of women with Pattern A consumption exhibits significant differences with regard to that of men, with women more strongly represented ($z = -3.18$; $p = 0.0014$), while in Pattern C the proportion of men is significantly higher compared to that of women ($z = 2.41$; $p = 0.016$). No statistically differences by sex are observed in either Pattern B ($z = 1.07$; $p = 0.28$) or in the atypical patterns of consumption ($z = 0.87$; $p = 0.38$).

Table 1
Frequency (percentage) of substance consumption by sex.

		Never	Occasional consumption	Once a week	More than once a week	Daily
Tobacco (*n* = 478)	Men	64.7%	10.0%	4.5%	3.0%	17.8%
	Women	60.4%	17.4%	1.9%	3.4%	16.9%
	Total	62.8%	13.2%	3.4%	3.2%	17.4%
Alcohol (*n* = 476)	Men	6.7%	43.9%	27.5%	20.4%	1.5%
	Women	5.4%	46.8%	28.3%	17.1%	2.4%
	Total	6.1%	45.1%	27.8%	19.0%	1.9%
Cannabis (*n* = 479)	Men	65.1%	20.1%	3.0%	4.8%	7.1%
	Women	74.5%	20.7%	1.9%	1.0%	1.9%
	Total	69.2%	20.3%	2.5%	3.1%	4.8%
Cocaine (*n* = 479)	Men	93.7%	5.6%	0.4%	0%	0.4%
	Women	97.1%	2.9%	0%	0%	0%
	Total	95.2%	4.4%	0.2%	0%	0.2%
Heroin (*n* = 479)	Men	99.3%	0.7%	0%	0%	0%
	Women	100%	0%	0%	0%	0%
	Total	99.6%	0.4%	0%	0%	0%
Inhalation sprays (*n* = 480)	Men	96.7%	3.3%	0%	0%	0%
	Women	97.6%	2.4%	0%	0%	0%
	Total	97.1%	2.9%	0%	0%	0%
Speed or amphetamines (*n* = 480)	Men	95.2%	4.5%	0.4%	0%	0%
	Women	97.6%	2.4%	0%	0%	0%
	Total	96.2%	3.6%	0.2%	0%	0%
Hallucinogens (*n* = 480)	Men	97%	2.2%	0%	0.4%	0.4%
	Women	98.1%	1.9%	0%	0%	0%
	Total	97.5%	2.1%	0%	0.2%	0.2%
Spice (*n* = 480)	Men	99.3%	0.4%	0%	0.4%	0%
	Women	100%	0%	0%	0%	0%
	Total	99.6%	0.2%	0%	0.2%	0%

Table 2
Porcentaje de participantes que consumen más de una sustancia según el policonsumo de sus referentes más próximos y resultados de la prueba ji-cuadrado.

	Best friend (*n*= 465)	**Father (*n*= 466)**	**Mother (*n*= 467)**	**Any sibling (*n*= 453)**	**Partner (*n*= 361)**
Reference person is not multiple consumer	20.3%	41.9%	42.8%	32.4%	30.5%
Reference person is multiple consumer	59.9%	58.4%	58.1%	68.0%	69.5%
χ^2 (*p*)	66.0 (<0.001)	10.5 (0.001)	7.6 (0.006)	55.1 (<0.001)	49.3 (<0.001)

Of the seven participants (3.2% of multiple consumers) who reported other polydrug use patterns, four consumed alcohol and cocaine, one used tobacco, alcohol and cocaine, one alcohol and inhalants and one amphetamines, hallucinogens and *Spice*.

Table 2 shows the percentage of multiple consumers in the sample in relation to the polydrug use of their closest reference persons: best friend, father, mother, siblings and partner and the results of the chi-square test. A close correlation can be observed between the polydrug use of the participants and that of their closest reference persons, so that if the reference person is a multiple consumer it is more likely that the participant will be one, too.

Table 3 shows the binary logistic regression results to predict polydrug use by age, sex and polydrug use of their closest reference persons. On analysis of the variables which predict the consumption by participants of more than one substance, the strongest is found to be the polydrug use of best friends, siblings and partners. If the best friend of the participant is a multiple consumer, the likelihood of the participant being a multiple consumer is between 3.29 and 11.43 times higher compared to those participants whose best friends are not multiple users; if a brother or sister is a multiple consumer, this likelihood is between 1.92 and 5.67 higher than for those who do not have a brother or sister who is a multiple consumer; if the partner is a multiple consumer, the likelihood is between 2.33 and 7.14 times higher than for those without a partner who is a multiple consumer. The model has a good fit (χ^2 = 123.05; $p < 0.001$), explains more than 40% of variability of polydrug use (Nagelkerke's $R^2 = 0.41$) and correctly classifies 76.3% of the participants.

Table 3
Results of binary logistic regression to predict polydrug consumption of the participants (n=342).

Variable	**B**	**O.R.**	**CI 95%**	*p*
Sex	-0.09	0.91	0.53:1.57	0.74
Age	0.05	1.05	0.97:1.14	0.26
Polydrug use of best friend	1.81	6.13	3.29:11.43	<0.001
Polydrug use of father	0.12	1.12	0.62:2.02	0.70
Polydrug use of mother	-.02	0.98	0.52:1.86	0.95
Polydrug use of a sibling	1.19	3.30	1.92:5.67	<0.001
Polydrug use of partner	1.41	4.08	2.33:7.14	<0.001

Discussion

The present study allows us to consolidate our knowledge of drug consumption behavior among Spanish undergraduates on health and sports science degrees. To this end, apart from providing results relative to the frequency of consumption of legal and illegal substances, the central features of polydrug use and their associations in the family and social contexts of the young students are described.

Firstly, one of the primary aims of this study to discover the link between the use of more than one substance and the polydrug use of other people in the subject's most immediate environment (parent/guardian, siblings, best friend, partner). A high correlation was found between the polydrug use of the participants and that of their closest reference persons, so if the reference person is a multiple consumer, there is a greater likelihood of the participant being one, too. Similarly, the polydrug use of best friends, brothers or sisters, or partners are the variables which most accurately predict the use of more than one substance by young people. In line with social learning theory, referred to at the beginning of this study, substance use is conceptualized as intentional behavior and socially learned through a process of modelling and reinforcement, as well as the interaction of personal and socio-environmental factors. Thus, the repeated exposure to substance using models directly influences the behavior of young people. The polydrug use of parents, however, is not relevant in predicting the multiple substance use among their children in comparison with the multiple consumption of other reference persons of similar age such as friends, siblings or partners. It is worth noting two points in connection with this result. Firstly, following Bandura's (1987) theory, the influence of the model is determined by the factors which facilitate the modeling effect; for example, similarity with the model in terms of factors such as age and/or sex, the attractiveness or interest the model holds for the partici-

pant, the emotional bonds forming part of the relationship, the level of normal interaction with the model or the social position of the model. Secondly, the features of this stage of a young person's development, together with the special experiences of university life, are emphasized. Life at university offers the student a period of personal growth, expectations, career plans and new challenges. Many of these students move away from home and start making new contacts with peers and with people of the opposite sex, which means adapting to new social surroundings. Polydrug consumption happens mostly in recreational contexts (e.g. raves) with other young people, and in such contexts polydrug use can represent a greater threat to health (Fernández-Calderón, Lozano-Rojas, & Rojas-Tejada, 2013). As a result, the influence of parents, once the primary reference persons (Ferrer & Ayneto, 1991), diminishes (Halley et al., 2014). In other words, as the adolescent grows and becomes more independent, the influence of parental attachment weakens (Becoña, Fernández, Calafat, & Fernández-Hermida, 2014). Finally, age and sex do not predict the use of two or more substances among young people if the patterns of polydrug use are not differentiated. The fact that consumption is undifferentiated by sex is supported by other authors who stress the importance of seeing polydrug use of tobacco and cannabis in the same way for both men and women (Ramo et al., 2012). Nevertheless, other studies have found sex differences in polydrug use (Substance Abuse and Mental Health Services Administration, 2009; Whitehorne-Smith et al., 2012). In terms of age, the results of this study are not consistent with differences found by other authors (OEDT, 2011; Ramo et al., 2012). More studies are therefore necessary in order to clear up possible inconsistencies with regard to sociodemographic variables of sex and age.

A further objective is to discover the frequency of drug consumption in a sample of young Spanish university students according to sex. Thus, the legal substance most often consumed on a daily basis is tobacco. At the same time, however, not many students claim never to drink alcohol (93.9% of the sample are consumers). The highest percentages of consumption on occasions and sometimes during the week belong to alcohol consumers. These data are in line with the last OEDT report (2011) on young people aged 15-34. In terms of illegal drugs, cannabis is the most frequently consumed. Our data on daily consumption of cannabis is above the levels found by the OEDT (2011), although it is in line with the increase in consumption from 2007 to the present and with findings in other studies (Font-Mayolas et al., 2006; Viña & Herrero, 2004). Moreover, cannabis is the only substance exhibiting differences by sex, with more men than women users, as also pointed out in other research (Font-Mayolas et al., 2006; OEDT, 2011). With regard to other substances, cocaine is the illegal substance most frequently used by undergraduates after cannabis. This is not unusual given that Spain is the country in Europe, alongside the United Kingdom, with the highest prevalence of cocaine use (OEDT, 2011). Finally, *Spice* is the substance least frequently used among students in the sample. Nevertheless, participation in *Spice* consumption is worth a special mention because although percentages are lower than those found in adolescents (OEDT, 2011), one of the participants uses it daily and all users are men. *Spice* is a mix of herbs for smoking with similar effects to those of cannabis about which little is known (Mustata et al., 2009). One of the first studies on this substance with a broad sample of university students (n = 2,349) shows that being male and a consumer of other substances increases the likelihood of consuming these synthetic cannabinoids (Stogner & Miller, 2014). However, not much research has been carried out in Spain in the university population, and more studies on the use of this type emergent drug among young people and earlier ages are needed, with special attention to patterns of consumption and demographics.

A final objective of the study was to describe the patterns of polydrug consumption among young people. Around half of the sample are multiple consumers of two or more substances. Of these, 29.4% correspond to Pattern A (alcohol + tobacco), 50.7% to Pattern B (cannabis + alcohol and/or tobacco) and 16.7% to Pattern C (cannabis + alcohol and/or tobacco + another illegal drug) and 3.2% to other patterns of polydrug use (alcohol + cocaine; tobacco + alcohol + cocaine; alcohol + inhalants; amphetamines + hallucinogens + *Spice*). These results are in line with the scientific literature, indicating a positive association between alcohol and tobacco as the most commonly consumed substances, combined with other drugs such as cannabis (Barret, Darredeau, & Pihl, 2006; McCabe, Cranford, Morales, & Young, 2006; O'Reilly & Jessen, 2005; Riquelme et al., 2012). Similarly, the polydrug use of tobacco and cannabis is also recognized as relevant (Burns, Ivers, Lindorff, & Clough, 2000; Calafat et al., 2000) given its use as one of the most frequent combinations among adolescents and young adults (Barrett et al., 2006; Ramo et al., 2012). Furthermore, Pattern A, is more common among women, and Pattern C among men, while Pattern B does not exhibit any differences by sex. A plausible explanation for these differences might be found by studying the data in OEDT (2011). Here, the type of consumption of certain substances among women in recent years, for example binge drinking and daily smoking, has undergone an increase to match consumption among men. With regard to men, the use of all drugs is more widespread than among women, especially illegal ones.

The present study suffers from some limitations. Given the transversal nature of the study, the direction of the links found cannot be investigated. A longitudinal study observing changes over time would be required to complete this research. A further limitation is related to the

way in which the consumption behaviour of people in the subject's closest circle is assessed. The measurement of this behaviour is based on the young participants' own perceptions. Similarly, given that the consumption of drugs may or may not be generally accepted by society, the answers given by the participants in the self-report could be inflated or deflated by a social desirability bias. Nevertheless, although confidentiality of responses was guaranteed in an effort to minimize this bias, it would be advisable to use other instruments alongside self-reports, such as peer evaluation scales. Future studies should analyze whether the same risk factors associated with the consumption of a single substance like tobacco, alcohol or cannabis could also be related to polydrug use of these substances. Finally, over recent years types of family structure have been changing from the traditional (with biological parents) or extended (living together with other relatives) to monoparental, or ones reconstituted by a new spouse and even those with same-sex parents (Becoña et al., 2012). Given the importance of such changes, it is recommended that future studies address the relationship between new types of family and polydrug use.

Despite these limitations, results suggest that multiple consumption of drugs in the young people's immediate environment is emerging as a key element to be taken into account in future drug prevention campaigns.

Acknowledgements

This study has been made possible thanks to the support provided by the Escola Universitària de la Salut i l'Esport (EUSES) in cooperation with the Universidad de Girona (UdG), 2014.

Conflict of interests

The authors declare no conflict of interests.

Referencias

Bandura, A. (1987). *Pensamiento y acción: Fundamentos sociales.* Barcelona: Martínez Roca (Original work published in 1986).

Bandura, A. & Walters, R.H. (1979). *Aprendizaje social y desarrollo de la personalidad.* Madrid: Alianza Universidad (Original work published in 1959).

Barrett, S. P., Darredeau, C., & Pihl, R. O. (2006). Patterns of simultaneous polysubstance use in drug using university students. *Human Psychopharmacology: Clinical and Experimental, 21*, 255-263. doi: 10.1002/hup.766.

Becoña, E., Fernández, E., Calafat, A., & Fernández-Hermida, J. R. (2014). Apego y consumo de sustancias en la adolescencia: Una revisión de aspectos conceptuales y metodológicos. *Adicciones, 26*, 77-86.

Becoña, E., Martínez, U., Calafat, A., Juan, M., Duch, M., & Fernández-Hermida, J. R. (2012). ¿Cómo influye la desorganización familiar en el consumo de drogas de los hijos? Una revisión. *Adicciones, 24*, 253-268.

Burns, C. B., Ivers, R. G., Lindorff, K. J., & Clough, A. R. (2000). Cannabis: A Trojan horse for nicotine? Australian and New Zealand. *Journal of Public Health, 24*, 637-637. doi: 10.1111/j.1467-842X.2000.tb00533.x.

Buu, A., Dipiazza, C.,Wang, J., Puttler, L. I., Fitzgerald, H. E., & Zucker, R. A. (2009). Parent, family, and neighborhood effects on the development of child substance use and other psychopathology from preschool to the start of adulthood. *Journal of Studies on Alcohol and Drugs, 70*, 489-498.

Calafat, A., Fernández, C., Becoña, E., Gil, E., Juan, M., & Torres, M. A., (2000). Consumo y consumidores de cannabis en la vida recreativa. *Adicciones, 12*, 197-230.

Connell, C. M., Gilreath, T. D., Aklin, W. M.,, & Brex, R. A. (2010). Social-ecological influences on patterns of substance use among non-metropolitan high school students. *American Journal of Community Psychology, 45*, 36-48. doi: 10.1007/s10464-009-9289-x.

Connor, J. P., Gullo, M. J., White, A., & Kelly, A. B. (2014). Polysubstance use: diagnostic challenges, patterns of use and health. *Current Opinion in Psychiatry, 27*, 269-275. doi: 10.1097/YCO.0000000000000069.

European Monitoring Centre for Drugs and Drug Addiction (2009a). *Polydrug use: Patterns and responses.* Luxembourg: Publications Office of the European Union. doi: 10.2810/26783.

European Monitoring Centre for Drugs and Drug Addiction (2009b). *Understanding the 'Spice' phenomenon.* Luxembourg: Office for Official Publications of the European Communities. doi: 10.2810/27063.

European Monitoring Centre for Drugs and Drug Addiction (2011). *Informe Anual 2011. El problema de la Drogodependencia en Europa.* Luxembourg: Office for Official Publications of the European Communities. doi:10.2810/4450.

European Monitoring Centre for Drugs and Drug Addiction (2014). *Informe Europeo sobre Drogas: Tendencias y Novedades.* Luxembuorg: Office for Official Publications of the European Communities. doi: 10.2810/32415.

Ferrer, X. & Ayneto, X. (1991). *Nuevos métodos en la formación de padres para la prevención del abuso de drogas.* Communication presented at the XIX Jornadas Nacionales de Socidrogalcohol, Santa Cruz de Tenerife.

Fernández-Calderón, F., Lozano-Rojas, O. M., & Rojas-Tejada, A. J. (2013). Raves y consumo de drogas desde una perspectiva epidemiológica y psicosocial: una revisión bibliográfica sistemática. *Adicciones, 25*, 269-279.

Font-Mayolas, S., Gras, M. E., Cebrián, N., Salamó, A., Planes, M., & Sullman, M. J. (2013). Types of polydrug use among Spanish adolescents. *Addictive Behaviors, 38*, 1605-1609. doi: 10.1016/j.addbeh.2012.09.007.

Font-Mayolas, S., Gras, M. E., & Planes, M. (2006). Análisis del patrón de consumo de cannabis en estudiantes universitarios. *Adicciones, 18*, 337-344.

Font-Mayolas, S. & Planes, M. (2000). Efectos del modelado por parte de la familia, pareja y amigos en la conducta de fumar de jóvenes universitarios. *Adicciones*, *12*, 467-477.

Gómez, A., Herde, J., Laffee, A., Lobo, S., & Martín, E. (2007). Consumo de drogas lícitas e ilícitas por estudiantes universitarios. Facultad de Ingeniería. Universidad de Carabobo, 2006. *Salus*, *11*, 41-45.

Halley, T. J., Forster, M., Wood, D., Baezconde-Garbanati, L., & Beth J. (2014). Problematic substance use among hispanic adolescents and young adults: implications for prevention efforts. *Substance Use and Misuse, 49*, 1025-1038. doi:10.3109/10826084.2013.852585.

Hawkins, J. D., Catalano, R. F., & Miller, J. Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance-abuse prevention. *Psychological Bulletin, 112*, 64-105. doi: 10.1037//0033-2909.112.1.64.

Herrera, A., Simich, L., Strike, C., Brands, B., Giesbrecht, N., & Khenti, A. (2012). Policonsumo simultáneo de drogas en estudiantes de pregrado del área de la salud en una universidad, León-Nicaragua. *Texto y Contexto Enfermagem, 21*, 79-86. doi: 10.1590/S0104-07072012000500011.

Hughes, K., Bellis, M. A., Whelan, G., Calafat, A., Juan, M., & Blay, N. (2009). Alcohol, drogas, sexo y violencia: riesgos y consecuencias para la salud entre los jóvenes turistas británicos en las Islas Baleares. *Adicciones, 21*, 265-278.

Lores, A. P., Murcia, J. A. M., Gutiérrez, M., & Sicilia, A. (2003). La práctica físico-deportiva en la Universidad. *Revista de Psicologia del Deporte, 12*, 39-54.

Mariño, N., Castro, J., & Torrado, J. (2012). Funcionamiento ejecutivo en policonsumidores de sustancias psicoactivas. *Revista de Psicología Universidad de Antioquia, 4*, 49-63.

Martín-Montañez, E., Barón-López, F. J., Rubio, L. O., Pavía, J., Miranda, J., & Santos, I. M. (2011). Consumo de alcohol, tabaco, cannabis y otras sustancias psicoactivas en estudiantes de la Universidad de Málaga. *Trastornos Adictivos*, *13*, 160-166. doi: 10.1016/S1575-0973(11)70032-0.

