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Can we increase risk perception among medical cannabis users?

¿Es posible crear la adecuada sensación de riesgo entre los consumidores de cannabis medicinal?

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Research regarding the possible therapeutic applications of cannabinoids continues to expand. Although the results obtained in some diseases are encouraging, developmental research is still in its initial stages. For some symptoms, the medicinal effectiveness of cannabinoids has been proven, but in many cases, adequate evidence is not yet available in this regard, nor are the existing data on the risks associated with the use of medicinal cannabis sufficient.

The lack of conclusive clinical research results does not stop social networks being flooded with messages proclaiming the efficacy of cannabis preparations for almost all diseases. Such propaganda does not usually indicate the potential appearance of side effects in this type of treatment. Perhaps the most insidious of all this biased information, however, is that the invitation to use it does not mention the need to consult with the true specialists in the treatment of diseases, namely, doctors.

When about to take any medicine, it is a matter of common sense to be aware of its potential risks as well as its benefits. Nevertheless, this rule is not followed by many of those currently using medical cannabis. The existence of risks associated with the recreational use of cannabis suggests such risks could also appear when used for therapeutic purposes.

It is therefore necessary that research on the therapeutic effects of cannabinoids be accompanied by the study of possible side effects linked to their medical use. The results obtained may serve to guide doctors in their proper clinical application and to warn those who decide to use them without proper medical control.

The aim is to discover the frequency with which the effects associated with cannabis use occur, such as addiction and dependence, myocardial infarction, stroke and schizophrenia, and other types of risk that, given their low incidence, would be difficult to identify in small clinical samples. Possible pharmacological interactions between cannabinoids and other drugs used by patients should also be identified (Bonn-Miller et al., 2019).

What is the state of the art regarding the medical use of cannabinoids?

Over time, many reviews have compiled information available on this matter. None of them, however, managed to reach the degree of systematization necessary to be able to adequately reflect the real situation. This aim was only achieved in 2017, after the appearance of several reports meeting this requirement.

Among these, three stand out, given the scale and rigour of the information contained:

- "The health effects of cannabis and cannabinoids", published in January 2017 by the Health and Medicine Division of the National Academy of Sciences, Engineering and Medicine of the United

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States (National Academies of Sciences, Engineering, and Medicine, 2017).

- "Information for health care professionals. Cannabis (marihuana, marijuana) and the cannabinoids. Dried or fresh plant and oil administration by ingestion or other means", issued in October 2018 by the Canadian Ministry of Health (Health Canada, 2018).
- "Medical use of cannabis and cannabinoids. Questions and answers for policymaking", issued by the European Monitoring Center for Drugs and Drug Addiction (2018).

These reports concluded that in relation to cannabinoids there is:

- Substantial evidence of its therapeutic effects in chronic pain in adults, antiemesis in chemotherapy and spasticity symptoms in multiple sclerosis.
- Moderate evidence of improvements in sleep disturbances associated with apnea, fibromyalgia, chronic pain and multiple sclerosis.
- Knowledge that an appreciable amount of limited evidence exists regarding its effectiveness or ineffectiveness in other cases.

To these conclusions must be added its most recent use in the treatment of two infrequent forms of epilepsy: Lennox-Gastaut syndrome and Dravet syndrome.

The above reports also indicated the danger that in some patients, medical prescription of cannabinoids may be responsible for the appearance of some of the problems linked to recreational use.

In this regard, there is substantial evidence that cannabis can:

- Increase the risk of traffic accidents or accidents involving the handling of machinery.
- Reduce the weight of the newborn.
- Lead to overdose in children under 6 years of age after accidental consumption.
- Cause schizophrenia or other psychoses.
- Increase the risk of cardiovascular problems.
- Worsen respiratory symptoms when smoked, which would increase episodes of chronic bronchitis and, with less evidence, contribute to the appearance of some type of cancer associated with the respiratory tract, such as lung cancer.
- Contribute to the appearance of cannabis dependence.
- Increase the risk of cognitive disorders.

Age of onset and frequency of consumption were also indicated as risk factors for the appearance of problems related to its use.

In summary, the reports presented some conclusive results regarding the medical applications of cannabinoids in some diseases and opened the door to the treatment of others. Nevertheless, they also warned of the risks that may arise during treatment.

Problems associated with cannabis use

The existence of risks associated with cannabis use raises the need to define them and to understand in what situations they may appear, above all, in those pathologies that may be related to disorders of the endocannabinoid system or in those patients whose clinical condition makes them vulnerable to the administration of cannabinoids.

To meet this objective, we may begin by consulting the data reported in those countries where medical treatment with cannabinoids is already approved and in operation.

Reviews published in this regard show that treatment had to be withdrawn in some patients. Others described the appearance of psychiatric, neurological, musculoskeletal or connective tissue disorders.

Adverse effects included: asthenia, loss of balance, dizziness, disorientation, diarrhoea, euphoria, drowsiness, headache, dry mouth, fatigue, euphoria, hallucinations, nausea and vomiting. Psychiatric symptoms included confusion, paranoia, psychosis, and substance dependence (EMCDDA, 2018; Mücke, Phillips, Radbruch, Petzke & Häuser, 2018; Whiting et al., 2015).

There is still not enough data to indicate the long-term effects produced by the medical use of cannabinoids. Knowledge of this would be interesting, since prolonged use can lead to negative consequences that do not necessarily appear in the initial stages.

Given the difficulties existing in Spain to implement this type of treatment, "verified" information on this subject is scarce. Nevertheless, this should not be an excuse for health professionals to ignore the necessary requirements for the proper treatment of patients and to identify and solve the problems associated with medical cannabis.

The guide issued by the College of Family Physicians of Canada for the prescription of medical cannabis can be very useful for advising those doctors who want to proceed with its use. The report provides recommendations for use in primary care, based on existing experience in the four clinical areas with the most evidence on cannabinoid treatment: pain, nausea and vomiting, spasticity, and adverse effects (Allan et al., 2018).

Although the Canadian guide is preferable, the information issued by the College of Pharmacists of Barcelona can also be consulted. This is aimed at those who self-administer certain types of cannabis preparations for the treatment of their illness. It is intended to warn of the risks associated with its use, given the lack of medical control and the variability in the active ingredients of the plant, which makes adequate dosage and appropriate monitoring of its use difficult (Borrás, 2019).

Effects of the legalization of medicinal cannabis on the perception of risk

Uruguay was the first country to legalize the use of cannabis for medicinal purposes; since then, a large number of countries, mainly European and American, have followed suit. It is interesting to assess how this legalization has managed to influence the perception of risk regarding cannabis.

The legalization of medicinal cannabis has involved an increase in THC content and, curiously, a decrease in CBD concentrations, which, a priori, is the one of greatest therapeutic interest and has fewer adverse psychoactive effects (Cash, Cunnane, Fan & Romero-Sandoval, 2020). At the same time, the consumption of new forms of cannabis has increased and the price has fallen, thus making it more accessible (Isorna, Pascual, Aso & Arias, 2022).

The legalization of medicinal cannabis is considered to have had little direct impact on recreational use among young people (Melchior et al., 2019). However, the marketing of cannabis products for therapeutic uses in some states may be influencing the perception of risk. A California study found that teens who had seen medical marijuana advertisements on billboards, in magazines or other media in the past three months were more likely to use cannabis and more likely to be using cannabis up to a year later (D'Amico, Miles & Tucker, 2015).

Conversely, in adults, the legalization of medical cannabis in the USA has involved an increase in recreational use and cannabis use disorder (CUD) (Cerdá et al., 2020). Using data from surveys carried out in the same country from 1991 to 2013 (NLAES and NESARC studies), Hassin et al. (2017) show that legal medicinal cannabis is accompanied by an increase in the prevalence of illegal consumption and CUD.

It has been observed that several years after the legalization of medicinal cannabis, the frequency of CUD has risen, especially in states where dispensaries and collective cultivation is permitted. The demand for treatment for CUD is increasing both globally and for young people (Smart & Pacula, 2019), and there is a link between higher density of medical cannabis dispensaries in California and CUD hospitalizations (Mair, Sumetsky, Kranich & Freisthler, 2021).

In addition to higher cannabis consumption, it has been observed that the sense of risk regarding cannabis use is lower and perception of its potential benefits for reducing pain or other medical or psychopathological problems is greater in states where medicinal cannabis is legal (Steigerwald et al., 2020).

Moreover, the legalization of medical cannabis can increase the concomitant use of cannabis and alcohol or tobacco, and there is no evidence that it has a positive role in reducing the use of prescription opioids (Isorna et al., 2022).

Regarding medical emergencies, after the liberalization of medical cannabis in Colorado, an increase in visits and calls to emergency departments due to cannabis use was observed (Wang et al., 2017; Wang, Davies, Halmo, Sass & Mistry, 2018).

Another relevant aspect is the impact that legalization may have among the pediatric population, since it increases the likelihood of minors being exposed to this substance. Thus, cases of accidental pediatric exposure to cannabis increased in Massachusetts after medical marijuana was legalized in 2012, despite the use of child-resistant packaging and warning labels (Whitehill et al., 2019). A review found an increase in pediatric patients with cyclic vomiting syndromes due to the intake of edible cannabis products. This is mainly attributed to the high concentrations of THC in the plants cultivated for medical cannabis and the greater appetite produced when incorporated into sweet foods, such as candies and baked goods, contributing to repeated visits to emergency departments (Wolf, Perhats, Clark, Frankenberger & Moon, 2020).

A further aspect of interest is that the legalization of medical cannabis does not imply that patients and clinicians know more about its therapeutic and adverse effects given the difficulty in distinguishing medical from recreational use (Lancaster, Seear & Ritter, 2017). Thus, among cancer patients in states with legal medicinal cannabis there was an increase in use, but despite wanting information about it, they did not obtain it (Pergam et al., 2017). One year after legalization in Thailand, a significant lack of information has also been noted for patients, with a significant percentage believing that it cured cancer, and for physicians, reporting frequent adverse effects (Zinboonyahgoon, Srisuma, Limsawart, Rice & Suthisisang, 2021).

How the problem should be tackled

The data from studies carried out on the possible risks linked to medical treatments with cannabis preparations allow us to conclude that there is evidence, especially at the level of short-term effects, of the appearance of side effects in some patients undergoing these types of treatments.

This means that medical cannabis users need to be aware that they cannot make the decision to medicate with cannabinoids on their own. It is the doctor who, in view of existing clinical data, has to advise on the possible benefits of the "new treatment".

Once the treatment has begun, the doctor must carry out a series of checks on the patient regarding the suitability of the cannabis preparations prescribed, and, in view of the results obtained, continue or abandon the treatment.

Patients must become used to understanding the existing data on possible complications that may accompany the

use of these preparations, in the same way as they would read the corresponding directions for use when taking other medications.

In addition, it should be taken into account whether the patient's previous or current use of cannabis can influence medication with cannabinoids. In both cases, a synergy may be generated in the occurrence of problems linked to uncontrolled cannabis use.

This argument should also be considered by those patients thinking about the possibility of taking up recreational use to reinforce the effects of treatment. This also applies to those who try to justify that the consumption of cannabis or any type of cannabis preparation can be used to prevent the appearance of diseases in which there is scientific evidence regarding the usefulness of cannabinoids.

Finally, it should be clear that therapeutic treatments with cannabinoids cannot serve as an argument in favour of their recreational use. It is necessary to learn to separate both types of consumption to avoid medical use serving as a justification for recreational use and the latter leading to the former.

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Validation of the Alcohol Smoking and Substance Involvement Screening Test (ASSIST) in acute psychiatric inpatients

Validación de la prueba de detección de consumo de alcohol, tabaco y sustancias (ASSIST) en pacientes con trastorno psiquiátrico ingresados en una unidad de agudos

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Abstract

The aims of this study were to examine the psychometric properties of The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in psychiatric inpatients, due to the scarcity of screening instruments validated in this population. Patients from Hospital Clínic's psychiatric ward (n = 202) completed: ASSIST, Addiction Severity Index (ASI), MINI-International Neuropsychiatric Interview (MINI), Alcohol Use Disorders Identification Test (AUDIT), Fagerström Test for Nicotine Dependence (FTND), Severity of Dependence Scale (SDS), and Drug Abuse Screening Test (DAST). Reliability and validity evidences based on internal structure (Exploratory and Confirmatory Factor Analyses) and on the relation to other variables were obtained. Excellent internal consistency was found for Total Substance Involvement (TSI) (α = .92 and ω = .93) and for Specific Substance Involvement (SSI) scores (α = .88 - .96 and ω = .89 - .95). Analysis of internal structure for tobacco, alcohol and cannabis subscales resulted in unidimensional models with adequate goodness-of-fit indices. ASSIST scores were significantly correlated with those of ASI (r = .795 to r = .953), AUDIT (r = .864), FTND (r = .808), DAST (r = .831), SDS (r = .519) and with "number of diagnoses of abuse/dependence" in MINI-Plus (TSI: r = .857 to r = .862; SSI: r = .646 to r = .834). Receiver operating characteristic analysis (ROC) and Mann-Whitney's U test found good discriminative validity evidences. ASSIST scores showed good reliability and there were validity evidences that support its use for identifying risk levels of tobacco, alcohol and other substance use in psychiatric patients.

Keywords: Addiction; alcohol use disorder; substance use disorder; ASSIST; mental health; screening.

Resumen

Los objetivos fueron examinar las propiedades psicométricas de la prueba de detección de consumo de alcohol, tabaco y sustancias (ASSIST) en pacientes con trastorno psiquiátrico. Un total de 202 pacientes ingresados en psiquiatría del Hospital Clínic completaron: ASSIST, Índice de gravedad de la adicción (ASI), MINI-Entrevista Neuropsiquiátrica Internacional (MINI), cuestionario de identificación de los trastornos debidos al consumo de alcohol (AUDIT), Test de Fagerström (FTND), Escala de gravedad de la dependencia (SDS) y Prueba de detección de abuso de drogas (DAST). Se obtuvieron la fiabilidad y evidencia de validez de la estructura interna (análisis factorial exploratorio/confirmatorio) y de la relación con otras variables. Se encontró excelente consistencia interna en puntuaciones de riesgo total (TSI) (α = ,92 y ω = ,93) y de cada sustancia (SSI) (α = ,88 - ,96 y ω = ,89 - ,95). La estructura interna de tabaco, alcohol y cannabis resultó en modelos unidimensionales con índices de bondad de ajuste adecuados. Las puntuaciones del ASSIST correlacionaron significativamente con: ASI (r = ,795 a r = ,953), AUDIT (r = ,864), FTND (r = ,808), DAST (r = ,831), SDS (r = ,519) y «número de diagnósticos de abuso/dependencia» en MINI-Plus (TSI: r = ,857 - ,862; SSI: r = ,646 - ,834). El análisis de curva ROC y U de Mann-Whitney mostraron evidencias de validez discriminativa. Las puntuaciones del ASSIST tienen buena fiabilidad y existen evidencias de validez para su uso en la detección del nivel de riesgo de consumo de tabaco, alcohol y sustancias en pacientes con trastorno psiquiátrico.

Palabras clave: Adicción; trastorno por consumo de alcohol; trastorno por consumo de sustancias; ASSIST; salud mental; cribado.

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Alcohol and substance use disorders (SUD), affect approximately 2.6% of the world's population each year (Degenhardt et al., 2017). Psychiatric disorders are associated with an increased risk of SUD. Among those with a comorbid mental disorder, the other psychiatric disorder often precedes the SUD (Degenhardt et al., 2019). The estimated prevalences of lifetime comorbidity of mood and anxiety disorders with any SUD is 40.9% and 29.9% respectively (Conway, Compton, Stinson & Grant, 2006) and those of bipolar disorder and schizophrenia with any SUD are higher than 40% (Dixon, 1999; Merikangas et al., 2011).

A low proportion of people with SUD receive addiction treatment (only 11% of those with a past year SUD), being this proportion slightly higher (18%) among those with a comorbid psychiatric disorder (Harris et al., 2019). When co-ocurring SUD disorders are undiagnosed and untreated in psychiatric patients, the course of illness is more severe and disabling, having these patients worse treatment outcomes than those with only SUD (Morisano, Babor & Robaina, 2014). To achieve effective diagnosis and treatment of comorbid SUD, it is important to integrate screening into everyday practice in psychiatric inpatients wards (Crome, Bloor & Thom, 2006). With the exception of the ASSIST, existing screening instruments neither cover all substances nor help deciding which type of intervention is more appropriate because most of them focus on dependence.

The World Health Organization (WHO) developed the ASSIST (Ali et al., 2002) which screens for all type of substances and has eight items (Q1: lifetime use, Q2: frequency of use during the last 3 months, Q3: compulsion to use substances, Q4: health, social, financial or legal problems associated with substance use, Q5: failure to meet role obligations, Q6: concern of family, friends or professionals with their use, Q7: failed attempts to quit or reduce and Q8: injection of drugs in their lifetime). Several domains or scores can be derived: Specific Substance Involvement score (SSI) for each substance (sum of response weights to items 1 to 7) and Total Substance Involvement score (TSI) (sum of response weights for items 1 to 8), as well as frequency, dependence and abuse. The SSI is a risk score for each substance, that determines the level of risk of substance use (low, moderate or high) and the most appropriate intervention for that level of use (no treatment, brief intervention or referral to addiction treatment respectively).

The proposed classification of SUD in ICD-11 covers different levels of substance use, from single harmful use to consolidated addictive behaviors, with the aims of facilitating early recognition of health problems derived from substance use and providing treatment interventions (Bascarán, Flórez, Seijo & García, 2019). Similarly, the ASSIST, can be a useful instrument for identifying different levels of risk in psychiatric patients and for increasing early access to appropriate interventions.

The original validation of the ASSIST (Humeniuk et al., 2008), and the validation in a Spanish sample (Rubio Valladolid et al., 2014), included patients from primary care and drug treatment settings. The only validation study in psychiatric population obtained good results but was limited to patients with first episode psychosis (Hides et al., 2009).

The aims of the study were to evaluate the reliability of the scores and to obtain validity evidences of the Spanish version of ASSIST to support its use to assess low, moderate and high level of risk of tobacco, alcohol and substance use in hospitalized psychiatric patients.

We expected that the reliability would be similar to that reported in previous studies (Hides et al., 2009; Humeniuk et al., 2008; Rubio Valladolid et al., 2014), that is, between .89 to .93 for TSI score and above .75 for SSI scores. We hypothesized a one factor model based on results of previous research (Pérez-Moreno, Calzada-Álvarez, Rovira-Guardiola & Torrico Linares, 2012; Tiburcio Sainz et al., 2016). We also hypothesized that ASSIST scores would have moderate to high correlations with the scores of instruments considered a gold-standard in addictions and other related variables.

Method

Participants

This cross-sectional study was undertaken in a general tertiary hospital that provides specialized services for a middle-income population mainly of Spanish nationality. Eligible subjects (Figure 1) included patients 18 years or older hospitalized in the psychiatric ward of Hospital Clinic of Barcelona, who had achieved stability from acute psychiatric symptoms and whose discharge date was within the next four days. Exclusion criteria were: 1) Mini Mental State Examination (Lobo, Ezquerra, Gómez, Sala & Seva, 1979) score below 27; 2) diagnosis of significant cognitive impairment or mental retardation; 3) inability to communicate due to language barrier, deafness or severe visual deficits; 4) aggressive behavior; 5) confusion or memory deficits due to recent electroconvulsive therapy; 6) presence of acute severe psychiatric symptoms. From 224 eligible candidates, 13 patients refused to participate and 211 patients gave informed consent. A convenience sample of 202 individuals was recruited after patients successfully completed all tests.

The sample (n = 202) consisted of 166 patients hospitalized for a psychiatric disorder and 36 patients hospitalized for detoxification of an alcohol or substance use disorder. The mean length of stay at the hospital was 19.6 days, (*SD* = 11.0). Age ranged from 19 to 84, with a mean of 44.0 ± 15.5 years. 47% of the sample were male, 52% were single, 32.2 % were

employed and 74.3% reported having completed secondary education or higher (see tables A and B in supporting material for a detailed description of the sample).

Procedure

The validation process followed the AERA, APA and NCME standards (American Educational Research Association, American Psychological Association, & National Council on Measurement in Education, 2014; Muñiz & Fonseca-Pedrero, 2019) for sources of validity evidence in educational and psychological testing. Reliability of the scores was estimated through internal consistency. Validity evidences based on internal structure and on the relation to other variables were obtained.

Before starting the recruitment, we ensured that items from the ASSIST Spanish version (Rubio Valladolid et al., 2014) were understandable for this population. Twenty randomly selected psychiatric inpatients were assessed with the ASSIST before starting the recruitment of the sample to check whether patients understood what was being asked in the test. Some comprehension difficulties were encountered with the self-administered version that were solved when a psychologist administered the test. Therefore, self-administration was disregarded. Patients consecutively admitted to the psychiatric ward were interviewed by a clinical psychologist with expertise in addictions and trained in the use of questionnaires. Patients were informed that their participation was voluntary. It took from 60 to 90 minutes to administer the whole battery and from 5 to 15 minutes to administer the ASSIST. Patients were assigned to the General Psychiatry Group (GPG) if they had been hospitalized due to a psychiatric disorder or to the Addiction Group (AG) if they had been hospitalized due to an alcohol or substance use disorder.

Measures

This study used the protocol developed by the WHO ASSIST group (Humeniuk et al., 2008). Sociodemographic data and independent and blind psychiatric diagnose of SUD if present were gathered. Participants completed the ASSIST V3.0 (Rubio Valladolid et al., 2014) and the following battery of tests (Figure 1) in their Spanish version:

Addiction Severity Index (ASI): a semi-structured interview to assess the severity of problems in several areas (medical, employment status, legal aspects, family/social, psychiatric, use of alcohol and drugs) in substance-abusing patients. The ASI-6, the latest version of the ASI, contains 257 items. The information is provided by the patient in the form of responses to closed questions and Likert-type responses with a range between 0 and 4. Only the section of drug and alcohol use was used. Internal consistency ranged between .47 and .95 and test-retest reliability ranged from .36 to 1. The study of the internal structure revealed a good fit to a unidimensional solution for all scales (Díaz-Mesa et al., 2010).

MINI International Neuropsychiatric Interview (MINI) (Ferrando et al., 1998): a structured diagnostic interview assessing the diagnostic criteria for DSM-IV and ICD-10 psychiatric disorders. Items have dichotomous responses. Only drug and alcohol use sections were used. It determines the presence or absence of diagnoses of dependence and/or abuse on alcohol and on the two most problematic drugs and whether there is a current and/or lifetime diagnosis. The kappa values for inter-rater reliability were above .75 and the majority were a .90 or higher, regarding test-retest reliability the majority of the values were higher than .75 and only one bellow .45 (Sheehan et al., 1998).

Severity of Dependence Scale (SDS) (González-Sáiz & Carulla-Salvador, 1998): a five-item scale that focus on psychological aspects of substance dependence and measures severity of substance use. Each item is scored on a 4 point scale (0 to 3). Adequate reliability coefficients were found for all substance dependence scales (α = .737 - .877; test-retest r = .796 - .952). Low internal consistency was found for the abuse scales (α = .329 - .694), and adequate test-retest coefficients on alcohol, cocaine and heroin (test-retest r = .708 - .902) (Vélez-Moreno et al., 2015).

Alcohol Use Disorder Identification Test (AUDIT): a screening test to identify hazardous and harmful drinking and alcohol dependence. It has ten items with three to four response options. Internal reliability measured by Cronbach's alpha coefficient was .86 and test-retest correlation coefficient was .90 (Rubio Valladolid, Bermejo Vicedo, Caballero Sánchez-Serrano & Santo-Domingo Carrasco, 1998).

Drug Abuse Screening Test (DAST-10): a self-administered test that has 10 items with dichotomous response, and provides a quantitative index of the extent to which drug abuse problems are suffered, measuring an underlying dimension of dependence. It has a high internal consistency (α = .89). The exploratory factor analysis in its Spanish version extracted two components that explained 62.18% of the variance. The cut-off points (≥ 3) showed a high degree of agreement with the diagnostic criteria DSM-IV TR (κ DAST-10 = .91), correctly classifying more than 90% of the subjects evaluated (Pérez-Gálvez, García-Fernández, de Vicente-Manzanaro, Oliveras-Valenzuela & Lahoz-Lafuente, 2010).

Fagerström Test for Nicotine Dependence Test (FTNDT): a six item self-report questionnaire, designed to measure the severity of nicotine dependence. Items have between two and four response options and provide a total score ranging between 0 and 10. Cronbach alpha coefficient for the Fagerstrom test was .66 (Becoña & Vázquez, 1998).

Data analysis

The SPSS statistical package (IBM Corp. Released, 2019) and R statistical software (R Core Team, 2020) were used.

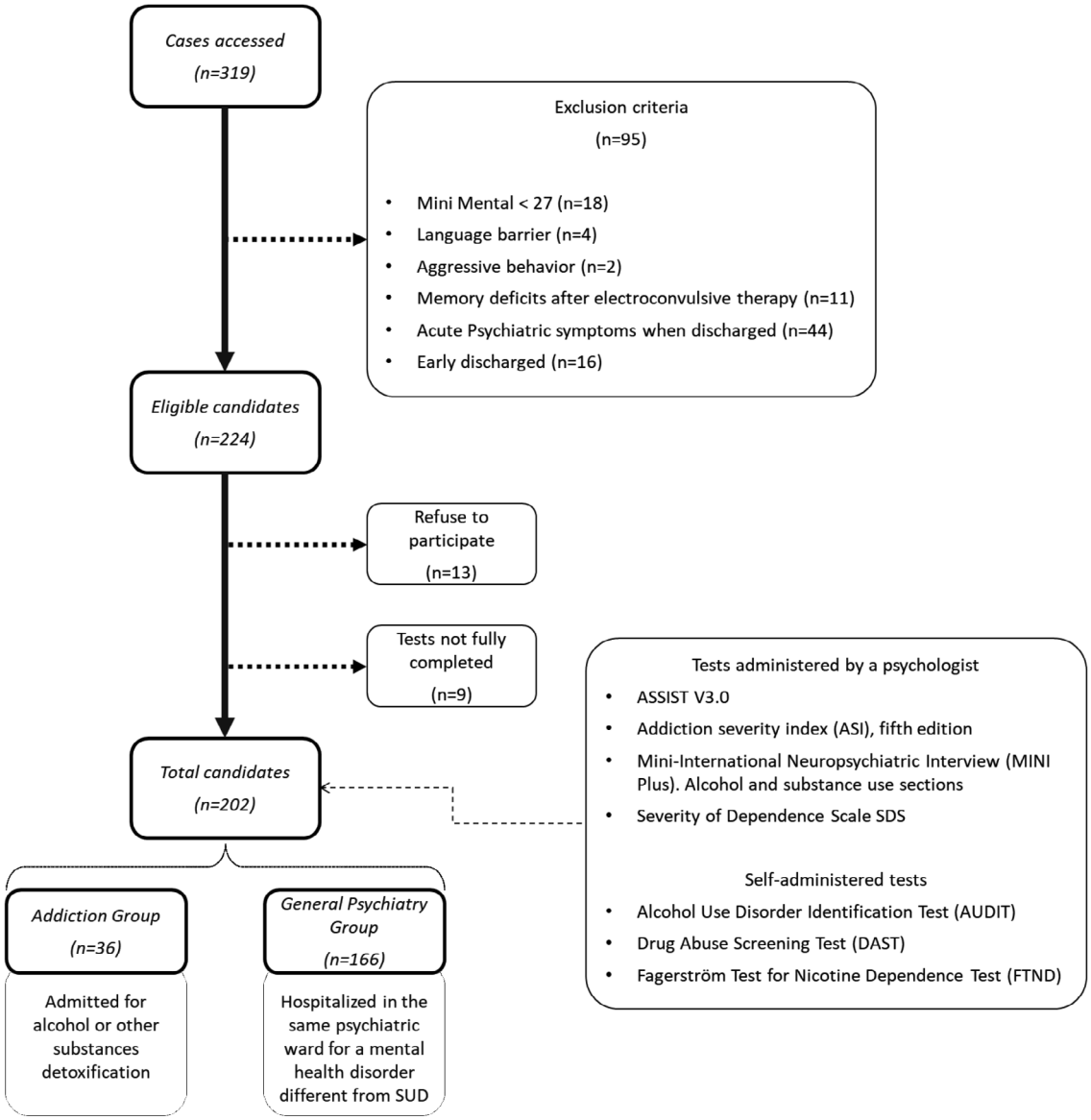

Figure 1. Flowchart showing the recruitment of patients and the battery of tests applied to the sample of candidates (n = 202).

