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

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

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Abstract

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

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

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

Keywords: Alcohol use disorder; Cohort study; Research.

Resumen

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Method

Study design

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

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

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

Ethical issues

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

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

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

Registered information

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

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

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

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

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

Note. *Coordination centre.

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

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

Table 2 displays a detailed summary of these variables.

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

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

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

Data collection process

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

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

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

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

Biobank

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

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

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

Authorship criteria

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

Data analysis

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

Results

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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Appendix

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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