Martínez, I., Fuentes, M., García, F., & Madrid, I. (2013). El estilo de socialización familiar como factor de prevención o riesgo para el consumo de sustancias y otros problemas de conducta en los adolescentes españoles. *Adicciones*, *25*, 235-242.

Mason, W. A., Kosterman, R., Haggerty, K. P., Hawkins, J. D., Redmond, C., Spoth, R. L., & Shin, C. (2009). Gender moderation and social developmental mediation of the effect of a family-focused substance use preventive intervention on young adult alcohol abuse. *Addictive Behaviors, 34*, 599-605. doi: 10.1016/j.addbeh.2009.03.032.

McCabe, S. E., Cranford, J. A, Morales, M., & Young, A. (2006). Simultaneous and concurrent poly-drug use of alcohol and prescription drugs: prevalence, correlates, and consequences. *Journal of Studies on Alcohol, 67*, 529-537.

Mustata, C., Torrens, M., Pardo, R., Pérez, C., The Psychonaut Web Mapping Group, & Farré, M. (2009). Spice drugs: los cannabinoides como nuevas drogas de diseño. *Adicciones*, *21*, 181-186.

Observatorio Español de la Droga y las Toxicomanías (2011). *Informe 2011. Situación y tendencias de los problemas de drogas en España.* Madrid: Ministerio de Sanidad, Política Social e Igualdad. Retrieved at: http://www.pnsd.msc.es/Categoria2/observa/pdf/oed2011.pdf.

Oliveira, E. B. & Furegato, A. R. F. (2008). El trabajo del estudiante de enfermería como un factor de riesgo para el consumo de alcohol y otras drogas. *Revista Latinoamericana Enfermagem, 16*, 565-571.

O'Reilly, B. & Jessen, J. (2005). Cannabis and other drug use by tertiary students in Darwin, Northern Territory, Australia. South Pacific. *Journal of Psychology*, *16*, 18-29.

Patiño-Masó, J., Gras-Pérez, E., Font-Mayolas, S., & Baltasar-Bagué, A. (2013). Consumo de cocaína y policonsumo de sustancias psicoactivas en jóvenes universitarios. *Enfermería Clínica*, *23*, 62-67. doi: 10.1016/j.enfcli.2013.02.003.

Prieto, R., Simich, L., Strike, C., Brands, B., Giesbrecht, N., & Khenti, A. (2012). Diversity and complexity in the phenomenon of drugs: simultaneous polydrug use in university students in one university, Cundinamarca-Colombia. *Texto y Contexto-Enfermagem*, *21*, 49-55. doi: 10.1590/S0104-07072012000500006.

Ramo, D. E., Liu, H., & Prochaska, J. J. (2012). Tobacco and marijuana use among adolescents and young adults: A systematic review of their co-use. *Clinical Psychology Review, 32*, 105-121. doi: 10.1016/j.cpr.2011.12.002.

Riquelme, G., Simich, L., Strike, C., Brands, B., Girsbrecht, N., & Khenti, A. (2012). Características del policonsumo simultáneo de drogas en estudiantes de pregrado de carreras de ciencias de la salud de una universidad, Santiago-Chile. *Texto y Contexto Enfermagem, 21*, 34-40. doi: 10.1590/S0104-07072012000500004.

Stogner, J. M. & Miller, B. L. (2014). A spicy kind of high: a profile of synthetic cannabinoid users. *Journal of Substance Use, 19*, 199-205. doi:10.3109/14659891.2013.770571.

Stone, A. L., Becker, L. G., Huber, A. M., & Catalano, R. F. (2012). Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addictive Behaviors, 37*, 747-775. doi: 10.1016/j.addbeh.2012.02.014.

Substance Abuse and Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health: National findings.* Rockville, MD: Office of Applied Studies, NSDUH.

Tirado, R., Aguaded, J. I., & Marin, I. (2009). Factores de protección y de riesgo del consumo de alcohol en alumnos de la universidad de Huelva. *Salud y Drogas, 9*, 165-183.

Trenz, R. C., Scherer, M., Harrell, P., Zur, J., Sinha, A., & Latimer, W. (2012). Early onset of drug and polysubstance use as predictors of injection drug use among adult drug users. *Addictive Behaviors, 37*, 367-372. doi: 10.1016/j.addbeh.2011.11.011.

Urrego, D. Z. (2002). Consumo de sustancias psicoactivas en estudiantes de especialidades médicas, Bogotá 2001. *Revista de Salud Pública, 4*, 59-73.

Varela, M., Salazar, I., Cáceres, D., & Tovar, J. (2007). Consumo de sustancias psicoactivas ilegales en jóvenes: factores psicosociales asociados. *Pensamiento Psicológico, 3*, 31-45.

Vázquez, F. & Becoña, E. (2000). Factores de riesgo y escalada cannabinoide. *Adicciones, 12 (Supl. 2)*, 175-184.

Veloza, M., Simich, L., Strike, C., Brands, B., Giesbrecht, N., & Khenti, A. (2012). Medio social y uso simultáneo de alcohol y tabaco en estudiantes universitarios de pregrado de carreras de ciencias de la salud de una universidad, Cundinamarca-Colombia. *Texto y Contexto Enfermagem, 21*, 41-48. doi:10.1590/S0104-07072012000500005.

Viña, C. & Herrero, M. (2004). El consumo de sustancias psicoactivas en estudiantes de Psicología de la Universidad de la Laguna. *International Journal of Clinical and Health Psychology, 4*, 521-536.

Whitehorne-Smith, P., Simich, L., Strike, C., Brands, B., Giesbrecht, N., & Khenti, A. (2012). Gender differences in simultaneous polydrug use among undergraduate students of one university, Kingston-Jamaica. *Texto y Contexto Enfermagem, 21*, 74-78. doi: 10.1590/S0104-07072012000500010.

Wish, E. D., Fitzelle, D. B., O'Grady, K. E., Hsu, M. H., & Arria, A. M. (2006). Evidence for significant polydrug use among ecstasy-using college students. *Journal of American College Health, 55*, 99-104. doi:10.3200/JACH.55.2.99-104

Opioid Receptor Antagonists in the Treatment of Alcoholism

Los Antagonistas de los Receptores Opioides en el Tratamiento del Alcoholismo

Josep Guardia Serecigni

Senior Consultant in Psychiatry. Addictive Behaviours Unit. Psychiatry Department.
Hospital de la Santa Creu i Sant Pau de Barcelona

Abstract

Objectives: On the basis of the recent advances in drug therapy of alcoholism, we conducted a review on opioid receptor antagonist drugs with approved indication for the treatment of alcoholism, such as naltrexone and nalmefene. *Methods:* We reviewed over 100 publications on peptides and opioid receptors, as well as studies conducted in experimental animals and in humans on the effect of opioid receptor antagonists on alcohol consumption in the treatment of alcoholism. We also reviewed the pharmacological characteristics of naltrexone and nalmefene, and the usefulness of these drugs in clinical practice. *Results:* Much evidence has demonstrated the efficacy of naltrexone and nalmefene for the reduction of alcohol consumption, in experimental animals as well as in humans examined under experimental bar conditions; however, due to its different receptor profile, nalmefene has been associated with higher efficacy levels in reducing alcohol consumption in alcohol-dependent rats. In addition, a great number of controlled clinical trials have demonstrated the efficacy of naltrexone for relapse prevention in patients with an alcohol dependence disorder. Recent controlled clinical trials have demonstrated the efficacy of nalmefene "as-needed" in the reduction of alcohol consumption in subjects with mild alcohol dependence. *Conclusions:* Both naltrexone and nalmefene have proved to be safe, well tolerated, easy to manage, and efficient drugs for the treatment of alcohol dependence disorder (currently known as alcohol use disorder). On the basis of recent controlled clinical trials, nalmefene has been shown to result in a significant reduction of alcohol consumption, thereby representing a new objective that extends the therapeutic possibilities for those patients who do not wish for a continuous abstinence, but rather a reduction of alcohol consumption.

Key words: Nalmefene, naltrexone, opioid receptor antagonist drugs, alcoholism treatment, reduction of alcohol consumption.

Resumen

Objetivos: A partir de los recientes progresos en la farmacoterapia del alcoholismo, hemos efectuado una revisión sobre los fármacos antagonistas de los receptores opioides, que tienen aprobada la indicación para el tratamiento del alcoholismo, como son naltrexona y nalmefeno. *Metodología:* Hemos revisado más de 100 publicaciones sobre péptidos y receptores opioides, el efecto de los fármacos antagonistas de los receptores opioides sobre el consumo de alcohol, tanto en animales como en humanos, tanto en el laboratorio como para el tratamiento del alcoholismo. También se describen las características farmacológicas de naltrexona y de nalmefeno y su utilidad en la práctica clínica. *Resultados:* Múltiples evidencias han demostrado la eficacia de naltrexona y nalmefeno para reducir el consumo de alcohol, tanto en animales de laboratorio como también en personas estudiadas en situación de bar experimental, aunque debido al diferente perfil receptorial, nalmefeno ha sido relacionado con una mayor eficacia para la reducción del consumo de alcohol, en ratas que presentan dependencia del alcohol. Además, un gran número de ensayos clínicos controlados han demostrado la eficacia de naltrexona para la prevención de recaídas, en personas que presentan un trastorno por dependencia del alcohol. Ensayos clínicos controlados recientes han demostrado la eficacia de nalmefeno "a demanda" para reducir el consumo de alcohol, en personas que presentan un trastorno por dependencia del alcohol de baja gravedad. *Conclusiones:* Tanto naltrexona como nalmefeno han demostrado ser fármacos seguros, bien tolerados, de manejo sencillo, y eficaces para el tratamiento del trastorno por dependencia del alcohol, (actualmente llamado trastorno por consumo de alcohol). A partir de recientes ensayos clínicos controlados se ha comprobado que nalmefeno produce una reducción significativa del consumo de alcohol, lo cual supone un nuevo objetivo que amplía las posibilidades de tratamiento para los pacientes que no desean la abstención continuada, sino una reducción de su consumo de alcohol.

Palabras clave: Nalmefeno, naltrexona, antagonistas de los receptores opioides, tratamiento del alcoholismo, reducción del consumo de alcohol.

Received: October 2014; Accepted: April 2015

Send correspondence to:
Dr. Josep Guardia Serecigni. Senior Psychiatric Consultant in Psychiatry. Addictive Behaviours Unit.
Psychiatry Department. Hospital de la Santa Creu i Sant Pau de Barcelona. E-mail: jguardia@santpau.cat

Alcoholism. currently known as alcohol use disorder, is the most common mental disorder among men and one with more scientific research behind it than most, both in the laboratory with animals and, in terms of diagnosis and treatment, in clinical practice (Guardia Serecigni, Jiménez-Arriero, Pascual Pastor, Flórez Menéndez, & Contel Guillamón, 2008).

Alcoholism is an addictive illness, probably associated with a malfunctioning of certain brain circuits that play a role in behavioral self-control when consuming alcoholic drinks. It is characterized by incentive-motivational aspects of alcohol consumption and their conditioned stimuli, but also by a deterioration in the capacity to inhibit inappropriate responses in the search for and consumption of alcohol (Kalivas & Volkow, 2005). If the course of the illness is not stopped, its medical, psychiatric, addictive, work and social consequences may progressively worsen, contributing to increased risk of relapse and also to making the illness more chronic and perpetuating it (Guardia, Surkov, & Cardús, 2011).

The main symptom of alcoholism is the difficulty in controlling alcohol consumption. This is linked to the impaired functioning of various neurotransmitter systems, among which the glutamatergic, GABAergic, dopaminergic and opioid systems stand out. Preclinical research studies have provided a great deal of scientific evidence, which has later been confirmed in clinical practice and have been extremely useful in the development and pharmacological treatment of alcoholism (Guardia Serecigni, 2015).

The majority of pharmaceutical drugs which have been studied for the treatment of alcoholism did not reach clinical practice, given that the clinical tests carried out did not show them to be more efficacious than the placebo. Drugs which have not displayed clear efficacy against alcoholism include dopaminergic agonists and antagonists, glutamatergicc antagonists and $GABA_A$ agonists (Guardia Serecigni et al., 2008; Pascual, Guardia, Pereiro, & Bobes, 2013). The majority, though not all, of the clinical trials carried out in Europe of acamprosate demonstrated its efficacy against relapse, but the most recent tests in the USA were not able to confirm that this drug was better than the placebo (Anton, O'Malley, Ciraulo, Cisler, Couper et al., 2006). Furthermore, the daily dosage of 6 tablets makes compliance very difficult for alcoholic patients, and without good compliance a drug is unlikely to be efficacious. As regards topiramate, only two controlled clinical trials, directed by the same researcher, have provided results better than placebo (Johnson, Ait-Daoud, Bowden, Di Clemente, Roache et al., 2003; Johnson, Rosenthal, Capece, Wiegand, Mao et. al., 2007). What is more, no health authority has approved its use in the treatment of alcoholism.

Among the drugs whose efficacy has been demonstrated, and which have been approved for the treatment of alcohol abuse, the opioid receptor antagonist drugs naltrexone and nalmefene stand out. They have a complex scientific background, having been researched in heavy drinking animals (mice, rats, monkeys) as well as people in experimental bar type laboratory settings and through clinical trials on the treatment of alcoholism (Guardia Serecigni, 2015).

The action of opioid antagonists on alcohol consumption has played a decisive role in both the neurobiological understanding of alcohol addiction and in the pharmacological treatment of the disorder. Some laboratory studies, carried out in experimental bars, have helped us to understand how naltrexone and nalmefene work to reduce alcohol consumption in a drinking session. And many controlled clinical trials on alcohol abuse treatment have assessed its efficacy and tolerability. In the initial studies in the 1990s, the medication was administered daily with the aim of furthering continuous abstention, while in the most recent trials the focus has rather been on a reduction of alcohol consumption and the dosage regimen has changed to "as needed use", limited to the days or occasions in which the person decides to drink alcoholic beverages (Guardia Serecigni, 2015).

Many people who have had problems as a consequence of excessive alcohol consumption decide to stop drinking, even without the help of treatment, when these problems start to overwhelm them. Such people can go without a drink for several weeks and can remain in remission even for months or years if they take a specialized course of treatment. However, the day when they decide to have an alcoholic drink it is likely that they will have serious difficulties to control alcohol consumption and will again take to drinking excessively, and that this will be accompanied by a rapid reappearance of the negative consequences associated with this behavior. This typical relapse sequence usually happens one or more times during the recovery process of alcohol abuse patients. Nevertheless, it always comes as a surprise and a disappointment to close relatives, and can be devastating for the patient (Guardia Serecigni, 2011).

There are various treatments which help the patient to "stop drinking" and "stay dry" for a period, but it is likely that sooner or later the patient will try an alcoholic drink, and from this moment on their lack of control regarding alcoholic drinks will return. This is the so called deprivation effect, proven in both animals and alcohol dependent humans. This effect can be blocked by opioid receptor antagonist drugs (Sinclair, 1990; Sinclair, 2001).

Previously, the only accepted goal of treatment was complete and continued abstinence from alcoholic drinks. However, when the patient starts treatment, he/she generally does not have the clear intention to stop drinking entirely. Rather, it is common that patients try to stop drinking habitually but leave themselves the option of the odd

drink on a particular day or occasion that they clearly associate with alcohol. This is where a common misunderstanding between doctor and patient arises. The doctor believes that the patient is determined to stop drinking completely, because that is what he/she has said. But the patient, not knowing the real nature of the addictive illness he/she is dealing with, believes that a small amount of alcohol on a special day would not interfere with his/her recovery. The problem is that when the patient tries a small alcoholic drink, the loss of control returns and this can lead back to drinking excessively and the negative consequences associated with it (Guardia Serecigni, 2011).

In other words, the real treatment goal that alcoholic patients set themselves in the initial recovery phase does not coincide with the expectation of complete and continued abstinence held by their doctors, but rather with the new objective of a REDUCTION of alcohol consumption, which does allow for the occasional low-risk drink.

Neurobiology of alcoholism

Acute administration of alcohol facilitates the inhibitory activity of GABA, which together with a reduction in the excitatory activity of glutamate, calcium channels and noradrenaline, generate a slowing down of the central nervous system (CNS) which, in extreme cases of (alcoholic) intoxication can lead to coma and death from cardio-respiratory failure.

Meanwhile, chronic administration of alcohol results in compensatory neuroadaptive changes that generate a state of hyperexcitability in the CNS, which can manifest clinically in withdrawal symptoms and which is due to glutamatergic, noradrenergic and calcium channel hyperfunction as well as GABAergic hypofunction.

In the midbrain ventral tegmental area (VTA), the dopaminergic neurons are under tonic inhibitory control by GABA neurons, which in turn can be activated by the glutamatergic neurons or inhibited by opioidergic neurotransmission. The functioning of these neurotransmission systems, which come together at the VTA intersection, can play a fundamental role in relapse.

When alcoholic patients stop drinking, their dopaminergic neurotransmission is usually at low levels (a transitory state of hypodopaminergia). An alcoholic drink in this state will trigger a rush of dopamine in the mesolimbic regions (due to the acute effect of alcohol on the glutamatergic, opioidergic and GABAergic neurotransmission), which can set off states of craving and search for, and consumption of alcohol (Clapp, Bhave, & Hoffman, 2008).

The opioid system and alcohol consumption

The endogenous opioid system is involved in a variety of physiological processes such as analgesia, stress, reward or adaptive homeostatic functions (temperature control, water and food intake). Acute administration of alcohol triggers the release of opioid peptides, which induce positive reinforcing effects and favor the acquisition of self-administrative behavior relating to alcohol.

Both opiate abstinence and opiate administration influence alcohol consumption. High and moderate doses of morphine reduce the preference for alcohol in inverse proportion to the dose taken on the day of injection, On the following day, however, the consumption of alcohol increases (Volpicelli, Ulm, & Hopson, 1991). A small dose of an opioid agonist (like morphine) can act as a primer and induce increased alcohol consumption (Reid & Hunter, 1984). People who have developed heroin dependence tend to drink more alcohol when suffering (heroin) withdrawal; high-dose methadone maintenance, meanwhile, can help them to reduce alcohol consumption (Siegel, 1986).

Ingesting alcohol can also trigger the activation of the opioid system, linked both to the positive reinforcement effect and to loss of control (Reid, 1990). This therefore produces an inverse relationship between the administration of opioid agonists and alcohol consumption, so that even small doses of opiates as well as opiate abstinence prompt an increase in the consumption of alcohol, while high doses of opiates reduce it. This suggests that alcohol and opiates have similar pharmacological effects and that alcohol consumption may be modified by manipulating the endogenous opioid system.

The reinforcing properties of alcohol are modulated (at least in part) by the cerebral opioid receptors. The initial hypotheses were focused on condensation products like acetaldehyde and dopamine, which could induce an increase in ethanol consumption by the direct stimulation of cerebral opioid receptors such as the tetrahydroisoquinolines (Davis & Walsh, 1970), salsolinol (Collins & Bigdeli, 1975) and tetrahydropapaveroline (Greenwald, Fertel, Wong, Schwartz, & Bianchine, 1979). But these hypotheses have been questioned since alkaloids, induced by alcohol consumption, were detected in such small quantities to make it unlikely that they are physiologically active.