Only the participants that answered the ASSIST and the whole battery of tests were included, therefore no procedure for imputation of missing values was required. Data were checked for normal distribution using the Kolmogorov-Smirnov test. Since ASSIST items did not follow a normal distribution, non-parametric tests were used. Mann-Whitney-U test was used to compare medians and Spearman test to perform correlation analyses. A p value of < .001 was considered statistically significant.

The items of the ASSIST were described using mean, standard deviation, median, interquartile range, skewness and kurtosis. Item discrimination indices were calculated by means of item-total corrected correlation considered adequate when it was above .30 (Nunnally & Bernstein, 1994).

Validity evidence based on internal structure was assessed through factor analysis. ASSIST dimensional structure was analyzed by randomly splitting the sample in two halves. The first of the two halves was used to perform an Exploratory Factor Analysis (EFA) to detect the latent structure of each substance subscale by means of a maximum likelihood estimation with varimax rotation.

With the second half of the sample, the structure resulting from the previous analysis was tested by means of a Confirmatory Factor Analysis (CFA) with the maximum likelihood estimation procedure. To check the global fit of the model χ^2 goodness of fit, the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA) indices were analyzed. An RMSEA < .06 and CFI > .95 values indicated a good fit (Hu & Bentler, 1999).

In order to assess the reliability of the scores, internal consistency for TSI and SSI scores was measured according to Cronbach's alpha (Cronbach, 1951). In addition, because of the drawbacks of the Cronbach's alpha coefficient for the assessment of reliability, the McDonald's omega (Dunn, Baguley & Brunsden, 2014) was also calculated.

Validity evidence based on the relationships to other variables was examined. Spearman's correlation was used to compare the scores of the ASSIST domains with the scores from other instruments administered simultaneously and considered gold standards in addictions (Figure 1). The AG was divided into two groups according to the presence vs. absence of a diagnosis of dependence in each substance made by an independent psychiatrist. ASSIST scores of both groups were compared using Mann-Whitney-U test.

Additionally, ASSIST domains that measure abuse and dependence were compared with the derived scores "total number of diagnoses of abuse" and "total number of diagnosis of dependence" in the MINI using Spearman's correlations. ASSIST domains "Lifetime substance use" and TSI were compared to ASI items: "number of previous treatments for alcohol or substance abuse" and "economic expenditure on alcohol or drugs over the last three months", which are risk factors considered as indirect measures of abuse or dependence.

Discriminative validity evidences were tested comparing the ASSIST scores of the following groups: low risk (patients from GPG without a diagnosis of abuse or dependence), moderate risk (patients from GPG with abuse or dependence diagnosis according to the MINI) and high risk (patients from the AG, admitted for a current SUD) using Mann-Whitney U test. Receiver operating characteristic analysis (ROC) and sensitivity and specificity of the cut-off scores were calculated when possible and compared to the sensitivity and specificity obtained using the cut-off scores suggested by the WHO.

Effect size estimates were calculated following Cohen's d recommendations (Cohen, 1988).

Ethical issues

The protocol was approved by the Ethics Committee of Hospital Clínic (CEIm, number 2011/6516), according to the Helsinki Declaration (World Medical Association Declaration of Helsinki, 2013), and the Spanish 14/2007 Law of July 3rd, of Biomedical Research. The anonymity of participants and confidentiality of data was guaranteed.

Results

The description of the first seven ASSIST items are presented in Table 1. Item-total corrected correlation indices were above .40, except for Q1 and Q2 for alcohol, meaning that the items show good discrimination.

Evidences of internal structure of the ASSIST

EFA for the tobacco, alcohol, cannabis, cocaine, amphetamines and sedatives subscales produced one factor each (with eigenvalues ranging 2.9 - 4.8) that explained between 57.3% to 80.3% of the variance. All factor loads were greater than .5 in all questions. The other substances subscales had insufficient data to carry out an EFA. Eigenvalues, the percentages of explained variance, factorial loadings and the Kaiser-Meyer Olkin index (KMO) are detailed in Table 2.

CFA results are shown in Figure 2. Analyses of substance subscales were based the results of the EFA, suggesting one-dimensional scales. For tobacco, using the Lagrange multipliers method, the best fit of the model was obtained by correlating Questions 6 and 7 ($r = .246$) ($\chi^2(3) = 5.298$, $p = .258$) (CFI = .995, RMSEA = .059, RMSEA 90% CI = .000-.177).

The same procedure was applied to the alcohol subscale. Question 2 was related to Question 6 ($r = .284$) and to Question 7 ($r = .241$) ($\chi^2(7) = 9.133$, $p = .243$) (CFI = .996, RMSEA = .058, RMSEA 90% CI = .000-.148). For the cannabis subscale, Question 2 was related to 3 (r = .541) and to 6 ($r = .372$) and Question 7 was related to 6 ($r = .250$) and to 5 ($r = .477$) ($\chi^2(5) = 5.728$, $p = .334$) (CFI = .999, RMSEA = .040, RMSEA 90% CI = .000-.155). The other substance subscales did not obtain an adequate adjustment in the analysis.

Reliability of ASSIST scores

Internal consistency, estimated by means of Cronbach's α coefficient was .92 for the TSI score and ranged from .88 to .96 for SSI scores. McDonald's Omega was .93 for the TSI score and between .89 to .96 for SSI scores (detailed results in supporting material, table C).

Evidences of validity based on the relation with other variables

Significant positive correlations were found between the ASSIST and gold standard instruments in addiction as summarized in Table 3.

SSI scores for subjects with a MINI diagnosis of "abuse or dependence" were significantly higher than the scores of those subjects without a diagnosis. SSI scores for those participants with an independent psychiatric diagnosis of current dependence were significantly higher than those from subjects without a diagnosis for tobacco, alcohol, cocaine, sedatives and opioids in the AG (see Table 4).

As for evidences of discriminative validity (see Table 5) there were significant differences in the SSI scores between low and moderate risk for alcohol, cannabis, cocaine, amphetamines and sedatives ($p < .001$) and between moderate and high risk for alcohol. There were no significant differences between moderate and high risk (dependence) for cannabis, cocaine and sedatives.

Table 1. *ASSIST items description.*

	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Tobacco							
Mean *(SD)*	2.58 (1.04)	3.39 (2.93)	3.3 (2.95)	1.57 (2.71)		2.79 (2.7)	1.56 (2.12)
Median *(IQR)*	3 (3 - 3)	6 (0 - 6)	6 (0 - 6)	0 (0 - 4)		3 (0 - 6)	0 (0 - 3)
Skewness	› 2.47	-1.91	-1.95	-.37		-1.76	-.34
Kurtosis	-2.11	-.27	-.22	1.22		.14	1.00
Discrimination index	.456	.868	.873	.537		.753	.597
Alcohol							
Mean *(SD)*	2.97 (.3)	2.65 (1.94)	1.1 (2.16)	1.4 (2.58)	.97 (2.43)	1.57 (2.42)	.91 (1.97)
Median *(IQR)*	3 (3 - 3)	3 (0 - 4)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 3)	0 (0 - 0)
Skewness	98.46	-.97	.57	.03	2.81	-.60	2.16
Kurtosis	-9.97	.00	1.54	1.38	2.16	1.07	1.94
Discrimination index	.107	.615	.853	.898	.761	.778	.806
Cannabis							
Mean *(SD)*	1.78 (1.48)	1.05 (2.07)	.95 (2.09)	1.06 (2.34)	.9 (2.37)	1.25 (2.19)	.65 (1.67)
Median *(IQR)*	3 (0 - 3)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 3)	0 (0 - 0)
Skewness	-1.87	1.14	1.45	1.40	3.51	.39	4.8
Kurtosis	-.39	1.67	1.82	1.81	2.31	1.42	2.47
Discrimination index	.527	.912	.891	.893	.802	.826	.708
Cocaine							
Mean *(SD)*	1.01 (1.42)	.3 (1.04)	.35 (1.27)	.34 (1.33)	.37 (1.55)	.49 (1.46)	.31 (1.17)
Median *(IQR)*	0 (0 - 3)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Skewness	-1.53	12.97	10.32	12.98	15.49	7.94	15.13
Kurtosis	.70	3.63	3.45	3.79	4.11	3.00	3.95
Discrimination index	.583	.857	.85	.86	.795	.792	.808
Amphetamines							
Mean *(SD)*	.65 (1.24)	.14 (.78)	.1 (.74)	.14 (.9)	.14 (.98)	.16 (.86)	.06 (.51)
Median *(IQR)*	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Skewness	-.10	37.94	51.29	44.69	48.79	33.12	98.69
Kurtosis	1.38	6.06	7.20	6.67	7.06	5.67	9.59
Discrimination index	.567	.814	.734	.767	.760	.714	.509
Sedatives							
Mean *(SD)*	.67 (1.25)	.75 (1.86)	.7 (1.89)	.78 (2.11)	.63 (2.06)	.64 (1.77)	.43 (1.45)
Median *(IQR)*	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Skewness	-.20	3.39	3.66	4.08	7.44	4.88	9.65
Kurtosis	1.34	2.25	2.35	2.43	3.03	2.56	3.32
Discrimination index	.789	.932	0.93	.901	.794	.815	.774
Opioids							
Mean *(SD)*	.28 (.88)	.12 (.76)	.13 (.82)	.13 (.92)	.11 (.9)	.18 (.93)	.19 (0.99)
Median *(IQR)*	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Skewness	5.91	43.33	39.53	49.75	68.00	30.28	27.52
Kurtosis	2.80	6.57	6.36	7.12	8.27	5.50	5.31
Discrimination index	.650	.907	.885	.814	.782	.826	.879

Note. Not enough data for Inhalants and Hallucinogens.

Table 2. *Exploratory factor analysis.*

Sub-scale	Number of factors	Eigenvalue	Variance explained	Factor loads	KMO	Barret's χ^2		
						χ^2	*df*	*p*
Tobacco	1	2.9	57.3%	› .50	.78	314.88	10	‹ .001
Alcohol	1	4.1	68.0%	› .70	.88	506.99	15	‹ .001
Cannabis	1	4.8	80.3%	› .80	.85	515.14	15	‹ .001
Cocaine	1	4.6	76.6%	› .70	.86	317.05	15	‹ .001
Amphetamines	1	4.2	70.3%	› .50	.84	171.68	15	‹ .001
Sedatives	1	3.6	59.7%	› .60	.80	113.89	15	‹ .001

Note. KMO = Kaiser-Meyer-Olkin.

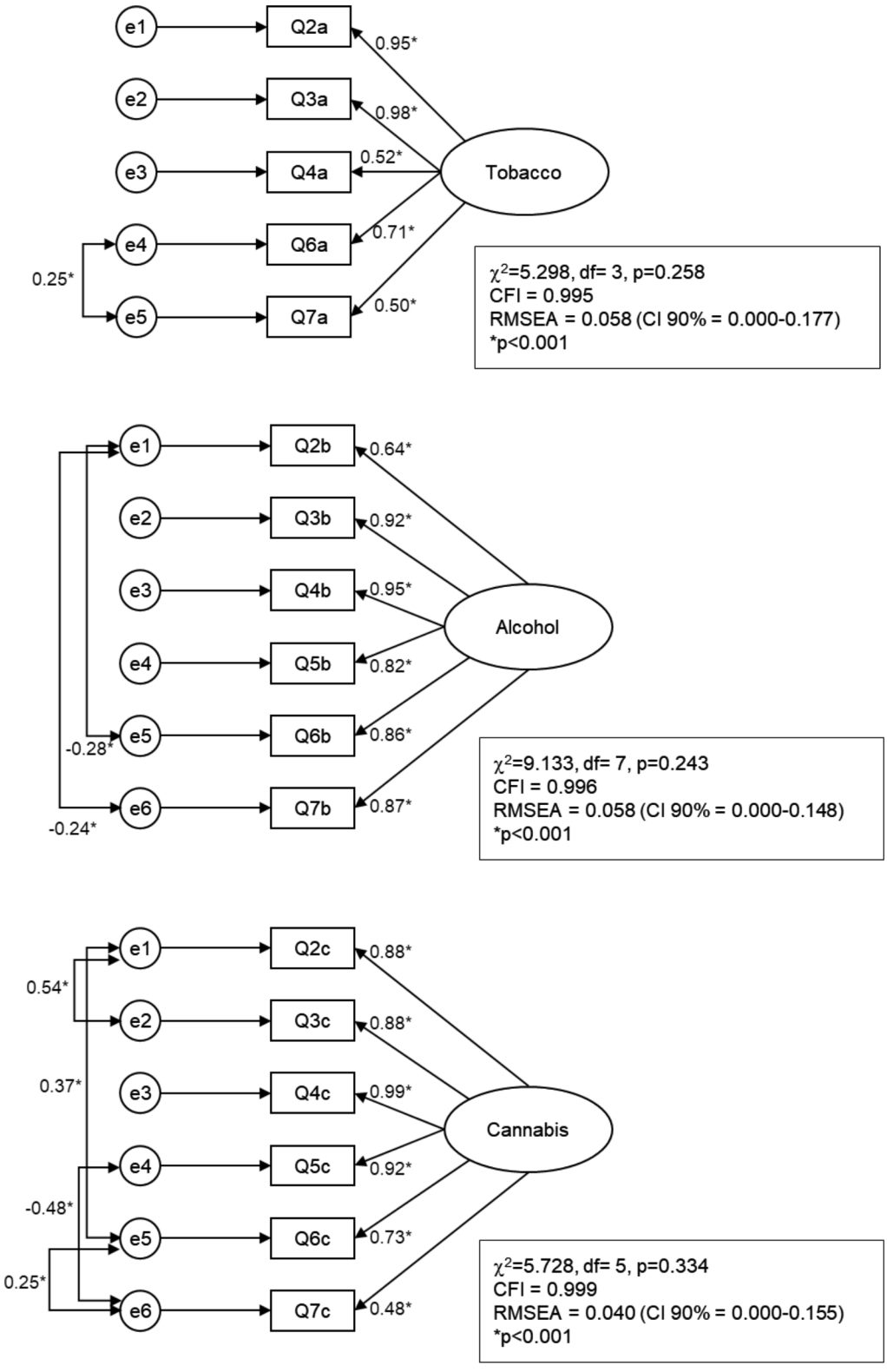

Figure 2. Confirmatory Factor Analysis for Tobacco, Alcohol and Cannabis ASSIST subscales.

Discrimination between moderate and high risk could not be investigated for amphetamines due to the absence of subjects with a dependence diagnosis (high risk) in the AG. For inhalants, opioids and hallucinogens ROC and Mann-Whitney's U could not be calculated due to insufficient data.

According to ROC analysis the ASSIST can discriminate better between low risk and moderate risk than between moderate risk and high risk. The area under the curve is higher for comparisons between low and moderate risk in all substances (cut-off-scores from 1.50 to 33.5, Area Under the Curve (AUC) from .386 to .991).

Table 3. *Evidences of validity based on the relation with other variables.*

Correlation between ASSIST domains & gold standard instruments	Spearman's r	*p*
TSI & SDS	.709	‹ .001
TSI illicit & SDS	.519	‹ .001
TSI illicit & DAST	.831	‹ .001
SSI Tobacco & FTND	.808	‹.001
SSI Alcohol & AUDIT	.864	‹ .001
TSI & MINI Plus "number of diagnoses" of current or lifetime abuse or dependence for alcohol and a maximum of two drugs	.862	‹ .001
TSI Illicit & MINI Plus "number of diagnoses" of current or lifetime abuse or dependence for alcohol and a maximum of two drugs	.857	‹ .001
SSI for all substances & MINI Plus "number of diagnoses"	.646 - .834	‹ .001
ASSIST "Dependence" for illicit substances & DAST	.821	‹ .001
ASSIST "Abuse" for illicit substances & DAST	.826	‹ .001
ASSIST "Total and Current Frequency" for all substances & ASI "Frequency of use of each substance"	.795 - .953	‹ .001
ASSIST "Dependence" for all substances & MINI Plus "Total number of diagnoses of dependence"	.795	‹ .001
ASSIST "Dependence" for illicit substances & MINI Plus "Total number of diagnoses of dependence"	.825	‹ .001
ASSIST "Abuse" for all substances & MINI Plus "Total number of diagnoses of abuse"	.842	‹ .001
ASSIST "Abuse" for all illicit & MINI Plus "Total number of diagnoses of abuse"	.837	‹ .001
ASSIST "Lifetime Substance Use" & ASI "Lifetime substance use"	.430	‹ .001
ASSIST "Lifetime Substance Use" & ASI "Number of previous treatments"	.460	‹ .001
TSI & ASI "Expenses in alcohol or drugs over the last three months"	.722	‹ .001

Table 4. *Specific Substance Involvement (SSI) scores according to presence of MINI plus criteria for current or lifetime diagnosis of abuse or dependence, and according to Addiction Group with Independent Psychiatric Diagnosis (IPD).*

SSI Score	Present abuse or dependence	Absent abuse or dependence	Mann-Whitney U test			Cohen's *d*
	Mean rank	*Mean rank*	*U*	*z*	*p*	
	MINI Plus current or lifetime abuse or dependence (n = 202)					
Alcohol	149.49	68.70	984.5	-9.74	‹ .001	1.00
Cannabis	166.60	78.93	515.0	-11.41	‹ .001	.69
Cocaine	161.54	93.02	711.5	-9.00	‹ .001	.40
Amphetamines	154.64	99.59	310.5	-5.98	‹ .001	.24
Sedatives	182.28	90.09	193.0	-11.33	‹ .001	.53
Opioids	182.00	99.04	105.0	-9.11	‹ .001	.25
	IPD (n = 36)					
Tobacco	21.29	12.92	77.0	-2.26	.024	2.68
Alcohol	23.46	8.58	25.0	-4.00	‹ .001	2.51
Cannabis	33.00	17.65	5.0	-2.54	.038	.60
Cocaine	32.90	16.18	5.5	-4.17	‹ .001	.72
Sedatives	29.94	15.23	20.5	-3.96	‹ .001	.97
Opioids	34.00	16.00	.0	-5.90	‹ .001	.50

Discussion

The aims of this study were to examine the reliability and to obtain sources of validity evidence of the ASSIST in psychiatric inpatients because there are few data about its use in this population. This research found that the ASSIST has good psychometric properties to measure different risk levels of substance use in hospitalized psychiatric patients. Items with adequate discrimination, evidences of unidimensional internal structure for tobacco, alcohol and cannabis, good internal consistency, and evidences of validity based on relations with other instruments (SDS, DAST, FTND, AUDIT, MINI, ASI) were found. EFA and CFA showed a unidimensional model for tobacco, alcohol, and cannabis which suggests that the total SSI score obtained for these substances is empirically supported in this sample. Other studies reported the same result for

Table 5. *Discrimination between low and moderate risk and moderate and high risk using Mann-Whitney's U test and receiver operating characteristic analysis (ROC).*

Risk level (n)	ROC (AUC)	ROC		ASSIST cut-off score	WHO cut-off score	ROC WHO		Mann-Whitney U test			
		Sensitivity	*Specificity*			*Sensitivity*	*Specificity*	*U*	*z*	*p*	*d*
SSI Alcohol											
Low (141) / Moderate (24)	.946	83.3%	86.5%	5.50	11	66.7%	99.3%	183.0	-7.08	< .001	1.95
Moderate (24) / High Alto (24)	.895	79.2%	75.0%	27.50	27	87.5%	70.8%	60.5	-4.70	< .001	1.66
SSI Cannabis											
Low (132) / Moderate (33)	.991	97.0%	97.0%	7.50	4	100%	94.7%	40.5	-10.57	< .001	3.94
Moderate (33) / High (2)	.386	50.0%	63.6%	32.50	27	50%	36.4%	25.5	-.54	= .61	.49
SSI Cocaine											
Low (159) / Moderate (9)	.932	88.9%	92.9%	1.50	4	77.8%	97.4%	95.0	-7.86	< .001	1.87
Moderate (9) / High (4)	.833	75.0%	77.8%	31.50	27	100%	66.7%	6.0	-1.86	= .06	1.38
SSI Amphetamines											
Low (162) / Moderate (3)	.988	100%	96.9%	1.50	4	66.7%	98.1%	6.0	-7.77	< .001	1.80
Moderate (3) / High (0)	n/a	n/a	n/a	n/a	27	n/a	n/a	n/a	n/a	n/a	n/a
SSI Sedatives											
Low (154) / Moderate (11)	1	100%	94.2%	1.50	4	100%	96.1%	.0	-9.76	< .001	7.32
Moderate (11) / High (9)	.606	66.7%	81.8%	33.5	27	66.7%	27.3%	39.0	-.80	= .42	.02

Note. ROC WHO: Sensitivity and Specificity values when using the ASSIST cut-off scores proposed by the WHO.

tobacco and alcohol in university students (Tiburcio Sainz et al., 2016) and for cocaine in a sample of cocaine users (Pérez-Moreno et al., 2012). Values of internal consistency ranging from .88 to .96 were similar to those reported by previous studies (Hides et al., 2009; Humeniuk et al., 2008; Rubio Valladolid et al., 2014).

SSI scores were significantly higher for those patients with a diagnosis of abuse or dependence on the MINI, showing that SSI scores reflect problematic substance use.

ROC analysis and Mann-Whitney's U test showed evidences of good discriminative validity, finding significant differences especially between groups of low and moderate risk for alcohol, cannabis, cocaine, amphetamines and sedatives. The AUC showed excellent results (AUC > .90). Good discriminative validity (AUC > .80) was also found between moderate (problematic use) and high risk (dependence) for alcohol. Similarly to previous studies (Humeniuk et al., 2008), ASSIST discriminates more effectively between low and moderate risk than between moderate and high risk, without differences for sedatives between moderate and high-risk groups.

The optimal cut-off points for moderate risk obtained in the present study for alcohol, cocaine, amphetamines and sedatives, are comparable to those established in the multi-site international study (Humeniuk et al., 2008), whereas in the Spanish version validation study (Rubio Valladolid et al., 2014) cut-off points for these substances were a bit higher. Cut off points for alcohol and amphetamines were congruent to those obtained in the study with first episode psychotic patients (Hides et al., 2009) while the cut-off point for alcohol in the study with adolescent population (Gryczynski et al., 2015) was lower.

In the present study the optimal cut-off point for cannabis is higher than the one obtained in the aforementioned studies. This may be due to the presence of only two subjects with a diagnosis of dependence in the AG compared to a high proportion of subjects with cannabis use disorder in the GPG.

Compared to the original validation study (Humeniuk et al., 2008), the proposed cut-off scores obtained higher or similar sensitivity and specificity scores. When using the WHO cut-off-scores, the values remained alike to previous studies, except for the cut-off for high risk in cannabis and sedatives that were lower.

In many substances, as cannabis, validation in sensible population is a clear need (López-Pelayo, Batalla, Balcells, Colom & Gual, 2015). Among the advantages of ASSIST, we can highlight its shorter application time compared to

Supporting materials

Table A. *Sociodemographic characteristics of the sample and differences between groups with Student's t for continuous and Chi-square for categorical variables.*

	Total n = 202	Addiction Group n = 36	General Psychiatry Group n = 166	Mean differences
Mean age in years *(SD)*	44.0 (15.5)	48.2 (12.4)	43.1 (16.0)	$t = 1.818$ $df = 200$ $p < .071$ Cohen's $d = .34$
Female	53.0	63.9	50.6	$\chi^2 = 2.09$ $df = 1$ $p < .148$
Civil status (%)				
Married or living together	32.7	44.4	30.1	$\chi^2 = 5.332$ $df = 5$ $p < .377$
Separated or divorced	11.9	11.1	12.1	
Widowed	3.5	2.8	3.6	
Never married	52.0	41.7	54.2	
Type of residence (%)				$\chi^2 = .290$ $df = 3$ $p < .962$
Own home or family home	63.4	63.9	63.3	
Rental property or room	36.6	36.1	36.8	
Ethnic group (%)				$\chi^2 = .932$ $df = 3$ $p < .818$
White/Caucasian	94.6	94.4	94.6	
Afro-American / Asian / Hispanic	5.5	5.6	5.4	
Employment status				
Employed	32.2	33.3	31.9	$\chi^2 = 7.360$ $df = 8$ $p < .498$
Not working due to medical illness	4.5	5.6	4.2	
Unemployed	24.8	19.4	25.9	
Disability	23.3	30.6	21.7	
Other (Retired, Student, or Stays at home)	15.4	11.1	16.3	
Level of schooling (%)				
Elementary school or lower	25.6	14.3	28.1	$\chi^2 = 5.07$ $df = 9$ $p < .828$
Secondary school	46.2	48.6	45.7	
University degree and higher	28.1	37.1	26.2	

Table B. *Clinical characteristics of Addiction Group (AG) and General Psychiatry Group (GPG).*

Addiction Group n = 36		General Psychiatry Group n = 166	
Alcohol Use Disorder n = 30	83.3%	Schizophrenia and Other Psychotic Disorders n = 79	47.6%
Sedative Use Disorder n = 14	38.9%	Mood Disorder (depressive or bipolar disorder) n = 61	36.7%
Cocaine Use Disorder n = 10	27.8%	Substance Induced Disorder n = 6	3.6%
Cannabis Use Disorder n = 6	16.7%	Miscellany n = 20	12.0%
Opioid Use Disorder n = 6	16.7%	Dual diagnosis n = 38	22.9%
Nicotine Use Disorder n = 24	66.7%		
Dual diagnosis n = 17	47.2%		
Polysubstance use n = 20	55.6%		

Note. Diagnosis according to DSM-IV criteria. Addiction Group (AG) includes patients admitted for alcohol or other substances detoxification. General Psychiatry Group (GPG) includes hospitalized in the same psychiatric ward for a mental health disorder different from SUD.