The opioid system is of great complexity due to the possible connections between the different peptide agonists, specific opioid receptors and their location in different cerebral areas. Endorphinergic neurons originating in the arcuate hypothalamic nucleus move towards other hypothalamic nuclei of the septum and the accumbens nucleus (important centers mediating the positive reinforcement and reward effects of many addictive drugs) and towards periaqueductal grey matter, amygdala and hypothalamus (Wise & Bozarth, 1982). The proenkephalinergic neurons are widely distributed in the brain, with a greater accumulation in the striatum, periaqueductal grey matter, hypothalamus, periventricular grey matter, hippocampus and raphe nucleus. And the prodynorphinergic neurons are found in the hypothalamus, periventricular nucleus, ce-

rebral cortex, amígdala, hipocampus, periaqueductal grey matter, solitary tract nucleus, spinal medulla, suprarenal and intestinal medulla.

The encephalines (Met- and Leu-encephaline) will link with the delta opioid receptor with an affinity 25 times greater than with the mu opioid receptor. The beta-endorphine recognizes the mu and delta connection points, although a preference for the mu receptor has been described. And the dynorphins interact selectively with the kappa opioid receptor (Gianoulakis, 1993).

In the VTA, opioids would act on the mu receptors, modulating rewarded behaviors. Its activation would result in hyperpolarization of the GABA interneuron, disinhibition of the dopaminergic neuron and increase of the dopamine release in the nucleus accumbens (Johnson & North, 1992), which could favor self-administration and may be related to the craving for alcohol and loss of control.

In the anterior limbic region, the opioids would activate the delta receptors, also triggering an increase in dopamine release in the accumbens nucleus which could be related to the maintenance of self-administration behavior, craving and relapse in people with alcohol dependence (Van Ree, 1987).

In strains of rats selected for their high consumption of ethanol, it has been suggested that this predisposition may be linked to the opioid system since delta opioid antagonists can reduce alcohol consumption (Altshuler, Phillips, & Feinhandler, 1980; Froehlich, Harts, Lumeng, & Li, 1990; Reid, 1990).

Low basal levels of beta-endorphin have been detected in people with risk of alcoholism (having a family record of alcoholism in the three previous generations), compared with people who did not have a family history of alcoholism. Furthermore, the consumption of 0.5 gr/kg of ethanol led to a temporary increase of the plasmatic beta-endorphin in the high risk group (Gianoulakis, Kirshnan, & Thavundayil, 1996). Similarly, alcoholic patients would also exhibit low levels of beta-endorphin after having stopped drinking which would return to normal after 6 months of continued abstention from alcohol (Gennazani, Nappi, Eacchinetti, Mezzella, & Parrini, 1982).

Acute administration of alcohol produces a release of endogenous opioids, especially beta-endorphin, which induces an increase in the release of dopamine in the accumbens nucleus (mediated by the inhibitory action of beta-endorphin on the GABA neurons of the VTA). This increase in dopamine availability may be linked to its positive reinforcing effect, craving and loss of control which can lead to relapse. Therefore, certain pharmaceutical drugs which can act on these neurotransmission systems may modulate the such changes and reduce the risk of relapse (Guardia et al., 2011).

Both mu receptors and delta opioids play a role in reducing alcohol consumption, produced by the antagonists in the opioid receptors. Delta opioids could act in the terminal areas, facilitating dopaminergic transmission; while the mu receptors could indirectly modulate the activity of the dopaminergic neurons, depressing the inhibitory tone applied by the GABA neurons on the dopaminergic neurons in the VTA (Johnson et al., 1992).

On the other hand, a patient with alcohol dependence may exhibit rebound or withdrawal symptoms after not drinking alcohol for several hours, after which a drink or consumption of benzodiazepines may produce a strong negative reinforcing effect since both can rapidly and efficiently neutralize alcohol withdrawal symptoms. Therefore, alcohol can have a double reinforcing effect: a positive one related to the release of endorphins (which will produce disinhibition of mesolimbic dopaminergic neurons) and a negative one linked to its ability to alleviate withdrawal, as well as certain psychiatric symptoms such as anxiety, difficulty falling asleep, phobias, posttraumatic stress or others (Guardia, Surkov, & Cardús, 2010).

The adaptation of kappa receptors to chronic consumption of alcohol

The consumption of alcohol, as with other drugs, triggers dopamine release in the accumbens nucleus, and this forms the neurological background of its reinforcing effect.

The stimulation of mu receptors (possibly caused by the release of beta-endorphin, induced by ethanol) in the VTA (origin of the A10 dopaminergic neurons) produces an increase in dopamine release; meanwhile, the selective blocking of the mu receptor results in a reduction of dopamine release. This is matched by stimulation of kappa receptors, in the interior of the nucleus accumbens, which causes lower dopamine release, while selective blocking triggers a marked rise in dopamine release (Spanagel, Herz, & Shippenbeerg, 1992).

In stressful situations, dynorphine increases in the central nucleus of the amygdala which also co-expresses CRF (corticotropin release factor), and this implies a close relationship between kappa opioid systems and CRF. In addition, dynorphinergic neurons move towards the noradrenergic neurons of the locus coeruleus, a region associated with arousal, attention and the response to stress. Kappa agonists can stimulate the hypothalamic-pituitary-adrenal axis and play a role in the analgesia induced by stress.

In states of drug dependence, inhibition of the kappa receptor can attenuate the compulsive intake of drugs and alcohol, while its activation can induce the restoration of drug or alcohol seeking behavior, generating stress-like symptoms.

The activation of kappa receptors weakens the release of dopamine induced by alcohol consumption and therefore its reinforcing effect, while the intracerebral administration of a kappa receptor antagonist, nor-binaltorphimine,

triggers a reduction of the operant response to ethanol, but only in animals with alcohol dependence. Therefore it appears that chronic consumption of alcohol would produce an increase in the activity of the kappa opioid system, which would be associated with a greater reinforcing effect of alcohol after withdrawal, and this in turn suggests that the drugs which modulate the kappa opioid system may be efficacious in the treatment of alcohol dependence (Shippenberg, Zapata, & Chefer, 2007).

Nalmefene is more efficacious than naltrexone for reducing alcohol consumption in rats with alcohol dependence. Both drugs would have a similar effect on mu receptors, but nalmefene would also have a modulating effect on the kappa opioid receptors and would produce a greater reduction in alcohol consumption than naltrexone in alcohol dependent rats (Keating, 2013; Nealey, Smith, Davis, & Walker, 2011; Walker & Koob, 2008).

Both the activation as well as the hyperfunction of kappa opioid receptors result in a reduction in the release of dopamine, in both the limbic system and the prefrontal cortex, generating a state of hypodopaminergia and hyperglutamatergia which runs parallel to a negative emotional state during abstention from alcohol and contributes to a greater negative reinforcing effect of a new alcoholic drink. This hypodopaminergia in the prefrontal cortex may furthermore contribute to more impulsive decision making, less cognitive control of addictive behavior and a certain impairment of the executive functions. The kappa receptor antagonists reduce the self-administration of alcohol in rats which have developed alcohol dependence and exhibit hyperfunction of the dynorphin/kappa system (Sirohi, Bakalkin, & Walker, 2012).

The alcohol deprivation effect

After a two-day period of deprivation, monkeys which self-administer alcohol increase their consumption. The longer the deprivation period, the greater the increase in alcohol consumption. Kornet, Goosen and Van Ree (1990) called this the "catch up" or "making up for lost time" phenomenon. It can be reverted by administering naltrexone (Kornet, Goosen, & Van Ree, 1991).

It is a phenomenon similar to that exhibited by alcoholic patients who stop drinking for a period. On the day they try an alcoholic drink again, they have greater problems than before to control consumption, and this effect can be neutralized by previously taking naltrexone or nalmefene (O'Brien, Volpicelli, & Volpicelli, 1996).

The neurological foundation of the deprivation effect is the powerful release of dopamine which takes place in the accumbens nucleus and other limbic structures in a brain which has adapted to alcohol, and which has a weakened dopaminergic tone (hypodopaminergia). Renewed alcohol consumption will produce a release of endogenous opioids, disinhibition of dopaminergic neurons and a significant increase in craving and loss of control regarding alcohol consumption (Clapp et al., 2008; Johnson et al., 1992). This is therefore not only a psychological effect, but also a neurobiological phenomenon which only takes place in people who are alcohol dependent and which can be attenuated or neutralized by opioid receptor antagonists.

Opioid Receptor Antagonists and Reduced Alcohol Consumption

The opioid system would act as a mediator of the reinforcing effects of alcohol which lead to drinking excessively. Naltrexone and nalmefene, which block the opioid receptors, would prevent an increase of in the activity of the opioid system after ingesting alcohol and this effect would be of decisive relevance for alcoholic patients who have a drink after a period of abstention. By reducing the reinforcing strength of alcohol in these circumstances, the risk of relapse into excessive alcohol consumption would be reduced (Guardia Serecigni, 2011).

Preclinical studies with animals

Studies with animals have shown that alcohol triggers an increase in beta-endorphin release in the pituitary (Seizinger, Holtz, & Herz, 1984), especially in rats who "prefer" alcohol in contrast to control rats (Froehlich, Zweifel, Harts, Lumeng, & Li, 1991). This preference, genetically determined and related to the the endorphinergic system, seems to be confirmed with respect to the sensitivity of the encephalinergic system to alcohol (Li, Li & Froehlic, 1992). In persons with a risk of alcoholism, consumption of alcohol can also trigger an increase in the β-endorphin in plasma (Gianoulakis et al., 1996).

The preference of Naltrexone for the mu receptor is elevated, medium for kappa and low for delta. The preferred ligands of the mu receptor are beta-endorphin and enkephalin, those of the delta receptor are the leu- and met-enkephalines, and dynorphins A and B are those preferred by kappa receptors. Therefore, although beta-endorphin is not a selective ligand, it has considerable affinity for the delta receptor (Terenius, 1996). Nalmefene has a greater modulation spectrum of the opioid receptors, being mu and delta receptor antagonist and partial agonist of kappa receptors (Keating, 2013; Nealey et al., 2011; Sirohi et al., 2012; Walker et al., 2008).

Laboratory trials with humans

In laboratory trials carried out in experimental bars with people exhibiting excessive alcohol consumption and who had not sought treatment for alcoholism, naltrexone achieved a reduction in the positive reinforcing effect of alcohol, the compulsion to drink, the number of units consumed, the speed of alcohol consumption and a possi-

ble increase in undesirable effects of alcohol intoxication, such as cephalea or nausea, compared to placebo (Davidson, Palfai, Bird, & Swift, 1999). In other words, people who took naltrexone noticed that alcoholic drinks did not have the same reinforcing effect on them (they said that it did not taste as good as before), that they drank more slowly (their drinks lasted longer), and the total number of drinks per session was lower. After several alcoholic beverages, they changed to non-alcoholic drinks and some said they felt more drunk than was normal for them, or had some unpleasant symptoms.

Both naltrexone (50 mg/day) and nalmefene (40 mg/day), managed to reduce the craving for more after the first alcoholic drink, the number of drinks consumed, the choice of an alcoholic drink when non-alcoholic alternatives were available, and the euphoria-inducing effect of alcohol (Drobes, Anton, Thomas, & Voronin, 2004).

Clinical trials on treatment of alcoholism

When alcoholic patients manage to reduce alcohol consumption, or to stop drinking for a period, they tend to recover rapidly from the consequences of alcohol, but the conditioned stimuli can again trigger a craving which leads to more alcohol consumption, after which the difficulties to control drinking and even the loss of control reappear, which can lead to relapse. Although some people manage to stop drinking without any help for long periods, others need specialized treatment to reduce their tendency to relapse (Work Group on Substance Use Disorders, 2007).

The neurobiological background of alcohol dependence are the persistent neuroadaptive changes induced by excessive and continued use of alcohol. Clinical manifestations are heightened tolerance, sensitization, craving, alcohol dependence and abstinence. Dependence is defined as the need to continue taking a substance to prevent withdrawal symptoms, but the traditional differentiation between physical and psychological dependence is artificial given that both are involved in the dysfunction of certain structures in the central nervous system (Guardia et al., 2010; Nestler, Hope, & Widnell, 1993).

Opioid receptor antagonists such as naltrexone and nalmefene reduce alcohol consumption in both animals (Froehlic & Li, 1993) and in social drinkers in an experimental bar situation (Davidson et al., 1999; Drobes et al., 2004), as well as in recovering alcoholic patients. This makes them very useful in the prevention of relapse (Anton et al., 2006; Guardia, Caso, Arias, Gual, Sanahuja et al., 2002; O'Malley, Jaffe, Chang, Scottenfeld, Meyer et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992).

Controlled clinical trials on the treatment of alcoholism have proven that opioid receptor antagonists trigger a reduction in the reinforcement or euphoria-inducing effects of alcohol consumption, a reduction in craving, improved control after a first drink or even a certain aversive effect on alcohol consumption (Swift, Whelihan, Kuznetson, Buongiorno, & Hsuing, 1994; Volpicelli, Watson, King, Sherman, & O'Brien, 1995).

The expected effect is, therefore, to improve the patient's self-control with regard to alcohol consumption and in the long term even eliminate the addictive conditioning, allowing the patient to progressively recover his/her freedom in decision-making and mitigating his/her obsession with drink (Guardia Serecigni, 2011).

The COMBINE study, carried out in USA (Anton et al., 2006), compares different modalities of pharmacological and psycho-social treatment of alcoholism, and concludes that one of the most useful indicators for evaluating the results of treatment is the number of heavy drinking days because this correlates well with the number of negative consequences that the patient suffers during the treatment as a consequence of excessive alcohol consumption (Falk, Wang, Liu, Fertig, Mattson et al., 2010). This correlation suggests that if patients manage to have fewer than 5 (men) or 4 (women) drinks per day, they would not suffer any, or just a few negative consequences, just like people who have stopped drinking. That is to say, the odd low-risk drink would have the same favorable results as complete and continued abstinence.

In other words, not drinking every day and remaining below heavy drinking limits at every sitting could be considered clinical remission since this behavior would not be associated with negative consequences. Therefore, treatment aimed at reducing alcohol consumption can be as satisfactory as continued abstinence, provided the patient does not exceed the limits of low-risk consumption at any sitting.

In the COMBINE study, naltrexone oral in 100mg/day doses for 16 weeks achieves a rise in the days of abstention (80.6% vs. 75.1%) and a reduction of the risk of excessive drinking (66.2% vs. 73.1%) compared to placebo. In addition, a criterion called "good clinical result" was used, defined by the authors as no more than 2 heavy drinking days per week, a maximum of 14 units per week for men (11 for women) and the absence of significant problems linked to alcohol during the last 8 weeks of the 16-week treatment (Anton et al., 2006; Anton, 2008).

Those patients who drank during the COMBINE study exhibited less serious symptoms and greater likelihood of achieving a personal target of controlled consumption. Furthermore, in various studies the therapeutic effect of naltrexone did not become statistically significant until the second month of treatment (Anton et al., 2006; Bouza, Magro, Muñoz, & Amate, 2004; Guardia et al., 2002), which suggests that its effect may be progressive and would not clearly manifest itself until the patient had a first alcoholic drink.

As with naltrexone, the first clinical trials with nalmefene were focused on achieving abstention from alcohol, but revealed some advantages over naltrexone such as, for example, not having a dose dependent risk of hepatic toxicity, higher bioavailability, and its opioid receptor antagonist effect being more competitive and lasting longer. Taken daily, nalmefene proved to be efficacious in preventing relapses into excessive alcohol consumption in the majority of studies (Karhuvaara, Simojoki, Virta, Rosberg, Loyttiniemi et al., 2007; Mason, Ritvo, Morgan, Salvato, Goldberg et al., 1994; Mason, Salvato, Williams, Ritvo, & Cutler, 1999), but not better than placebo in the study reported by Anton, Pettinati, Zweben, Kranzler, Johnson et al. (2004).

Following this, the study by Karhuvaara et al. (2007) led to a new procedure called targeted nalmefene, in which people with excessive alcohol consumption were instructed to take the drug when they felt that they were about to drink alcohol. With simple medical management this procedure achieved a significant reduction of excessive alcohol consumption in comparison with placebo. Another study of targeted nalmefene concluded that polymorphic variations in the genes of opioid receptors do not modify the response to treatment with nalmefene, in contrast to what happens in the treatment with naltrexone, where ASN40ASP polymorphism of the mu OPRM1 receptor affects the response to naltrexone treatment (Arias, Armeli, Glernter, Covault, Kallio et al., 2008)

The Pharmacology of Naltrexone and Nalmefene

Trials carried out with naltrexone have confirmed its **efficacy** in reducing alcohol consumption and relapse rate at the end of three months of treatment for alcoholism (Anton et al., 2006; Bouza et al., 2004; Pettinati, O'Brien, Rabinowitz, Wortman, Oslin et al., 2006; Srisurapanont & Jarusuraisin, 2005). Cochrane's meta-analyses have confirmed that naltrexone (50mg/day for 12 weeks) achieves a 36% reduction in the relapse rate and reduces the number of days of alcohol consumption, excessive drinking, total consumption of alcohol, craving, and also the levels of gamma-glutamyltransferase. Nevertheless, the effect size has been considered small to moderate (Kranzler, Modesto-Lowe, & Van Kirk, 2000; Rösner, Hackl-Herrweth, Leucht, Vecchi, Srisurapanant et al., 2010).

In some controlled trials, naltrexone has not proved to be better than placebo in terms of preventing relapse (Gueorguieva, Wu, Pittman, Cramer, Rosenheck et al., 2007; Krystal, Cramer, Krol, Kirk, & Rosenheck, 2001; Oslin, Lynch, Pettinati, Kampmann, Gariti et al., 2008;). However, a reanalysis of two negative studies suggests that naltrexone can reduce the risk of excessive consumption and raise the likelihood of abstention (Chick, Anton, Checinski, Croop, Drummond et al., 2000).

Adhering to the medication regimen can be decisive if the reduction in the relapse rate or craving are to reach statistical significance compared to placebo (Anton, 2008). It is therefore possible that the efficacy of naltrexone increases if administration is supervised by a relative or nurse, in which case the patient can also be intensively monitored and urine tests carried out periodically (Guardia Serecigni et al., 2008).

Extended-release injectable naltrexone is adminstered in 380mg doses every four weeks and produces a reduction in heavy drinking days of 25%, and in the alcohol consumed on the days the patient drinks again. The onset of the therapeutic effect may be very fast (from the second day onwards) and may be sustained throughout the treatment, which means that the patient's commitment to the treatment and specialized psychotherapeutic intervention may be more easily maintained (Ciraulo, Dong, Silverman, Gastfried, & Pettinati, 2008; Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati et al., 2005). A study carried out with 624 patients has shown that extended-release naltrexone did not have hepatotoxic effects, not even among patients who continued heavy drinking during the treatment, and achieved a reduction in GGT better than placebo in weeks 4, 8, 12 and 20 of the treatment (Lucey, Silverman, Illeperuma, & O'Brien, 2008).

Pharmacokinetics and Pharmacodynamics

Naltrexone is a cyclopropyl derivative of oxymorphone, structurally similar to naloxone and nalorphine. Taken orally, it is rapidly and almost completely (95%) absorbed. It reaches peak concentration after one hour and circulates 21% bound to plasma proteins. It has a half life of 3.9 hours (reaching 9.7 hours after chronic administration), its levels decline during the first 24 hours. It undergoes intense first-pass hepatic metabolism through the cytosol system, mediated by the 3 hydrodiol-dehydrogenase. Approximately 95% of the naltrexone absorbed is metabolized and converted in its principal active metabolite, 6-beta-naltrexol, a pure opioid antagonist with a longer half life than naltrexone (12.9 hours), which facilitates its longer lasting action. It is mainly eliminated by the kidneys. Equilibrium is quickly established and the drug does not accumulate.

It is believed that naltrexone acts as a competitive antagonist of the mu, delta and kappa opioid receptors, with a greater affinity for the mu receptor (Ortiz Camúñez, 1996). A 50 mg administration blocks the opioid receptors for 24 hours. Long-term studies (21 months) show that tolerance for naltrexone opioid antagonist properties does not appear to develop (González & Brogden, 1988).

Nalmefene has a partial agonist effect on the kappa opioid receptors, but with a kappa receptor system in up-regulation as a result of chronic drinking it acts as a functional antagonist (Keating, 2013; Kisler, Sirohhi, Reis, Jansen,

Quock et al., 2013). This receptor profile of nalmefene has been linked to its superior efficacy over naltrexone for reducing alcohol consumption in rats with alcohol dependence (Walker et al., 2008).

The recommended therapeutic dose is 50 mg per day for naltrexone and 18 mg/day for nalmefene. In the first few days of treatment it may be advisable to administer only 25 mg/day to reduce the possible adverse effects of naltrexone. However, in the COMBINE study, as well as some other studies carried out the USA, doses of 100 mg/day for 16 weeks of treatment were used (Anton et al., 2006; Anton, 2008).

Nalmefene has a methylene radical (C=CH2) substituted by a ketonic group (C=O) in position 6 with respect to naltrexone, and in comparison with naltrexone it has greater bioavailability (40-50%), a longer half life and greater affinity for delta and kappa opioid receptors.

Nalmefene is absorbed rapidly, reaches peak plasmatic concentration after 2-3 hours and does not modify the ECG QTc interval, nor the T-wave morphology. It does not, therefore, disrupt cardiac rhythm, nor require QTc monitoring in clinical practice (Matz, Graff, Vainio, Kaillio, Hojer et al., 2011). It has a half life of 13.4 hours and linear pharmacokinetics. After two hours, mu receptor occupation is 93%-100% and is kept at a high level for longer than 24 hours, at the same time as its plasmatic concentration diminishes progressively, which suggests a slow dissociation of the mu opioid receptor. Its prolonged occupation of mu opioid receptor after isolated or repeated administration makes it very suitable for non-daily administration (Ingman, Hagelberg, Aalato, Nagren, Juhakoski et al., 2005; Niciu & Arias, 2013).

It is held that nalmefene metabolites do not contribute significantly to its pharmacological effect. Nalmefene is extensively and rapidly metabolized by glucuronide conjugation and is eliminated by the kidneys. While naltrexone is metabolized oxidatively, nalmefene metabolizes primarily by glucuronide conjugation and does not display dose dependent hepatotoxicity, which improves its safety profile for patients with hepatic dysfunction (Salvato & Mason, 1994; Niciu & Arias, 2013).

The side effects of naltrexone may affect 30% percent of patients, with nausea and cephalea being the most frequent, followed by dizziness, vomiting, stomach pain or discomfort, anorexia, asthenia, agitation, insomnia or anxiety. These can appear in the initial days of treatment, are usually of low intensity and tend to disappear (Croop, Faulkner, & Labriola, 1997). Starting treatment with a lower dose (25 mg/day) and accompanied by a meal can minimize adverse effects and favor progressive adaptation of the organism. Over the following days, the dose is raised to the normal level of 50 mg/day.

Of the possible adverse effects of nalmefene, the most frequent are dizziness, nauseas and sleep disorder. Other less frequent symptoms are dry mouth, cephalea, tachycardia/palpitations, sweating, muscle spasms, anorexia, weight loss, asthenia. Most of them are light or moderate, appear at the beginning of the treatment and are short-lived. Exceptional cases of confusion, hallucination and dissociative symptoms have been reported. Most of the side effects tend to diminish without the need to modify treatment and do not reappear with new administration.

Nalmefene does not modify the ECG QTc interval, nor the T-wave morphology (Keating, 2013) and during treatment in the ESENSE trials no clinically relevant changes or differences between nalmefene and placebo took place with regard to vital signs, laboratory analysis, body weight, electrocardiographic registers and scores on the Profile Mood States scale which assesses possible emotional symptoms (Gual, He, Torup, van den Brink, & Mann, 2013; Keating, 2013; Mann, Bladstrom, Torup, Gual, & van den Brink, 2013).

Tolerability and Safety

At doses of 50 mg/day, naltrexone is a well-tolerated drug with few adverse effects, especially when the patient does not drink alcoholic beverages excessively. Alcoholic patients treated with naltrexone for 12 weeks tend to show an improvement in their hepatic enzymes. Possible side effects tend to diminish within 7 to 14 days and can be minimized by starting the treatment with 25 mg/day during the first week.

Instead of an increase, naltrexone triggers a decrease of certain hepatic enzymes such as gamma-glutamyltransferase (GGT) and aspartate-aminotransferase (AST). While in the control group GGT is also reduced, this is not the case with AST. At the end of the treatment, no significant differences were detected in terms of GGT and AST levels between the experimental and control groups when comparing with basal levels of these hepatic enzymes (Croop et al., 1997; Guardia et al., 2002; O'Brien et al., 1996). In a pilot study carried out with obese patients who received doses six time higher than normal (300 mg/day), elevated transaminase was detected, due to hepatocellular damage, but this receded when naltrexone was stopped.

The ESENSE trials have shown that the treatment with nalmefene is associated with a reduction of the hepatic enzymes alanine-aminotransferase (ALT) and gamma-glutamyltransferase (GGT), significantly greater than in patients taking the placebo (Mann et al., 2013; Gual et al., 2013).

Indications and Contraindications

Before prescribing naltrexone or nalmefene, it is advisable to rule out consumption of opiates since both drugs antagonize their possible therapeutic effects and would trigger serious withdrawal symptoms in people who have de-

veloped opiate dependence. And should the patient need surgical intervention he/she would have to stop taking naltrexone or nalmefene 3-7 days before the intervention, particularly in the case of major surgery (Anton, 2008).

It is advisable to take into account the patient's hepatopathy background and associated drugs with hepatotoxic potential. In the analyses prior to starting treatment, patients should be asked for indicators of hepatic and renal function, complete hemogram, pregnancy test (women of fertile age) and urine tests for the presence of opiates and other substances.

Due to its posible hepatotoxic effect, naltrexone is contraindicated in pregnancy, lactation, acute hepatitis, hepatic insufficiency, hepatocellular damage, recent consumption of opiates, active dependence on heroin or other opiates, withdrawal symptoms from opiates, acute withdrawal from alcohol and patients who need opioid analgesics, antitussives or antidiarrheals (González et al., 1988; Ortiz Camuñez, 1996). In patients with acute hepatitis, liver failure or serious hepatocellular problems, reflected in elevated hepatic enzymes at three times the normal limit and/or the bilirrubinemia, precautions need to be taken if the patient is suffering from a less serious hepatic dysfunction or have a recent history of hepatopathy (Berg, Pettinati, & Volpicelly, 1996).

Nalmefene is contraindicated in pregnancy, lactation, serious deterioration of hepatic or renal function, recent consumption of opiates, dependence on heroin or other opiates, withdrawal symptoms from opiates, acute withdrawal from alcohol, patients who need opioid analgesics, antitussives or antidiarrheals (Keating, 2013; European Medicines Agency, 2013).

Nalmefene treatment should be interrupted one week before surgical interventions which could require the administration of opioid analgesics. Care is advised when treating patients with transaminases (ASAT and ALAT) more than 3 times above the normal limit, and hepatic and renal function should be monitored in patients with deteriorated liver or kidney function. Given that the results of trials with animals show potential reproductive toxicity, it is not advised to take nalmefene during pregnancy or the lactation period since the drug is excreted through milk. Nevertheless, the possible advantages of the treatment should be considered if the patient has had a favorable prior experience with nalmefene and suffers from excessive alcohol consumption during lactation.

Possible interactions

Naltrexone presents a low level of interaction due to its hepatic metabolism by the cytosolic and not the cytochrome P450 system. Some authors consider that it could be administered with disulfiram and other psychotropic medication, at usual doses, taking care to monitor hepatic function periodically (Berg et al., 1996).

Nalmefene is metabolized by CYP450 and UGT enzymes. Long-term treatment alongside powerful inhibitors of enzyme UGT2B7 (such as diclofenac, fluconazole, medroxyprogesterone or meclofenamic acid) may increase the exposure to nalmefene. On the other hand, simultaneous treatment with UGT enzyme inductors (such as dexametasone, phenobarbital, rifampicin and omeprazol) may diminish the efficacy of nalmefene due to reduced plasma concentrations.

Both naltrexone and nalmefene block the analgesic, antitussive or antidiarrheal effects of opioid drugs prescribed to these ends and can trigger serious opiate withdrawal symptoms in people actively dependent on heroin, methadone, buprenorphin or other opiates.

There is no clinically significant pharmacokinetic interaction between nalmefene and alcohol, which means that nalmefene neither raises nor lowers alcohol intoxication.

Differential characteristics of nalmefene

Nalmefene has been considered a modulator of the opioid system. It acts as an antagonist of the mu and delta receptors (opioids), and partial agonist of the kappa receptors, but some author propose that in up-regulation of the kappa receptors it could act as antagonist (Keating, 2013). Compared to naltrexone, it has greater affinity for delta and kappa receptors, greater bioavailability, a longer half life and, therefore, a longer-lasting effect. Moreover, no indications have been found of dose-dependent hepatotoxicity (Nutt, 2014).

Some authors claim that, given its differential effect on the kappa opioid receptors, nalmefene is more efficacious than naltrexone in reducing alcohol consumption when the organism has developed a dependence on alcohol (Walker et al., 2008; Walker, Zorrilla, & Koob, 2011). Chronic alcohol ingestion leads to an up-regulation of the dynorphin/kappa opioid system in the person who has developed alcohol dependence, which would be associated with a state of hypodopaminergia linked to higher levels of craving. Nalmefene could renormalize such a state of hypodopaminergia and, therefore, reduce craving for alcohol (Spanagel & Vengeliene, 2012).

With regard to the aim of continued abstention, nalmefene has proven efficacious in preventing relapses in some clinical trials (Mason et al., 1994; 1999), although in one case this could not be confirmed (Anton et al., 2004). In terms of the new objective of reducing alcohol intake, some pilot studies signalled that naltrexone and nalmefene could be of use since they would result in a reduction of the number of days in which a person drank alcohol, the number of drinks per sitting, the number of heavy drinking days and the numbers for the biological markers ALT and GGT (Heinala, Alho, Kiianmaa, Lonquist, & Sinclair, 2001; Hernández–Avila, Song, Kou, Tennen, Armeli et al., 2006; Kranzler, Tennen, Armeli, Chan, Covault et al., 2009).

The efficacy of nalmefene in connection with the new treatment target of alcohol intake reduction has been assessed on the basis of three placebo controlled multicenter studies in Europe, with a new procedure in which the alcoholic patient takes an 18 mg pill of nalmefene only on the day in which alcohol consumption is likely or when facing a situation with a risk of relapse.

Based on the results of the ESENSE 1 and 2 studies (Gual et al., 2013; Mann et al., 2013), the indication of nalmefene for reducing alcohol consumption in alcohol dependent persons has been confirmed, and the European Medicines Agency approved this new indication in 2013.

A New Target in the Treatment of Alcoholism

Treatment with nalmefene leads to a reduction in alcohol consumption. Not drinking alcohol every day and drinking less per sitting is a realistic objective for low-risk alcoholic patients if they take nalmefene, above all if they are motivated and committed to cutting down their alcohol intake.

Therefore, people with difficulty in controlling alcohol consumption, those who have already suffered some of the negative consequences and recognize the need to reduce their alcohol intake, can benefit from the treatment with nalmefene.

The profile of the ideal patient would probably be of a middle-aged person with mild alcohol dependence, who does not have clear withdrawal symptoms, who has applied for alcoholism treatment for the first time, who does not have serious medical, psychiatric or addictive comorbidity, and who is determined to cut down substantially on his/her alcohol consumption. A stable family, social and work environment, furthermore, will favor the results of the treatment (Van Amsterdam & Van den Brink, 2013).

Excessive alcohol consumption tends to be associated with negative consequences. The majority of those who suffer such negative consequences do not have an alcohol consumption disorder. They can be said to have such a habit but are capable of modifying it when they wish to because they have not yet developed an addiction. They can, therefore, reduce their intake when they seriously decide to do so, without needing specialized treatment.

When a person has developed alcohol addiction it is unlikely that he/she will be able to reduce consumption and effectively maintain it at low levels for a prolonged period of time. The cardinal symptom of alcoholism is precisely the difficulty in controlling alcohol intake, above all the first drink, and the opioid receptor antagonists would neutralize this symptom. The effort to reduce alcohol intake is a necessary but insufficient condition; nalmefene helps the person who is determined to reduce drinking to achieve his/her aim.

Alcoholism treatment with nalmefene achieves something similar to the medical model of treatment in which a specific drug neutralizes a specific symptom. In people suffering from alcoholism, the symptom is behavioral, the difficulty to control or the loss of control.

Nalmefene for reducing alcohol consumption

The ESENSE trials were carried out on patients with mild or moderate alcohol dependence disorder, that is without alcohol withdrawal symptoms (which did not exceed 10 points on the CIWA scale), and without serious medical, psychiatric or addictive comorbidity. These were patients, then, who did not need alcohol detoxification treatment and who could begin nalmefene treatment as outpatients and without having to stop drinking.

In each visit, the motivational and psychoeducational intervention procedure was applied to enhance adherence to the treatment. This procedure is known as BRENDA, an acronym representing the six successive actions which can be carried out on each patient visit: a biopsychosocial evaluation is first carried out, a report of the biopsychosocial evaluation is presented to the patient, empathy with the patient and his/her response to the report is necessary, the needs of the patient are identified, direct advice is given to the patient regarding attainment of treatment targets, an assessment of the patient's response to the clinician is prepared and the clinician adapts to the patient's preferences in order to reach final consensus on future goals (Volpicelli, Pettinati, McLellan, & O'Brien, 2001).

With the aim of introducing the new procedure "as needed", the patient is instructed to take a 20 mg nalmefene pill only on those days when he/she intends to have an alcoholic drink or in situations in which it is likely he/she will have an alcoholic drink, in which case it is recommended that, if possible, the pill be taken one hour before the first alcoholic drink or if not, as soon as possible, even together with the first alcoholic drink.

Patients on the ESENSE program took nalmefene (or placebo) for six months in a randomized, double blind manner. The ESENSE 1 study took place in northern European countries, while ESENSE 2 was carried out in southern Europe. The treatment goal was to achieve change from the beginning to month 6 in the number of heavy drinking days and the average of total alcohol consumption per session. Patients who were given the active ingredient took it on 48% and 57% of the days, while those who were assigned the placebo did so on 63.9% and 65.2% of the days in ESENSE 1 and 2 respectively.

Between the selection and randomization interviews, a high percentage of patients (18% in ESENSE 1 and 33% in ESENSE 2) had already reduced their alcohol consumption to below 6 heavy drinking days during the 4 previous weeks, or to below the average level of risk of drinking,

which were the criteria for inclusion in the study and which had been confirmed in the selection interview.

In the next step in the procedure, nalmefene resulted in a reduction in the number of heavy drinking days significantly greater than placebo in both ESENSE studies, as well as a reduction of total alcohol consumption in ESENSE 1 but not in ESENSE 2.

The concept RESPONSE to the treatment was defined as a reduction from a very high level of risk of alcohol consumption to a mid- or low level, or from high or mid-level risk to low-level risk. Logically, patients who managed a significant reduction in alcohol intake between the selection visit and the beginning of treatment could not reduce their consumption further during the course of treatment, that is they began the treatment with a low level of risk and maintained this level throughout. Nevertheless, a subanalysis of the group of patients who at the start of treatment still had high risk consumption (>60 gr/day for men, >40 gr/day for women) confirmed nalmefene's efficacy in reducing consumption, with significantly better results in comparison with placebo.

Moreover, those taking nalmefene exhibited a greater reduction in their scores on the global clinical impression scales, both those for severity and for improvement, and also in the ALT and GGT levels, with significant differences in favor of nalmefene.

In a third study, called SENSE, in which treatment lasted for 12 months, the same procedure was followed to assess the safety, tolerability and efficacy of nalmefene in patients with alcohol dependence. A substantial reduction of alcohol intake between the selection interview and beginning of treatment was achieved by 39% of patients. Retention after 12 months was 63% and the reduction, both in terms of heavy drinking days and total alcohol consumption, was significantly higher with nalmefene than placebo after 12 months of treatment, as were the reduction of scores on the global clinical impression scales (severity and improvement) and in ALT and GGT levels (Van den Brink, Aubin, Bladström, Torup, Gual et al., 2013; Van den Brink, Sorensen, Torup, Mann, & Gual, 2014).

An analysis of the subgroup of those who continued high-risk consumption at the start of the nalmefene treatment confirmed a satisfactory response in 72% of those who took nalmefene, in contrast to 57% who took the placebo by the end of the treatment.

Nalmefene was well-tolerated and the adverse effects which appeared most frequently (>5%) were dizziness, nausea, cephalea, insomnia, vomiting, fatigue and loss of appetite. Other less frequent symptoms were hyperhidrosis, somnolence, tachycardia, nasopharyngitis and sleep disorder.

The adverse effects appeared from the first day of treatment with nalmefene, the majority were transitory (3-7 days) and of light to moderate severity (Van den Brink et al., 2013; 2014). Those which led most frequently to abandonment of treatment were dizziness, nausea, fatigue and cephalea. Comparing the serious side effects which appeared in patients taking nalmefene or placebo produced the following figures respectively, 5.9% vs. 6.7% in the ESENSE 1 study, 2.2% vs. 4.7% in ESENSE 2 and 6.9% vs. 5,4% in the SENSE study. This suggests that the majority of adverse effects were not attributable to nalmefene but rather to the patients' own pathology since patients did not stop drinking during the nalmefene treatment and also because the procedure for data collection means that any symptom that the patient mentions in any of the visits is registered as a possible side effect, irrespective of whether or not it can be attributed to the drug (Keating, 2013).

A state of confusion, or hallucinatory or dissociative symptoms appeared only exceptionally and only at the beginning of the treatment, were of light or moderate severity and short-lived, and did not reappear when nalmefene administration was repeated (European Medicines Agency, 2013).

Advantages of nalmefene treatment to reduce alcohol consumption

Treatment with nalmefene is safe, well-tolerated and simple. It leads to a reduction in heavy drinking days and the amount of alcohol consumed per session in patients with alcohol dependence (Gual et al., 2013; Mann et al., 2013).

Lower alcohol consumption is associated with a reduction in the number of accidents, hostile or self-destructive behavior and heart rhythm disorders (Rehm, Baulinas, Borges, Graham, Irving et al., 2012). The COMBINE study detected a reduction in negative consequences parallel to lower alcohol intake, to the extent that those patients who did not have a single day of excessive consumption also avoided the negative consequences normally associated with it (Anton et al., 2006; Falk et al., 2010).