Table C. *Cronbach's α and McDonald's Omega coefficients.*

	Cronbach's α	McDonald's Omega
Total Substance Involvement (TSI)	.92	.93
TSI Illicit substances	.91	.93
SSI Tobacco	.88	.89
SSI Alcohol	.93	.92
SSI Cannabis	.95	.95
SSI Cocaine	.96	.93
SSI Amphetamines	.93	.89
SSI Sedatives	.95	.96
SSI Opioids	.96	.94

MINI (Ferrando et al., 1998) or PRISM (Torrens, Serrano, Astals, Pérez-Domínguez & Martín-Santos, 2004), and that unlike other tests adapted to psychiatric population, it covers all substances. For example, the DALI (Rosenberg et al., 1998) does not screen for tobacco, amphetamines, sedatives or opioids or the DAST (Pérez-Gálvez et al., 2010) that does not include alcohol or tobacco. The fact that this study was carried out with patients suffering from an acute episode, whose cognitive processes and ability to complete a test could be compromised, shows that it can be applied in inpatient settings and to patients suffering not only from a first psychotic episode but also from other mental illnesses. Screening for SUDs with validated instruments in psychiatric patients (Greenberg & Rosenheck, 2014; Langås, Malt & Opjordsmoen, 2011b, 2011a; Torrens, Martin-Santos & Samet, 2006) and other vulnerable populations that may have dual diagnoses (Vargas-Cáceres et al., 2020) is essential in order to provide accurate identification of risky behaviors regarding substance use, diagnosis, and a brief motivational intervention or a referral to specialized addiction treatment when needed. An early intervention can improve the course of their illness.

The present study has several limitations, the more relevant being the sample size and the resulting small representation of certain substances such as inhalants, hallucinogens or amphetamines that made it impossible to calculate the sensitivity and specificity for some substances. Recruitment was only done in one hospital setting being generalization of results modest. However, both limitations are common in validation studies. Test-retest reliability was not done because patients were discharged soon after the first administration. Evidences of predictive validity were not calculated either. An additional limitation is that using similar indices to those used in previous studies to assess the correlations with the ASSIST scores introduces a potential redundancy bias. Lastly, the sample was limited to inpatients. Generalization to mental health outpatients should not be difficult due to their milder symptoms and better cognitive state. Evidences of validity have not been gathered for the self-administered version of the ASSIST.

Despite those limitations, the excellent properties of the Spanish version of the ASSIST in psychiatric population encourage its implementation as part of our regular practice. The study has several strengths. First, it has a dimensional approach of mental disorders and did not focus on just one mental disorder or substance. Second, it was conducted following a well-established method of validation (Humeniuk et al., 2008). The inclusion of every relevant parameter of validation in the same study is not common (López-Pelayo et al., 2015).

Considering that a moderate risk in a primary care population can be regarded as high risk in patients with psychiatric disorders, it is important to detect problematic use (moderate risk) in this population and to implement early interventions.

The Spanish version of ASSIST is available for improving early detection and intervention of substance use disorders in psychiatric inpatients. Its implementation may help reducing re-hospitalizations and relapses, increasing adherence to treatment, and improving quality of life of people suffering from a mental health disorder.

ASSIST showed good validity and reliability evidence in assessing the level of risk of substance use in psychiatric inpatients.

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Conflict of interests

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Plasma midkine levels in patients with cocaine use disorder during abstinence

Niveles plasmáticos de midkina en pacientes con trastorno por uso de cocaína en abstinencia

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Abstract

Preclinical evidence suggests that endogenous midkine could play a key modulatory role on the neurotoxic and addictive effects of different kinds of drugs of abuse, including psychostimulants. However, this hypothesis has not yet been explored in humans. As a first approach to progress in this knowledge, we have comparatively studied plasma midkine levels in 75 patients with cocaine use disorder under abstinence and 26 control subjects matched for sex, age and body mass index. Patients were further segmented into early-abstinent (up to one month of abstinence, $n = 30$) and late-abstinent (more than one month of abstinence, $n = 45$). Midkine levels were quantified in plasma samples of all the participants by enzyme-linked immunosorbent assays. Early-abstinent patients exhibited a 60% increase of midkine plasma concentration in comparison with the controls. This elevation tended to normalize upon the progression of abstinence. The results obtained demonstrate that peripheral midkine levels are closely related to cocaine use and are consistent with the idea that this cytokine could play a protective role by limiting the biological activity of psychostimulants.

Keywords: Midkine; cocaine use disorder; cocaine abstinence; neuroprotection; psychostimulants.

Resumen

Diversos estudios preclínicos han sugerido que la midkina endógena podría jugar un papel modulador clave sobre los efectos neurotóxicos y adictivos de distintas drogas, incluidos los psicoestimulantes. Esta hipótesis no ha sido aún explorada en humanos. Como primer paso en esta dirección, en el presente trabajo hemos medido los niveles plasmáticos de midkina en 75 pacientes con trastorno por uso de cocaína en abstinencia y 26 controles apareados con los anteriores por sexo, edad e índice de masa corporal. Los pacientes fueron además divididos en un grupo de abstinencia temprana (menos de un mes, $n = 30$) y otro de abstinencia tardía (más de un mes, $n = 45$). Se cuantificaron los niveles plasmáticos de midkina de todos los participantes mediante un ensayo por inmunoabsorción ligado a enzimas. Los pacientes en abstinencia temprana mostraron un incremento del 60% en su concentración plasmática de midkina con respecto a los controles que tendió a desaparecer en los pacientes con periodos de abstinencia más prolongados. Los resultados demuestran que los niveles periféricos de midkina están estrechamente relacionados con el uso de cocaína y apoyan la idea de que dicha citoquina podría jugar un papel protector limitando la actividad biológica de los psicoestimulantes.

Palabras clave: Midkina; trastorno por abuso de cocaína; abstinencia de cocaína; neuroprotección; psicoestimulantes.

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Midkine is a heparin-binding cytokine that promotes the survival and differentiation of different cell types and seems to play an important role in central nervous system development and repair after injury (Muramatsu, 2011). A growing amount of experimental data tend to show that endogenous midkine function could be critical to limit the neurotoxic and addictive properties of different drugs of abuse (Herradón & Pérez-García, 2014; Alguacil & Herradón, 2015). In the particular case of psychostimulants, it has been reported that midkine knockout mice exhibit enhanced amphetamine-induced astrocytosis in the striatum (Gramage, Martín, Ramanah, Pérez-García & Herradón, 2011) and are particularly resistant to extinguish cocaine-induced conditioned place preference (Gramage et al., 2013). Despite these interesting results, there is no data to our knowledge supporting a possible relationship between psychostimulant abuse and midkine function in humans. As a first step to increase this knowledge, we have compared plasma midkine levels between abstinent cocaine abusers and control subjects and have also studied possible correlations between plasma midkine levels and variables related to cocaine use such as years of drug consumption, severity of cocaine addiction and duration of abstinence.

Method

This study was approved by the Ethical Committees of both the Hospital Regional Universitario de Málaga and Universidad San Pablo-CEU and fulfilled The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, as well as the General Data Protection Regulation of the European Union (2016/679). Informed consent was obtained from the subjects included. The study was conducted in white Caucasian population, and included a sample of patients diagnosed with Cocaine Use Disorder (CUD) currently in abstinence, as well as healthy control subjects. Patients were recruited at the addiction treatment facilities of the Centro Provincial de Drogodependencias (Málaga, Spain). Those subjects who fitted criteria of alcohol or cannabis dependence within the month before the study were excluded. Control participants were included from data bases of healthy subjects willing to participate in medical research projects at the Hospital Regional Universitario de Málaga (Málaga, Spain) and were matched to patients for sex, age and body mass index. CUD was evaluated according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) using the Spanish version of the Psychiatric Research Interview for Substance and Mental Diseases (PRISM) (Torrens, Serrano, Astals, Pérez-Domínguez & Martín-Santos, 2004). The group of CUD patients consisted of 75 subjects, 88% males, with 34.1 ± 7.5 years of age and BMI = 24.9 ± 4.6 kg/m^2 (means ± standard deviations). These subjects had been consuming cocaine for 5.7 ± 5.4 years, reached a score of 7.1 ± 3.7 in the cocaine trait severity scale for cocaine abuse and dependence (which reflects a heavy consumption) and had been abstinent from cocaine for 13.7 ± 32.2 months; 32.4% of them had shown a problematic use of alcohol earlier in life (27% within the last year) and had been abstinent to alcohol a mean of 127.8 days before recruitment. The control group consisted of 26 subjects, 85% males, with 36.8 ± 10.1 years of age and BMI = 24.6 ± 2.8 kg/m^2.

Blood samples from the participants were obtained by experienced nurses in the morning after fasting for 8–12 h. Venous blood was extracted into 10 ml EDTA tubes (BD, Franklin Lakes, NJ, USA), immediately centrifuged at 2,200 x g for 15 min (4˚C) and individually assayed to detect infectious diseases by 3 commercial rapid tests for HIV, hepatitis B, and hepatitis C (Strasbourg, Cedex, France). Plasma samples were individually characterized, registered, and stored at -80˚C until the day of analysis, which was performed by using a sandwich ELISA Midkine kit (MKELISA, Cellmid, Sydney, Australia) according to the instructions of the manufacturer (which include the use of duplicates). This particular kit was selected because it was specifically developed for human samples, provides a high sensitivity (limit of detection = 8 pg/ml), high specificity (0 reactivity to pleiotrophin, a cytokine closely related to midkine) and reliable quantification of the analyte at concentrations up to 10 µg/ml.

According to the literature showing that the most prominent phenomenological and neurobiological features of cocaine abstinence happen within the first weeks of cocaine withdrawal (Pathiraja, Marazziti, Cassano, Diamond & Borison, 1995), we split the patients for statistical analysis into an early-abstinent group (up to one month of abstinence, n = 30) and a late-abstinent group (more than one month of abstinence, n = 45). Midkine levels were comparatively studied in these two groups and control subjects by using one-way ANOVA followed by Bonferroni post-hoc tests. The possible correlations between midkine levels and each of the three variables related to cocaine use (severity score, duration of consumption and length of abstinence) were first studied by using Pearson coefficients. Besides, we also investigated these correlations after segmentation of the former variables into 5 groups according to percentile criteria by applying Spearman coefficients. The level of statistical significance was always established at $p < 0.05$.

Results

CUD patients under early abstinence exhibited a significant, 60% increase of plasma midkine levels with respect to control subjects; this difference was later reduced

and did not achieve statistical significance when abstinence exceeded one month, as shown in the late abstinent group (Figure 1).

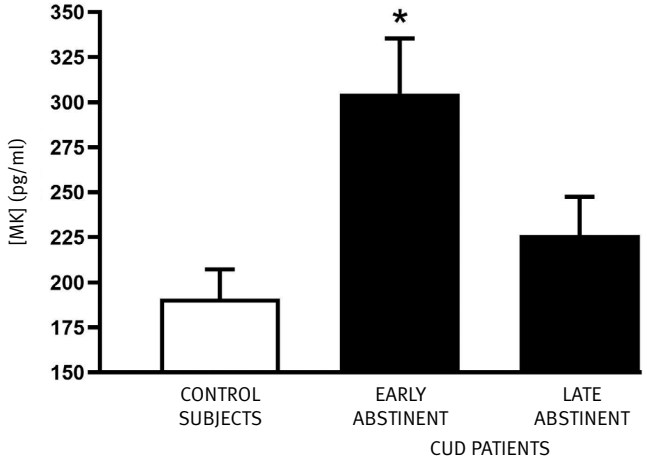

Figure 1. Midkine concentration in the plasma of control subjects and CUD patients. * $p < 0.05$ vs control subjects.

Midkine concentration did not correlate with the duration of lifetime cocaine use or the severity of cocaine addiction, but interestingly it was found to be inversely related to the time elapsed from cocaine withdrawal (Table 1, Figure 2).

Discussion

The results obtained in this study provide the first evidence of a significant relationship between cocaine use and midkine regulation in humans. Bearing in mind that our patients were abstinent to cocaine in the moment of the collection of the samples, it remains to be established if the elevation of plasmatic midkine was a consequence of the previous use of cocaine or was triggered by cocaine withdrawal; in any case, the levels of the cytokine consistently came back to control values upon the progression of abstinence, hence they seemed to be inversely parallel with cocaine dependence. Up to our knowledge the correlation between central and peripheral midkine levels has been poorly addressed both in health and disease; in spite of this, blood midkine changes have been associated to several neuropsychiatric conditions such as schizophrenia (Shimizu et al., 2003), Alzheimer disease (Salama et al., 2005) or autism (Esnafoglu & Cirrik, 2018), thus suggesting that plasma midkine levels could be sensitive to pathological changes affecting midkine levels or function in the brain. According to this idea, it is possible that our finding of elevated plasma midkine in patients could be secondary to an upregulation of central midkine triggered by cocaine use and/or cocaine withdrawal. Such an effect would be consistent with preclinical data suggesting a neuroprotective role of midkine upregulation in situations involving brain tissue injury, which include exposition to drugs, ischemia and neurodegenerative alterations (Muramatsu, 2011; Herradón & Pérez García, 2014; Alguacil & Herradón, 2015). Obviously, this hypothesis needs further testing since elevations of midkine levels in the periphery could also reflect other alterations related to cocaine use, not necessarily of central origin. Thus, for instance, vascular endothelial cells are known to release

Table 1. *Analysis of correlations between midkine levels and variables associated to cocaine abuse.*

	UNGROUPED DATA ANALYSIS		SEGMENTED DATA ANALYSIS	
	Correlation Coefficient	***p*-value**	**Correlation Coefficient**	***p*-value**
CUD severity (DSM score)	-0.061	0.601	-0.072	0.538
Duration of consumption (years)	-0.117	0.318	-0.045	0.699
Length of abstinence (months)	-0.140	0.231	**-0.253**	**0.029**

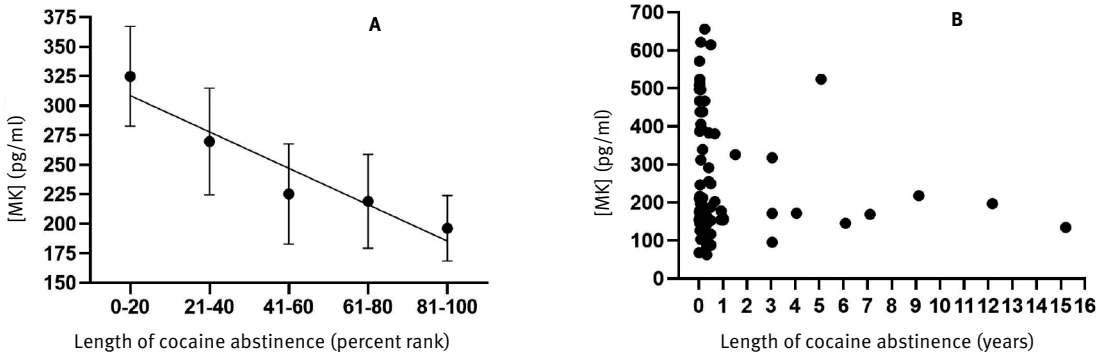

Figure 2. Midkine concentration in the plasma of abstinent CUD patients. Panel A shows the linear regression obtained ($r^2 = 0.91$) after segmenting the length of cocaine abstinence into 5 percentile groups (points represent means ± SEM). Panel B shows ungrouped data.

midkine (Fujisawa et al., 1998) and this could be affected by the potent cardiovascular actions of cocaine. Besides, some other conditions with higher incidence among drug addicts could also contribute to an elevation of blood midkine in these subjects, i.e. chronic kidney disease (Campbell et al., 2017), malignancies (Jones, 2014) or immune disorders (Sorrelle, Dominguez & Brekken, 2017). One limitation of this study is the impossibility to rule out any influence of alcohol or tobacco use on the observed changes of plasma midkine levels. Although our patients were not abusing alcohol when the samples were collected, a mild to moderate use cannot be discarded and this may affect midkine expression in the brain (Flatscher-Bader & Wilce, 2008). Smoking should be specifically monitored in future studies, since it has been also shown to increase midkine serum levels in some previous works (Ito et al., 2019), but not in others (but not in others: see Salaru et al., 2014). Accordingly, further work is needed to confirm the present results and provide a better understanding of the precise involvement of midkine function in cocaine use disorder; in this way, cerebrospinal fluid and plasma correlation studies appear to be especially relevant.

Acknowledgements

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Conflict of interests

The authors declare they have no conflict of interest.

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Concomitant use of direct-acting antivirals (DAA) and central nervous system drugs in patients with hepatitis C virus infection

Uso concomitante de antivirales de acción directa (AAD) y fármacos con acción sobre el sistema nervioso central: Consideraciones en el perfil actual del paciente con hepatitis C

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Abstract

Our objective was to determine potential drug interactions (DI) between pangenotypic direct-acting antivirals (pDAA) and concomitant central nervous system (CNS) medication in patients with chronic hepatitis C virus (HCV). Transversal design. Patients aged ≥ 18 years on treatment with pDAA during 2017 were included. The variables collected were comorbidity, concomitant CNS medication and potential DI. The pDAA analyzed were a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) and c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). Descriptive statistical analysis. We recruited 1,170 patients (mean age 60.1 years, 56.4% male). Mean concomitant drug use was 3.2 per patient/year. The percentages of potential / possible DI between the DAAs and the concomitant drugs on the CNS were: 2.7% contraindications, 11.3% significant and 4.2% weak. By pDAA, the percentages were: SOF/VEL (2.7%; 0.0%; 4.4%), GLE/GDP (2.7%; 26.5%; 1.6%) SOF/VEL/VOX (2.7%; 6.8%; 4.4%), respectively. Concomitant CNS medication was used in one third of HCV patients. It is important to select a pDAA with a low rate of potential DI to simplify treatment. SOF/VEL is a good alternative compared with the other pDAA studied, mainly due to the concomitant use of antipsychotics and analgesics.

Keywords: HCV; central nervous system; drug interactions; pangenotypic direct-acting antivirals.

Resumen

El objetivo fue determinar las potenciales interacciones farmacológicas (IF) entre los antivirales de acción-directa pangenotípicos (AADp) y la medicación-concomitante sobre el sistema nervioso central (SNC) asociada a los pacientes portadores del virus de la hepatitis C crónica (VHC). Se realizó un diseño transversal. Se incluyeron pacientes ≥18 años en tratamiento con AADp durante el año 2017. Las variables recogidas fueron: comorbilidad, medicación-concomitante (SNC) y potenciales IF. Los AADp analizados fueron: a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) y c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). Análisis-estadístico descriptivo. Se reclutaron 1.170 pacientes; edad-media de 60,1 años y el 56,4% varones. El promedio de medicamentos-concomitantes fue de 3,2 por paciente/año. El porcentaje de potenciales/posibles IF entre los AADp y los medicamentos-concomitantes sobre el SNC fueron: 2,7% contraindicaciones, 11,3% significativas y 4,2% débiles. En función de los AADp, estos porcentajes fueron los siguientes: SOF/VEL (2,7%; 0,0%; 4,4%), GLE/PIB (2,7%; 26,5%; 1,6%) y SOF/VEL/VOX (2,7%; 6,8%; 4,4%), respectivamente. Un tercio de los pacientes con VHC muestran un uso de medicación-concomitante de acción sobre el SNC. Será importante seleccionar un AADp que tenga una baja tasa de potenciales IF para simplificar el tratamiento. SOF/VEL se presenta como una buena alternativa en comparación con los AADp seleccionados, principalmente en el uso concomitante de antipsicóticos y analgésicos.

Palabas clave: VHC; sistema nervioso central; interacciones medicamentosas; antivirales de acción directa pangenotípicos.

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Chronic hepatitis C virus (HCV) infection is a worldwide health problem, affecting 120-150 million people, with a prevalence of between 0.5-2% of the general population (European Association for the Study of the Liver, 2018; World Health Organization, 2018). New cases of the disease continue to be detected, especially among young people and parenteral drug users. Early detection and treatment are therefore important aspects in the prevention of the disease (European Association for the Study of the Liver, 2018).

In the fight against HCV, new DAA molecules taking advantage of the numerous therapeutic targets offered by the virus replication cycle have revolutionized HCV treatment (Calleja et al., 2018). The serve the purpose of achieving greater efficacy and a reduction of possible side effects (Calleja et al., 2018; Zoratti et al., 2020). Advances in research on the virus' replication mechanisms have allowed potential therapeutic targets to be identified. Three different families of DAAs are available, with clear pharmacokinetic differences: a) NS3/4A protease inhibitors, b) NS5A replication complex inhibitors, and c) NS5B polymerase inhibitors. With these pharmacological groups, it is possible to act on three phases of the HCV replication process (inhibiting: viral protease, NS5A protein and NS5B polymerase). With protease inhibitors, potential drug interactions (DI) should be checked before recommending their use; NS5A protein inhibitors are potent and effective but have a low resistance barrier and variable toxicity profiles, while NS5B polymerase inhibitors have a high genetic barrier and their metabolism generally does not depend on cytochrome P450 (Morozov & Lagaye, 2018). A single DAA cannot by itself prevent the reproduction of HCV (mutations); for this reason, the recommended treatment consists of the use of two/three drugs from different families of inhibitors (Laursen, Sandahl, Kazankov, George & Grønbæk, 2020). Current DAAs are pangenotypic (pDAA), that is, they are effective against all HCV genotypes (Paolucci et al., 2019). In addition, they require shorter treatment durations and have a better safety profile, with lower rates of DI (Benet, Bowman, Koleske, Rinaldi & Sodhi, 2019).

Some studies have shown that two-thirds of patients may have potential DIs with DAAs, with figures close to 20% observed in contraindicated drugs (Lauffenburger et al., 2014; Keast, Holderread, Cothran & Skrepnek, 2019). In Spain, high rates of comorbidity and concomitant medication have been reported as being associated with these HCV patients; the most prescribed therapeutic groups with potential DIs were those related to the cardiovascular system (37.5%) and the central nervous system (34.1%; [CNS]) (Sicras Mainar, Navarro Artieda, Hernández & Morillo, 2019).

Comorbidities are common in patients with HCV. These patients may be on multiple medications, a circumstance that can cause adverse effects and/or potential DIs (Calleja et al., 2018). In general, a careful review of the medication patients are taking is advised when prescribing a pDAA. However, little information is available on the risk of presenting a DI when administering a pDAA to these patients (concomitant medication) at the population level, so reporting data is necessary to advance current scientific knowledge. The objective of this study was thus to determine the potential DIs among the DAAs associated with concomitant CNS treatment in patients with HCV infection.

Patients and methods

A cross-sectional study was carried out. Electronic medical records (EMRs) were obtained from the dissociated BIG-PAC database (data source: secondary; owner: Atrys Health; enrolled population: 1.8 million patients). Primary data are from the computerized medical records from seven integrated health areas (primary care centers and hospitals), part of the Spanish public health service, in seven autonomous communities of Spain. Before being exported to BIG-PAC, EMRs undergo rigorous anonymization in the centers/hospitals of origin, in accordance with Organic Law 3/2018, of December 5, regarding the Protection of Personal Data and Guarantee of Digital Rights. Atrys Health does not have access to the primary data sources (Sicras-Mainar et al., 2019).

Patients included in the study were ≥18 years of age with a diagnosis of HCV (ICD-10-CM [B18.2]), seen and treated with pDAAs during 2017, and meeting the following criteria: a) age ≥ 18 years, b) HCV diagnosis at least 12 months prior to the start of the study, c) participation in the chronic prescription program (≥2 prescriptions of any concomitant medication during the study period), and d) guarantee of regular follow-up of these patients (≥ 2 medical visits). Patients who transferred to other centers and/or moved away and/or out of the health area were excluded. Patients' concomitant medication was detailed in the study to calculate the percentage of potential DIs based on the administration of the different DAAs. The result is a theoretical exercise based on a real distribution in practice.

The variables included in the study were demographic as well as the main associated comorbidities (ICD-10-CM). As a summary variable of general comorbidity, we used the Charlson comorbidity index (relating patient comorbidity to long-term mortality) (Charlson, Pompei, Ales & MacKenzie, 1987). Of the 3,430 patients with HCV, only those subjects receiving concomitant chronic medication acting on the CNS were selected for the study (N=1,170). The therapeutic groups were: anticonvulsants, opioid

analgesics, antidepressants, anxiolytics, antipsychotics, sedatives or hypnotics.

Treatment description (concomitant medication, CNS) was obtained in accordance with the Anatomical Therapeutic Chemical Classification System (The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses, 2019). Assigning a pDAA to a patient was based on the criteria of the specialist (prescribing physician). The selected DAAs (most frequently prescribed in Spain) were: a) Sofosbuvir/Velpatasvir (SOF/VEL), b) Glecaprevir/Pibrentasvir (GLE/PIB) and c) Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). It should be noted that the concomitant medication was analyzed during the antiviral treatment period and only with the chronic or habitual medication administered to the patients. Concomitant medications having potential DIs with action on the CNS are detailed in Figure 1A. To determine the potential effect of possible DIs, the University of Liverpool recommendations were followed (University of Liverpool HIV and Hepatitis Pharmacology Group Drug Interaction Charts, 2020), in collaboration with the European Association for the Study of Hepatic Diseases (European Association for the Study of the Liver, 2018) and HCV treatment guidelines (World Health Organization, 2018). The potential DIs were identified as: a) contraindication, b) significant and c) weak. In addition, the main indications/reasons for prescription were identified for some active ingredients such as quetiapine and oxcarbazepine. Quetiapine was reviewed as it was the most frequently prescribed drug, and oxcarbazepine as it is contraindicated with all three pDAAs analyzed.

Database search criteria were structured using SQL script. Data were carefully reviewed through exploratory analysis and preparation for analysis, observing frequency distributions and checking for possible recording or coding errors. A descriptive statistical analysis was carried out with absolute and relative frequencies for qualitative, and means and standard deviations (SD) for quantitative data. The respective 95% confidence intervals (CI) were calculated.

Results

We identified 1,170 patients (34.1%) with HCV who were receiving concomitant medication acting on the CNS. Mean age was 60.1 years (SD: 10.8), 56.4% were men, and mean Charlson index was 1.0 (SD: 1.1). The following stood out among the comorbidities: arterial hypertension (33.4%), anxiety disorder (31.9%), dyslipidemia (21.6%),

A) By active principle.

pDAA	N (%)	CNS drug	DI magnitude
SOF/VEL	32 (2.7%)	Oxcarbazepine	Contraindicated
	51 (4.4%)	Buprenorfine	Weak
GLE/PIB	32 (2.7%)	Oxcarbazepine	Contraindicated
	117 (10%)	Quetiapine	Significant
	79 (6.8%)	Fentanyl	
	79 (6.8%)	Paliperidone	
	33 (2.8%)	Aripiprazole	
	26 (2.2%)	Oxycodone	
	19 (1.6%)	Clotiapine	Weak
SOF/VEL/VOX	32 (2.7%)	Oxcarbazepine	Contraindicated
	79 (6.8%)	Paliperidone	Significant
	51 (4.4%)	Buprenorfine	Weak

B) By pDAA.

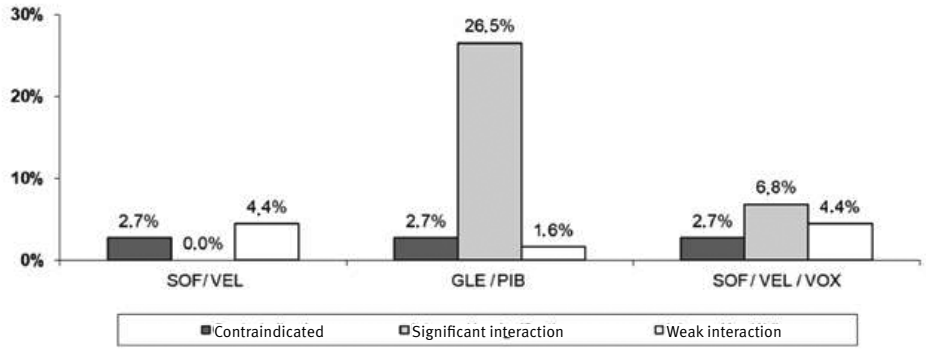

Figure 1. Potential drug interactions between pDAAs and concomitant drugs of the central nervous system.

Note. pDAA: pangenotypic direct-acting antivirals; CNS: central nervous system; DI: drug interaction; SOF/VEL: sofosbuvir/velpatasvir; GLE /PIB: glecaprevir/pibrentasvir; SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir.

diabetes mellitus (17.4%), addictions (6.7%), liver cirrhosis (5.8%) and AIDS/HIV (1.0%).

The average number of concomitant medications (active ingredients) was: 3.2 (SD: 2.1) per patient/year. The breakdown by CNS therapeutic groups was: a) psycho-anxiolytic (N=744, 64%), b) psychoanalytic-antidepressant (N=679, 58%), c) antiepileptic (N=494, 42%) and d) analgesics (N=429, 37%). Prominent among the active ingredients in these therapeutic groups and showing potential DI with a pDAA were: quetiapine (N=117), fentanyl (N=79), paliperidone (N=79), buprenorphine (N=51), aripiprazole (N=33), oxcarbazepine (N=32), oxycodone (N=26), and clotiapine (N=19) (Figure 1A).

The percentage of potential DIs on the CNS were: 2.7% (95% CI: 1.8-3.6%) contraindications, 11.3% (95% CI: 9.5-13.1%) significant and 4.2% (95% CI: 3.1-5.3%) weak. Based on the DAAs, these percentages [95% CI] were as follows: SOF/VEL (2.7% [1.8-3.6%]; 0.0% [0.0-0.0%]; 4.4% [3.2-5.6%]), GLE / GDP (2.7% [1.8-3.6%]; 26.5% [24.0-29.0%]; 1.6% [0.9-2.3%]) and SOF/VEL/VOX (2.7% [1.8-3.6%]; 6.8% [5.4-8.2%]; 4.4% [3.2-5.6%]), respectively (Figure 1B).

Grounds for prescribing the selected active ingredients were: a) quetiapine (N=117): states of agitation / personality disorder (N=65, 56%), bipolar disorder (N=38, 32%) and schizophrenia (N=14, 12%); and b) oxcarbazepine (N=32): unspecified seizures (N=18, 56%) and epileptic seizures (N=14, 44%).

Discussion

The results of the study show that people with HCV are associated with significant comorbidity and use of medication, leading to greater exposure to potential DIs on receiving antiviral treatment. Although the study was carried out only on concomitant CNS medications, 11.3% had significant DIs and 2.7% were contraindicated. Awareness of DIs represents a challenge for treating HCV infection.

DIs in patients with HCV are common. Maasoumy (2013), for example, investigated the risk of potential DIs in subjects treated with protease inhibitors (telaprevir, boceprevir) in a German hospital and found that half of the patients were exposed to a drug with potential interaction (Maasoumy et al., 2013). Some systematic reviews have shown high rates of potential DIs and their potential interaction mechanisms from a theoretical perspective (Ahmed, Lutchman & Kwo, 2017; Garrison, German, Mogalian & Mathias, 2018; Talavera et al., 2017). Langness (2017) determined that hypertensive agents, analgesics, and psychiatric medications cause frequent interactions with DAAs (sofosbuvir/simeprevir, sofosbuvir/ledipasvir, sofosbuvir/ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir). The authors conclude that drug interactions are frequent (1.2 per patient), and that DAA treatment may require adjustments to concomitant medications (Langness et al., 2017). Kondili (2017) (study on sofosbuvir/ribavirin, sofosbuvir/simeprevir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir/dasabuvir), highlighted that 30-44% of patients undergoing DAA treatment are at risk of significant interactions. The authors underlined the need for greater awareness in the administration of these drugs, especially in patients with moderate/severe liver disease (Kondili et al., 2017). Our results are in line with these contributions, although we observed a lower rate of relevant DIs. This circumstance may be due to the fact that the study was performed on pDAAs (later marketed) and that we only included drugs acting on the CNS.

Furthermore, SOF/VEL presented a lower rate of DI. SOF is an inhibitor of the NS5B polymerase, while VEL is an inhibitor of the NS5A replication complex. GLE is a pangenotypic inhibitor of the HCV NS3/4A protease essential for viral replication. While PIB is a pangenotypic inhibitor of HCV NS5A, concomitant administration of GLE/PIB can increase exposure to certain medications (digoxin, dabigatran, statins, ethinyl estradiol) (Ahdmed et al., 2017; Talavera et al., 2017). The intracellular metabolic activation pathway of SOF is mediated by nucleotide phosphorylation pathways and hydrolases, generally of low affinity and high capacity, so they are unlikely to be affected by concomitant medications (Kondilii et al., 2017). Recent reviews show that drug combinations with SOF generally have fewer interactions than regimens based on protease inhibitors. However, the analysis of each interaction is theoretical and more interaction studies would be needed to confirm their real effects (Roncero, Villegas, Martínez-Rebollar & Buti, 2018). It appears that the key to interpreting DIs is based on knowledge of the pharmacokinetic profiles of drugs and their ability to inhibit CYP450-3A4 and transporters (hepatic, intestinal) in relation to their potential clinical consequences (Talavera et al., 2017). It should be noted that there may be some discrepancies between the licensed indications for a drug and its actual therapeutic use.

On a practical level, it should be noted that the potential DIs of contraindicated medication and significant interactions are the most clinically relevant and, therefore, those requiring greater vigilance (European Association for the Study of the Liver, 2018). Thus, given the short period of DAA administration, some concomitant medications could be substituted or the administered dose reduced when introducing DAAs. In other cases, for example patients coinfected with HIV/HCV, perhaps another kind of intervention would be preferable, such as selecting the DAA type more carefully. Additionally, it will always be necessary to ask the patient about the use of other drugs, such as those paid for privately (homeopathic,

supplements, vitamins, etc.) or those bought without a prescription.

The article shows the limitations inherent in cross-sectional/retrospective studies, such as underreporting of the disease, or the possible variability among professionals and patients. As a cross-sectional study, it did not take possible confounding factors into account, so the results of the study should be interpreted with caution. Furthermore, the study did not quantify the degree of liver fibrosis (liver damage) in patients at baseline; in our opinion, however, this circumstance should already have been taken into account by the specialist prior to prescribing the pDAA. The efficacy and safety of the concomitant medication associated with certain chronic diseases (indication and prescription in dementia, psychosis, etc.) were also not taken into consideration, which may have an impact on the manifestation of DI. It would have been relevant to know the specialist doctor's criteria for prescribing a DAA, possible drug addictions and/or the indicated doses of drugs with action on the CNS, to mention a few examples, since these are circumstances that can cause real DIs in patients (Roncero et al., 2018).

Potential interactions can pose problems in clinical practice, although many could be avoided by adjusting the pharmacological dose or selecting a safer alternative, provided sufficient knowledge and experience are available to handle these pharmacokinetic issues (Keast et al., 2019). In conclusion, a third of patients with HCV show concomitant use of medication with action on the CNS. It is important to select a pDAA with a low rate of potential DIs to simplify treatment. SOF/VEL is shown to be a good alternative to the selected pDAAs.

Conflict of interests

A. Sicras is an independent consultant in connection with the development of this manuscript. A. Sicras is an employee of Atrys Health. R. Morillo has no conflict of interest. Atrys Health has received fees for carrying out this study.

Author contributions

Conception and design of the manuscript by A. Sicras. Data collection and statistical analysis by A. Sicras. All authors contributed to data interpretation, drafting, revision and approval of the submitted manuscript.

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Gender-based differences in perceptions about sexual violence, equality and drug-facilitated sexual assaults in nightlife contexts

Diferencias de género en percepciones sobre violencia sexual, igualdad y agresiones sexuales facilitadas por drogas en ocio nocturno

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Abstract

Sexual violence, including drug-facilitated sexual assaults, is a serious issue that is becoming increasingly common in leisure nightlife contexts. This study provides information about the attitudes and perceptions of Spanish youths towards sexual violence within that setting. The participants were recruited by a snowball sampling scheme. A bivariate analysis was performed to identify possible sociodemographic and nightlife recreational habit factors related to gender. The statistical significance of the differences between the studied variables was assessed using the chi-squared and Fisher's exact tests. Women perceived a low level of personal security, as well as the existence of social perceptions penalizing female more than male drug use, and blaming women for the sexual violence they suffer. Women also recognised less explicit violent behaviours as violence significantly more than men did. Men were more willing to have sexual intercourse with someone unable to express consent because of drugs. In addition, they believed more strongly that sexual assaults take place because of the victim's use of alcohol or other drugs. In a leisure nightlife context, women are prone to perceive a lack of social support for themselves and the feeling of impunity for the perpetrators. Furthermore, numerous misconceptions surround drug-facilitated sexual assaults, with the majority of respondents believing that assaults happen after the surreptitious administration of substances to the victim by an unknown assailant. Moreover, the involvement of alcohol was underestimated. Our findings are useful for designing prevention efforts, demystifying the drug-facilitated sexual assaults and enhancing social support for victims.

Keywords: Drug-facilitated sexual assault; sexual violence; youth prevention; rape myths; cultural violence.

Resumen

La violencia sexual, incluyendo las agresiones sexuales facilitadas por drogas, es un serio problema cada vez más común en los contextos de ocio nocturno. Este trabajo estudia las actitudes y percepciones de la juventud española en torno a la violencia sexual en dicho ámbito. Los participantes se reclutaron mediante muestreo en bola de nieve. Se realizó un análisis bivariado para identificar posibles factores sociodemográficos y de ocio nocturno relacionados con género. La significación estadística de las diferencias entre estas variables se evaluó mediante las pruebas de chi-cuadrado y exacta de Fisher. Las mujeres percibieron un menor nivel de seguridad personal, así como la existencia de percepciones sociales que penalizan en mayor medida el consumo de drogas femenino que el masculino, y que culpabilizan a las mujeres por la violencia que sufren. Además, ellos mostraron mayor disposición a mantener relaciones sexuales con personas incapaces de otorgar su consentimiento debido a los efectos de las drogas. Los hombres creen en mayor medida que las agresiones sexuales ocurren debido al uso de alcohol u otras drogas por parte de las víctimas. En el contexto de ocio nocturno, las mujeres son propensas a percibir la existencia de una falta de apoyo social hacia ellas, así como un sentimiento de impunidad social hacia los agresores. Además, existen numerosas concepciones erróneas en torno a las agresiones sexuales facilitadas por drogas. La mayoría cree que las agresiones ocurren tras la administración encubierta de sustancias a la víctima por parte de un agresor desconocido. Además, se subestimó la participación del alcohol. Nuestros hallazgos son útiles para diseñar esfuerzos preventivos bien dirigidos, desmitificar el fenómeno de las agresiones sexuales facilitadas por drogas y mejorar el apoyo social a las víctimas.

Palabras clave: Agresión sexual facilitada por drogas; violencia sexual; prevención juvenil; mitos de la violación; violencia cultural.

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Sexual violence is a form of interpersonal violence, typically directed towards women, that includes any sexual act, comments or unwanted sexual advances. As such, sexual violence represents one of the most serious public health and human rights problems-worldwide (World Health Organization, 2013, 2014). Around 11% of European women aged 18 to 74 years have suffered sexual violence at some point in their life, with 5% being subjected to non-consensual sexual intercourse by restraining them or hurting them in some way (European Union Agency for Fundamental Rights, 2014). By age group, young and college-aged women are particularly affected (Bird, Gilmore, George & Lewis, 2015; Carey, Durney, Shepardson & Carey, 2015; Krebs, Lindquist, Warner, Fisher & Martin, 2007). In Spain, according to recent research into violence against women in a university population (Valls, Puigvert, Melgar & Garcia-Yeste, 2016), only 56% of women and 42% of men considered all the presented violent situations as violence. Likewise, in this country, the highest prevalence of sexual violence during the last year affected women aged 16-29 years (Government Delegation against Gender Violence, 2015). However, most of the incidents of sexual violence are not reported, therefore epidemiological studies are of particular importance to gain some idea of the burden of this problem in different populations (Hellmann, Kinninger & Kliem, 2018).

Perceptions, attitudes and social norms have been repetitively suggested as being contributors to sexual violence. This means to a marked extent that culture defines the boundaries between acceptable and abusive behaviours (Government Delegation for National Plan on Drugs, 2018; World Health Organization, 2002). Thus, cultural violence refers to culture aspects justifying direct or structural violence and repressing the victims´ response (Galtung, 1990). In this sense, a society that does not perceive all kinds of sexual violence, not only will not repress and persecute it but, more importantly, will not be able to implement policies to prevent it, especially among young people (Sasson & Paul, 2014). There is a gap in the perception of definitions and causes of sexual violence, and also regarding the ideas about victims and offenders, between the general population and people actively involved in the field of sexual violence (O'Neil & Morgan, 2010). Indeed, studies concerning sexual violence show that the general population seem to identify specific acts, such as rape, as sexual violence but not the subtler forms, such as sexually degrading language (about women) or harassment (McMahon & Farmer, 2011). These differences may be due, in part, to differing views of the causes of sexual violence (McMahon, 2010). In Spain, the only survey studying the social perception of sexual violence observed the invisibility of violent behaviours different from unwanted sexual intercourse. This study stated that most youths fall midway between rejection and tolerance to sexism, and also found significant differences in the perception of sexual violence between sexes (Government Delegation against Gender Violence, 2018). However, this study paid little attention to the relationship between sexual violence and drugs use. There is currently a marked convergence in gender relations in leisure nightlife contexts that can increase the negative consequences for women (Calafat et al., 2003; Calafat, Juan, Becona, Mantecon & Ramon, 2009; Gilbert & Pearson, 2003; Hughes et al., 2011). Thus, young women have begun to impinge on traditionally male spaces in the absence of a true gender equality (Prego-Meleiro, Montalvo, Quintela-Jorge & García-Ruiz, 2020a). As an example, the prevalence of binge drinking has increased steadily in women since the second half of the 1990s, approaching the levels typically found for males (Government Delegation for National Plan on Drugs, 2018).

Sexual violence also occurs when someone is unable to consent or to refuse a sexual approach due to the effects of psychoactive substances (World Health Organization, 2002). That is the case in drug-facilitated sexual assaults (DFSA) (Advisory Council of the Misuse of Drugs, 2007). This is an intersectional form of sexual violence (Prego-Meleiro, Montalvo, Quintela-Jorge & García-Ruiz, 2020b) particularly common in recreational contexts (Folgar, Rivera, Sierra & Vallejo-Medina, 2015; Lawyer, Resnick, Bakanic, Burkett & Kilpatrick, 2010; Resnick, Walsh, Schumacher, Kilpatrick & Acierno, 2012) as these situations entail the convergence of potential victims, motivated offenders and lack of capable guardians (Mustaine & Tewksbury, 2002). In Spain, parties and festivals are considered as the main contexts in which sexual aggression against women occurs (Government Delegation against Gender Violence, 2018). Nevertheless, little is known about either people's usual perception concerning DFSA or any gender-based differences in this perception. Cultural violence implies negative social reactions, including the victim´s blaming, which makes self-acknowledgment of unwanted sexual experiences more difficult (Bondurant, 2001; Fisher, Daigle, Cullen & Turner, 2003), triggers psychological health problems in the victims (Ullman & Filipas, 2001; Ullman & Najdowski, 2010), and increases the risk of revictimization (Lorenz & Ullman, 2016). In that framework, this study suggests the following hypotheses: (i) the perceptions of equality, safety, and the risk of suffering sexual violence in leisure nightlife contexts vary significantly between genders; (ii) there is a social gap between genders in the identification of some specific acts as sexual violence; (iii) the willingness to conduct sexual intercourse with someone unable to express consent because of drugs is greater among men than women; (iii) there are several widespread myths or misconceptions about the DFSA phenomenon, which significantly affect the social conception of this form of sexual violence; and (v) women

experience a lack of social support in leisure nightlife contexts, resulting from the different social perceptions about the drug use based on gender.

In the context of equality, the modification of incorrect assumptions and cultural expectations about sexual violence is a key step to reducing this problem. For that purpose, the university is a special interest context because it shows the cultural environment of younger generations. Therefore, this work aimed to determine gender-based perceptions about different aspects of sexual violence in the leisure nightlife context, especially the normalization and justification of violence, paying particular attention to the role played by drug use. This aim aligns with the need to increase social awareness about the DFSA phenomenon as a form of sexual violence severely affecting women in the leisure nightlife context.

Materials and methods

Subjects

The participants were recruited by a snowball sampling scheme using a closed two-phases online questionnaire. First, 229 students from the University of Alcalá (Spain) participating in the educational Project UAH/EV951 completed the questionnaire. These students were then instructed to send the same questionnaire to a minimum of ten contacts belonging to their immediate circle, using the instant messaging services available within social networks. The students involved in this phase were adequately instructed about the inclusion criteria of the study, *i.e.,* being aged between 16 and 35 years and residing in Spain at the time of the study. Their participation was completely anonymous via electronic devices, such as mobile phones or computers. This process was carried out between October and December 2017. After the initial sampling, any participant which did not meet the requirements were excluded, reaching a final sample size of 2,355 young people.

During the development of the study, before accessing the online questionnaire, all participants faced a previous page informing them in detail about the reason and purposes of the research, as well as the inclusion criteria of the study. Likewise, the topics addressed by the questionnaire were presented on that previous page before the participants could access the survey, and an estimate of the time needed to complete the questionnaire (15 minutes). Hence, the previous page requested the participants a consent for their voluntary and anonymous participation before accessing the questionnaire, which constituted the positive consent for their participation. The access to the survey was provided only through a link available after the presentation of that aforementioned information. Special attention was given to the questions' design to avoid obtaining any identifying data from the participants. For instance, people were asked to report their age in years rather than their date of birth, and no questions about the place of residence or the geographical origin of the participants were included. In addition, neither Internet protocol addresses nor cookies were collected. The evaluation commission of the "Call for Projects for the Promotion of Teaching Innovation in the Teaching-Learning Process" of the University of Alcalá (course 2017-18) approved the implementation of the project within which this study was framed (reference number UAH/EV951). The project approval within this institutional frame requires complying with specific ethical requirements.

Data Collection and Measures

The variables studied were collected into four groups: sociodemographic; nightlife recreational habits, including drug use; perceptions about sexual violence and equality in a nightlife context; and perceptions about DFSA also in the nightlife context.

Sociodemographic. Age was measured as a stratified variable following the most frequent ranges used in similar studies: under 18 (pre-university age), 18-24 (university) and > 24. Other variables were: educational level and parents educational level (university/upper cycle; bachelor/medium or basic/no studies) and self-perceived family income. Sociodemographic questions were limited to avoid collecting information that could identify the students since the first phase, i.e., anonymity was guaranteed.

Nightlife recreational habits. The questionnaire included six items, structured as follows: frequency of going out during the last year; frequency of consuming alcohol, cannabis, cocaine, amphetamines or benzodiazepines in leisure time, and level of importance regarding the use of alcohol and other drugs in leisure time. Regarding the frequency of going out, the response options included five categories ranging from "*more than once a week*" to "*never*". Other five response categories were used for questions about the frequency of using psychoactive substances, grouped as "*always or often*", "*sometime or a few times*" and "*never*". In turn, the optional response of the questions focussed on the level of importance of the substance use included other five categories ranging from "*indispensable*" to "*indifferent*".

Perceptions about sexual violence and equality in nightlife context. In order to ensure the comparability of our findings, questions were adapted from previous studies. Those concerning equality, security and impunity were based on Spanish (Government Delegation against Gender Violence, 2015; Observatorio Noctámbul@S, 2017, 2018) and European (European Union Agency for Fundamental Rights, 2014) survey-based studies. The questions focused on perceptions about equality between women and men

in the nightlife, including the level of security, worries about the risk of suffering from sexual violence, and the legal consequences for assailants. Five items were included, which required a dichotomous response (*yes* or *no*). Here some sample items: "*Are you worried due to the risk of sexual violence when you go out?*", "*Do you think that nightlife spaces are egalitarian for women and men?*" Questions regarding several behaviours as forms of sexual violence included rape, unwanted physical contact, corralling, invasive sexual comments and insistence against negatives. These items were selected from the Sexual Experiences Survey (Koss et al., 2006), previous Spanish studies (Observatorio Noctámbul@S, 2017, 2018), as well as definitions from the World Health Organization. The Sexual Experiences Survey Long Form Victimization (SES-LFV) is one version of the Sexual Experiences Survey (SES) that assesses victimization by unwanted sexual encounters including rape. Respondents were asked to place a checkmark showing the experiences they think are forms of sexual violence, among the following: "*rape*", "*unwanted physical contact*", "*corraling*", "*invasive sexual comments*", and "*insistence against negatives*". Other questions about the normalization of sexual violence and justification for forced sexual intercourse were also based on approaches used in official surveys (European Union Agency for Fundamental Rights, 2014; Government Delegation against Gender Violence, 2015). Seven items requiring dichotomous responses (*yes* or *no*) were included regarding the questions about the normalization and justification of the sexual violence. The Acceptance of Modern Myths about Sexual Aggression (AMMSA) scale (Megías, Romero-Sánchez, Durán, Moya & Bohner, 2011) was used for designing these items. Concretely, those related to the intersectionality between sexual violence and drug use. As such, four items encompassed the normalization study. Two of those items are: "*Do you think that women who have fun in nightlife environments must assume the risks of being sexually assaulted?*", "*Do you think that sexual assaults happen due to the greater use of drugs by women?*" Other three items approached the justification for forced sexual intercourse, for example: "*Do you think forced sexual intercourse is justified if a woman is under the influence of drugs?*"

Perceptions about DFSA. The authors developed several questions concerning DFSA due to the lack of questionnaires regarding this phenomenon at the time of the study. Previous reviews of the issue allowed relevant items to be identified (Anderson, Flynn & Pilgrim, 2017; Lorenz & Ullman, 2016). These questions included eight items encompassing the willingness to conduct DFSA; risky practices for DFSA victimization (sharing the own drink and accepting drinks with unknown content); the type of consumption and the type of drugs, and the relationship between victim and assailant in most DFSA cases. Besides, four other items were included concerning the social perception of using drugs based on gender. Concretely, the existence of an equal consideration regarding male and female drug use, the greater normalization of images of drunken men and social tolerance towards men and women under the influence of drugs; and, finally, the social support in risky situations, especially the social men penalization for trying to take advantage of a woman who has motor difficulties due to the effects of psychoactive substances.

Data analysis

All variables were described for the whole sample and stratified by gender. A bivariate analysis was performed to identify possible sociodemographic and nightlife recreational habit factors related to gender. The statistical significance of the differences between these variables was assessed using the Chi-square and Fisher's exact tests. The significance was set at two-tailed $p < 0.05$.

Gender-based differences in the perceptions about sexual violence, equality and DFSA in a nightlife context were calculated using the crude (OR) and adjusted odds ratio (ORa). The ORa was determined using logistic regression models. These models were fitted to assess that no other sociodemographic or nightlife recreational habits affected the gender-relations differences in the perceptions. The models included all variables with $p < 0.10$ in the bivariate analysis. Possible interactions amongst the related factors were also evaluated. OR, ORa, and their corresponding 95% confidence intervals (95% CI), were obtained as measures of the relation strength.

Results

From the 2,355 respondents, 66.0% were women, 74.0% were aged between 18 and 24 years (mean age 20.6 years, SD=4.2), 73.4% had an educational level above basic studies, 40.3% came from families in which at least one parent had university or higher studies and 66.7% came from families with a middle, low or very low income. With respect to nightlife recreational habits in the last 12 months, 64.3% had gone out at least once a month, using alcohol or cannabis always or often 72.8% and 7.5%, respectively. Around 33.3 % thought that the use of alcohol and/or other drugs was very important in their leisure time. The women were younger ($p < 0.001$), had a higher maternal educational level ($p = 0.016$) and used less cannabis and cocaine in their leisure time ($p < 0.001$). The sociodemographic characteristics can be found in Table 1.