In comparison to continued abstinence, the target of reduced intake has the advantage of adapting better to the need for help of the alcoholic patient. Patients frequently state that they wish to stop drinking, but equally often, they hope that at some point in the future they can have an alcoholic drink. In other words, patients' expectation, and often that of their families, is that after a period of abstention the problem will have been resolved and that they will have recovered control over their drinking; the belief that control is voluntary and depends exclusively on the patient's willpower to succeed is widespread.

In reality, unfortunately, due to the deprivation effect, the day they try an alcoholic drink again after a period of abstention, it is most likely that they will lose control over their drinking.

Moreover, patients who hope to be able to enjoy a drink at some time in the future without the risk of problems will

not accept the goal of complete and continued abstention, and will reject medication which prevents them from having the odd drink. Some patients will refuse treatment for alcoholism if they have to stop drinking entirely.

The treatment with nalmefene aimed at reducing alcohol intake adapts better to the needs of a majority of patients beginning treatment for alcoholism. It may favor the acceptance of, adherence to, and retention in the treatment program, as well as the commitment to the new goal of reducing alcohol consumption.

For patients it might be difficult to understand: (1) controlling alcohol consumption is a function of the nervous system and is not governed by the patient's willpower; (2) this control depends on the proper functioning of certain brain structures; (3) intervening in the opioid receptors can result in a normalization of control over alcohol consumption; (4) one simple pill can achieve this. The COMBINE study has shown that both naltrexone (100 mg/day) and cognitive behavioral therapy achieve greater efficacy than placebo. However, the combination of both does not achieve better results than naltrexone accompanied by simple medical management, that is in order to attain the greatest therapeutic benefit with naltrexone, it is not necessary to apply psychological treatment (Anton et al., 2006).

In the ESENSE studies with nalmefene, a small motivational intervention known as BRENDA was employed to optimize management and adherence to the medication (Volpicelli et al., 2001). Any motivational intervention aimed at reducing alcohol consumption and keeping to the program can therefore be helpful in terms of optimizing the efficacy of nalmefene.

It is advisable to carry out a good analysis of the alcohol consumption patterns of the patient, give him/her clear and simple instructions and recommendations (both verbal and written) about the reduction of alcohol and managing nalmefene, and monitor the patient to support ongoing learning about the new therapeutic procedure, helping him/her to overcome potential hurdles and circumstances that may appear during the course of treatment.

The active participation of the alcoholic patient, in the initial decision as to the goal of the therapy and the individualized management of it, improves adherence to the therapy and retention in the treatment program. It is the patients themselves who decide when the medication is taken and even when alcohol can or cannot be drunk. It adapts better to the patients' own objectives and prevents an occasional drink turning into relapse, helping patients to successfully overcome situations with risk of relapse. If the patients do not consider an occasional drink as a relapse, that is if they do not feel as if they have relapsed, it is less likely that they will abandon the treatment program. Remaining on the program furthers doctor-patient rapport, offering more opportunities to become aware of problems, progressively changing attitudes with respect to alcohol consumption, and progressively reducing the tendency to drink heavily.

Among the advantages of treatment with nalmefene we can highlight (1) patients being well-disposed to the treatment, probably due to their greater participation and implication in decision-making. (2) A more specific effect on the "difficulty of control" symptom which facilitates the understanding of the way nalmefene works, both for the patients as well as their families. (3) An increase in the likelihood that patients will request treatment, and at an earlier stage in their illness. (4) The possibility, in this case, of halting the development of the illness in its initial stages, thereby preventing the increase and progressive worsening of the negative consequences of excessive alcohol consumption that both patients and their families would have suffered in the future. (5) The treatment with nalmefene is safe, well-tolerated, simple, and does not require psychotherapy, just the instructions of a medical expert.

On each visit during the course of treatment with nalmefene, an analysis can be made of the factors which increase the risk of loss of control over drinking and work on coping strategies to make sure that the patient keeps to low-risk levels of consumption. At the same time, it is possible to consolidate the parallel psychiatric comorbidity diagnosis (anxiety, affective or personality disorders) and detect possible concomitant consumption of other drugs or medicines of abuse, which can interfere with the recovery from alcoholism. These data enrich the understanding and personalized diagnosis of each alcoholic patient and permit the optimization of each patient's development.

If the patient is motivated to take the treatment, it is more likely that he/she will be willing to change attitudes, behavior, lifestyle, etc., essential for making progress in his/her recovery. If there is a bout of heavy drinking during the course of treatment with nalmefene, the patient is more likely to ask for help and, if a good analysis is made of the relapse, the patient is more likely to accept a new plan of treatment which he/she may have rejected at the start of the treatment, given that he/she had not yet become aware of the severity of the problem.

Finally, it is important to bear in mind that nalmefene is the only medication which has been approved by the health authorities for use in reducing alcohol consumption in patients with alcohol dependence.

Conclusions

1. Opioid receptor antagonist drugs (nalmefene and naltrexone) lead to a reduction in alcohol consumption
2. Opioid receptor antagonists can prevent an occasional alcoholic drink from turning into a relapse because they can attenuate the deprivation effect.

3. Both naltrexone and nalmefene manage to reduce craving after a first alcoholic drink, the amount of alcohol drunk per sitting, the choice of alcoholic drinks over non-alcoholic drinks, and the euphoria-inducing effect of alcohol.
4. The treatment target of reducing alcohol consumption can obtain the same results as continued abstention, as long as the patient does not exceed the limits of low-risk consumption at each sitting.
5. Nalmefene may be more effective than naltrexone in reducing alcohol consumption in people with alcoholism thanks to its modulating effects on the kappa opioid receptors.
6. Nalmefene helps the person who decides to reduce his/her consumption to achieve this goal.
7. The profile of the ideal patient would probably be of a middle-aged person with mild alcohol dependence, who does not have clear withdrawal symptoms, who has applied for alcoholism treatment for the first time, who does not have serious medical, psychiatric or addictive comorbidity, and who is determined to cut down substantially on his/her alcohol consumption.
8. Among the advantages of treatment with nalmefene it is worth highlighting that it is safe, well-tolerated, and simple; that it does not need psychotherapy but rather psychosocial support or the instructions of a medical expert; and that it is better accepted by patients, probably due to their greater participation in decision-making.
9. Treatment with nalmefene, aimed at reducing alcohol consumption, better adapts to the needs of the majority of patients who start alcoholism treatment and can favor the acceptance of, adherence to and retention in the treatment program, and the commitment to this new therapeutic objective.
10. Nalmefene is the only drug which has been approved by the health authorities for use in reducing alcohol consumption in patients with alcohol dependence.

Conflict of Interests

The author participated as principal researcher in the ESENSE 2 study and has been a member of the Lundbeck España advisory committee on nalmefene.

References

Altshuler, H. L., Phillips, P. E., & Feinhandler, D. A. (1980). Alterations of ethanol self-administration by naltrexone. *Life Sciences, 26,* 679-688.

Anton, R. F., Pettinati, H., Zweben, A., Kranzler, H. R., Johnson, B., Bohn, M. J.,… Karhuvaara, S. (2004). A multisite dose ranging study of nalmefene in the treatment of alcohol dependence. *Journal of Clinical Psychopharmacology, 24*, 421-428.

Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M.,… Zweben, A., COMBINE Study Research Group. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence – the COMBINE study: a randomized controlled trial. *Journal of American Medical Association, 295*, 2003-2017.

Anton, R. F. (2008). Naltrexone for the management of alcohol dependence. *New England Journal of Medicine, 359*, 715-721.

Arias, A. J., Armeli, S., Glernter, J., Covault, J., Kallio, A., Karhuvaara, S.,... Kranzler, H. R. (2008). Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. *Alcoholism: Clinical and Experimental Research, 32*, 1159-1166.

Berg, B. J., Pettinati, H. M., & Volpicelli, J. R. (1996). Valoración riesgo-beneficio de la naltrexona en el tratamiento de la dependencia del alcohol. *Drug Safety, 15*, 274-282.

Bouza, C., Magro, A., Muñoz, A., & Amate, J. M. (2004). Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a thematic review. *Addiction, 99*, 811-828.

Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, D. C., Farmer, R.,… Ritson, B. (2000). A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol & Alcoholism, 35*, 587-593.

Ciraulo, D. A., Dong, Q., Silverman, B. L., Gastfriend, D. R., & Pettinati, H. M. (2008). Early treatment response in alcohol dependence with extended-release naltrexone. *Journal of Clincal Psychiatry, 69*, 190-195.

Clapp, P., Bhave, S. V., & Hoffman, P. L. (2008). How adaptation of the brain to alcohol leads to dependence. A pharmacological perspective. *Alcohol Research & Health, 31*, 310-339.

Collins, M. A. & Bigdeli, M. B. (1975). Tetrahydroisoquinolines in vivo. Rat brain formation of salsolinol, a condensation product of dopamine and acetaldehyde under certain conditions during ethanol intoxication. *Life Sciences, 16,* 535-601.

Croop, R. S., Faulkner, E. B., & Labriola, D. F. (1997). The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study. *Archives of General Psychiatry, 54,* 1130-1135.

Davidson, D., Palfai, T., Bird, Ch., & Swift, R. (1999). Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcoholism: Clinical and Experimental Research, 23*, 195-203.

Davis, V. E. & Walsh, M. D. (1970). Alcohol, amines and alkaloids; a possible basis for alcohol addiction. *Science, 167,* 1005-1007.

Drobes, D. J., Anton, R. F., Thomas, S. E., & Voronin, K. (2004). Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. *Alcoholism: Clinical and Experimental Research, 28*, 1362-1370.

European Medicines Agency. (2013). Selincro (nalmefene): EU summary of product characteristics. http://www.emea.europa.eu/docs/en_GB/document_library/EPARProduct_Information/ European Medicines Agency. Selincro (nalmefene): EU summary of product characteristics. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002583/WC500140255.pdf. Accessed 28 June 2013.

Falk, D., Wang, X. Q., Liu, L, Fertig, J., Mattson, M., Ryan, M.,… Litten, R. Z. (2010). Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. *Alcoholism: Clinical and Experimental Research, 34*, 2022-20343.

Froehlic, J. C., Harts, J., Lumeng, L., Li, T. K. (1990). Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. *Pharmacology Biochemistry and. Behavior, 35,* 385-390.

Froehlic, J. C., Zweifel, M., Harts, J., Lumeng L., & Li, T. K. (1991). Importance of delta opioid receptors in maintaining high alcohol drinking. *Psychopharmacology (Berlin), 103*, 467-472.

Froehlic, J. C., Li, T. K. (1993). Opioid peptides. In: Galanter, M. (Ed.) *Recent Developments in Alcoholism, Volume 11: Ten Years of Progress.* New York: Plenum Press.

Garbutt, J. C., Kranzler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H.M., Silverman, B. L.,… Ehrich, E. W. for the Vivitrex Study Group. (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. *Journal of American Medical Association, 293*, 1617-1625.

Gennazi, A. R., Nappi, G., Eacchinetti, F., Mezzella, G. L., Parrini, D., Sinforiani, E.,… Savoldi, F. (1982). Central deficiency of beta-endorphin in alcoholic addicts. *Journal of Clinical Endocrinology and Metabolism, 55,* 583-586.

Gianoulakis, C. (1993). Endogenous opioids and excessive alcohol consumption, *Journal of Psychiatry and Neuroscience, 18,* 148-156.

Gianoulakis, C., Kirshnan, B., & Thavundayil, J. (1996). Enhanced sensitivity of pituitary β-endorphin to ethanol in subjects at high risk of alcoholism. *Archives of General Psychiatry, 53,* 250-257.

Gonzalez, J. P. & Brogden, R. N. (1988). Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs, 35,* 192-213.

Greenwald, R. D., Fertel, R. H., Wong, J. K., Schwartz, R. D., & Bianchine, J. R. (1979). Salsolinol and tetrahydropapaveroline bind opiate receptors in the brain. *Federation proceedings, 63rd Annual Meeting.*

Gual, A., He, &., Torup, L., van den Brink, W., & Mann, K. (2013). A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *European Neuropsychopharmacology 23*, 1432-1442. doi: 10.1016/j.euroneuro.2013.02.006.

Guardia, J., Caso, C., Arias, F., Gual, A., Sanahuja, J., Ramírez, M.,… Casas, M. (2002). A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder. Results from a multicenter clinical trial. *Alcoholism: Clinical and Experimental Research, 26*, 1381–1387.

Guardia Serecigni, J., Jiménez Arriero, M. A., Pascual Pastor, F., Flórez Menéndez, G., & Contel Guillamón, M. (2008). *Alcoholismo. Guía clínica de Socidrogalcohol basada en la evidencia científica.* 2ª Edición. Barcelona. SOCIDROGALCOHOL.

Guardia, J., Surkov, S., & Cardús, M. (2010). Neurobiología de la Adicción. En C. Pereiro (Ed.) *Manual de Adicciones.* (pp. 37-130). Barcelona. Socidrogalcohol.

Guardia Serecigni, J. (2011). Cambio de paradigma en el tratamiento del alcoholismo de baja gravedad. *Adicciones, 23*, 299-316.

Guardia, J., Surkov, S., & Cardús, M. (2011). Bases neurobiológicas de la Adicción. En J. Bobes, M. Casas, M. Gutiérrez (Eds.). *Manual de Trastornos Adictivos.* 2ª Edición. (pp. 25-33). Valladolid. ADAMED. Enfoque Editorial.

Guardia Serecigni, J. (2015). La reducción del consumo de alcohol. Un nuevo objetivo en el tratamiento del alcoholismo de baja gravedad. *Adicciones, 27*, 3-7.

Gueorguieva, R., Wu, R., Pittman, B., Cramer, J., Rosenheck, R. A., O'Malley, S. S., & Krystal, J. H. (2007). New insights into the efficacy of naltrexone based on trajectory-based reanalyses of two negative clinical trials. *Biological Psychiatry, 61*, 1290-1295.

Heinala, P., Alho, H., Kiianmaa, K., Lonnqvist, J., & Sinclair, J. D. (2001). Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *Journqal of Clinical Psychopharmacology, 21*, 287-292.

Hernández-Ávila, C. A., Song, Ch., Kou, L., Tennen, H., Armeli, S., & Kranzler, H. R. (2006). Targeted versus daily naltrexone: second analysis of effects on average daily drinking. *Alcoholism: Clinical and Experimental Research, 30*, 860-865.

Ingman, K., Hagelberg, N., Aalato, S., Nagren, K., Juhakoski, A., Karhuvaara, S.,... Scheinin, H. (2005). Prolonged central mu-opioid receptor occupancy alter single and repeated nalmefene dosing. *Neuropsychopharmacology, 30*, 2245-2253.

Johnson, S. W. & North, R. A. (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *Journal of Neuroscience, 12*, 483-488.

Johnson, B. A., Ait-Daoud, N., Bowden, Ch. L., Di Clemente, C., Roache, J. D., Lawson, K. (2003) Oral topiramamte for the treatment of alcohol dependence: a randomised controlled trial. *The Lancet 361,* 1677-1685.

Johnson, B. A., Rosenthal, N., Capece, J. A., Wiegand, F., Mao, l., Beyers, K.,… Swift, R. M. (2007). Topiramate for treating alcohol dpendence. A randomized controlled trial. *Journal of American Medical Association 298*, 1641-1651.

Kalivas, P. W. & Volkow, N. D. (2005).The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry, 162*,1403-1413.

Karhuvaara, S., Simojoki, K., Virta, A., Rosberg, M., Loyttiniemi, E., Nurminen, T.,… Makela, R. (2007). Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcoholism: Clinical and Experimental Research, 31*, 1179-1187.

Keating, G. M. (2013). Nalmefene: A review of its use in the treatment of alcohol dependence. *CNS Drugs, 27*, 761-772.

Kissler, J. L., Sirohi, S., Reis, D. J., Jansen, H. T., Quock, R. M., Smith, D. G., & Walker, B. M. (2013). The one-two punch of alcoholism: role of central amygdale dynorphins/kappa-opioid receptors. *Biological Psychiatry, 75*, 774-782. doi:10.1016/j.biopsych.2013.03.014.

Kornet, M., Goosen, C., & Van Ree, J. M. (1990). The effect of interrupted alcohol supply on spontaneous alcohol consumption by rhesus monkeys. *Alcohol and Alcoholism, 25,* 407-412.

Kornet, M., Goosen, C., & Van Ree, J. M. (1991). The effect of naltrexone on alcohol consumption during chronic alcohol drinking, and after a period of imposed abstinence in free-choice drinking rhesus monkeys. *Psychopharmacology (Berlin), 104,* 367-376.

Kranzler, H. R., Modesto-Lowe, V., & Van Kirk, J. (2000). Naltrexone vs. nefazodone for the treatment of alcohol-dependence. A placebo-controlled trial. *Neuropsychopharmacology, 22*, 493-503.

Kranzler, H. R., Tennen, H., Armeli, S., Chan, G., Covault, J., Arias, A., & Oncken, C. (2009). Targeted naltrexone for problem drinkers. *Journal of Clinical Psychopharmacology, 29*, 350-357.

Krystal, J. H., Cramer, J. A., Krol, W. F., Kirk, G. F., & Rosenheck, R. A, for the Veterans Affairs Naltrexone Cooperative Study 425 Group. (2001). Naltrexone in the treatment of alcohol dependence. *New England Journal of Medecine, 345*, 1734-1739.

Li, X. W., Li, T. K., Froehlic, J. C. (1992). The encephalinergic system and alcohol preference. *Alcoholism: Clinical and Experimental Research, 16*, 359.

Lucey, M. R., Silverman, B. L., Illeperuma, A., & O'Brien, C. P. (2008). Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcoholism: Clinical and Experimental Research, 32*, 498-504.

Mann, K., Bladstrom, A., Torup, L., Gual, A., & van den Brink, W. (2013). Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biological Psychiatry, 73*, 706–713.

Mason, B. J., Ritvo, E. C., Morgan, R. O., Salvato, F. R. , Goldberg, G., Welch, B., & Mantero-Atienza, E. (1994). A doble-blind placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCL for alcohol dependence. *Alcoholism: Clinical and Experimental Research, 18*, 1162-1167.

Masson, B. J., Salvato, F. R., Williams, L. D., Ritvo, E. C., & Cutler, R. B. (1999). A double-blind placebo-controlled study of oral nalmenfene for alcohol dependence. *Archives of General Psychiatry, 56*, 719-724.

Matz, J., Graff, C., Vainio, P. J., Kallio, A., Hojer, A. M., Struijk, J. J.,… Toft, E. (2011). Effect of namefene 20 and 80 mg on the corrected QT interval and T-wave morphology: a randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled, single-centre study. *Clinical Drug Investigation, 31*, 799-811.

Nealey, K. A., Smith, A. W., Davis, S. M., & Walker, B. M. (2011). K-opioid receptors are implicated in the increased potency of intra-accumbens nalmefene in ethanol-dependent rats. *Neuropharmacology, 61*, 35-42.

Nestler, E. J., Hope, B. T., & Widnell, K. L. (1993). Drug addiction: A model for the molecular basis of neural plasticity. *Neuron, 11,* 995-1006.

Niciu, M. J. & Arias, A. J. (2013). Targeted opioid receptor antagonists in the treatment of alcohol use disorders. *CNS Drugs, 27*, 777-787.

Nutt, D. J. (2014). The role of the opioid system in alcohol dependence. *Journal of. Psychopharmacology 28*, 8-22. DOI: 10.1177/0269881113504017.

O'Brien, C. P., Volpicelli, L. A., & Volpicelli, J. R. (1996). Naltrexone in the treatment of alcoholism: A clinical review. *Alcohol, 13,* 35-39.