The perceptions of equality, security and impunity in the nightlife contexts are shown in Table 2 and are clearly different for men and women. Of all respondents, 86.0% perceived leisure nightlife spaces as not egalitarian (88.6% women and 81% men, $p>0.001$), 80.7% considered them as being less safe (84.1% vs. 74.1%, $p<0.001$) and 61.5% were worried about the risk of sexual violence

in the leisure nightlife, with this concern being fifteen times more frequent amongst women (81.7%) than men (21.1%) ($p < 0.001$). With regard to the perception about what is sexual violence, rape and unwanted physical contact were considered to be sexual violence for 98% of the respondents, with no significant differences between genders. Some differences were found for corralling, which was considered to be sexual violence for 91.0% of the respondents (92.5% women and 88.0% men ($p < 0.001$)), and invasive sexual comments (90.6%; 92.1% women and 87.8% men ($p<0.001$)). The difference regarding the perception about insistence against negatives (81.1%; 84.4% women and 74.5% men; ($p<0.001$)) should be highlighted: the consideration of this behavior as a form of violence is two times more frequent among women. With respect to the normalization of the sexual violence in the leisure nightlife, 9.5% thought that women must assume the risk of being sexually assaulted (12.7% men and 7.9% women, $p<0.001$) and 19.4% linked sexual violence against women in nightlife with greater female drug use, with no differences between genders. Around 91.2% of the respondents thought that the drug use acts as a trigger

Table 1. *Demographic results.*

	Total	Women	Men	
Age* **	**N (%)**	**N (%)**	**N (%)**	***p***
16 – 17	353 (15.0)	272 (17.5)	81 (10.1)	
18 – 24	1742 (74.0)	1129 (72.6)	613 (76.6)	‹ .001
› 24	260 (11.0)	154 (9.9)	106 (13.3)	
Formative level				
University and/or higher education	854 (36.5)	557 (35.8)	297 (37.5)	.131
Secondary/Upper secondary	863 (36.9)	592 (38.3)	21 (34.2)	
Basic or with no studies	623 (26.6)	398 (25.7)	225 (28.4)	
Maternal educational level**				
University and/or higher education	942 (40.3)	644 (41.7)	298 (37.4)	.016
Secondary/Upper secondary	331 (21.4)	156 (19.6)	487 (20.8)	
Basic studies or without studies	911 (38.9)	569 (36.9)	342 (42.8)	
Father formative level				
University and/or higher education	894 (38.8)	604 (39.7)	290 (36.8)	.258
Secondary/Upper secondary	466 (20.2)	310 (20.4)	156 (19.8)	
Basic studies or without studies	947 (38.9)	606 (39.9)	341 (43.3)	
Family income				
Very high, high, medium-high	780 (33.3)	510 (32.8)	270 (33.8)	.677
Medium, low, very low	1559 (66.7)	1034 (66.5)	525 (65.6)	
Frequency going out in last year				
Several times/week-once/month	1515 (64.3)	989 (63.6)	526 (65.8)	.565
Once/month/three months	648 (27.5)	435 (28.0)	213 (26.6)	
Three times/year-never	132 (8.2)	131 (8.4)	61 (7.6)	
Frequency of alcohol use in leisure time (ILT)				
Always or often	1708 (72.8)	1127 (72.6)	581 (73.1)	.868
Sometimes or a few times	522 (22.2)	345 (22.2)	177 (23.3)	
Never	117 (5.0)	80 (5.2)	37 (4.7)	
Importance of alcohol and other drug use ILT				
Indispensable, very important	784 (33.3)	521 (33.5)	263 (32.9)	.924
Not very important	780 (33.1)	516 (33.2)	264 (33.0)	
Indifferent	789 (33.5)	517 (33.3)	272 (34.0)	
Frequency of cannabis use ILT***				
Always or often	173 (7.5)	99 (6.5)	74 (9.5)	‹ .001
Sometimes or a few times	725 (31.5)	451 (29.7)	174 (35.2)	
Never	1400 (60.9)	969 (63.8)	431 (55.3)	
Frequency of cocaine or amphetamine use ILT**				
Sometimes or a few times	137 (5.8)	73 (4.8)	64 (8.3)	.001
Never	2145 (94.0)	1442 (95.2)	703 (91.7)	
Frequency of benzodiazepine use ILT				
Always or often	14 (0.6)	9 (0.6)	5 (0.7)	.952
Sometimes or a few times	38 (1.7)	26 (1.7)	12 (1.6)	
Never	2223 (97.7)	1476 (97.7)	747 (97.8)	

Note. ILT: in leisure time. *p ‹ 0.10; **p ‹ 0.05; ***p ‹ 0.001.

Table 2. *Perceptions about sexual violence and equality in a nightlife context.*

	Total	Women	Men		
	N (%)	N (%)	N (%)	Crude OR	Adjusted[a] OR
Perceptions about equality, safety and impunity in nightlife contexts. "Nightlife contexts/spaces...					
Are not egalitarian for women and men"***	2024 (86.0)	1376 (88.6)	648 (81.0)	1.82 (2.32-1.45)	1.75 (2.27-1.39)
imply a lower level of safety"***	1897 (80.7)	1305 (84.1)	592 (74.1)	1.85 (1.5-2.28)	1.80 (1.45-2.23)
worry me due to the risk of sexual violence"***	1446 (61.5)	1270 (81.7)	176 (22.1)	15.78 (12.78-19.49)	15.03 (12.08-18.69)
imply fewer legal consequences for assailants"***	1417 (61.4)	979 (64.7)	438 (55.1)	1.49 (1.25-1.78)	1.62 (1.35-1.94)
Perceptions about behaviours that constitute forms of sexual violence. This behaviour is sexual violence:					
Rape	2322 (98.6)	1534 (98.6)	788 (98.5)	1.11 (0.54-2.27)	0.92 (0.43-1.97)
Unwanted physical contact	2308 (98.0)	1529 (98.3)	779 (97.4)	1.58 (0.89-2.84)	1.61 (0.86-3.01)
Corralling***	2143 (91.0)	1439 (92.5)	704 (88.0)	1.69 (1.27-2.25)	1.655 (1.23-2.23)
Invasive sexual comments***	2134 (90.6)	1432 (92.1)	702 (87.8)	1.62 (1.23-2.15)	1.60 (1.2-2.15)
Insistence against negatives***	1909 (81.1)	1313 (84.4)	596 (74.5)	1.86 (1.5-2.29)	2.01 (1.62-2.51)
Normalization of sexual violence in leisure nightlife contexts (ILNC)					
"women must assume the risks of being sexually assaulted ILNC"***	223 (9.5)	122 (7.9)	101 (12.7)	0.59 (0.44-0.78)	0.53 (0.4-0.71)
"sexual assaults happen due to the greater use of drugs by women"	454 (19.4)	278 (17.9)	176 (22.1)	0.77 (0.63-0.96)	0.70 (0.56-0.88)
"drug use acts as a trigger facilitating violent sexual behavior"**	2140 (91.2)	1431 (92.3)	709 (88.6)	1.49 (1.12-1.99)	1.44 (1.06-1.96)
"preventing drug use would end sexual violence INLC"	170 (7.2)	108 (6.9)	62 (7.8)	0.89 (0.64-1.23)	0.85 (0.6-1.19)
Justification of sexual violence. "Forced sexual intercourse is justified if...					
a woman dresses provocatively"	44 (1.9)	27 (1.7)	17 (2.1)	0.81 (0.44-1.5)	0.97 (0.5-1.88)
a woman is under the influence of drugs"*	62 (2.6)	34 (2.2)	27 (3.5)	0.62 (0.37-1.02)	0.58 (0.34-0.99)
a woman agrees to leave a nightlife space with the assailant**	151 (6.5)	83 (5.4)	68 (8.6)	0.61 (0.44-0.85)	0.57 (0.4-0.8)

Note. ILNC: ILNC: in leisure nightlife contexts. *p ‹ 0.10; **p ‹ 0.05; ***p ‹ 0.001a adjusted by age, maternal educational level, cannabis use and cocaine/amphetamines use.

facilitating sexually violent conducts (92.3% vs. 89.0%; p < 0.05), but only 7.2% thought that cessation of the drug use would end the sexual violence in the nightlife, with no significant differences between sexes. Similarly, forced sexual intercourse against women in nightlife was justified by 1.9% of the respondents if a woman dresses provocatively (no differences between genders), 2.6% (3.5% men and 2.2% women, p < 0.10) if a woman is drugged and 6.5% (8.6% men and 5.4% women, p < 0.05) if a woman agrees to leave with her assailant.

Perceptions about the DFSA phenomena are shown in Table 3. Around 1.7% of the respondents would be willing to conduct sexual intercourse with someone unable to express consent because of the drug use. This willingness was five times higher in men (3.6%) than in women (0.8%; p < 0.001). Regarding the risk practices related to DFSA: 67.7% share their drinks (73.5% men and 64.7% women, p < 0.001); 27.7% accepted drinks with unknown content (35.2% vs. 24.2%, p < 0.001) and 14.4% thought they may have ingested a substance involuntarily (17.1% vs. 12.9%, p < 0.001). As for their DFSA substance knowledge, 48.4% thought that *burundanga* (scopolamine) was present in most DFSA cases (44.7% men and 55.3% women, p < 0.001) and 34.0% thought that alcohol was present (39.2% vs. 31.3%, p<0.001). Around 36.9% of the respondents thought that DFSA usually happens after a voluntary use of some substance by the victim (42.0% men, 34.3% women, p<0.001) and 35.4% believed that most crimes are committed by someone the victim knows personally (no differences by gender). Concerning the social perception of drug use, 37.5% of men and 23.7% of women (p < 0.001) thought that the social consideration of drug use is equal for men and women. Likewise, 22.8% vs. 8.9% (p < 0.001) thought that men and women under the effect of drugs face the same social judgment. As such, the perception that drugged women and men are equally tolerated is three times more frequent amongst men. Around 81.3% thought that the image of a drunk man is more normalized than the image of a drunk woman, with the frequency being more than twice as high among women (85.3%) than among men (74.3%) (p < 0.001). Moreover, 28.7% believed that the social opinion about male's drug use is the same as the social opinion about the female's drug use (37.5% men and 23.7% women, p < 0.001). Finally, 48.9% believe that the society penalizes a man trying to take advantage of a woman who has motor difficulties due to

Table 3. *Perceptions about DFSA.*

	Total	Women	Men		
To be willing to conduct DFSA	**N (%)**	**N (%)**	**N (%)**	**Crude OR**	**Adjusted[a] OR**
"I would be willing to have sexual intercourse with someone unable to express consent because of drugs use"***	41 (1.7)	12 (0.8)	29 (3.6)	0.21 (0.10-0.41)	0.19 (0.09-0.39)
Risky practices for DFSA victimization in leisure nightlife contexts (ILNC)					
"I share my own drink ILNC"***	1579 (67.7)	998 (64.7)	581 (73.5)	0.66 (0.55-0.8)	0.635 (0.52-0.79)
"I accept drinks with unknown content ILNC"***	653 (27.9)	374 (24.2)	279 (35.2)	0.59 (0.49-0.71)	0.59 (0.49-0.73)
"I think I have ingested a substance involuntarily ILNC"***	338 (14.4)	201 (12.9)	137 (17.1)	0.71 (0.57-0.91)	0.81 (0.63-1.05)
Type of consumption/substances involved in most DFSA cases. "In most DFSA cases...					
...the victim uses drugs voluntarily"***	857 (36.9)	526 (34.3)	331 (42.0)	1.38 (1.16-1.65)	1.36 (1.13-1.63)
...alcohol consumption is involved"***	787 (33.4)	479 (31.3)	308 (39.2)	0.71 (0.59-0.85)	0.76 (0.63-0.91)
...scopolamine (Burundanga) consumption is involved"***	1119 (48.4)	768 (50.3)	351 (44.7)	0.71 (0.59-0.85)	0.76 (0.63-0.91)
Relationship between victim and assailant in most DFSA cases					
"the assailant is someone known by the victim in most DFSA cases"	826 (35.4)	557 (36.1)	269 (34.1)	1.09 (0.90-1.30)	1.16 (0.96-1.40)
Social perception of drug use based on gender					
"social consideration of drug use is equal for men and women"***	666 (28.4)	367 (23.7)	299 (37.5)	0.51 (0.43-0.62)	0.52 (0.43-0.64)
"an image of a drunken man is socially more normalized than that of a drunken woman"***	1912 (81.3)	1326 (85.3)	586 (74.3)	2.1 (1.70-2.60)	2.21 (1.77-2.76)
"social tolerance is equal for men and women under the effects of drugs"***	320 (13.6)	138 (8.9)	182 (22.8)	0.33 (0.26-0.42)	0.32 (0.25-0.42)
Social support in situations with possible DFSA risk					
"society penalizes *a man trying to take advantage of a woman who has motor difficulties due to the effects of psychoactive substances* ILNC"***	1146 (48.9)	720 (46.5)	426 (53.6)	0.75 (0.63-0.89)	0.7 (0.59-0.84)

Note. ILNT: ILNT: in leisure nightlife contexts. *p‹0.10; **p‹0.05; ***p‹0.001a adjusted by age, maternal educational level, cannabis use and cocaine/amphetamines use.

the effects of psychoactive substances in a leisure nightlife context; 53.6% men and 46.5% women ($p < 0.001$).

Discussion

A worrying proportion of youths still hold incorrect basic beliefs about sexual violence, with marked differences between the two genders. Many of them internalize nightlife as a predominantly male environment, where women, simply because of who they are, must assume the risk of suffering sexual violence, as well as a certain degree of social condemnation if this violence occurs. In addition, there is little knowledge or, even worse, misconceptions, about DFSA among young people.

This research was carried out in a context of young university students, which we consider to be representative of the young, middle and medium-to-high social group in the Spanish population. In this regard, the gender-based differences were more remarkable at a socio-demographic than a leisure nightlife level. However, despite the context being representative, the sample is not probabilistic, a limitation resulting from the difficulties of researching this topic. Women were slightly younger than men, their parents had a slightly higher educational level, and they presented a leisure nightlife pattern rather close to the male pattern than for previous generations. These data show that a convergence between men and women regarding consumption patterns (Calafat et al., 2009) was reached in a short period of time (Cortés Tomás, Espejo Tort, Martín del Río & Gómez Iñíguez, 2010). However, although an increasing number of women are entering nightlife, severe gender inequalities remain. (Calafat et al., 2009). As previously hypothesized, in our study, perceptions of equality, safety and impunity in leisure nightlife contexts differ between women and men, with only 11.4% and 19.0%, respectively, thinking that nightlife spaces are egalitarian, which is in line with other Spanish studies (European Union Agency for Fundamental Rights, 2014; Government Delegation against Gender Violence, 2018). Similarly, our results show an important female perception of nightlife as a context characterized by a low personal safety level. More than 80% of women are concerned about the risk of sexual violence in leisure nightlife (fifteen times more than men). This perception limits the female freedom of action and movement. Indeed, in a related study, up to half of the European women were found to avoid some situations or places for fear of suffering a sexual assault (European Union Agency for Fundamental Rights, 2014). Consequently, women could be suffering more negative consequences in this process of convergence that is occurring in leisure nightlife contexts (Calafat et al., 2009).

Almost everyone in our sample perceived certain behaviour, such as rape and unwanted physical contact, as sexual violence. Nevertheless, the opinion varies as to whether other, less explicit behaviours, such as corralling or invasive sexual comments, are forms of sexual violence, as already indicated in previous studies (Government Delegation against Gender Violence, 2018; McMahon & Farmer, 2011). As initially hypothesized, there is a social gap between genders regarding identifying some specific acts as sexual violence. These differences are more marked regarding the consideration of insistence against a negative as a form of violence, which is two times more frequent among women. This misperception has two consequences. On the one hand, with regard to the possible victims, the perceptions about what constitutes violence conditions the ability of a victim to self-acknowledged as such (Prego-Meleiro et al., 2020a). Many people do not identify their unwanted sexual experiences as a crime and conceptualize them as miscommunication, bad sex or they simply do not know how to identify them (Bondurant, 2001; Fisher et al., 2003; Littleton, Axsom, Breitkopf & Berenson, 2006). This difficulty is more common among victims of sexual assault who had consumed alcohol around the attack time (Bondurant, 2001; Littleton, Axsom & Grills-Taquechel, 2009). These victims feel that their experiences do not represent a "real rape" (Littleton & Axsom, 2003). Similarly, with regard to the culture of protecting the offenders, the normalization of attitudes, beliefs and distorted socialization experiences results in aggressive sexual behaviors by the assailants (Benson, Charlton & Goodhart, 1992; Margolin, Miller & Moran, 1989).

Drug use plays an important role in sexual violence from two different perspectives. First, drugs, especially alcohol, are highly linked and integrated into the recreational activity of the nightlife context (Calafat et al., 2009; Hughes et al., 2011; Olszewski, 2008; Romo-Avilés, García-Carpintero & Pavón-Benítez, 2019). Indeed, alcohol consumption was found to be an indispensable or very important activity for a third of the respondents during their leisure nightlife activities, which is higher than for previous studies in the same context (Calafat et al., 1999). Second, drug use appears to be one of the main causes of sexual violence for many young people. Around 20% attribute sexual violence against women in a nightlife context to the greater use of drugs by women nowadays. This perception involves blaming women for the violence they suffer and can be explained by social adherence to gender stereotypes, which penalize more the female consumption because of the transgression of roles traditionally assigned to women. According to this belief, drinking alcohol before the assault causes the victim to be perceived as promiscuous responsible for the attack (Grubb & Turner, 2012). These observations are consistent with one of our original hypotheses: women experience a lack of social support in leisure nightlife contexts, resulting from the different social perceptions about the drug use based on gender. Finally, drugs use is also largely considered as a factor triggering the manifestation of violent sexual behaviours. At this point, we focus only on male consumption since sexually violent behaviour is mainly realized by men against women (World Health Organization, 2002). However, sexual violence in the leisure nightlife context should not be considered only based on drug use. Thus, although up of 90% of the respondents think that drug use facilitates sexual violence, only 7.2% believe that stopping the consumption would end the violence. Cultural violence against women is an essential component of sexual violence, thereby configuring a socio-structural reality that supports and justifies violent behaviours. In Spain, around 50% of men and 45% of women think that alcohol is often the reason why a man rapes a woman (Government Delegation against Gender Violence, 2018). However, this statement can be interpreted as if the population were somehow "exempting" the offenders from their actions. Indeed, a person may share perceptions for justifying the violence subtly and never blaming the victim directly. For instance, when thinking that the assaults happen because of how a woman dresses or because the victims consume alcohol or other drugs (Lorenz & Ullman, 2016), which this study found for a large number of men. Similarly, it is striking the differences between genders regarding the willingness to conduct sexual intercourse with someone unable to express consent because of drugs. In this sense, the observations support our previous hypothesis that men show greater willingness than women to conduct sexual intercourse with someone unable to express consent because of drugs. As such, male willingness reaches 3.6%, with this figure being almost five times higher than in females, although similar to estimates from other countries (Victorian Health Promotion Foundation, 2015). In this sense, previous studies suggested that the use of alcohol by victims of alcohol-involved sexual assault is frequently encouraged by another person, often the assailant (Lynch, Wasarhaley, Golding & Simcic, 2013). It should be noted that in situations of dating and hooking up, sexual goals are more often the primary motivation among men than among women (Bradshaw, Kahn & Saville, 2010). Consistent with this observation, significant proportions of male college students admit to encouraging their female counterparts to consume alcohol in an attempt to engage them in sexual intercourse (Lynch et al., 2013; Romero-Sánchez & Megías, 2010; Sipsma, Carrobles, Montorio & Everaerd, 2000). Similarly, undergraduate women report sexual assaults after someone else got them drunk twice as frequently as after being held down (Tyler, Hoyt & Whitbeck, 1998).

In this study, three myths were related to the DFSA phenomenon, which fits another of our original hypotheses: there are several widespread myths or misconceptions about the DFSA phenomenon, which significantly affect

the social conception of this form of sexual violence. Firstly, most young people believe that assaults happen after the surreptitious administration of some type of substance to the victim by the assailant. However, it is much more frequent that victims voluntarily intake the drugs before the assault (García-Caballero, Quintela-Jorge & Cruz-Landeira, 2017; Hagemann, Helland, Spigset, Espnes, Ormstad & Schei, 2013; Scott-Ham & Burton, 2005). In addition, 48.4% believe that the *burundanga* (scopolamine) is the substance involved in most DFSA cases, with this figure decreasing to 34% for alcohol. However, confirmed DFSA cases involving the use of scopolamine in Spain are anecdotal (Gomila, Puiguriguer & Quesada, 2016), whereas at both a national (García-Caballero et al., 2017; Navarro & Vega, 2013; Xifró-Collsamata et al., 2015) and international level (Hagemann et al., 2013; Scott-Ham & Burton, 2005), there is significant evidence for the involvement of alcohol in DFSA cases. Both myths are related, since the media have helped to spread the idea about the covert administration of "rape drugs" such as flunitrazepam, gamma-hydroxybutyrate (GHB) (Hagemann et al., 2013) and scopolamine (Gomila et al., 2016). The greater extent of these myths among women is remarkable, probably resulting from their greater concern about suffering sexual violence. This may lead them to further consider these scare stories concerning the surreptitious administration of certain substances (Prego-Meleiro et al., 2020a). Finally, another misconception identified in this work sustains that, in most cases, assailants are unknown people to the victim, an idea not fitting the reality. (Panyella-Carbó, Agustina & Martin-Fumadó, 2019; Prego-Meleiro et al., 2020a).

It is essential to bear in mind that these myths and incorrect perceptions difficult that people suffering DFSA to acknowledge themselves as victims, which is crucial for reporting the assault and seeking proper help. (Lorenz & Ullman, 2016; Prego-Meleiro et al., 2020a). However, even if they identify themselves as such, the decision to report an incident is influenced by the negative social reactions expected by the victims (Burt, 1980; Heider, 1958; Lerner, 1980). When a sexual assault involved drug use by the victim, social reactions to the incident depend on cultural perceptions about drug use, which vary based on the consumer's gender (Prego-Meleiro et al., 2020a). Young women tend to believe that females' drug use is socially more penalized than drug use by males. The perception that drugged women and men are equally tolerated by society is three-time more frequent among men. Similarly, women believe twice as frequently as men that the image of a drunk man is socially more normalized than that of a drunk woman. In this way, as we previously suggested, women experience a lack of social support in leisure nightlife contexts, resulting from the different social perceptions about drug use based on gender. Social negative reactions towards victims negatively affect their recovery (Relyea & Ullman, 2015), thus implying a higher risk of re-victimization (Lorenz & Ullman, 2016). The absence of a suitable social support may also lead the victims to not recognize the need to take precautions against future aggressions (Littleton et al., 2009) or to take refuge in alcohol as a coping strategy (Lorenz & Ullman, 2016). This situation can lock victims in spirals of cyclical re-victimization (Prego-Meleiro et al., 2020a). In this sense, when we asked about expected social support in a risky DFSA situation, only 48.9% believe that the society would penalize a man trying to take advantage of a woman who has motor difficulties due to the effects of psychoactive substances in a leisure nightlife context. This perception of a lack of social support is more extended among women and is associated with the greater female perception of impunity for the perpetrators in a nightlife context. Finally, the performance of statistical adjustments must be taken into consideration. The balance between women and men was not altered when the analyses were carried out adjusting the data by proxy variables for education level and frequency of going out. Consequently, the differences observed are not attributable to factors other than gender.

Limitations

This study presents several limitations. Although a non-probabilistic sampling method was used, the representativeness of the sample is valid as the composition is consistent with the sociodemographic profile of any other Spanish university. Likewise, results come from a population group with a medium-to-high social level, so that the misconception could be considerably greater in other population groups. In addition, this study did not use validated questions giving the pioneering nature of this work in Spain, where limited research into sexual violence and DFSA has been conducted despite the relevance of this phenomenon. Consequently, the studied parameters have not yet been included in psychometric scales.

Conclusions

A significant segment of university students does not perceive certain forms of sexual violence and shares several attitudes and perceptions justifying it. The use of drugs, especially alcohol, is widely viewed as a factor originating and justifying the sexual violence against women, with this idea being particularly prevalent among men. This tolerance to sexual violence leads women to suffer disadvantageous situations, particularly in leisure nightlife contexts, where drug use is widespread. In this sense, this study's findings may prove useful when designing prevention efforts targeted to increasing the social awareness of teenagers and young adults against sexual violence in leisure nightlife contexts. These efforts must demystify the DFSA phenomenon, enhance the social support before, during

and after the assault, and avoid blaming the victims. Identifying misconceptions regarding sexual violence should encourage the development of preventive and informative intervention programs, particularly targeted to men, to promote the generation of equitable and secure spaces. All forms of sexual violence must be well defined and understood by the possible offenders, victims and society as a whole. A mindset change is necessary to get a more supportive and active society against sexual violence, concretely against the DFSA phenomenon.

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Conflict of interests

The authors declare that they have no competing interests.

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Substance use, mental health and dual disorders on pregnancy: Results of prevalence and treatment rates in a developed country

Salud mental, abuso de sustancias y trastornos duales en el embarazo: Tasas de prevalencia y tratamiento en un país desarrollado

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Abstract

Smoking and substance use during pregnancy are major preventable causes of mortality and morbidity, having a bidirectional and deleterious relationship with the mental health of the mother and child. As part of the WOMAP (Woman Mental Health and Addictions on Pregnancy) initiative, our study aimed to describe the prevalence of co-occurring mental illness and substance use problems, diagnoses and severity of those considered at risk and rates of treatment.

A screening of 2,014 pregnant women was done using the AC-OK scale and they were asked about their smoking habits and services use for mental health/substance abuse. Of these, 170 women were considered at risk of co-occurring mental illness and substance use problems (≥ 2 positive responses to the AC-OK-Mental Health subscale, ≥ 1 positive response to the AC-OK-Substance Abuse subscale and/or smoking more than once a month and no use of specialized services) and were assessed with a more

Resumen

El tabaquismo y el consumo de sustancias durante el embarazo son importantes causas prevenibles de morbimortalidad, teniendo una relación bidireccional y deletérea con la salud mental de la madre y el niño.

Como parte de la iniciativa WOMAP (Woman Mental Health and Addictions on Pregnancy), se estudiaron 2,014 embarazadas buscando describir la prevalencia de trastornos mentales y por uso de sustancias concurrentes, las tasas de tratamiento y los diagnósticos y la gravedad. Las participantes fueron evaluadas con la escala AC-OK y se les preguntó sobre sus hábitos tabáquicos y uso de servicios de salud mental/sustancias. De las participantes, 170 mujeres resultaron positivas para un trastorno mental y por uso de sustancias concurrentes (≥ 2 positivos a la subescala AC-OK-Salud Mental, ≥ 1 positivos a la subescala AC-OK-Sustancias y/o fumar más de una vez al mes y no estar en tratamiento) y fueron evaluadas en profundidad mediante una batería de escalas (Patient Health

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extensive battery of measures (Patient Health Questionnaire [PHQ-9], General Anxiety Disorder [GAD-7], Posttraumatic stress disorder [PTSD] Checklist for DSM-5 [PCL-5], Alcohol Use Disorders Identification Test [AUDIT], Drug Abuse Screening Test [DAST] and Fagerström).
In the last year, 614 women (30.5%) smoked tobacco (42.5% daily) and 9.8% were positive for both substance use and mental illness per the AC-OK. Only 11.1% of them received specific treatment in the previous three months while another 13.6% were scheduled to attend services in the following month. From the subsample assessed in depth, 62(36.5%) endorsed at least moderate depression, 35(20.6%) endorsed at least moderate anxiety, 32(18.8%) endorsed PTSD on the PCL, and 37 out of 88 alcohol users scored above the threshold in AUDIT (≥ 3).
In conclusion, high prevalence and low treatment rates suggest that effective detection mechanisms should be integrated into usual care, allowing for early interventions.
Keywords: Perinatal care; perinatal mental health; dual disorders; smoking; drug use; screening.

Questionnaire [PHQ-9], General Anxiety Disorder [GAD-7], Post-traumatic stress disorder Checklist [PCL-5], Alcohol Use Disorders Identification Test [AUDIT], Drug Abuse Screening Test [DAST] y Fagerström).
En el último año, 614 mujeres (30,5%) fumaron tabaco (42,5% diariamente) y el 9,8% fueron positivas para problemas por uso de sustancias y salud mental según la AC-OK. Solo el 11,1% había recibido tratamiento en los tres meses previos y solo un 13,6% tenía una cita en el siguiente mes. De las 170 pacientes evaluadas secundariamente, 62(36,5%) presentaron al menos depresión moderada, 35(20,6%) al menos ansiedad moderada, 32(18,8%) fueron positivas a la PCL-5, y 37 de las 88 que reconocieron uso de alcohol puntuaron por encima del umbral en AUDIT (≥ 3).
En conclusión, la combinación de una prevalencia significativa junto con bajas tasas de tratamiento, remarcan la necesidad de mecanismos de detección efectivos en la atención habitual, permitiendo una intervención temprana.
Palabras clave: Atención perinatal; salud mental perinatal; patología dual; tabaquismo; consumo de drogas; cribado.

During the first weeks of pregnancy, proper monitoring of risk factors related to fetal complications, through an adequate anamnesis, is crucial for optimal follow up. Antecedents such as previous pre-eclampsia or preterm birth are screened by almost all obstetricians in a new pregnancy in order to prevent and provide an early diagnosis of recurrences. However, despite the fact that substance use, especially tobacco use, is even more frequent (Lange, Probst, Rehm & Popova, 2018), and has a crucial impact in both the short and long term, it is usually underdiagnosed and not always part of the systematic evaluation of all obstetricians (Hankin, McCaul & Heussner, 2000). Moreover, unidentified substance use can lead to gestational complications, such as preterm birth, premature rupture of membranes or fetal growth restriction (Cnattingius, 2004; Dahlin, Gunnerbeck, Wikstrom, Cnattingius & Edstedt Bonamy, 2016; England, Benjamin & Abenhaim, 2013; Gouin, Murphy & Shah, 2011; Ko et al., 2014) and is therefore a potentially preventable cause of complications. Substance use becomes even more problematic considering that women who use substances during pregnancy usually use more than one illicit substance, multiplying the risk of fetal disease (Forray & Foster, 2015). Exposure to illicit drugs during pregnancy has also been linked to structural effects on the fetus and a range of neurobehavioral consequences during childhood and later (Holbrook & Rayburn, 2014).

When facing substance use among pregnant women, we must consider the inter-relationships between specific congenital malformations, prematurity, restriction in birth weight, stillbirth, and later fetal withdrawal syndrome or neonatal death, and other less frequent complications (Dahlin et al., 2016; Gauthier, Guidot, Kelleman, McCracken & Brown, 2016; Ko et al., 2014; Pereira, Da Mata, Figueiredo, de Andrade & Pereira, 2017; Pineles, Hsu, Park & Samet, 2016).

The two most relevant complications of tobacco use are prematurity and low birth weight. In both cases, first trimester cessation leads to a risk similar outcome to that of non-smokers (Blatt, Moore, Chen, Van Hook & DeFranco, 2015). These complications are dose dependent (Cnattingius, 2004). The same is known for licit substances, with studies describing physical complications (Cook et al., 2017) and behavioral and psychiatric problems related to tobacco use (Ekblad, Gissler, Lehtonen & Korkeila, 2010; Tiesler & Heinrich, 2014) and alcohol (Donald et al., 2015; Sarman, 2018).

This is of particular interest given that some women do not alter their pattern of substance use until pregnancy is confirmed (Holbrook & Rayburn, 2014). Thus smoking prevalence during pregnancy is similar to that of the general population (Cnattingius, 2004). A recent meta-analysis estimates smoking prevalence during pregnancy in Spain of 26% (Lange et al., 2018), a likely underestimate of the problem given well-known under-reporting (Garg et al., 2016). Perinatal mental health problems, bidirectionally and deleteriously related to substance use, are recognized as a major public health issue in pregnant women. Depression and anxiety prevalence studies in multiple countries described a range of between 10 to 30% in pregnant women (Austin, Priest & Sullivan, 2008; Bayrampour, Hapsari & Pavlovic, 2018; Fairbrother, Janssen, Antony, Tucker & Young, 2016; Martinez-Paredes & Jacome-Perez, 2019; Woody, Ferrari, Siskind, Whiteford & Harris, 2017). Similar to substance use, perinatal mental health problems are related to several adverse pregnancy outcomes (Kramer et al., 2009) and abnormal neurodevelopment and mental health disorders in children (Kingston, Tough & Whitfield, 2012).

Despite several initiatives revealing under-identification (Hankin et al., 2000) and recommending systematic screening, there are no universal clear guidelines, and consequently mental health conditions during pregnancy are still under-diagnosed (Bayrampour et al., 2018). Yet, few studies have analyzed the co-occurrence of mental health and substance use problems in this population. The lack of services to deal with perinatal mental health in many health care settings, highlights the need to improve detection and care of these women (Howard, Piot & Stein, 2014).

Different barriers for a proper approach to mental health during pregnancy have been identified (Bayrampour et al., 2018). One way to overcome barriers to identification and care is the development of screening questionnaires of easy use for obstetricians and midwives. The AC-OK screening tool is a useful instrument validated in Spanish and with good psychometric properties for routine screening of mental health and substance use problems in clinical settings (Chavez et al., 2017).

In this study, we use data obtained from the WOMAP (Woman Mental Health and Addictions on Pregnancy) research project, a study designed to test the feasibility, acceptability and efficacy of two different interventions for pregnant women with tobacco, benzodiazepines or other substance use problems and/or mental health disorders. Our aims were to: 1) describe the prevalence of substance use and mental health problems using the AC-OK questionnaire, including the prevalence of smoking; 2) depict whether these women received treatment or not, and 3) identify the mental illness and drug use diagnoses and severity in a subsample of women considered eligible for the WOMAP clinical trial.

Methods

Setting and participants

From July 2016 to December 2019, 2014 pregnant women were screened. Participants were selected among pregnant women under 26 weeks of pregnancy who were over 18 years of age and undergoing obstetric visits in five hospitals in the Madrid (Spain) metropolitan area: Jiménez Díaz Foundation (Madrid urban area), Infanta Leonor Hospital (Madrid urban area), Tajo University Hospital (Aranjuez), General Hospital of Villalba (Villalba) and Infanta Elena Hospital (Valdemoro). The five participating hospitals cover a health area of more than 1.300.000 inhabitants from diverse socioeconomic backgrounds.

Participants were approached in two ways: in situ, when the woman finished the obstetric visit, or by telephone, after the obstetrician in charge obtained the contact authorization from the patient. In both cases, the study was explained to the participants by research assistants, and the screening interview administered to those who accept to participate. Usual care for pregnant women in the recruitment hospitals begins with a first appointment between 8-12 gestational weeks in which a detailed anamnesis and fetal ultrasound are conducted. First trimester analytical results (week 10-12) are also evaluated and chromosomal abnormalities screened. In weeks 20, 28 and 32-34 of gestation, morphological ultrasounds measuring fetal growth are performed and analytical results of each trimester are evaluated. Subsequently, at week 38-39, a static ultrasound, fetal growth and assessment of the amniotic fluid are carried out. From weeks 40-41, fetal monitoring and ultrasound controls are performed to assess the biophysical profile.

Assessment

Participants were first screened to identify those considered to be at risk for co-occurring mental health/substance use problems. Those who tested positive on the screening were offered to participate in the WOMAP clinical trial and were later evaluated with a more comprehensive questionnaire. Data were collected and stored using MEmind clinician interface (www.memind.net), a web-based application developed to merge different data sources, including clinician and patient data (Barrigon et al., 2017).

Screening assessment

2014 women who agreed to be assessed were screened for mental health (MH), substance abuse (SA) and co-occurring mental health/substance use problems (dual disorder) with the AC-OK screen (Chavez et al., 2017; Cherry & Dillon, 2013). AC-OK is an easy-to-use questionnaire, validated in Spanish speaking populations in Spain and USA, designed to be a useful screener for mental health and substance abuse problems. The AC-OK includes 15 items, nine items related to mental health and six items related to substance abuse. The Spanish version has good psychometric properties, with good internal consistency (Mental Health Screen [$\alpha = 0.82$]; Substance Abuse Screen [$\alpha = 0.90$]) and excellent sensitivity and specificity. A cut-off point of 2 or more positive answers were selected for mental health subscale and one or more for substance use subscale (Chavez et al., 2017). Those women that answered "yes" to AC-OK questions 9 or 10, regarding death desire and suicidal behavior, were screened for suicide risk in the previous month with the Paykel Suicide Scale (Paykel, Myers, Lindenthal & Tanner, 1974) and referred to an immediate psychiatric evaluation as part of a safety protocol if they answer yes to Paykel questions 4 or 5 (i.e. had a suicidal plan or attempt). This questionnaire consists of five questions about suicide including life-weariness, wishes of death, suicidal ideation, suicidal plans and suicide attempts.

Furthermore, women were asked about cigarette smoking in the last 12 months (yes/no) and, among those who answered yes, how often they smoked (number of days they smoked cigarettes per week). They also were asked about mental health and/or drug/alcohol abuse services

used in the last three months and whether they had an appointment scheduled in the next month. Finally, socio-demographics characteristics were collected: age, country of origin, racial group and education level.

Assessment for women at risk

Women were considered at risk (and therefore included in the clinical trial) if they had: 1) two or more positive responses to the AC-OK-Mental Health (AC-OK MH) subscale, 2) one or more positive responses to the AC-OK-Substance Abuse (AC-OK SA) subscale and/or reported smoking more than once a month, 3) no use of specialized services, defined as not having an appointment in the following month and have not seen a clinician in the past three months and 4) if the Paykel Suicide Scale was administered, they answered NO to questions 4 and 5 (Paykel et al., 1974). Exclusion criteria for entering the clinical trial were: 1) had received a diagnosis of psychotic or bipolar-related disorders or 2) lacked capacity to consent, as determined by not being able to answer questions of the study purpose or process.

Due to WOMAP study clinical trial protocols, only eligible women (n=170) were assessed with a more extensive battery of mental health and substance use questionnaires. For mental health, we used the Patient Health Questionnaire (PHQ-9) which addresses the nine DSM-IV diagnostic criteria for major depressive disorder (Kroenke, Spitzer & Williams, 2001), the General Anxiety Disorder 7-item screener (GAD-7) for anxiety (Spitzer, Kroenke, Williams & Lowe, 2006), and the Post-Traumatic Stress Disorder Checklist (PCL-5), a self-report measure for the 17 DSM-IV symptoms of PTSD (Blanchard, Jones-Alexander, Buckley & Forneris, 1996). For substance use, the questionnaires administered were the Alcohol Use Disorders Identification Test (AUDIT), a screener developed by the World Health Organization (WHO) (Bohn, Babor & Kranzler, 1995), the Drug Abuse Screening Test (DAST), a brief self-report instrument designed for drug abuse and dependence disorders detection (Yudko, Lozhkina & Fouts, 2007); and the Fagerström Test for Nicotine Dependence, a six item instrument that evaluates the amount of cigarette consumption, compulsion to smoke, and smoking dependence (Heatherton, Kozlowski, Frecker & Fagerstrom, 1991). In addition, women with a positive screen were asked about the number of days in the last month they used the following substances: alcohol, opioids, barbiturates, benzodiazepines, cocaine, amphetamines, cannabis, hallucinogens and inhalants.

Statistical analysis

A descriptive study of the total sample was made regarding demographical variables with means and standard deviations or percentages as were appropriate. Rates of positive screen to the AC-OK and its subscales was calculated for total sample and compared by educational level and racial group using chi-square tests. Smoking habit was described in the total sample using percentages. For the subsample assessed in depth scores of questionnaires were calculated.

Ethical considerations and data protection

The study was carried out in compliance with the Declaration of Helsinki and approved by the Jiménez Díaz Foundation Ethics Committee for Clinical Investigation (Ref. 2015/43). After a complete description of the study, all screened participants gave informed consent.

Concerning data protection, access to the MEmind clinician user interface was restricted to researchers. Only the Principal Investigator, clinicians and researchers, using a username and password, had access to identifiable information. The data provided by the clinician were encrypted by Secure Socket Layer/Transport Layer Security (SSL/TLS) between the investigator's computer and the server. Data were stored in an external server created for research purposes. Data were encrypted using the industry-standard AES-256 algorithm. Furthermore, an external auditor guaranteed that security measures met the Organic Law for Data Protection (Spanish Government, Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales, 2018) standards at a high protection level.

Results

Total sample description

The total sample was 2014 women aged 33.0 ± 5.6 years old (range 18-46). 67.6% of the women were born in Spain, 19.8% were from South or Central America, 6.2% from the rest of Europe, 2.5% from Morocco, and 3.9% from other non-European countries.

Regarding racial group identification, 75.4% (1518) of women who provided information (1965), identified themselves as white; and 14.3% (287) stated their ethnicity as Latin American. Other minority racial groups included: 1.9% (n=39) gypsy, 2.3% (n=46) Arab, 2.2% (n=45) mixed race/ethnicity, 1% (n=20) Afro-American and 0.5% (n=10) Asian. Regarding education, 880 women (43.7%) had a university degree or higher, half of the women (49.6%; n=998) completed high school or vocational-technical school, , and 129 women (6.4%) only completed primary studies.

Considering mental health and substance abuse, out of the 2014 women screened, 9.8%(198) had two or more positive responses to AC-OK-MH subscale and one or more positive responses to AC-OK-SA subscale and therefore were considered at high risk of having co-occurring mental health/substance use problems , rate that increases to 17.1% (344) if smoking in the last year was added to the AC-OK as criteria for being considered at risk. For each subscale, percentages of positive items are shown in Figure 1.

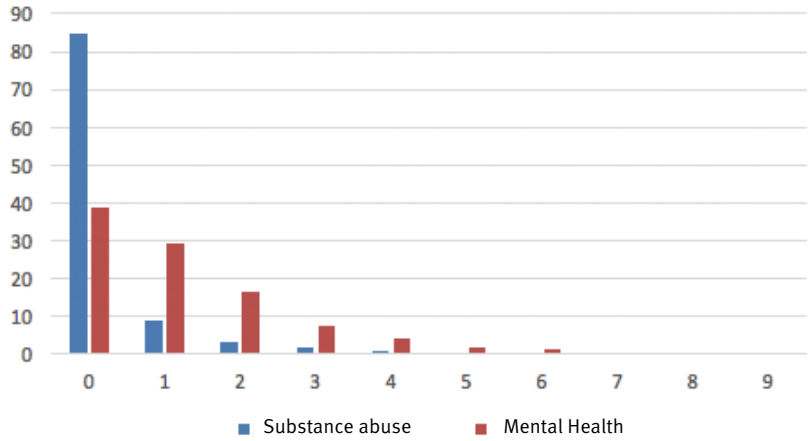

Figure 1. Percentage of women per the number of AC-OK affirmative answers in SA (6 items) and MH subscales (9 items).

Differences were observed by educational level, with 14.7% (n=19) of women considered at high risk for a co-occurring disorder in those with primary studies, compared to 11.2% (n=112) among those with high school studies and 7.5% with university studies (n=66) (p=0.004). Differences that remain when tobacco was added to the AC-OK as a criteria for being considered at risk: 24% (n=31) with primary studies, 19.9% (n=119) with high school studies and 12.7% (n=112) with university (p<0.001).

Regarding mental health, 32% of women (n=645) affirmatively answered two or more items, while 15% (n=302) affirmatively answered one or more items regarding substance abuse. No differences were found in the AC-OK-SA by race or educational level. A greater percentage of women with only primary studies were positive on the AC-OK-MH (43.4%; n=56) compared to 36.7% (n=366) among those with high school or vocational-technical school studies and 25% (n=220) with university studies (p<0.001). When evaluating differences by race, those self-identifying as Asians (20%), Gipsy (20.5%), white (30.4%) or from Latin America (34.8%) had lower positive rates on the AC-OK-MH as compared to Afro-American (55.0%), those of mixed race (46.7%) or Arab (41.3%) (p=0.006).

Among the 198 considered at risk according to the AC-OK, 22 (11.1%) received treatment at a mental health or drug abuse facility in the previous three months and 27 (13.6%) were scheduled to attend services in the following month.

Of the 99 women who answered "yes" to AC-OK questions 9 or 10, concerning death desire and suicidal behavior, they were asked about suicide risk in with Paykel Suicide Scale. Of those, two (2%) reported having made a suicide attempt, six (6.1%) had made a suicide plan, 21 (21.2%) had suicidal thoughts, 30 (30.3%) expressed death wishes, and 28 (29.3%) reported life weariness. Out of the total sample, 614 women (30.5%) had smoked tobacco during the past year (Table 1).

Table 1. *Frequency of smoking (n= 614)*[1].

Frequency	N	Percent
Daily	261	42.5 %
5 to 6 days/week	10	1.6 %
3 to 4 days/week	13	2.1 %
1 to 2 days/week	18	2.9 %
2 to 3 days/month	10	1.6%
Less than once a month	296	48.2%

Note. [1] Data from six patients is missing (1%).

Description of women at risk

One hundred and seventy women (8.4%) who fulfilled the study inclusion criteria were assessed with an in-depth questionnaire battery. Results are shown in Tables 2 and 3.

When asked about substance use in the previous month, 23 women reported alcohol use (from 12 women drinking one single day to a maximum of 1 woman drinking daily), eight used sedative drugs (five of them during the whole month, another one during 23 days, and two women more than 4 and 3 days each one), five women smoked cannabis (three in a daily basis and two twice during the month); and one woman reported cocaine use during 7 days. The rest of the drugs were not used by the 170 evaluated women.

Discussion

Analysis of the sample of 2014 pregnant women, showed tobacco consumption figures higher than those of a recent meta-analysis that estimated a prevalence of smoking during pregnancy of 26% (Lange et al., 2018) . Almost a third of our sample (30.5% of women) smoked tobacco in the last year, with 261 of smokers (42.5% of smokers) reporting daily smoking. In Spain, a recent study found a prevalence of substance use in each of the pregnancy trimesters of 21.2%, 18.5% and 13.3% respectively for tobacco use, 40.7%, 23.1%

Table 2. *Mental health and drug abuse questionnaires results (n= 170).*

	N	Percent
Depression (PHQ-9)[a]		
Negative (0-4)	40	23.5%
Mild depression (5-9)	68	40.0%
Moderate depression (10-14)	41	24.1%
Moderately severe depression (15-19)	16	9.4%
Severe depression (20-27)	5	2.9%
Positive (PHQ-9 ≥ 10)	62	36.5%
Generalized Anxiety (GAD-7)		
Negative (0-4)	70	41.2 %
Mild anxiety (5-9)	65	38.2%
Moderate anxiety (10-14)	22	12.9%
Severe anxiety (15-21)	13	7.6%
Positive (GAD-7 ≥ 10)	35	20.6%
PTSD (PCL)[b]		
Negative	138	81.2%
Positive (PCL ≥ 33)	32	18.8%
Alcohol Use (AUDIT)c		
Negative	51	58.0%
Positive (AUDIT ≥ 3)	37	42.0%
Drug Abuse (DAST)[d]		
Negative	37	21.8%
Positive (DAST ≥ 3)	0	0

Note. a: data not available for one woman; b: 5 women did not report traumatic events; c: 82 women did not use alcohol; d: 133 women did not use drugs.

Table 3. *Fagerström questionnaire results (only those reporting use in the last year (87) were assessed).*

	N	Percent
Very low dependence	51	58.6 %
Low dependence	21	24.1 %
Moderate dependence	10	11.5 %
High dependence	4	4.6 %
Very high dependence	1	1.1%

and 17.1% for alcohol and 4.8%, 1.9% and 1.2% for cannabis (Blasco-Alonso et al., 2015). Like this apparent progressive smoking cessation when pregnancy is confirmed, our sample revealed that, of the 614 women who claimed to have smoked in the last year at the time of evaluation, 48.2% reported smoking less than once a month.

A relevant contribution of this study to the scarce information existing in the literature regarding co-occurring problems in pregnant women, is that 9.8% (198 women) were considered at risk for a dual disorder of both mental illness and substance use disorder. In addition, 17.1% were at risk if they reported tobacco use in the last year.

While substance abuse among pregnant women has been reported in the literature (Blasco-Alonso et al., 2015; Chang et al., 2011), dual pathology has been rarely described. From the subsample of 170 women eligible for the WOMAP trial who were evaluated in depth, 36.5 %were positive to at least moderate depression, 20.6% were positive to at least moderate anxiety, 18.8% were positive to the PTSD scale and 37 scored above the threshold in AUDIT (21.8%). These rates, again, are clinically relevant and agree with those obtained in previous studies that describe rates of up to 20% in depression and anxiety in pregnancy (Austin et al., 2008; Bayrampour et al., 2018). The significant prevalence rates of mental health, substance abuse and dual problems found in the sample of pregnant women screened positive in the AC-OK highlight the need for exploring additional efforts to treat dual disorders during initial pregnancy services, moreover when a 4,91% (99)of the women screened recognized death or suicidal thoughts.

Of note, is that only a small proportion of the patients identified as being at risk for dual disorders using the AC-OK instrument were in treatment. Only 11.1% (22 women) had received treatment in mental health or drug abuse services in the last three months and 13.6% (27 women) had scheduled an appointment in the following month. This finding highlights the significant lack of mental health and addictions care during pregnancy and suggests that new actions should be established to allow professionals involved in the care of the pregnant woman to recognize substance use and mental health disorders, and to provide proper referrals to treatment.

All pregnant women, should be asked regularly about substance use (Siu, 2015). Low treatment rates in our sample suggest that not all obstetricians, nor other professionals involved in the care of the pregnant woman, are identifying substance use and mental health problems. Considering the consequences of substance use, it should be part of usual care, not only in the first visit, but also throughout the following appointments, to evaluate and promote the cessation of consumption. Several reasons may be behind this lack of adequate recognition and identification of substance use disorder and mental illness. Among them, and added to the frequent underreport, could be the lack of knowledge of the extent of the fetal repercussion, which is probably underestimated in the short and long term. And on the other hand, as it has been described in the literature (Ebrahim & Gfroerer, 2003), the patient profile is usually more complex, being usually younger, with low socioeconomic status and higher rates of inadequate gestational control. Our findings of higher AC-OK positives on those patients with lower educational levels support this hypothesis. In addition, these patients may also deny consumption to avoid the legal repercussions that are often associated with disclosure.

Anamnesis is the essential tool for the identification of patients with mental health and substance use problems but screening tools validated for their use in pregnant

women are limited (ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy, 2012). One of these tools is the CRAFFT, which has been reported to be better than medical report and the T-ACE alcohol screen for identification of prenatal substance use young patients (under 25 years old), but it has not been validated in older patients (Chang et al., 2011). It could be considered if, due to the usual lack of time in medical appointments, other additional screening tools should be applied universally or only in those patients who respond affirmatively to questions about consumption. On the other hand, the use of biological tests as screening tool could improve detection and minimize underreporting but would be less feasible to use them in routine care (Garg et al., 2016). A very simple questionnaire such as the AC-OK shows promise and could be adequate for accurate identification in the usual care of pregnant women.

There are several limitations to consider when drawing conclusions from the obtained results. First, when evaluating the prevalence results in pregnancy, it must be considered that the sample is not extracted from the entire Madrid region in which the hospitals are located. Second, a possible underestimation of prevalence, given the usual under-reporting of substance use and mental health problems, may influence the figures (Garg et al., 2016).

Despite these limitations, it can be concluded that due to the combination of significant prevalences, low rates of treatment, and the severe but preventable consequences on the mother and child, new actions, including efficient detection mechanisms should be integrated into usual clinical practice. This would allow for adequate access to treatment and promoting early cessation of substance consumption.

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Conflict of interests

The authors declare that there is no conflict of interest in any aspect of this study.

The authors declare no conflicts of interest in relation to the study, its authorship, and/or the publication of this manuscript.

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Cognitive functioning after six months of follow-up in a sample of alcohol use disorder outpatients

Funcionamiento cognitivo después de seis meses de seguimiento en una muestra de pacientes ambulatorios con trastorno por uso de alcohol

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Abstract

Until now, no follow-up studies had simultaneously evaluated executive functions, other non-executive functions related cognitive functions, and impulsivity in a large enough sample of moderate to severe alcohol use disorder (AUD) patients. The main objective of the present study was to compare neuropsychological performance and its relation to alcohol use in patients with AUD and healthy controls, and to determine the evolution of cognitive impairment and alcohol use over time. For this purpose, a 6-month follow-up study was designed to compare a sample of 100 outpatients with AUD (DSM-5 criteria) with 100 matched healthy controls. The patient group was recruited from three different health centres in Spain located in Orense, Gijón and Barcelona. The assessment consisted of a systematic battery of cognitive tests to evaluate the following functions: attention, anterograde memory, processing speed, verbal fluency, executive function, and implicit attitude toward alcoholic beverages. We also compared clinical variables associated with alcohol use, such as alcohol craving and impulsivity. After 6 months, anterograde memory, working memory, and resistance to interference improved remarkably in AUD patients, although not enough to match the normal population. With regard to clinical variables, there was a small but significant cognitive improvement related to a reduction in alcohol use and impulsivity. Executive dysfunction and other non-executive functions related cognitive functions impairment can be considered prognostic factors in outpatients with moderate to severe AUD.

Keywords: Alcohol use disorder; cognitive impairment; executive function; impulsivity; follow-up study.

Resumen

Hasta la fecha, ningún estudio de seguimiento había evaluado simultáneamente la función ejecutiva, otras funciones no ejecutivas relacionadas con funciones cognitivas y la impulsividad en una muestra suficientemente grande de pacientes con trastorno por uso de alcohol (TUA) entre moderado y grave. Este estudio tuvo como objetivo principal comparar el desempeño neuropsicológico y su relación con el uso de alcohol en pacientes con TUA y en controles sanos, y determinar la evolución del deterioro cognitivo y el uso de alcohol a largo plazo. Con este fin, se diseñó un estudio de seguimiento de seis meses para comparar una muestra de 100 pacientes ambulatorios con TUA (criterios del DSM-5) emparejados con 100 controles sanos. Los pacientes se reclutaron de tres centros sanitarios diferentes de España, Orense, Gijón y Barcelona. La evaluación consistió en una batería sistematizada de pruebas cognitivas para evaluar las siguientes funciones: atención, memoria anterógrada, velocidad de procesamiento, fluidez verbal, función ejecutiva y actitud implícita hacia bebidas alcohólicas. También se compararon variables clínicas asociadas al consumo de alcohol, como el *craving* y la impulsividad. Después de seis meses, la memoria anterógrada, memoria de trabajo y resistencia a la interferencia mejoraron notablemente en los pacientes con TUA, aunque no llegaron a igualar la población general. Respecto de las variables clínicas, hubo una pequeña pero significativa mejoría cognitiva relacionada con una reducción del consumo de alcohol y de la impulsividad. La disfunción ejecutiva y otras funciones no ejecutivas relacionadas con el deterioro cognitivo pueden considerarse factores pronósticos en pacientes ambulatorios con TUA entre moderado y grave.

Palabras clave: Trastorno por uso de alcohol; deterioro cognitivo; función ejecutiva; impulsividad; estudio de seguimiento.