O'Malley, S. S., Jaffe, A., Chang, G., Schottenfeld, R. S., Meyer, R. E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence a controlled study. *Achives of General Psychiatry, 49,* 881-887.

Ortiz Camuñez, M. A. (1996). Naltrexona. *Terapéutica en Atención Primaria de Salud, 3,* 535-540.

Oslin, D. W., Lynch, K. G., Pettinati, H. M., Kampman, K. M., Gariti, P., Gelfand, L.,... O'Brien, C. P. (2008). A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. *Alcoholism: Clinical and Experimental Research, 32*, 1299-1308.

Pascual Pastor, F., Guardia Serecigni, J., Pereiro Gómez, C., & Bobes García, J. (2013). Alcoholismo. *Guías Clínicas de SOCIODROGALCOHOL basadas en la EVIDENCIA CIENTÍFICA. 3ª Edición.* Madrid. SANED (Sanidad y Ediciones).

Pettinati, H. M., O'Brien, C. P., Rabinowitz, A. R., Wortman, S. P., Oslin, D. W., Kampman, K. M., & Dackis, C. A. (2006). The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. *Journal of Clinical Psychopharmacology, 26*, 610-625.

Rehm, J., Baliunas, D., Borges, G. L., Graham, K., Irving, H., Kehoe, T.,... Taylor, B. (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction 105,* 817–843.

Reid, L. D. (1990). Summary. In L. D. Reid (ed.) *Opioids, bulimia and alcohol abuse & alcoholism* (pp. 289-304). New York: Springer-Verlag.

Rösner, S., Hackl-Herrweth, A., Leucht, S., Vecchi, S., Srisurapanant, M., & Soyka, M. (2010). Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev, 12*, CD001867.

Seizinger, B. R., Hollt, V., & Herz, A. (1984). Effect of chronic ethanol treatment on the in vitro biosynthesis of pro-opiomelanocortin and its post-translational processing to β-endorphin in the intermediate lobe of the rat pituitary. *Journal of Neurochemistry, 43,* 607-613.

Shippenberg, T. S., Zapata, A., & Chefer, V. I. (2007). Dynorphin and the pathophysiology of drug addiction. *Pharmacology and Therapeutics, 116*, 306-321.

Siegel, S. (1986). Alcohol and opiate dependence: Re-evaluation of the Victorian perspective. In H.D. Capell, F. B. Glaser, Y. Israel, et al. (Eds.): *Research Advances in Alcohol and Drug Problems.* (pp. 279-314). New York: Plenum Press.

Sinclair, J. D. (1990). Drugs to decrease alcohol drinking. *Annals of Medicine, 22*, 357-362.

Sinclair, J. D. (2001). Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism, 36*, 2-10.

Sirohi, S., Bakalkin, G., & Walker, B. M. (2012). Alcohol-induced plasticity in the dynorphin/kappa-opioid receptor system. *Frontiers in Molecular Neuroscience, 5*, 1-12.

Spanagel, R., Herz, A., & Shippenbeerg, T. S. (1992). Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. *Proceeding of National Academy of Sciences, 89,* 2046-2050.

Spanagel, R. & Vengeliene, V. (2012). New pharmacological treatment strategies for relapse prevention. *Current Topics in Behavioral Neurosciences, 13*, 583-609.

Srisurapanont, M. & Jarusuraisin, N. (2005). Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *International Journal of Neuropsychopharmacology, 8*, 267-280.

Swift, R. M., Whelihan, W., Kuznetson, O., Buongiorno, G., & Hsuing, H. (1994). Naltrexone-induced alterations in human ethanol intoxication. *American Journal of. Psychiatry, 151*, 1463-1467.

Terenius, L. (1996). Alcohol addiction (alcoholism) and the opioid system. *Alcohol, 13,*31-34.

Van den Brink, W., Aubin, H. J., Bladström, A., Torup, L., Gual, A., & Mann, K. (2013). Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results of a subgroup analysis of two randomized controlled 6-month studies. *Alcohol and Alcoholism, 48*: 570-578.

Van den Brink, W., Sørensen, P., Torup, L., Mann, K., & Gual, A., for the SENSE Study Group. (2014). Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *Journal of Psychopharmacology, 28,* 733-744. DOI: 10.1177/026988111452/362.

Van Ree, J. M. (1987). Reward and abuse: opiates and neuropeptides. In J. Engel, & L. Oreland (Eds.). *Brain Reward Systems and Abuse.* New York: Raven press.

Volpicelli, J. R., Ulm, R. R., & Hopson, N. (1991). Alcohol drinking in rats during and following morphine injections. *Alcohol, 8*, 288-292.

Volpicelli, J. R., Alterman, A. I., Hayashida, M., & O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry, 49,* 876-880.

Volpicelli, J. R., Watson, N. T., King, A. C., Sherman, C. E., & O'Brien, Ch. P. (1995). Effect of Naltrexone on Alcohol "high" in alcoholics. *American Journal of Psychiatry, 152,* 613-615.

Volpicelli, J. R., Pettinati, H. M., McLellan, A. T., & O'Brien, C. P. (2001). Combining Medication and Psychosocial Treatments for Addictions. *The BRENDA approach.* The Guilford Press: New York.

Walker, B. W. & Koob, G. (2008). Pharmacological evidence for motivational role of kappa-opioid systems in ethanol dependence. *Neuropsychopharmacology, 33*, 643-652.

Walker, B. W., Zorrilla, E. P., & Koob, G. F. (2011). Systemic k-opioid receptor antagonism by norbinaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. *Addiction Biology, 16*, 116–119.

Wise, R. A. & Bozarth, M. A. (1982). Action of drugs of abuse on brain reward systems: an update with specific attention to opiates. *Pharmacology Biochemistry and Behavior,17,* 239-243.

Work Group on Substance Use Disorders. (2007). Treatment of patients with substance use disorders, second edition. American Psychiatric Association Practice Guidelines. *American Journal of Psychiatry, 164*, 4.

World Health Organization (2000). *International Guide for Monitoring Alcohol Consumption and Related Harm*. Geneva: WHO.

New Psychoactive Drugs

Nuevas Drogas Psicoactivas

Helen Dolengevich-Segal*, Beatriz Rodríguez Salgado**, Jorge Gómez-Arnau Ramírez*, Daniel Sánchez-Mateos

*Servicio de Psiquiatría. Hospital Universitario del Henares. Coslada (Madrid). **Hospital Ramón y Cajal. Centro de Salud Mental de San Blas, Madrid. ***Hospital La Fe, Valencia.

Drugs that are not regulated by the Convention on Psychotropic Drugs of the United Nations of 1971 are called New Psychoactive Drugs (NPD) (United Nations Office on Drugs and Crime, 2013). These are uncontrolled molecules that emulate the effects of illegal psychoactive drugs. Not only new synthetic substances but also other already known substances that are consumed outside of the traditional contexts are included in the concept, as well as new distribution pathways for them. In this sense, the internet plays a key role, as it is relatively easy to obtain drugs known as *legal highs*, or *research chemicals,* through the network. They are sold as "mystical incense", "water pipe cleaners", "dietary supplements", "bath salts", "collector's items" or "fertilizer for plants", with the warning that they are not suitable for human consumption. However, it is possible to find numerous websites in which are listed dose, forms of consumption, combinations, possible complications, and expected effects. The nature of these substances is varied: from herbal products—in which the false idea is exploited that because they natural, they are harmless—to chemical, synthetic and semi-synthetic, and pharmaceutical substances (chemical intermediates used to prepare other substances), or mixtures of the above. The exact composition of the products, where adulteration is also common, is often not detailed. The psychoactive activity is also diverse: stimulants, sedatives, empathogens, hallucinogens, and analgesics. In fact, with the modern composition of substances, there are some that in themselves can be considered a "poly-drug consumption", as they are able to influence different neuronal receptors and present different effects. Such is the case of synthetic cannabinoid STS-35, which acts as a ligand of cannabinoid receptors, as a glutamate antagonist of type NMDA receptors (the same action performed by MK-801, a molecule used to induce experimental psychosis in animals), and as a serotonin agonist; or synthetic opioid MT-45, which has a piperazine structure, from which a stimulating effect is expected, while at the same time, it acts on μ opioid receptors (Siddiqi, Verney, Dargan, & Wood, 2015). Outside the usual commercial networks, there is a *Deep web,* in which the encrypted information evades the authorities' surveillance, which allows the traffic of illegal products. In recent years, several portals that sold classic illicit drugs such as cocaine, heroin, MDMA, or amphetamines have been closed down.

The latest report of the European Observatory for Drugs and Drug Addictions, based on the data collected through the Early Warning System of the European Union points out that in 2014, 101 new psychoactive substances were detected out of a total of 450 identified by the system since its initiation in 1997. Among them, synthetic cannabinoids and synthetic cathinones (European Monitoring Centre for Drugs and Drug Addiction, 2015) stand out because of their frequency. Recent scientific literature also echoes the arrival of new drugs in Europe, both through the toxicological

Received: May 2015; Accepted: May 2015

Send correspondence to:
Helen Dolengevich Segal Servicio de Psiquiatría. Hospital Universitario del Henares. Avda. de Marie Curie s/n, 28822, Coslada (Madrid).
E-mail: e.dolengevich@gmail.com

analysis and through case reports of clinical complications linked to consumption (Wood, Sedefov, Cunningham, & Dargan, 2015).

The emergence of psychopathological disorders among the population that consumes NPD invites us to reflect about the possible presence of a dual pathology, which refers not only to the comorbidity between a psychiatric diagnosis and a substance use disorder, but also to the existence of a common vulnerability. The term dual pathology refers to psychopathological phenotypes in which an association of genetic and environmental factors is postulated. At the confluence of the two pathologies, the possible existence of a common neuronal substrate containing responses to different types of stress has been pointed out, as well as the hypothesis of self-medication and self-regulation or the influence of environmental factors and lifestyle (Szerman et al., 2013; Volkow, 2001).

In this sense, the definition of psychonaut, coined by Jünger (1952) when referring to people who use entheogens to explore their psyche, has been updated. The term *e-psychonaut* has been proposed in reference to the importance of the Network to obtain both psychoactive material and information about the effects, pharmacology, risks or possible combinations (Davey, Schifano, Corazza, Deluca, & Psychonaut Web Mapping Group, 2012). Epidemiologically, psychonauts tend to be male, between the third and fourth decade of life, with a high educational level and a marked inclination to polydrug use. In recent years, late adolescents and young adults of both sexes have also been added, all of them with scarce experience (Government Delegation for the National Plan on Drugs, 2015). In the case of consumption of NPD and the presence of psychopathology, the term *dual psychonaut* refers to subjects with a possible mental illness looking for the specific management of these substances, as well as those in whom perseverant psychopathological symptoms emerge after consumption, highlighting an underlying vulnerability (Dolengevich-Segal, Rodríguez-Salgado, Gómez-Arnau, Rabito-Alcón, & Correas-Lauffer, 2014).

The data warn us of the importance of the phenomenon, as it implies a change both in the substances themselves and in their consumption patterns and even in the epidemiological profile of the consumers, all of which entails the need to update our knowledge of the approach to the possible medical and psychopathological complications (Kersten & McLaughlin, 2014).

References

Davey, Z., Schifano, F., Corazza, O., Deluca, P., & Psychonaut Web Mapping Group. (2012). e-Psychonauts: Conducting research in online drug forum communities. *Journal of Mental Health, 21*, 386-94.

Delegación del Gobierno para el Plan Nacional sobre Drogas (2015). *Encuesta sobre alcohol y drogas en la población general en España (EDADES 2013/2014).* Ministerio de Sanidad, Servicios Sociales e Igualdad.

Dolengevich-Segal, H., Rodríguez-Salgado, B., Gómez-Arnau, J., Rabito-Alcón, M. F., & Correas-Lauffer, J. (2014). Psychoactive substance use in the Internet era. *Revista de Patología Dual, 1*, 3-9.

European Monitoring Centre for Drugs and Drug Addiction (2015). *New psychoactive substances in Europe. An update from the EU Early Warning System.* Publications Office of the European Union, Luxembourg.

Jünger, E. (1987). *Visita a Godenholm.* Madrid: Alianza Editorial (original version published in 1952).

Kersten, B. P. & McLaughlin, M. E. (2015). Toxicology and management of novel psychoactive drugs. *Journal of Pharmacy Practice, 28,* 50-65. doi: 10.1177/08971900014544814

Siddiqi, S., Verney, C., Dargan, P., & Wood, D. M. (2015). Understanding the availability, prevalence of use, desired effects, acute toxicity and dependence potential of the novel opioid MT-45. *Clinical Toxicology (Philadelphia), 53*, 54-59. doi:10.3109/15563650.2014.983239.

Szerman, N., Martínez-Raga, J., Peris, L., Roncero, C., Basurte, I., Vega, P., & Casas, M. (2013). Rethinking Dual Disorders/Pathology. *Addictive Disorders & Their Treatment, 12*, 1-10. doi: 10.1097/ADT.0b013e31826e7b6a.

United Nations Office on Drugs and Crime (2013*). The challenge of new psychoactive substances.* Available at: http://www.unodc.org/documents/scientific/NPS_2013_SMART.pdf

Volkow, N. (2001). Drug abuse and mental illness: Progress in understanding comorbidity. *American Journal of Psychiatry, 158*,1181–1183.

Wood, D. M., Sedefov, R., Cunningham, A., Dargan, P. I. (2015). Prevalence of use and acute toxicity associated with the use of NBOMe drugs. *Clinical Toxicology (Philadelphia), 53,* 85-92. doi:10.3109/15563650.2015.1004179

MENSUAL suspensión inyectable de liberación prolongada

XEPLION®

palmitato de paliperidona

EFICACIA PARA SENTIRSE EFICACIA

FARMACOCINÉTICA[1, 2]

EFICACIA[1]

SIN SUPLEMENTACIÓN ORAL[3]

MONOTERAPIA[1, 4, 5]

TOLERABILIDAD CONTRASTADA[3, 6-9] *

SIN METABOLISMO HEPÁTICO[3]

CLARIDAD DE PENSAMIENTO[10-13]

FLEXIBILIDAD DE PAUTA POSOLÓGICA[3]

En España no se comercializa la presentación de 25 mg.

*Para más información sobre efectos adversos consultar apartado 4.8 de la Ficha Técnica

Janssen-Cilag, S.A.

Paseo de las Doce Estrellas, 5-7
28042 Madrid
www.janssen.es

janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

PHES/XEP/0315/0010 Marzo 2015

1. NOMBRE DEL MEDICAMENTO. 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.** XEPLION 50 mg. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. XEPLION 75 mg. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. XEPLION 100 mg. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. XEPLION 150 mg. 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 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, 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 o risperidona oral.* El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con XEPLION. XEPLION debe iniciarse según se describe al principio de la sección 4.2 anterior. *Cambio desde Risperidona inyectable de acción prolongada.* Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con XEPLION en lugar de la siguiente inyección programada. A partir de entonces, XEPLION se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de XEPLION según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y XEPLION necesaria para alcanzar una exposición a paliperidona similar en estado estacionario

Dosis previa de risperidona inyectable de acción prolongada	Inyección de XEPLION
25 mg cada 2 semanas	50 mg mensualmente
37,5 mg cada 2 semanas	75 mg mensualmente
50 mg cada 2 semanas	100 mg mensualmente

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de XEPLION, se deben considerar sus características de liberación prolongada. Tal y como se recomienda con otros medicamentos antipsicóticos, 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 cido 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 cido de inyección recomendado de XEPLION es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de XEPLION, la recomendación es la siguiente: *Para los pacientes estabilizados con dosis de 25 a 100 mg:* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg:* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de XEPLION, inicie la administración según las pautas recomendadas para la iniciación de XEPLION recogidas anteriormente. Poblaciones especiales. Población de edad avanzada. No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de XEPLION en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado XEPLION sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar XEPLION con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. XEPLION no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes. *Otras poblaciones especiales.* No se recomienda ajustar la dosis de XEPLION por motivos de sexo, raza o tabaquismo. *Población pediátrica.* No se ha establecido la seguridad y la eficacia de XEPLION en niños <18 años de edad. No hay datos disponibles. Forma de administración. XEPLION se utiliza únicamente para uso intramuscular. Se debe inyectar lentamente, profundamente en el músculo. 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. La dosis no se debe administrar por vía intravascular o subcutánea. 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, 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 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 todos los antipsicóticos, incluido paliperidona. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con antipsicóticos, incluido XEPLION. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia postcomercialización. 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. Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente durante el tratamiento con paliperidona. En algunos casos, se ha notificado un aumento de peso previo que puede ser un factor de predisposición. Se ha notificado en muy raras ocasiones la asociación con cetoacidosis y en raras ocasiones con coma diabético. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con antipsicóticos atípicos, incluido 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. Hiperprolactinemia. Los estudios de cultivo de tejidos sugieren que 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 dara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona debe utilizarse con precaución en pacientes con posibles tumores dependientes 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 3 a 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 precínicos 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 alfa antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir XEPLION con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que XEPLION afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dado que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), XEPLION debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se administra XEPLION con otros tratamientos que también tengan esta posibilidad, p.ej., otros antipsicóticos, tricíclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódico de liberación prolongada (de 500 mg a 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre XEPLION y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a XEPLION. Los estudios *in vitro* indican que 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. Risperidona administrada por vía oral o intramuscular se metaboliza en un grado variable a paliperidona. Se debe proceder con cautela en caso de administración concomitante de risperidona o paliperidona oral con XEPLION. **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 antipsicóticos (como paliperidona) durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. XEPLION no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. XEPLION no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a XEPLION. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con XEPLION. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1000 a <1/100), *raras* (≥1/10.000 a <1/1000), *muy raras* (<1/10.000), y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Clasificación por órganos y sistemas	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas
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, infección de ojos, amigdalitis, celulitis, acarodermatitis, absceso subcutáneo	onicomicosis	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, anemia, disminución del hematocrito, aumento del recuento de eosinófilos	agranulocitosis[e] neutropenia, trombocitopenia	
Trastornos del sistema inmunológico			hipersensibilidad	reacción anafiláctica[e]	
Trastornos endocrinos		hiperprolactinemia[a]		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, aumento de los triglicéridos en sangre	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, aumento del colesterol en sangre	intoxicación por agua[e], cetoacidosis diabética[e], hipoglucemia, polidipsia	
Trastornos psiquiátricos	insomnio[d]	agitación, depresión, ansiedad	trastorno del sueño, manía, estado de confusión, disminución de la líbido, nerviosismo, pesadillas	embotamiento afectivo[e], anorgasmia	
Trastornos del sistema nervioso	cefalea	parkinsonismo[b], acatisia[b], sedación/somnolencia, distonia[b], mareos, discinesia[b], temblor	discinesia tardía, convulsión[e], 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, coma diabético[e], trastorno del equilibrio, coordinación anormal[e], titubeo de la cabeza[e]	
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma[e], trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		
Trastornos cardiacos		bradicardia, taquicardia	fibrilación auricular, bloqueo auriculoventricular, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	embolismo pulmonar[e], trombosis venosa, isquemia[e], rubor	
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión pulmonar, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño[e], hiperventilación[e], neumonía por aspiración[e], congestión del tracto respiratorio disfonía[e]	
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, obstrucción del intestino[e], íleo, hinchazón de la lengua, incontinencia fecal, fecaloma, disfagia, queilitis[e]	
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas	ictericia[e]	
Trastornos de la piel y del tejido subcutáneo		erupción cutánea	urticaria, prurito, alopecia, eccema, sequedad de la piel, eritema, acné	angioedema[e], erupción debida al medicamento, hiperqueratosis, decoloración de la piel[e], dermatitis seborreica[e], caspa	
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda	espasmos musculares, rigidez en las articulaciones, dolor de cuello, artralgia	rabdomiólisis[e], aumento de la creatina fosfoquinasa en sangre, anomalía postural[e], inflamación de las articulaciones, debilidad muscular	
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6)[e]	
Trastornos del aparato reproductor y de la mama			disfunción eréctil, trastorno de la eyaculación, amenorrea, retraso en la menstruación, trastornos menstruales[d], ginecomastia, galactorrea, disfunción sexual, secreción vaginal	priapismo[e], dolor de las mamas, malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción mamaria	
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[e], alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, disminución de la temperatura corporal[e], escalofríos, aumento de la temperatura corporal, sed, síndrome de abstinencia a medicamentos[e], absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección[e], hematoma en el lugar de la inyección	
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[a]Referido a "Hiperprolactinemia" a continuación. [b]Referido a "Síntomas extrapiramidales" a continuación. [c]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 0,47% en todos los pacientes tratados con XEPLION. [d]**Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** menstruación irregular, oligomenorrea. [e]No se observaron en estudios clínicos de XEPLION pero sí en la experiencia tras la comercialización con paliperidona.

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. Además de las reacciones adversas anteriormente mencionadas, se han notificado las siguientes reacciones adversas con el uso de risperidona, las cuales se espera que aparezcan con XEPLION. **Trastornos del sistema nervioso:** trastorno cerebrovascular. **Trastornos oculares:** síndrome del iris flácido (intraoperatorio). **Trastornos respiratorios, torácicos y mediastínicos:** estertores. **Trastornos generales y alteraciones en el lugar de administración:** (observadas con la formulación inyectable de risperidona): necrosis en el lugar de la inyección, úlcera en el lugar de la inyección. 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. *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. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poco frecuente) y nódulos (raro). *Síntomas extrapiramidales (SEP).* SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano y reflejo de la glabella anormal, temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y miodonía), distonía (incluye distonía, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotótonos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzosamente su origen en el trastorno extrapiramidal. *Aumento de peso.* En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de XEPLION, respectivamente. Durante el período abierto de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recidivas a largo plazo, el 12% de los pacientes tratados con XEPLION cumplieron este criterio (aumento de peso de ≥7% desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo 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.** 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. Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: psicolépticos, otros antipsicóticos. Código ATC: N05AX13. XEPLION contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. *Tratamiento agudo de la esquizofrenia.* La eficacia de XEPLION en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de XEPLION en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con XEPLION. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de XEPLION (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de XEPLION fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntua-

ción de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de XEPLION en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de XEPLION, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

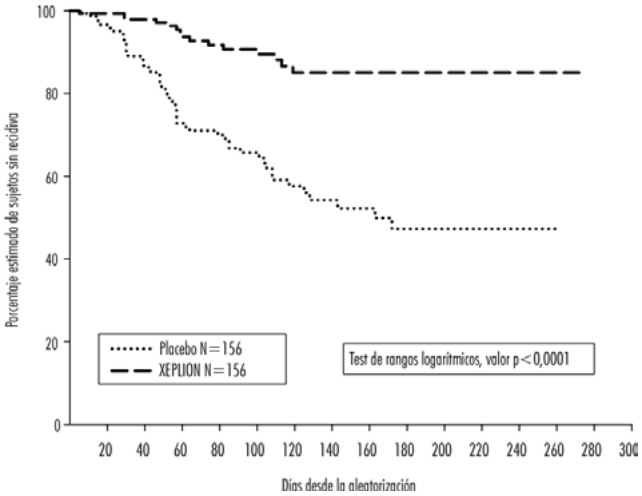
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con XEPLION en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de XEPLION se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de XEPLION fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de XEPLION fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de XEPLION a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de XEPLION es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la 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 (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque XEPLION no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a los de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (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_{inf}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con XEPLION en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. No se recomienda ajustar la dosis únicamente en función de la edad. Sin embargo, puede ser necesario realizar el ajuste de la dosis debido a las disminuciones en el aclaramiento de creatinina relacionadas con la edad (ver Insuficiencia renal más arriba y la sección 4.2). Peso. 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. 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. No se evaluó el tabaquismo con XEPLION. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico 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: 197,72 €; PVP: 243,63 €; PVP (IVA): 253,38 €. XEPLION 75 mg suspensión inyectable de liberación prolongada: PVL: 287,86 €; PVP: 338,77 €; PVP (IVA): 352,32 €. XEPLION 100 mg suspensión inyectable de liberación prolongada: PVL: 345,43 €; PVP: 396,34 €; PVP (IVA): 412,19 €. XEPLION 150 mg suspensión inyectable de liberación prolongada: PVL: 449,06 €; PVP: 499,97 €; PVP (IVA): 519,97 €. **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-Glag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** XEPLION 50 mg: EU/1/11/672/002. XEPLION 75 mg: EU/1/11/672/003. XEPLION 100 mg: EU/1/11/672/004. XEPLION 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** 04 de marzo de 2011. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 10/2014. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

Bibliografía:

1. Pandina GJ, et al., A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. J Clin Psychopharmacol. 2010;30: 235-244.
2. Samtani MN et al. Population Pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia. Clin Pharmacacokinet. 2009; 48 (9): 585-600.
3. Ficha Técnica de Xeplion®.
4. Mesones Peral JE et al. Comparative analysis of the prevention of relapse in psycotic patients following the introduction of Paliperidone Palmitate. XVI Congreso Mundial de Psiquiatría. Madrid, España, 14-18 de septiembre de 2014. Póster 309.
5. Benito A et al. Outcomes económicos del tratamiento con palmitato de paliperidona: Dos años de seguimiento. XVI Congreso Mundial de Psiquiatría. Madrid, España, 14-18 de septiembre de 2014. Póster 393.
6. Jones MP et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia.International Journal of Clinical Pharmacology and Therapeutics. 2010; 48 (6): 383-399.
7. Manzano Callejo JM et al. Antipsicóticos atípicos, esquizofrenia y síndrome metabólico. Póster presentado en el XVII Congreso Nacional de Psiquiatría. Sevilla, 2013.
8. Bergmans P, et al. Flexibly dosed paliperidone palmitate in non-acute but symptomatic patients with schizophrenia previously unsuccessfully treated with long-acting injectable risperidone. Póster presentado en el Congreso DGPPN, 27-30 de noviembre de 2013, Berlín, Alemania, Póster P003 (sesión P-06).
9. Montalvo I et al. Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate. Int Clin Psychophacol. 2012; 28: 46.49.
10. Schreiner A. Paliperidone palmitate in acute patients with schizophrenia - Treatment response, safety and tolerability: a prospective flexible dose study in patients previously unsuccessfully treated with oral antipsychotics. Póster presentado en congreso internacional del Royal College of Psychiastrists, 2-5 de julio de 2013, Edimburgo, Reino Unido.
11. Vázquez JM, et al. Evolución de la Brief Psychiatric Rating Scale (BPRS) y la UdvalgfürKliniskeUndersogelser (UKU) en pacientes con trastorno por uso de sustancias y diagnóstico adicional en el espectro psicótico: "Palmitato de Paliperidona versus antipsicóticos orales / R.I.L.". Póster presentado en el XVII Congreso Nacional de Psiquiatría. Sevilla, 2013.
12. Schreiner A, et al. Paliperidone palmitate - Impact on negative, disorganized and depressive symptoms, subjective well-being and patient satisfaction in non-acute patients with schizophrenia previously unsuccessfully treated with oral antipsychotics. Póster presentado en el congreso DGPPN, 27-30 de noviembre de 2013, Berlín, Alemania, póster P006 (sesión P-08).
13. Hargarter L, et al. Functional outcomes with once monthly paliperidone palmitate in acute and non-acute patients with schizophrenia: data from a prospective fexible dose study in patients with schizophrenia previously unsuccessfully treated with oral antipsychotics. Póster presentado en el congreso del Royal College of Psychiastrists's International, 2-5 de julio de 2013, Edimburgo, Reino Unido.

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.

Reducir para ganar

Único fármaco indicado para la reducción del consumo de alcohol[2]

(2) Ficha técnica Selincro 2013

Lundbeck

Selincro®
nalmefeno

Selincro®
nalmefeno

Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8, en la que se incluye información sobre cómo notificarlas. **1. NOMBRE DEL MEDICAMENTO** Selincro 18 mg comprimidos recubiertos con película. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA** Cada comprimido recubierto con película contiene 18,06 mg de nalmefeno (como dihidrato de hidrocloruro). Excipiente con efecto conocido: cada comprimido recubierto con película contiene 60,68 mg de lactosa. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA** Comprimido recubierto con película (comprimido). Comprimido recubierto con película de color blanco, ovalado, biconvexo, de 6,0 x 8,75 mm y grabado con "S" en una cara. **4. DATOS CLÍNICOS 4.1 Indicaciones terapéuticas** Selincro está indicado para la reducción del consumo de alcohol en pacientes adultos con dependencia del alcohol que presentan un nivel de consumo de alcohol de alto riesgo (NCR) [ver sección 5.1], sin síntomas de abstinencia físicos y que no requieran una desintoxicación inmediata. Selincro solo se debe prescribir junto con apoyo psicosocial mantenido dirigido a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. El tratamiento con Selincro se debe iniciar únicamente en los pacientes que mantienen un NCR alto dos semanas después de la evaluación inicial. **4.2 Posología y forma de administración** Posología En la visita inicial, se deben evaluar el estado clínico, la dependencia del alcohol y el nivel de consumo de alcohol del paciente (según el paciente). Por lo tanto, se debe solicitar al paciente que registre su consumo de alcohol durante aproximadamente dos semanas. En la siguiente visita, se puede iniciar el tratamiento con Selincro en los pacientes que mantienen un NCR alto, (ver sección 5.1) durante este periodo de dos semanas, junto con una intervención psicosocial dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Durante los ensayos clínicos pivotales la principal mejoría se observó durante las 4 primeras semanas. Se debe evaluar la respuesta del paciente al tratamiento y la necesidad de mantener farmacoterapia con regularidad (p. ej., mensualmente) (ver sección 5.1). El médico debe seguir evaluando la evolución del paciente en cuanto a la reducción del consumo de alcohol, el funcionamiento general, la adherencia al tratamiento y los posibles efectos adversos. Se dispone de datos clínicos para el uso de Selincro en condiciones controladas y aleatorizadas para un periodo de 6 a 12 meses. Se recomienda precaución al prescribir Selincro durante más de 1 año. Selincro se toma a demanda: cada día que el paciente perciba un riesgo anticipado de consumo de alcohol debe tomar un comprimido, preferiblemente 1-2 horas antes del momento de consumo. Si el paciente ha empezado a beber alcohol sin haber tomado Selincro, el paciente debería tomar un comprimido lo antes posible. La dosis máxima de Selincro es un comprimido al día. Selincro se puede tomar con o sin alimentos (ver sección 5.2). *Poblaciones especiales Población de edad avanzada (≥ 65 años de edad)* No se recomienda el ajuste de la dosis para este grupo de pacientes (ver secciones 4.4 y 5.2). *Insuficiencia renal* No se recomienda el ajuste de la dosis para los pacientes con insuficiencia renal leve o moderada (ver secciones 4.4 y 5.2). *Insuficiencia hepática* No se recomienda el ajuste de la dosis para los pacientes con insuficiencia hepática leve o moderada (ver secciones 4.4 y 5.2). *Población pediátrica* No se ha establecido la seguridad y eficacia de Selincro en niños y adolescentes de < 18 años. No se dispone de datos (ver sección 5.1). Forma de administración Selincro es un medicamento que se administra por vía oral. El comprimido recubierto con película se debe tragar entero. El comprimido recubierto con película no se debe dividir ni aplastar porque el nalmefeno puede provocar sensibilización cutánea en contacto directo con la piel (ver sección 5.3). **4.3 Contraindicaciones** Hipersensibilidad al principio activo o a alguno de los excipientes incluidos en la sección 6.1. Pacientes en tratamiento con agonistas opioides (como analgésicos opioides, opioides para terapia de sustitución con agonistas opioides (por ejemplo metadona) o agonistas parciales (por ejemplo buprenorfina)) (ver sección 4.4). Pacientes con una actual o reciente adicción a opiáceos. Pacientes con síntomas agudos de abstinencia de opiáceos. Pacientes con sospecha de uso reciente de opiáceos. Pacientes con insuficiencia hepática grave (clasificación de Child-Pugh). Pacientes con insuficiencia renal grave (eGFR < 30 ml/min por 1,73 m2). Pacientes con historia reciente de síndrome de abstinencia del alcohol agudo (incluyendo alucinaciones, convulsiones y delirium tremens). **4.4 Advertencias y precauciones especiales de empleo** Selincro no está indicado en pacientes cuyo objetivo terapéutico sea la abstinencia inmediata. La reducción del consumo de alcohol es un objetivo intermedio en el camino hacia la abstinencia. Administración de opiáceos En una situación de urgencia en la que se deban administrar opiáceos a un paciente que toma Selincro, la cantidad de opiáceo requerida para lograr el efecto deseado puede ser superior a la habitual. El paciente se debe someter a un estricto control para detectar síntomas de depresión respiratoria como consecuencia de la administración de opiáceos, así como otras reacciones adversas. Si se precisan opiáceos en una urgencia, la dosis siempre se debe ajustar de forma individual. Si se requieren dosis excepcionalmente altas, será necesaria una estrecha observación. El tratamiento con Selincro se debe interrumpir temporalmente 1 semana antes del uso previsto de opiáceos (p. ej., cuando se vayan a utilizar analgésicos opioides en una intervención quirúrgica programada). El médico prescriptor deberá advertir a los pacientes de la importancia de informar a su médico de la última toma de Selincro en caso de que sea necesario el uso de opiáceos. Se debe tener precaución cuando se utilicen medicamentos que contengan opiáceos (p. ej., antitusígenos, analgésicos opioides (ver sección 4.5)). Comorbilidad *Trastornos psiquiátricos* Se han registrado efectos psiquiátricos en estudios clínicos (ver sección 4.8). Si los pacientes presentan síntomas psiquiátricos no asociados al inicio del tratamiento con Selincro, y/o que no son transitorios, el médico prescriptor deberá considerar otras causas de los síntomas y valorar la necesidad de continuar el tratamiento con Selincro. Selincro no se ha investigado en pacientes con enfermedad psiquiátrica inestable. Se debe proceder con precaución al prescribir Selincro a pacientes con comorbilidad psiquiátrica presente como el trastorno depresivo mayor. *Trastornos convulsivos* Se dispone de experiencia limitada en pacientes con antecedentes de trastornos convulsivos, incluidas las convulsiones por abstinencia de alcohol. Se recomienda precaución si se inicia un tratamiento para reducir el consumo de alcohol en estos pacientes. *Insuficiencia renal o hepática* Selincro se metaboliza principalmente en el hígado y se elimina predominantemente por la orina. Por lo tanto, se debe tener precaución cuando se prescriba Selincro a pacientes con insuficiencia renal o hepática leve o moderada, por ejemplo, realizando controles más frecuentes. Se debe proceder con precaución al prescribir Selincro a pacientes con valores altos de ALAT o ASAT (> 3 veces el LSN), ya que estos pacientes fueron excluidos del programa de desarrollo clínico. Pacientes de edad avanzada (≥ 65 años de edad) Se dispone de datos clínicos limitados sobre el uso de Selincro en pacientes ≥ 65 años de edad con dependencia del alcohol. Se debe tener precaución al prescribir Selincro a pacientes ≥ 65 años de edad (ver secciones 4.2 y 5.2). Otras Se recomienda precaución si Selincro se administra conjuntamente con un inhibidor potente de la enzima UGT2B7 (ver sección 4.5). Lactosa Los pacientes con intolerancia hereditaria a galactosa, insuficiencia de lactasa de Lapp o problemas de malabsorción de glucosa o galactosa no deben tomar este medicamento. **4.5 Interacción con otros medicamentos y otras formas de interacción** No se han llevado a cabo estudios de interacción farmacológica *in vivo*. Según estudios *in vitro*, no se prevén interacciones clínicamente relevantes entre el nalmefeno, o sus metabolitos, y medicamentos administrados simultáneamente metabolizados por las enzimas más comunes CYP450 y UGT o transportadores de membrana. La administración conjunta con medicamentos que sean inhibidores potentes de la enzima UGT2B7 (p. ej., diclofenaco, fluconazol, acetato de medroxiprogesterona, ácido meclofenámico) puede aumentar significativamente la exposición a nalmefeno. Es improbable que esto suponga un problema con el uso ocasional, pero si se inicia un tratamiento a largo plazo simultáneo con un inhibidor potente de la UGT2B7, no se puede descartar la posibilidad de un aumento en la exposición a nalmefeno (ver sección 4.4). Por el contrario, la administración conjunta con un inductor de la UGT (p. ej., dexametasona, fenobarbital, rifampicina, omeprazol) puede dar lugar a concentraciones plasmáticas subterapéuticas de nalmefeno. Si se toma Selincro de manera simultánea con agonistas opioides (p. ej., algunos tipos de antitusígenos y antigripales, determinados antidiarreicos, y analgésicos opioides), puede que el paciente no se beneficie del agonista opioide. No existe ninguna interacción farmacocinética clínicamente relevante entre el nalmefeno y el alcohol. Se produce un pequeño deterioro en la función cognitiva y psicomotora tras la administración de nalmefeno. No obstante, el efecto de la combinación de nalmefeno y alcohol no superó la suma de los efectos de cada uno de ellos por separado. El consumo simultáneo de alcohol y Selincro no previene los efectos de la intoxicación del alcohol. **4.6 Fertilidad, embarazo y lactancia** Embarazo No hay datos o estos son limitados (menos de 300 resultados en embarazos) relativos al uso de nalmefeno en mujeres embarazadas. Los estudios en animales han mostrado toxicidad en la reproducción (ver sección 5.3). No se recomienda Selincro durante el embarazo. Lactancia Los datos farmacodinámicos/toxicológicos disponibles en animales muestran que nalmefeno/metabolitos se excretan en la leche (ver sección 5.3). Se desconoce si nalmefeno se excreta en la leche materna. No se puede excluir el riesgo en recién nacidos/lactantes. Se debe decidir si es necesario interrumpir la lactancia o interrumpir/abstenerse de iniciar el tratamiento con Selincro tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad En estudios de fertilidad en ratas, no se observaron efectos de nalmefeno sobre la fertilidad, el apareamiento, el embarazo o los parámetros espermáticos. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas** No se ha estudiado la influencia de nalmefeno sobre la capacidad para conducir y utilizar máquinas. Selincro puede provocar reacciones adversas como náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, relacionadas con el inicio del tratamiento y tuvieron una corta duración. La influencia de Selincro sobre la capacidad para conducir y utilizar máquinas es nula o insignificante. **4.8 Reacciones adversas** Resumen del perfil de seguridad Más de 3.000 pacientes han sido expuestos a nalmefeno en estudios clínicos. En general, el perfil de seguridad concuerda en todos los estudios clínicos realizados. Las frecuencias de las reacciones adversas en la Tabla 1 se calcularon basándose en tres estudios aleatorizados, a doble ciego y controlados con placebo en pacientes con dependencia del alcohol (1.144 pacientes expuestos a Selincro a demanda y 797 expuestos a placebo a demanda). Las reacciones adversas más frecuentes fueron náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración. En los estudios clínicos se comunicaron estados confusionales y, en raras ocasiones, alucinaciones y disociación. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración (de unas pocas horas a unos pocos días). La mayoría de estas reacciones adversas se resolvieron con el tratamiento continuo y no recurrieron con la administración repetida. Si bien estos acontecimientos tuvieron generalmente una corta duración, podrían tratarse de psicosis alcohólica, síndrome de abstinencia alcohólica o enfermedad psiquiátrica comórbida. Tabla de reacciones adversas Las frecuencias se definen como: 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) o frecuencia no conocida (no puede estimarse a partir de los datos disponibles). 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** En un estudio en pacientes diagnosticados de ludopatía, se investigaron dosis de nalmefeno de hasta 90 mg/día durante 16 semanas. En un estudio en pacientes con cistitis intersticial, 20 pacientes recibieron 108 mg/día de nalmefeno durante más de 2 años. Se ha registrado la toma de una dosis única de 450 mg de nalmefeno sin cambios en la tensión arterial, la frecuencia cardiaca y respiratoria o la temperatura corporal. No se ha observado un patrón atípico de reacciones adversas en estos contextos, si bien la experiencia es limitada. En caso de sobredosis, se recomienda realizar un tratamiento sintomático y someter al paciente a observación. **5. PROPIEDADES FARMACOLÓGICAS 5.1 Propiedades farmacodinámicas** Grupo farmacoterapéutico: Otros fármacos del sistema nervioso utilizados en la dependencia del alcohol. Código ATC: N07BB05 Mecanismo de acción El nalmefeno es un modulador del sistema opioide con un perfil definido de receptores μ, δ y κ. - Estudios *in vitro* han demostrado que el nalmefeno es un ligando selectivo de los receptores opioides con actividad antagonista en los receptores μ y δ y actividad agonista parcial en el receptor κ. - Estudios *in vivo* han demostrado que el nalmefeno reduce el consumo de alcohol, posiblemente como resultado de la modulación de las funciones corticomesolímbicas. Los datos de estudios no clínicos, estudios clínicos y literatura médica no indican ninguna forma de posible dependencia o abuso de Selincro. Eficacia clínica y seguridad En dos estudios de eficacia se evaluó la eficacia de Selincro en la reducción del consumo de alcohol en pacientes con dependencia del alcohol (DSM-IV). Se excluyó a los pacientes con antecedentes de delirium tremens, alucinaciones, convulsiones, comorbilidad psiquiátrica significativa, o alteraciones significativas de la función hepática así como a aquellos que presentaban síntomas de abstinencia físicos apreciables en la selección o la aleatorización. La mayoría (80%) de los pacientes incluidos tenían un NCR alto o muy alto (consumo de alcohol > 60 g/día en hombres y > 40 g/día en mujeres según los NCR de alcohol de la OMS) en la selección, y de estos el 65% mantuvieron un NCR alto o muy alto entre la selección y la aleatorización. Ambos estudios fueron aleatorizados, a doble ciego, con grupos paralelos y controlados con placebo, y al cabo de 6 meses de tratamiento, los pacientes que recibieron Selincro se volvieron a aleatorizar para recibir placebo o Selincro durante un periodo de lavado final de 1 mes. La eficacia de Selincro también se evaluó en un estudio aleatorizado, a doble ciego, con grupos paralelos, controlado con placebo y de 1 año de duración. En conjunto, en los estudios participaron 1.941 pacientes, de los cuales 1.144 fueron tratados con Selincro 18 mg a demanda. En la visita inicial se evaluaron el estado clínico, la situación social y el patrón de consumo de alcohol de los pacientes (según la información del paciente). En la visita de aleatorización, que tuvo lugar al cabo de 1 a 2 semanas se reevaluó el NCR, y se inició el tratamiento con Selincro junto con una intervención psicosocial (BRENDA) dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Selincro se prescribió a demanda, y los pacientes lo tomaron, de promedio, aproximadamente la mitad de los días. La eficacia de Selincro se evaluó utilizando dos criterios de valoración principales: el cambio desde la visita basal al mes 6 en el número de días de consumo excesivo de alcohol (DCE) al mes y el cambio desde la visita basal al mes 6 en el consumo de alcohol total diario (CAT). Un DCE se definió como un día con un consumo ≥ 60 g de alcohol puro en hombres y ≥ 40 g en mujeres. Se produjo una reducción significativa del número de DCE y CAT en algunos pacientes en el periodo entre la visita inicial (selección) y la aleatorización debido a efectos no farmacológicos. En los estudios 1 (n = 579) y (n = 655) 2, el 18% y el 33% de la población total, respectivamente, redujeron considerablemente su consumo de alcohol en el periodo comprendido entre la selección y la aleatorización. Con respecto a los pacientes con un NCR alto o muy alto en la visita basal, el 35% de los pacientes experimentaron mejorías debido a los efectos no farmacológicos en el período entre la visita inicial (selección) y la aleatorización. En la aleatorización, estos pacientes consumían una cantidad tan baja de alcohol que era poco el margen para seguir mejorando (efecto suelo). Por lo tanto, los pacientes que mantuvieron un NCR alto o muy alto en la aleatorización se definieron a posteriori como la población objetivo. En esta población post hoc, el efecto terapéutico fue mayor en comparación con el de la población total. La eficacia y relevancia clínicas de Selincro se analizaron en pacientes con un NCR alto o muy alto en la selección y la aleatorización. En la visita basal, los pacientes tenían, de promedio, 23 DCE al mes (11% de los pacientes tenían menos de 14 DCE al mes) y consumían 106 g/día. La mayoría de los pacientes tenían una dependencia del alcohol baja (55% con una puntuación de 0 a 13) o intermedia (36% con una puntuación de 14 a 21) según la Escala de Dependencia de Alcohol. *Análisis post-hoc de la eficacia en pacientes que mantuvieron un NCR alto o muy alto en la*