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It is commonly accepted that alcohol use disorder (AUD) is associated with cognitive deficits. AUD is often a long-term relapsing condition and tends to become a chronic disease (Breese, Shina & Heilig, 2011; Koob, Sanna & Bloom, 1998; Volkow & Li, 2005).

Even moderate levels of alcohol use are associated with adverse brain outcomes including hippocampal atrophy. This is one of the reasons why the recommended alcohol use limits are being lowered (Topiwala et al., 2017). Reducing global use in the population, delaying the onset of alcohol use, and insistence on treatment of those who already present alcohol abuse problems are fundamental actions (Florez, Espandian, Villa & Saiz, 2019).

Executive functions is an umbrella term encompassing a set of high-level control mechanisms mediating the ability to successfully regulate thoughts and behaviours in order to fulfil a goal (Dohle, Diel & Hofmann, 2018; Miyake & Friedman, 2012), adapt to novel everyday life situations, and manage social interactions (Cristofori, Cohen-Zimerman & Grafman, 2019).

AUD is associated with cognitive impairments, particularly in executive functions (Stephan et al., 2017). These deficits constitute an important factor in AUD, increasing relapse risk (Brion et al., 2017). Among the most commonly reported cognitive sequelae in AUD are deficits in hippocampal-related functions (Bartels et al., 2006) and frontal cortex dysfunction (Nowakowska-Domagala, Jablkowska-Górecka, Mokros, Koprowicz & Pietras, 2017).

Many studies have evaluated the effect of periods of alcohol abstinence on executive functions, but the duration of these periods is not clearly established. Short-term abstinence is usually considered to be from the first few days of detoxification to several months, and long-term abstinence from several months to one year or more (Bartsch et al., 2007; Nowakowska-Domagala et al., 2017; Stavro, Pelletier & Potvin, 2013; Zahr & Pfefferbaum, 2017). Recovery from alcohol dependence contributes to functional improvement in memory, visuospatial abilities, and attention (Crews et al., 2005; Sullivan, Rosenbloom, Lim & Pfefferbaum, 2000).

Even short-term sobriety has been found to be beneficial (Bartsch et al., 2007). Long-term abstinence is also associated with cognitive recovery in patients with cognitive impairments related to alcohol use. Improvement in cognitive functions is achieved only after a period of several months of abstinence. After one year of abstinence, cognitive enhancement is more remarkable, but even in this case, certain residual cognitive impairments may persist (Bernardin, Maheut-Bosser & Paille, 2014). It has been demonstrated that after long-term abstinence (two years), there is a slow recovery process, which may continue beyond the two years (Bartels et al., 2006).

Two meta-analyses have studied cognitive deficits in alcoholism, in samples of short- and long-term sober alcoholics. Stavro *et al.* (2013) noted that alcoholic patients had similar levels of neuropsychological deficits in several cognitive domains after one month and after one year of sobriety. A more recent meta-analysis came to the conclusion that cognitive deficits and especially memory functioning among recently detoxified alcoholics persisted even in long-term abstinent alcoholics (Crowe, Cammisuli & Stranks, 2019). It is generally accepted that certain deficits, such as frontal cortex dysfunctions affecting verbal and working memory and executive functions (Nowakowska-Domagala et al., 2017), can persist even with prolonged sobriety (Le Berre, Fama & Sullivan, 2017; Romero-Martínez, Vitoria-Estruch & Moya-Albiol, 2020).

In addition to cognitive dysfunction, patients with AUD have greater impulsivity and inability to plan (Villa et al., 2021). Impulsivity is a heterogeneous concept encompassing a variety of behaviours which can be defined as a predisposition to perform quick, unplanned actions, without considering potential negative consequences of these actions (Herman & Duka, 2019).

Impairment in cognitive abilities may lead to loss of self-control. Impulsivity is a symptom that reflects this lack of executive control, and it is a risk factor for alcohol addiction (Mujica-Parodi, Carlson, Cha & Rubin, 2014). People whose cognitive function is lower are more predisposed to lose control with alcohol. Acute alcohol use interferes with executive functions, and chronic abuse damages brain structures responsible for such executive functions, in both cases resulting in reduced cognitive control and increased risk of losing control (Draper, Karmel, Gibson, Peut & Anderson, 2011).

Until now, no follow-up studies had simultaneously evaluated executive functions, additional cognitive functions, and impulsivity in a large enough sample of moderate to severe alcohol use disorder patients. The aim of the study was two-fold (investigation of the evolution of EF, impulsivity and other cognitive functions throughout treatment AND investigation of the relationship between cognitive variables and clinical measures). So, the main objective of this study was to determine whether executive dysfunction and cognitive impairment in patients with moderate to severe alcohol use disorders can be considered a prognostic factor in outpatient treatment. Our hypothesis was that after 6 months of follow-up, although there would be at least partial recovery from these deficits, they will have become a prognostic factor. So, the patients who presented the strongest cognitive impairment would be the ones with the least improvement in their alcohol use.

Methods

Subjects

Two different groups of participants were recruited: 1) an alcohol use disorder (AUD) group (DSM-5 criteria for moderate to severe AUD) (n=100) and 2) a control

group of healthy volunteers (n=100). The drop-out rate between baseline and follow-up evaluation was 11 patients (n=111 at baseline), who did not attend the evaluation, refused to perform it or did not show commitment during treatment and therefore maintained the same level of consumption. The AUD group was recruited from three different health centres: The Addictive Behavior Unit of the Psychiatry Service at the Hospital of Orense, the La Calzada Mental Health Center in Gijón, and the Institute of Neuropsychiatry and Addictions at Parc de Salut Mar in Barcelona. The control group was matched to the AUD group for demographic criteria, sex, age, and years of education. The main study characteristics and the inclusion/exclusion criteria have been thoroughly described elsewhere (Villa et al., 2021).

All participants were fully informed about the nature and characteristics of the study and provided written informed consent to participate. They were all given a 50-euro gift card for their participation in the study.

The study was approved by the local ethics committees in Orense, Asturias and Barcelona, and was conducted in compliance with the ethical principles of the Declaration of Helsinki (World Medical Association General Assembly, 2013).

Procedure

The study was designed as a prospective longitudinal 6-month follow-up study of moderate to severe alcohol use disorder outpatients. These patients may or may not have achieved abstinence. This was confirmed by self-report and by blood analysis (MCV, GOT, GPT, and GGT).

Assessment

All participants were assessed by well-trained qualified clinicians using the following tools: 1) An ad-hoc questionnaire was used to gather sociodemographic variables including sex, age, marital status, living situation, education level, and employment situation; clinical characteristics including age of onset of alcohol and tobacco use, alcohol and tobacco use during the last month, inclusion and exclusion criteria, age of onset of AUD (patients), and family history of alcoholism; 2) Levels of biomarkers related to alcohol use (GOT, GPT, GGT, and MCV) were measured in serum; 3) Clinical assessment: 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960), Barratt Impulsiveness Scale Version 11 (BIS-11; Patton, Stanford & Barratt, 1995); and Obsessive Compulsive Drinking Scale (OCDS; Anton, Moak & Latham, 1995); 4) Neuropsychological variables: Two Wechsler adult intelligence scale (WAIS-IV; Wechsler, 2008) subtests, Symbol Search and Arithmetic were used to assess information processing speed and abstract reasoning; the d2 Test of Attention (Steinborn, Langner, Flehmig & Huestegge, 2018) was used to assess attention; the California Verbal Learning Test (CVLT; Elwood, 1995); and two WAIS-IV subtests, Digit Symbol Coding and Retained Digit (Hagen et al., 2016) were used to measure memory; the FAS Verbal Fluency Test and Category Fluency Test (animals; del Ser Quijano et al., 2004); the Stroop Test (SCWT; Scarpina & Tagini, 2017), the Wisconsin Card Sorting Test (WCST; Nyhus & Barcelo, 2009), the Iowa Gambling Test (IGT; Steingroever, Wetzels, Horstmann, Neumann & Wagenmakers, 2013) were used to examinate executive function; and lastly, an

Table 1. *Battery of neuropsychological tests.*

Neuropsychological test	Main function evaluated	Characteristics
Symbol search (from WAIS-IV)	Processing speed	Measures the ability to quickly identify the presence of figures in a series. Nonverbal.
Arithmetic (from WAIS-IV)	Abstract reasoning	Measures the mental solving of arithmetic problems given a time limit. Verbal.
Attention Test D2	Sustained attention / inhibition of response **(Attention)**	Measures the ability to focus on relevant visual stimuli and ignore irrelevant ones. Nonverbal.
California Verbal Learning Test (CVLT)	Immediate recall, delayed recall, and identification **(Memory)**	Measures the ability to remember lists of words over several attempts, with and without interference. Verbal.
Digit Symbol (from WAIS-IV)	Working memory **(Memory)**	Measures speed in converting numbers into symbols according to an established sequence. Nonverbal.
Digit Span (from WAIS-IV)	Short-term memory **(Memory)**	Measures the ability to remember and follow a sequence of numbers. Verbal.
FAS and semantic category of animals	Verbal fluency **(Executive function)**	Measures the ability to generate word lists by categories. Verbal.
Stroop Test (SCWT)	Divided attention and interference resistance **(Executive function)**	Measures the ability for color recognition. Nonverbal.
Wisconsin Card Sorting Test (WCST)	Abstract reasoning and cognitive flexibility **(Executive function)**	Measures the ability to select cards based on categories. Nonverbal.
Iowa Gambling Test (IGT)	Decision-making and cognitive flexibility **(Executive function)**	Measures the ability to select stimuli based on short- and long-term rewards. Nonverbal.
Implicit Association Test (IAT)	Implicit attitude to a stimulus **(Automatic processing)**	Measures speed of matching words based on implicit attitudes related to alcohol. Nonverbal.

Table 2. *Evolution of parameters related to alcohol consumption and impulsivity at 6-month follow-up.*

	Baseline (SD)	6 months (SD)	*p*
SDU	9.27 (5.90)	2.14 (4.30)	‹ .001
GOT	39.63 (25.99)	29.54 (21.67)	.002
GPT	37.92 (20.56)	28.41 (12.65)	‹ .001
GGT	135.10 (174.30)	82.00 (135.60)	.001
MCV	94.83 (6.43)	91.13 (7.75)	‹ .001
BIS11 Cognitive	17.77 (7.98)	16.00 (5.56)	.013
BIS11 Motor	16.27 (6.94)	15.82 (5.99)	.531
BIS11 Non-planning	19.58 (8.52)	18.66 (7.29)	.022
BIS11-TOTAL	53.85 (19.86)	50.54 (15.80)	.044
OCDS Obsessive	6.25 (4.80)	2.95 (3.85)	‹ .001
OCDS Compulsive	10.54 (4.44)	3.85 (4.33)	‹ .001
OCDS TOTAL	16.77 (8.08)	6.90 (7.87)	‹ .001

Note. SD: standard deviation; SDU: standard drink unit; BIS: Barratt Impulsiveness Scale; OCDS: Obsessive Compulsive Drinking Scale; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma-glutamyl transferase; MCV: mean corpuscular volume.

alcohol Implicit Association Test (IAT; Ostafin, Marlatt & Greenwald, 2008) was used to assess automatic processing. The cognitive battery used to obtain neuropsychological variables is summarized in Table 1.

The instruments described above were administered at baseline and at 6 months follow-up.

The patients had no symptoms of intoxication prior to the evaluation, as determined by experienced clinicians.

Once detoxification was completed, treatment with 1-3 mg of lorazepam or equivalent doses of other benzodiazepines was allowed. Approved pharmacological treatments for alcohol dishabituation were also allowed.

No remediation cognitive intervention was carried out in addition to the detoxification treatment.

Statistical analysis

The continuous variables of the two groups in the study were compared using Student's t-test, while the analysis of differences between the two groups in the distribution of categorical variables was carried out with a chi-square test. The criterion for statistical significance in all tests was $p<0.05$, set as the maximum acceptable value for the probability of making a type I error. Bonferroni corrections were conducted for multiple comparisons.

Results

Variables related to drinking and impulsivity

Six months after starting outpatient treatment, patients showed significant differences from baseline, with a decrease in the number of SDUs (standard drink units) (t=2.14, $p<0.001$), decrease in the analytical variables related to alcohol use: GOT (t= 29.54, $p=0.002$), GPT (t=28.41, $p<0.001$), GGT (t=82.00, $p=0.001$), and MCV (t=91.13, $p<0.001$), and lower pathological alcohol use scores as measured by OCDS - Obsessive (t=2.95, $p<0.001$), OCDS - Impulsive (t=3.85, $p<0.001$), and OCDS - Total (t=6.90, $p<0.001$). There were also significant differences with respect to impulsivity as measured using the BIS, which showed a decrease in all subscales, BIS - Cognitive (t=16.00, $p=0.013$), BIS - Non-planning (t=18.66, $p=0.022$), and BIS - Total (t=50.54, $p=0.044$), except for the BIS - Motor (t=15.82, $p=0.531$) (Table 2).

Cognitive variables

Table 3 shows the results yielded by the different cognitive tests in each group (controls and patients) at the 6-month follow-up, with respect to neuropsychological variables. All tests yielded significant results, which indicated better cognitive function in the control group, with the exception of the IGT and IAT, for which no significant between-group differences were found.

Table 4 presents the same cognitive tests, but comparing the results between patients at baseline and 6-month follow-up. The results reflected statistically significant differences on the following tests: California Verbal Learning Test (CVLT), Digit Symbol Coding and Retained Digits, and the Stroop Test (SCWT), which means an improvement in anterograde memory, divided attention, and interference resistance after 6 months of outpatient treatment: CVLT-A1 first attempt (t=6.86, $p<0.001$), CVLT-A5 fifth attempt (t=11.93, $p=0.001$), CVLT-AToT total attempts (t=48.66, $p<0.001$), CVLT-Free immediate (t=10.396, $p=0.002$), CVLT-Free delayed (t=11.08, $p=0.001$), CVLT - Guided (t=12.31, $p<0.001$), Digit Symbol correct (t=49.24, $p=0.004$), Digit Symbol standard score (t=8.22, $p<0.001$), Digits cumulative (t= 6.99, $p=0.041$), Digits total (t= 22.21, $p=0.020$), SCWT proportion correct (t=0.92, $p=0.001$), SCWT mean RTCC (t=2412, $p=0.004$, SCWT mean RTCCO (t=2550, $p=0.035$),

Table 3. *Comparison of neuropsychological tests between controls and patients at 6-month follow-up assessment (The cases column at baseline has been retrieved from Villa et al. (2021).*

	Controls (SD) N=100	Cases 6 months (SD) N=100	*P*	Cases (SD) at baseline N=111
Processing speed				
SYMBOL SEARCH Correct	30.78 (8.33)	24.31 (7.91)	‹ .001	23.95 (7.45)
SYMBOL SEARCH Error	0.95 (1.30)	1.30 (1.54)	.086	1.54 (1.88)
SYMBOL SEARCH Raw Score	29.57 (9.31)	22.71 (8.44)	‹ .001	22 (7.69)
SYMBOL SEARCH Standard score	10.46 (3.12)	8.41 (3.05)	‹ .001	8.10 (2.83)
Abstract reasoning				
ARITHMETICS Raw score	13.79 (3.93)	11.68 (3.12)	‹ .001	11.32 (321)
ARITHMETICS Standard score	10.70 (3.53)	8.90 (3.02)	‹ .001	8.43 (3.06)
Attention				
D2	163.70 (43.2)	113.69 (43.20)	‹ .001	113 (44.50)
Memory				
CVLT-A1 first attempt	6.91 (2.75)	6.86 (2.35)	.893	5.77 (1.92)
CVLT-A5 fifth attempt	13.38 (2.51)	11.93 (2.68)	‹ .001	11.26 (2.93)
CVLT-AToT total attempts	53.20 (9.80)	48.66 (12.15)	.004	45.80 (11.60)
CVLT- Free immediate	12.31 (2.82)	10.40 (3.31)	‹ .001	9.77 (3.32)
CVLT- Free delayed	12.98 (2.90)	11.08 (3.20)	‹ .001	10.32 (3.35)
CVLT- Guided	13.64 (2.70)	12.31 (2.74)	.001	11.42 (2.38)
CVLT- Recognition	15.34 (1.08)	14.73 (1.70)	.003	14.20 (2.12)
DIGIT SYMBOL Correct	63.10 (19.10)	49.24 (17.48)	‹ .001	46.40 (15.80)
DIGIT SYMBOL Standard score	10.26 (3.26)	8.22 (3.22)	‹ .001	7.34 (2.86)
DIGITS Direct	9.33 (2.10)	8.34 (2.26)	.001	8.11 (2.21)
DIGITS Reverse	8.07 (2.18)	6.92 (1.89)	‹ .001	6.71 (2.01)
DIGITS Cumulative	8.19 (2.33)	6.99 (2.25)	‹ .001	6.64 (2.27)
DIGITS Total	25.54 (5.39)	22.21 (5.50)	‹ .001	21.42 (5.57)
Executive Function				
FAS Direct score correct	36.50 (11.70)	28.82 (11.73)	‹ .001	27.30 (11.30)
FAS Perseveration errors	0.81 (1.28)	0.98 (1.28)	.348	0.78 (1.53)
FAS Intrusion errors	0.23 (0.63)	0.55 (1.04)	.010	0.64 (1.03)
FAS Derivation errors	0.48 (1.14)	0.49 (0.80)	.970	0.58 (0.95)
ANIMALS Direct Score	21.56 (6.23)	18.01 (6.09)	‹ .001	17.14 (4.77)
SCWT prop correct	0.95 (0.07)	0.92 (0.11)	.032	0.89 (0.12)
SCWT mean RTCC	1972 (1288)	2412 (1465)	.025	2654 (1610)
SCWT mean RTCI	1874 (1170)	2860 (2186)	‹ .001	3033 (2635)
SCWT mean RTCCO	2349 (1921)	2550 (1516)	.412	3179 (2958)
SCWT PROPCC	1776 (188)	750 (1012)	‹ .001	1459 (1822)
SCWT PROPCI	0.99 (0.09)	0.87 (0.19)	‹ .001	0.85 (0.26)
SCWT PROPCCO	0.88 (0.18)	0.92 (0.15)	.320	0.85 (0.26)
SCWT mean RT	49 (351)	1709 (1993)	‹ .001	1181 (1633)
WCST Completed categories	4.59 (1.98)	3.31 (2.16)	‹ .001	3.08 (2.04)
WCST Correct	70.70 (11.30)	69.78 (12.54)	.562	67.20 (13.40)
WCST Error	36.10 (23.30)	47.09 (22.50)	.001	54 (21.00)
WCST SUMPE	6.77 (3.08)	5.99 (4.26)	.132	7.30 (11.00)
WCST PE	30.2 (21.20)	19.60 (18.25)	‹ .001	17 (18.20)
WCST PR	9.48 (4.41)	7.40 (5.15)	.002	9.30 (13.60)
WCST SFMS	0.90 (1.22)	1.39 (1.35)	.009	1.03 (1.28)
WCST TRIAL FIRST	22.60 (26.70)	30.02 (29.87)	.071	30.30 (34.30)
WSCT CI	18.40 (16.80)	22.86 (16.85)	.080	22.60 (19.40)
WCST FI		32.14 (19.68)	.012	33.20 (20.10)
WSCT NI	28.50 (22.90)	27.79 (26.54)	.875	31.60 (26.30)
WSCT C2	15.8 (15.30)	12.9 (18.90)	.229	32 (176)
WSCT DIFFC1F1	-1315 (13095)	-9.28 (26.00)	.321	-9.50 (30.30)
WSCT DIFFF1N1	-1.70 (28.30)	4.81 (34.83)	.169	1.50 (36.40)
WSCT DIFFN1C2	12.20 (24.70)	14.83 (31.11)	.488	16.70 (29.10)
WSCT DIFFC2F2	-0.20 (21.40)	0.94 (22.21)	.728	1.70 (22.80)
WSCT DIFFF2N2	3.30 (22.30)	5.27 (22.09)	.544	1836 (822)
IGT Total	2039 (964)	1841 (1013)	.156	46.50 (15.50)
IGT CA	49.90 (16.10)	48.09 (18.14)	.467	53.50 (15.50)
IGT CDA	50.10 (16.10)	51.91 (18.14)	.467	9.72 (4.60)
IGT NET 5 AD	10.56 (4.85)	10.01 (5.10)	.434	10.28 (4.60)
IGT NET 5 DIS	9.44 (4.85)	10.05 (5.06)	.385	30.30 (34.30)
Automatic processing				
IAT	-0.57 (0.52)	-0.48 (0.52)	.152	-0.48 (0.48)

Note. SD: Standard deviation; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage on the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

Table 4. *Comparison of neuropsychological tests between patients at baseline and at 6-month follow-up assessment.*

	Baseline (DS) N = 111	6 months (DS) N = 100	*P*
	Processing speed		
SYMBOL SEARCH Correct	23.73 (7.52)	24.31 (7.91)	.369
SYMBOL SEARCH Error	1.48 (1.91)	1.30 (1.54)	.439
SYMBOL SEARCH Raw Score	21.91 (7.57)	22.71 (8.44)	.333
SYMBOL SEARCH Standard score	8.19 (2.86)	8.41 (3.05)	.446
	Abstract reasoning		
ARITHMETICS Raw score	11.28 (3.10)	11.68 (3.12)	.102
ARITHMETICS Standard score	8.44 (2.30)	8.90 (3.02)	.069
	Attention		
D2	111.95 (43.60)	113.69 (43.20)	0.665
	Memory		
CVLT-A1 first attempt	5.74 (1.94)	6.86 (2.35)	‹ .001
CVLT-A5 fifth attempt	11.07 (2.84)	11.93 (2.68)	.001
CVLT-AToT total attempts	45.09 (11.49)	48.66 (12.15)	‹ .001
CVLT- Free immediate	9.55 (3.26)	10.40 (3.31)	.002
CVLT- Free delayed	10.16 (3.29)	11.08 (3.20)	.001
CVLT- Guided	11.31 (2.79)	12.31 (2.74)	‹ .001
CVLT- Recognition	14.20 (2.09)	14.73 (1.70)	.005
DIGIT SYMBOL Correct	46.09 (15.54)	49.24 (17.48)	.004
DIGIT SYMBOL Standard score	7.42 (2.83)	8.22 (3.22)	‹ .001
DIGITS Direct	8.09 (2.14)	8.34 (2.26)	.168
DIGITS Reverse	6.68 (1.89)	6.92 (1.89)	.137
DIGITS Cumulative	6.55 (2.21)	6.99 (2.25)	.041
DIGITS Total	21.30 (5.37)	22.21 (5.50)	.020
	Executive Function		
FAS Direct score correct	27.38 (11.04)	28.82 (11.73)	.119
FASPerseveration errors	0.85 (1.59)	0.98 (1.28)	.452
FAS Intrusion errors	0.67 (1.06)	0.55 (1.04)	.369
FAS Derivation errors	0.58 (0.97)	0.49 (0.80)	.397
ANIMALS Direct Score	17.30 (4.70)	18.01 (6.09)	.174
SCWT prop correct	0.88 (0.12)	0.92 (0.11)	.001
SCWT mean RTCC	2671 (1634)	2412 (1465)	.049
SCWT mean RTCI	3102 (2730)	2860 (2186)	.359
SCWT mean RTCCO	3194 (3046)	2550 (1516)	.035
SCWT PROPCC	1384 (1852)	750 (1012)	.002
SCWT_PROPCI	0.83 (0.26)	0.87 (0.19)	.108
SCWT_PROPCCO	0.86 (0.22)	0.92 (0.15)	.011
SCWT mean RT	1298 (1668)	1709 (1993)	.041
WCST Completed categories	3.00 (1.99)	3.31 (2.16)	.116
WCST Correct	66.79 (13.57)	69.78 (12.54)	.061
WCST Error	55.30 (20.44)	47.09 (22.50)	‹ .001
WCST SUMPE	7.14 (11.28)	5.99 (4.26)	308
WCST PE	15.82 (17.58)	19.60 (18.25)	.083
WCST PR	9.11 (14.03)	7.40 (5.15)	.242
WCST SFMS	1.03 (1.29)	1.39 (1.35)	.070
WCST TRIAL FIRST	31.33 (35.37)	30.02 (29.87)	.716
WSCT CI	23.56 (19.37)	22.86 (16.85)	.759
WCST FI	33.02 (20.27)	32.14 (19.68)	.699
WSCT NI	32.15 (26.76)	27.79 (26.54)	.180
WSCT C2	33.50 (184.70)	12.90 (18.90)	.268
WSCT DIFFC1F1	-8.26 (30.72)	-9.28 (26.00)	.770
WSCT DIFFF1N1	0.83 (36.75)	4.81 (34.83)	.365
WSCT DIFFN1C2	17.15 (30.04)	14.83 (31.11)	.469
WSCT DIFFC2F2	1.83 (23.66)	0.94 (22.21)	.774
WSCT DIFFF2N2	8.91 (19.6)	5.27 (22.9)	.224
IGT Total	1845 (819)	1841 (1013)	.975
IGT CA	46.49 (15.63)	48.09 (18.14)	.411
IGT CDA	53.51 (15.63)	51.91 (18.14)	.411
IGT NET 5 AD	9.79 (4.66)	10.01 (5.10)	.724
IGT NET 5 DIS	10.21 (4.66)	10.050 (5.06)	.796
	Automatic processing		
IAT	-0.50 (0.47)	-0.48 (0.52)	.671

Note. SD: Standard deviation; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage on the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

Table 5. *Influence of baseline cognitive variables and impulsivity on severity of use at 6-month follow-up.*