Tabla 1: Frecuencias de las reacciones adversas

Sistema de clasificación de órganos	*Frecuencia*	*Reacción adversa*
Trastornos del metabolismo y de la nutrición	Frecuente	Apetito disminuido
Trastornos psiquiátricos	Muy frecuente	Insomnio
	Frecuente	Trastorno del sueño
		Estado confusional
		Inquietud
		Libido disminuida (incluida la pérdida de líbido)
	No conocida	Alucinación (incluidas alucinaciones auditivas, alucinaciones táctiles, alucinaciones visuales y alucinaciones somáticas)
		Disociación
Trastornos del sistema nervioso	Muy frecuente	Mareo
		Cefalea
	Frecuente	Somnolencia
		Temblor
		Alteración de la atención
		Parestesia
		Hipoestesia
Trastornos cardiacos	Frecuente	Taquicardia
		Palpitaciones
Trastornos gastrointestinales	Muy frecuente	Náuseas
	Frecuente	Vómitos
		Boca seca
Trastornos de la piel y del tejido subcutáneo	Frecuente	Hiperhidrosis
Trastornos musculoesqueléticos y del tejido conjuntivo	Frecuente	Espasmos musculares
Trastornos generales y alteraciones en el lugar de administración	Frecuente	Fatiga
		Astenia
		Malestar general
		Sensación anormal
Exploraciones complementarias	Frecuente	Peso disminuido

Tabla 2: Resultados de los análisis de respondedores con datos agrupados de pacientes con un NCR alto o muy alto en la selección y la aleatorización

Respuesta[a]	Placebo	Nalmefeno	Odds ratio (IC del 95%)	Valor p
CAT R70[b]	19,9%	25,4%	1,44 (0,97; 2,13)	0,067
0-4 DCE[c]	16,8%	22,3%	1,54 (1,02; 2,35)	0,040

a En el análisis se trata a los pacientes que abandonaron como no respondedores
b Reducción del CAT ≥ 70% respecto al valor basal en el mes 6 (periodo de 28 días)
c De 0 a 4 DCE/mes en el mes 6 (periodo de 28 días)

aleatorización En el estudio 1, el porcentaje de abandonos fue más elevado en el grupo de Selincro que en el grupo de placebo (50% frente a 32%, respectivamente). En cuanto a los DCE, se registraron 23 días/mes en la visita basal en el grupo de Selincro (n = 171) y 23 días/mes en la visita basal en el grupo de placebo (n = 167). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el número de DCE fue de 9 días/mes en el grupo de Selincro (n = 85) y 14 días/mes en el grupo de placebo (n = 114). El CAT fue de 102 g/día en la visita basal en el grupo de Selincro (n = 171) y 99 g/día en la visita basal en el grupo de placebo (n = 167). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el CAT fue de 40 g/día en el grupo de Selincro (n = 85) y 57 g/día en el grupo de placebo (n = 114). En el estudio 2, el porcentaje de abandonos fue superior en el grupo de Selincro que en el grupo de placebo (30% frente a 28%, respectivamente). En cuanto a los DCE, se registraron 23 días/mes en la visita basal en el grupo de Selincro (n = 148) y 22 días/mes en la visita basal en el grupo de placebo (n = 155). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el número de DCE fue de 10 días/mes en el grupo de Selincro (n = 103) y 12 días/mes en el grupo de placebo (n = 111). El CAT fue de 113 g/día en la visita basal en el grupo de Selincro (n = 148) y 108 g/día en la visita basal en el grupo de placebo (n = 155). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el CAT fue de 44 g/día en el grupo de Selincro (n = 103) y 52 g/día en el grupo de placebo (n = 111). Los análisis de respondedores con los datos agrupados de los dos estudios se incluyen en la Tabla 2. Se dispone de datos limitados sobre Selincro en el periodo de lavado final de 1 mes. *Estudio de 1 año* En este estudio participaron un total de 665 pacientes: 52% de ellos tenían un NCR alto o muy alto en la visita basal, y de estos el 52% (que representan el 27% de la población total) siguieron teniendo un NCR alto o muy alto en la aleatorización. En esta población objetivo post-hoc, abandonaron más pacientes que recibían nalmefeno (45%) que aquellos que recibían placebo (31%). En cuanto a los DCE, se registraron 19 días/mes en la visita basal en el grupo de Selincro (n = 141) y 19 días/mes en la visita basal en el grupo de placebo (n = 42). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia al cabo de 1 año, el número de DCE fue de 5 días/mes en el grupo de Selincro (n = 78) y 10 días/mes en el grupo de placebo (n = 29) E l CAT fue de 100 g/día en la visita basal en el grupo de Selincro (n = 141) y 101 g/día en la visita basal en el grupo de placebo (n = 42). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia al cabo de un año, el CAT fue de 24 g/día en el grupo de Selincro (n = 78) y 47 g/día en el grupo de placebo (n = 29). Población pediátrica La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Selincro en los diferentes grupos de la población pediátrica en el tratamiento de la dependencia del alcohol (ver sección 4.2 para consultar la información sobre el uso en la población pediátrica). **5.2 Propiedades farmacocinéticas** Absorción El nalmefeno se absorbe rápidamente tras una única administración oral de 18,06 mg, con una concentración máxima (C_{max}) de 16,5 ng/ml al cabo de aproximadamente 1,5 horas, y una exposición (AUC) de 131 ng*h/ml. La biodisponibilidad oral absoluta de nalmefeno es del 41%. La administración de alimentos ricos en grasas aumenta la exposición total (AUC) en un 30% y la concentración máxima (C_{max}) en un 50%; el tiempo hasta la concentración máxima (t_{max}) se retrasa 30 minutos (t_{max} es de 1,5 horas). Se considera poco probable que este cambio tenga relevancia clínica. Distribución La fracción media de nalmefeno unida a proteínas en plasma es de aproximadamente el 30%. El volumen de distribución (Vd/F) estimado es de aproximadamente 3200 l. Los datos de ocupación obtenidos en un estudio PET tras la administración diaria única y repetida de 18,06 mg de nalmefeno muestran un 94-100% de ocupación de los receptores 3 horas después de la administración, lo que indica que el nalmefeno atraviesa fácilmente la barrera hematoencefálica. Biotransformación Tras la administración oral, el nalmefeno sufre un extenso y rápido metabolismo para formar su principal metabolito, el nalmefeno-3-O-glucurónido, siendo la enzima UGT2B7 la principal responsable de la conversión, y con las enzimas UGT1A3 y UGT1A8 como factores contribuyentes secundarios. Un pequeño porcentaje de nalmefeno se convierte en nalmefeno-3-O-sulfato por sulfatación y en nornalmefeno por CYP3A4/5. El nornalmefeno se convierte posteriormente en nornalmefeno 3 O glucurónido y nornalmefeno-3-O-sulfato. Se considera que los metabolitos no contribuyen con un efecto farmacológico significativo sobre los receptores opioides en humanos, salvo en el caso de nalmefeno-3-O-sulfato, que posee una potencia comparable a la de nalmefeno. No obstante, el nalmefeno-3-O-sulfato está presente a concentraciones inferiores al 10% de la de nalmefeno, por lo que es muy poco probable que constituya un factor contribuyente principal en el efecto farmacológico de nalmefeno. Eliminación El metabolismo por conjugación del glucurónido es el principal mecanismo de aclaramiento de nalmefeno, y la excreción renal es la principal vía de eliminación de nalmefeno y sus metabolitos. El 54% de la dosis total se elimina por la orina en forma de nalmefeno-3-O-glucurónido, mientras que el nalmefeno y sus otros metabolitos están presentes en la orina en cantidades inferiores al 3% cada uno. Se calcula que el aclaramiento oral de nalmefeno (CL/F) es de 169 l/h y la semivida de eliminación de 12,5 horas. De los datos de distribución, metabolismo y eliminación se desprende que el nalmefeno tiene un coeficiente de extracción hepática elevado. Linealidad/No linealidad El nalmefeno muestra un perfil farmacocinético lineal independiente de la dosis en el intervalo de dosis de 18,06 mg a 72,24 mg, con un aumento de 4,4 veces en la C_{max} y un aumento de 4,3 veces en el AUC_{0-tau} (en estado estacionario o casi). El nalmefeno no muestra diferencias farmacocinéticas importantes entre sexos, entre jóvenes y ancianos, o entre diferentes grupos étnicos. Sin embargo, el tamaño corporal parece afectar mínimamente al aclaramiento de nalmefeno (el aclaramiento aumenta cuanto mayor es el tamaño corporal), si bien se considera poco probable que tenga relevancia clínica. Insuficiencia renal No se dispone de datos tras la administración oral en pacientes con insuficiencia renal. La administración IV de 1 mg de nalmefeno en pacientes con insuficiencia renal grave produjo una exposición 1,6 veces mayor (AUC_{inf} ajustada por dosis), y una menor C_{max} (en un factor de aproximadamente 2,1 a 4,6) que en voluntarios sanos. La semivida de eliminación (26 horas) fue más larga que la de los voluntarios sanos (10 horas) (ver secciones 4.3 y 4.4). Insuficiencia hepática La administración de una dosis única de 18,06 mg de nalmefeno a los pacientes con insuficiencia hepática leve o moderada aumentó la exposición respecto a la de los voluntarios sanos. En pacientes con insuficiencia hepática leve, la exposición aumentó 1,5 veces y el aclaramiento oral se redujo en aproximadamente un 35%. En pacientes con insuficiencia hepática moderada, la exposición aumentó 2,9 veces para el AUC y 1,7 veces para la C_{max}, mientras que el aclaramiento oral se redujo en cerca del 60%. No se observaron cambios clínicamente relevantes en el t_{max} o la semivida de eliminación en ninguno de los grupos. No se dispone de datos farmacocinéticos tras la administración oral de nalmefeno a pacientes con insuficiencia hepática grave (ver secciones 4.3 y 4.4). Pacientes de edad avanzada No se ha realizado ningún estudio específico con administración oral en pacientes de ≥ 65 años. Un estudio con administración IV indicó que no existen cambios relevantes en la farmacocinética en pacientes de edad avanzada en comparación con adultos más jóvenes (ver secciones 4.2 y 4.4). **5.3 Datos preclínicos sobre seguridad** El nalmefeno ha mostrado potencial de sensibilización cutánea en el ensayo de ganglio linfático local en ratones tras la aplicación tópica. Los estudios en animales no sugieren efectos perjudiciales directos con respecto a la fertilidad, el embarazo, el desarrollo embrionario o fetal, el parto o el desarrollo posnatal. En un estudio de toxicidad para el desarrollo realizado en conejos, se observaron efectos en los fetos en términos de reducción de peso fetal y retraso en la osificación, pero no anomalías graves. La AUC a dosis máximas sin efecto adverso observado (NOAEL), para estos efectos fue inferior a la exposición en humanos a la dosis clínica recomendada. Se observó un aumento de la viabilidad natal y una disminución de la viabilidad posnatal de las crías en estudios de toxicidad prenatal y posnatal en ratas. Este efecto se consideró un efecto indirecto relacionado con la toxicidad materna. Los estudios en ratas han mostrado excreción de nalmefeno o sus metabolitos en leche. Los datos no clínicos no muestran riesgos especiales para los seres humanos según los estudios convencionales de farmacología de seguridad, toxicidad a dosis repetidas, genotoxicidad o potencial carcinogénico. **6. DATOS FARMACÉUTICOS 6.1 Lista de excipientes** Núcleo del comprimido Celulosa microcristalina Lactosa anhidra Crospovidona, tipo A Estearato de magnesio Recubrimiento del comprimido Hipromelosa Macrogol 400 Dióxido de titanio (E171) **6.2 Incompatibilidades** No procede. **6.3 Periodo de validez** 3 años. **6.4 Precauciones especiales de conservación** Este medicamento no requiere condiciones especiales de conservación. **6.5 Naturaleza y contenido del envase** Blísters transparentes de PVC/PVdC/aluminio en cajas de cartón. Tamaños de envases de 7, 14, 28, 42, 49 y 98 comprimidos recubiertos con película. Puede que solamente estén comercializados algunos tamaños de envases. **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** H. Lundbeck A/S Ottiliavej 9 DK-2500 Valby Dinamarca **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN** EU/1/12/815/001 7 comprimidos EU/1/12/815/002 14 comprimidos EU/1/12/815/003 28 comprimidos EU/1/12/815/004 42 comprimidos EU/1/12/815/005 98 comprimidos EU/1/12/815/006 49 comprimidos EU/1/12/815/007 14 comprimidos, tarjeta EU/1/12/815/008 28 comprimidos, tarjeta **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN** Fecha de la primera autorización: 25 de Febrero de 2013 **10. PRESENTACIÓN Y PRECIO PVP (IVA)** Selincro 18 mg, envase con 14 comprimidos. P.V.P 63,04 € P.V.P iva 65,57 € **11. CONDICIONES DE DISPENSACIÓN POR LA SEGURIDAD SOCIAL** Con receta médica. Especialidad reembolsable por el Sistema Nacional de Salud. Con visado de inspección. Cícero de aportación reducida. **12. FECHA DE LA REVISIÓN DEL TEXTO:** Mayo 2015 La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu/.

Reducir para ganar

Único fármaco indicado para la reducción del consumo de alcohol[2]

(2) Ficha técnica Selincro 2013

Lundbeck

Selincro®
nalmefeno