Impulsivity and cognitive variables	SDU ≤ 2 mean/mean *(p)*	GGT ≤ 50 mean/mean *(p)*	MCV ≤ 88 mean/mean *(p)*	OCDS OBSESSIVE ≤ 5 mean/mean *(p)*	OCDS COMPULSIVE ≤5 mean/mean *(p)*	OCDS TOTAL ≤ 10 mean/mean *(p)*
BIS-11						
BIS Cognitive	18.59/ 18.52 (.975)	19.58/ 16.8 (.112)	17.45/ 1916 (.280)	18.17/ 20.23 (.245)	18.07/ 19.91 (.322)	18.17/ 19.72 (.342)
BIS Motor	16.23/ 18 (.327)	16.73/ 16.35 (.783)	16.31/ 16.74 (.764)	15.95/ 19.18 **(.049)**	16.33/ 17.21 (.540)	15.82/ 18.79 **(.041)**
BIS Non-planning	18.95/ 22.65 (.071)	20.59/ 18.17 (.138)	19.87/ 19.64 (.895)	19.25/ 21.64 (.213)	18.87/ 21.72 (.083)	18.68/ 22.65 **(.020)**
BIS Total	54.02/ 59.17 (.320)	52.21/ 51.32 (.150)	53.95/ 55.68 (.659)	53.50/ 61.50 (.060)	53.37/ 59.15 (.167)	52.82/ 61.52 **(.030)**
Processing speed						
SYMBOL SEARCH Correct	23.57/ 25.39 (.309)	23.69/ 24.40 (.628)	22.89/ 24.49 (.297)	23.65/ 25.14 (.427)	23.15/ 25.82 (.088)	23.61/ 24.90 (.427)
SYMBOL SEARCH Error	1.54/ 1.52 (.947)	1.55/ 1.52 (.943)	1.47/ 1.57 (.769)	1.61/ 1.27 (.376)	1.70/ 1.15 (.087)	1.67/ 1.17 (.140)
SYMBOL SEARCH Raw Score	22.04/ 21.83 (.898)	22.17/ 21.70 (.75)	21.68/ 22.16 (.759)	22.07/ 21.72 (.845)	21.47/ 23.24 (.250)	21.96/ 22.10 (.928)
SYMBOL SEARCH Standard score	8.07/ 8.22 (.804)	8.00/ 8.27 (.612)	7.76/ 8.27 (.389)	7.94/ 8.73 (.251)	7.73/ 8.97 (.034)	7.88/ 8.72 (.179)
Abstract reasoning						
ARITHMETIC Raw score	10.91/ 12.91 **(.010)**	11.07/ 11.77 (.266)	7.58/ 9.10 **(‹ .001)**	11.10/ 12.23 (.139)	11.10/ 11.85 (.278)	11.08/ 12.00 (.225)
ARITHMETIC Standard score	8.08/ 9.74 **(.026)**	8.17/ 8.9 (.226)	7.15/ 9.10 **(‹ .001)**	8.32/ 8.86 (.453)	8.38/ 8.54 (.793)	8.34/ 8.65 (.662)
Attention						
D2	113.96/ 109.17 (.681)	110.48/117.40 (.437)	106.76/ 116.20 (.25)	108.44/ 131.32 **(.032)**	111.68/ 116.03 (.654)	111.67/ 116.65 (.636)
Memory						
CVLT-A1 first attempt	5.62/ 6.30 (.117)	5.75/ 5.80 (.889)	5.71/ 5.79 (.837)	5.62/ 6.36 (.090)	5.58/ 6.21 (.108)	5.56/ 6.34 (.068)
CVLT-A5 fifth attempt	11.34/ 10.96 (.604)	11.35/ 11.10 (.670)	11.45/ 11.16 (.623)	11.20/ 11.50 (.694)	11.10/ 11.63 (.373)	11.13/ 11.62 (.462)
CVLT-AToT total attempts	45.51/ 46.69 (.672)	45.58/ 46.07 (.828)	44.92/ 46.19 (.593)	45.28/ 47.68 (.428)	44.63/ 48.42 (.102)	44.94/ 48.07 (.240)
CVLT-Free immediate	9.76/ 9.83 (.926)	9.72/ 9.87 (.809)	9.58/ 9.88 (.673)	9.62/ 10.41 (.294)	9.55/ 10.30 (.240)	9.60/ 10.27 (.327)
CVLT-Free delayed	10.28/ 10.43 (.845)	10.22/ 10.47 (.715)	10.03/ 10.46 (.517)	10.12/ 11.09 (.201)	10.23/ 10.51 (.669)	10.13/ 10.83 (.315)
CVLT-Guided	11.28/ 11.96 (.229)	11.29/ 11.65 (.528)	11.34/ 11.46 (.829)	11.25/ 12.14 (.144)	11.18/ 12.00 (.117)	11.22/ 12.00 (.162)
CVLT-Recognition	14.12/ 14.48 (.407)	14.28/ 14.05 (.597)	14.39/ 14.09 (.483)	14.16/ 14.26 (.698)	14.28/ 14.00 (.536)	14.15/ 14.34 (.678)
DIGIT SYMBOL Correct	45.46/ 49.91 (.210)	46.01/ 47.05 (.745)	44.53/ 47.36 (.393)	44.46/ 54.18 **(.015)**	44.65/ 50.48 (.061)	44.47/ 51.79 **(.031)**
DIGIT SYMBOL Standard score	7.16/ 8.04 (.123)	7.20/ 7.60 (.462)	6.81/ 7.62 (.180)	7.01/ 8.68 **(.017)**	7.05/ 8.03 (.073)	7.05/ 8.17 (.063)
DIGITS Direct	7.77/ 9.39 **(.001)**	7.93/ 8.42 (.260)	7.50/ 8.48 **(.026)**	7.80/ 9.36 **(.003)**	7.69/ 9.09 **(‹ .001)**	7.76/ 9.10 **(.003)**
DIGITS Reverse	6.57/ 7.26 (.076)	6.62/6.87 (.498)	5.87/ 7.15 **(‹ .001)**	6.44/ 7.82 **(.002)**	6.51/ 7.18 (.082)	6.46/ 7.41 **(.017)**
DIGITS Cumulative	6.51/ 7.13 (.099)	6.79/ 6.37 (.349)	6.03/ 6.96 **(.026)**	6.47/ 7.32 (.106)	6.33/ 7.36 **(.011)**	6.41/ 7.27 (.063)
DIGITS Total	20.81/ 23.78 **(.003)**	21.31/ 21.62 (.774)	19.34/ 22.51 **(.001)**	20.66/ 24.5 **(.004)**	20.49/ 23.64 **(.002)**	20.58/ 23.79 **(.006)**
Executive function						
FAS Direct score correct	26.90/ 28.83 (.429)	27.15/ 27.55 (.859)	24.21/ 28.9 **(.027)**	26.74/ 29.54 (.277)	26.87/ 28.30 (.518)	26.51/ 29.52 (.207)
FAS Perseveration errors	0.78/ 0.78 (996)	0.82/ 0.72 (.735)	1.00/ 0.671 (.366)	0.74/ .095 (.550)	0.72/ 0.94 (.477)	0.74/ 0.90 (.62)
FAS Intrusion errors	0.62/0.69 (.754)	0.60/ 0.70 (.664)	0.84/ 0.53 (.138)	0.67/ 0.50 (.051)	0.60/ 0.73 (.578)	0.62/ 0.69 (.773)
FAS Derivation errors	0.56/ 0.65 (.640)	0.60/ 0.52 (.645)	0.63/ 0.55 (.685)	0.59/ 0.50 (.636)	0.64/ 0.42 (.205)	0.60/ 0.52 (.662)
ANIMALS Direct Score	17.10/ 17.26 (.894)	16.96/ 17.45 (.61)	16.89/ 17.26 (.695)	16.61/ 19.27 **(.024)**	16.78/ 17.97 (.24)	16.39/ 19.24 **(0.005)**
SCWT prop correct	0.88/0.91 (.341)	0.89/ 0.88 (.795)	0.85/ 0.91 **(.016)**	0.88/ 0.93 **(.009)**	0.87/ 0.92 **(.012)**	0.87/ 0.93 **(.002)**
SCWT mean RTCC	2781.26/ 2167.57 **(.009)**	2766.21/ 2455.09 (.300)	3016.60/ 2465.40 (.130)	2850.62/ 1859.08 **(‹ .001)**	2847.00/ 2198.16 **(.012)**	2880.03/ 2015.27 **(‹ .001)**
SCWT mean RTCI	3288.10/2055.28 **(.001)**	3317.72/ 2526.65 (.078)	3935.78/ 2562.53 **(.038)**	3297.83/ 1959.8 **(‹ .001)**	3394.66/ 2177.01 **(.003)**	3358.89/ 2110.20 **(.001)**
SCWT mean RTCCO	3179.60/ 3177.89 (.999)	3189.87/ 3160.39 (.964)	3342.79/ 3094.11 (.660)	3462.60/ 2032.94 **(‹ .001)**	3258.51/ 2991.89 (.705)	3535.98/ 2170.53 **(.001)**
SCWT PROPCC	1517.22/ 1237.57 (.382)	1519.33/ 1352.67 (.635)	1444.11/ 1467.17 (.954)	1554.60/ 1073.63 (.102)	1546.05/ 1254.16 (.347)	1590.93/ 1086.99 (.083)
SCWT PROPCI	0.84/ 0.87 (.569)	0.84/ 0.85 (.899)	0.75/0.89 **(.012)**	0.82/ 0.95 **(‹ .001)**	0.82/ 0.91 (.052)	0.82/ 0.93 **(.005)**
SCWT PROPCCO	0.84/ 0.87 (.716)	0.86/0.83 (.469)	0.85/ 0.85 (.963)	0.84/ 0.87 (.507)	0.84/ 0.88 (.254)	0.84/ 0.89 (.161)
SCWT mean RT	1263.03/ 866.84 (.201)	1234.17/ 1086.45 (.625)	1571.47/ 97765 (.103)	1279.69/ 781.45 (.105)	1304.87/ 888.01 (.17)	1273.14/ 920.22 (.259)
WCST Completed categories	3.02/ 3.17 (.734)	2.90/ 3.32 (.280)	2.92/ 3.12 (.626)	2.95/ 3.45 (.290)	3.01/ 3.15 (.739)	2.88/ 3.55 (.118)
WCST Correct	65.78/ 69.69 (.132)	65.13/ 69.20 (.122)	64.1/ 67.89 (.239)	65.22/ 72.14 **(.034)**	64.83/ 70.76 **(.031)**	64.83/ 71.59 **(.019)**
WCST Error	53.60/ 5317.00 (.920)	54.59/ 51.60 (.464)	54.08/ 53.22 (.847)	54.30/ 50.32 (.386)	54.37/ 51.48 (.483)	55.11/ 49 (.165)
WCST SUMPE	7.78/ 5.04 (.059)	6.55/ 8.40 (.418)	5.81/ 7.94 (.200)	7.32/ 6.77 (.713)	7.91/ 5.57 (.144)	7.46/ 6.52 (.537)
WCST PE	18/ 12.18 (.062)	15.47/ 19.15 (.330)	14.71/ 17.89 (.331)	16.75/ 16.97 (.951)	17.7/ 14.66 (.366)	16.57/ 17.46 (.798)
WCST PR	9.89/ 6.52 (.071)	7.58/ 12.05 (.139)	6.99/ 10.34 (.106)	8.48/ 12.08 (.321)	9.12/ 9.35 (.935)	8.57/ 10.94 (.426)
WCST SFMS	1.09/ 0.74 (.063)	0.98/ 1.07 (.742)	0.87/ 1.09 (.357)	0.99/ 1.14 (.69)	0.95/ 1.18 (.436)	1.00/ 1.07 (.819)
WCST TRIAL FIRST	30.40/ 28.43 (.765)	33.10/ 24.47 (.158)	29.55/ 30.22 (.921)	31.84/ 22.50 (.190)	30.82/ 28.03 (.669)	31.55/ 25.59 (.365)
WSCT CI	22.67/ 21.49 (.772)	24.45/ 18.83 (.111)	23.97/ 21.62 (.556)	23.78/ 16.93 (.137)	22.86/ 21.4 (.714)	23.31/ 19.92 (.425)
WCST FI	31.18/ 31.62 (.736)	33.17/ 32.31 (.823)	31.52/ 33.56 (.613)	33.94/ 28.50 (.220)	32.74/ 33.14(.923)	34.73/ 27.56 (.071)
WSCT NI	30.36/ 34.89 (.455)	28.89/ 35.58 (.191)	33.67/ 30.07 (.508)	30.24/ 35.61 (.374)	32.55/ 28.34 (.417)	29.79/ 35.58 (.278)
WSCT C2	35.03/ 17.76 (.429)	38.32/ 19.26 (.470)	61.32/ 15.91 (.356)	34.43/ 19.41 (.480)	37.39/ 17.41 (.410)	35.68/ 19.49 (.481)
WSCT DIFFC1F1	-9.44/ -9.08 (.948)	-8.72/ -10.5 (.743)	-5.80/ -11.22 (.398)	-9.88/ -7.27 (.706)	-9.89/ -8.14 (.77)	-11.42/ -3.55 (.216)
WSCT DIFFF1N1	3.05/ -4.32 (.426)	4.28/ -3.37 (.291)	-1.61/ 3.16 (.509)	3.43/ -6.16 (.26)	0.19/ 4.68 (.549)	4.94/ -8.14 (.076)
IGT Total	1758.52/ 2134.78 (.059)	1785.91/ 1926.25 (.381)	1675/ 1920.55 (.131)	1803.37/ 1970.45 (.401)	1766.03/ 2003.03 (.188)	1785.97/ 1979.31 (.296)
IGT CA	45.46/ 50.43 (.158)	46.73/ 46.07 (.829)	46.47/ 46.51 (.991)	46.11/ 48.04 (.574)	46.14/ 47.33 (.695)	46.04/ 47.79 (.582)
IGT CDA	54.53/ 49.56 (.158)	53.27/ 53.92 (.829)	53.53/ 53.49 (.992)	53.89/ 51.95 (.574)	53.86/ 52.67 (.695)	53.96/ 52.21 (.582)
IGT NET 5 AD	9.45/ 10.74 (.196)	9.75/ 9.67 (.937)	9.21/ 9.99 (.402)	9.67/ 9.91 (.813)	9.42/ 10.42 (.254)	9.45/ 10.48 (.258)
IGT NET 5 DIS	10.54/ 9.26 (.196)	10.25/ 10.32 (.937)	10.79/ 10.01 (.402)	10.32/ 10.09 (.813)	10.58/ 9.57 (.254)	10.55/ 9.52 (.258)

Note. SDU = 0 patients who have consumed 0 standard drink unit per day in the last month; SDU ≤ 2 patients who have consumed 2 or less standard drink unit per day in the last month; patients with a GGT (gamma-glutamyl transferase) equal or lesser value than 50; patients with a MCV (mean corpuscular volume) equal or lesser value than 88; OCDS: Obsessive Compulsive Drinking Scale; OCDS OBSESSIVE ≤ 5 patients with a score less than or equal to 5 in the obsessive subscale of the OCDS; OCDS COMPULSIVE ≤5 patients with a score less than or equal to 5 in the compulsive subscale of the OCDS; OCDS TOTAL ≤ 10 patients with a score less than or equal to 10 in the total subscale of the OCDS. SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

SCWT PROPCC (t=750, p=0.002), SCWT PROPCCO (t=0.92, p=0.011), and SCWT mean RT (t=1709, p=0.041).

Table 5 shows the comparison between cognitive performance at baseline versus treatment response after 6 months, measured with the OCDS, blood analysis (MCV and GGT), and alcohol use during the previous month (SDUs). Our results show that patients who had worse cognitive performance at baseline also had a worse response to treatment as indicated by the following significant findings: *OCDS Obsessive≤5:* BIS – Motor p=0.049; d2 p=0.032, Digit Symbol correct p=0.015; Digit Symbol standard score p=0.017; Digit Direct p = 0.003, Digit Reverse p=0.002; Digit Total p=0.004; Animals direct score p=0.024; SCWT proportion correct p=0.009; SCWT mean RTCC p<0.001; SCWT mean RTCI p<0.001; SCWT mean RTCCO p<0.001; SCWT PROPCI p<0.001, and WCST correct p=0.034. *OCDS Compulsive≤5:* Digit direct p<0.001; Digit cumulative p=0.011; Digit total p=0.002; SCWT proportion correct p=0.012; SCWT mean RTCC p=0.012; SCWT mean RTCI p=0.003, and WCST correct p=0.031. *OCDS Total≤10:* BIS - Motor p=0.041; BIS - Non-planning p=0.020; BIS Total p=0.030; Digit Symbol correct p=0.031; Digit direct p=0.003; Digit reverse p=0.017; Digit total p=0.006; Animals direct score p=0.005; SCWT proportion correct p=0.002; SCWT mean RTCC p<0.001; SCWT mean RTCI p=0.001; SCWT mean RTCCO p=0.001; SCWT PROPCI p=0.005; WCST correct p=0.019. *MCV≤88:* Arithmetic raw score p<0.001; Arithmetic standard score p<0.001; Digit direct p=0.026; Digit reverse p<0.001; Digit cumulative p=0.026; Digit total p=0.001; FAS direct score correct p=0.027; SCWT proportion correct p=0.016; SCWT mean RTCI p=0.038, and SCWT PROPCI p=0.012. *GGT≤50:* none. *SDU≤2:* Arithmetic raw score p=0.010; Arithmetic standard score p=0.026; Digit direct p=0.001; Digit total p=0.003; SCWT mean RTCC p=0.009, and SCWT mean RTCI p=0.001.

Table 6 shows the comparison between cognitive performance at 6 months versus treatment response after 6 months as measured with the OCDS, blood analysis (MCV, GGT), and alcohol use during the previous month (SDUs). Our results show that patients who had a better response to treatment had better cognitive performance at 6 months as indicated by the following significant findings: *OCDS Obsessive≤5:* BIS - Cognitive p=0.001; BIS - Motor p=0.007; BIS - Non-planning p=0.025; BIS Total p=0.001; Symbol Search error p=0.019; Symbol Search raw score p=0.042; Arithmetic raw score p=0.025; Digit reverse p=0.013; FAS direct score correct p=0.006; FAS intrusion errors p=0.028; SCWT proportion correct p=0.028; SCWT mean RTCC p=0.006; SCWT mean RTCI p=0.010; SCWT mean RTCCO p=0.016; SCWT PROPCI p=0.016; SCWT mean RT p=0 .009; WCST correct p=0.008; WCST error p=0.029, and WCST SUMPE p=0.036. *OCDS Compulsive≤5:* BIS - Cognitive p<0.001; BIS - Motor p=0.011; BIS - Non-planning p<0.001; BIS Total p<0.001; Symbol Search error p=0.045; Arithmetic raw score p=0.006; Arithmetic standard score p=0.014; CVLT-A5 fifth attempt p=0.013; Digit reverse p=0.016; Digit cumulative p=0.006; Digit total p=0.009; FAS direct score correct p=0 .001; FAS intrusion errors p=0.040; SCWT proportion correct p=0.003; SCWT mean RTCC p=0.025; SCWT mean RTCI p=0.003; SCWT mean RTCCO p=0.021; SCWT PROPCC p=0.045; SCWT PROPCI p<0.001; SCWT mean RT p=0.002; WCST correct p=0.031, and WCST error p=0.004. *OCDS Total≤10:* Symbol Search error p=0.005; Arithmetic raw score p=0.001; Arithmetic standard score p=0.018; FAS direct score correct p=0.013; SCWT proportion correct p=0.003; SCWT mean RTCC p=0.008; SCWT mean RTCI p=0.007; SCWT mean RTCCO p=0 .025; SCWT PROPCI p=0.001; SCWT mean RT p=0.005; WCST correct p=0.005, and WCST error p=0.011. *MCV≤88:* BIS - Cognitive p=0.003; BIS Total p=0.029; Symbol Search raw score p=0.012; Symbol Search standard score p=0.011; Arithmetic raw score p=0.010; Arithmetic standard score p=0.005; Digit reverse p<0.001; Digit cumulative p=0.006; Digit total p=0.002; SCWT mean RTCC p=0.017; SCWT mean RTCCO p=0.037; SCWT PROPCI p=0.022; SCWT mean RT p=0.012; WCST completed categories p=0.030, and WCST error p=0.048. *GGT≤50:* Arithmetic raw score p=0.048; Arithmetic standard score p=0.019; Digit reverse p=0.008; Digit cumulative p=0.029; Digit total p=0.025, and FAS derivation errors p=0.012. *SDU≤2:* BIS - Cognitive p=0.044; Arithmetic raw score p<0.001; Arithmetic standard score p<0.001; Digit direct p=0.046; Digit cumulative p=0.006; Digit total p=0.008; FAS direct score correct p=0.002, and WSCT DIFFC1F1 p=0.014.

Discussion

The present study used a systematized battery of verbal and non-verbal tests to compare the cognitive performance of a group of outpatients with AUD seeking cessation treatment after 6 months of follow-up to that of a group of healthy volunteers, matched for the main sociodemographic variables influencing cognitive capacity (age, sex, and completed years of schooling).

Data from this evaluation demonstrated statistically significant deficits in the patient group compared with healthy volunteers in almost all tests, with the exception of two: the IGT and IAT. These results are consistent with those already obtained in the previous study (Villa et al., 2021), which compared the same assessment in the same patients with controls, but at baseline. Based on these data, after 6 months of follow-up, cognitive functioning in the patients was still lower than in the healthy controls (Bernardin et al., 2014; Le Berre et al., 2017; Nowakowska-Domagala et al., 2017).

When comparing the results of the cognitive evaluation of patients at baseline and after 6 months of follow-up, it

Table 6. *Influence of the severity of use on cognitive variables and impulsivity at 6-month follow-up.*

Impulsivity and cognitive variables	SDU ≤ 2 mean/mean *(p)*	GGT ≤ 50 mean/mean *(p)*	MCV ≤ 88 mean/mean *(p)*	OCDS OBSESSIVE ≤ 5 mean/mean *(p)*	OCDS COMPULSIVE ≤5 mean/mean *(p)*	OCDS TOTAL≤ 10 mean/ mean *(p)*
BIS-11						
BIS Cognitive	15.35/ 18.22 **(.044)**	15.72/ 16.43 (.525)	13.6/ 17.01 **(.003)**	15.02 /19.50 **(.001)**	14.48/ 19.12 **(< .001)**	14.71/ 19.21 **(< .001)**
BIS Motor	15.59/ 16.61 (.457)	15.53/ 16.26 (.543)	14.53/ 16.37 (.167)	15.15/ 18.23 **(.007)**	14.85/ 17.82 **(.011)**	14.93/ 18.03 **(.004)**
BIS Non-planning	17.93/ 21.13 (.053)	18.76/ 18.51 (.868)	17.47/ 19.17 (.248)	17.77/ 21.86 **(.025)**	16.93/ 22.24 **(< .001)**	17.24/ 22.21 **(.001)**
BIS Total	48.93/ 56 (.076)	50.08/ 51.28 (.714)	45.67/ 52.60 **(.029)**	47.95/ 59.86 **(.001)**	46.2/ 59.48 **(< .001)**	46.80/ 59.83 **(< .001)**
Processing speed						
SYMBOL SEARCH Correct	24.00/ 25.35 (.43)	23.66/ 25.33 (.295)	21.9/ 25.32 (.053)	23.62/ 26.77 (.119)	23.40/ 26.18 (.075)	23.54/ 26.21 (.118)
SYMBOL SEARCH Error	1.38/ 1.00 (.231)	1.34/ 1.23 (.734)	1.67/ 1.14 (.216)	1.44/ 0.77 **(.019)**	1.48/ 0.91 **(.045)**	1.51/ 0.76 **(.005)**
SYMBOL SEARCH Raw Score	22.23/ 24.35 (.231)	21.84/ 24.10 (.172)	19.23/ 24.18 **(.012)**	21.80/ 26 **(.042)**	21.91/ 24.36 (.166)	22.03/ 24.41 (.22)
SYMBOL SEARCH Standard score	8.24/ 8.96 (.267)	8.03/ 9.00 (.113)	7.23/ 8.90 **(.011)**	8.11/ 9.45 (.102)	8.04/ 9.15 (.083)	8.07/ 9.24 (.093)
Abstract reasoning						
ARITHMETIC Raw score	11.04/ 13.87 **(< .001)**	11.21/12.43 **(.048)**	10.50/ 12.18 **(.010)**	11.32/ 13 **(.025)**	11.06/ 12.97 **(.006)**	11.17/ 12.96 **(.010)**
ARITHMETIC Standard score	8.31/ 11.00 **(< .001)**	8.37/ 9.79 **(.019)**	7.70/ 9.44 **(.005)**	8.62/ 10 (.057)	8.37/ 10.06 **(.014)**	8.46/ 10.07 **(.018)**
Attention						
D2	112.18/ 118.83 (.498)	111.93/ 116.49 (.611)	111.83/ 114.48 (.783)	109.38/ 129.18 (.082)	108.06/ 125.30 (.055)	109.15/ 124.96 (.106)
Memory						
CVLT-A1 first attempt	6.77/ 7.17 (.524)	6.76/ 7.02 (.595)	6.77/ 6.90 (.789)	6.73/ 7.32 (.394)	6.79/ 7.00 (.701)	6.75/ 7.14 (.463)
CVLT-A5 fifth attempt	11.86/ 12.17 (.642)	11.79/ 12.15 (.508)	11.60/ 12.07 (.467)	11.73/ 12.64 (.157)	11.50/ 12.82 **(.013)**	11.65/ 1.62 (.090)
CVLT-AToT total attempts	48.15/ 50.39 (.477)	48.03/ 49.67 (.525)	47.47/ 49.17 (.536)	47.70/ 52.14 (.158)	47.07/ 51.94 (.057)	47.25/ 52.17 (.062)
CVLT-Free immediate	10.32/ 10.65 (.706)	10.5/ 10.23 (.709)	10.33/ 10.42 (.904)	10.24/ 10.95 (.349)	10.12/ 10.97 (.221)	10.32/ 10.59 (.716)
CVLT-Free delayed	11.11/ 10.96 (.862)	11.22/ 10.85 (.587)	11.27/ 11.00 (.689)	10.89/ 11.77 (.239)	10.84/ 11.57 (.302)	10.9/ 11.52 (.416)
CVLT-Guided	12.33/ 12.22 (.885)	12.39/ 12.18 (.734)	12.43/ 12.25 (.755)	12.19/ 12.73 (.369)	12.12/ 12.7 (.351)	12.25/ 12.45 (.766)
CVLT-Recognition	14.74/ 14.69 (.908)	14.87/ 14.51 (.35)	14.73/ 14.73 (.998)	14.71/ 14.82 (.792)	14.59/ 15.03 (.189)	14.62/ 15.00 (.292)
DIGIT SYMBOL Correct	48.74/ 50.91 (.601)	49.6/ 48.66 (.794)	48.70/ 49.46 (.850)	47.73/ 54.64 (.123)	48.51/ 50.73 (.52)	47.79/ 52.83 (.187)
DIGIT SYMBOL Standard score	8.10/ 8.61 (.506)	8.14/ 8.33 (.775)	7.90/ 8.35 (.548)	7.97/ 9.09 (.179)	8.15/ 8.36 (.738)	7.99/ 8.79 (.263)
DIGITS Direct	8.10/ 9.13 **(.046)**	8.10/ 8.72 (.185)	7.90/ 8.52 (.156)	8.18/ 8.91 (.260)	8.04/ 8.94 (.074)	8.18/ 8.72 (.307)
DIGITS Reverse	6.74/ 7.52 (.109)	6.52/ 7.56 **(.008)**	5.97/ 7.32 **(< .001)**	6.66/ 7.86 **(.013)**	6.60/ 7.57 **(.016)**	6.75/ 7.34 (.165)
DIGITS Cumulative	6.67/ 8.09 **(.006)**	6.60/ 7.61 **(.029)**	6.07/ 7.38 **(.006)**	6.86/ 7.45 (.259)	6.57/ 7.85 **(.006)**	6.80/ 7.44 (.195)
DIGITS Total	21.46/ 24.74 **(.008)**	21.21/ 23.79 **(.025)**	19.93/ 23.17 **(.002)**	21.63/ 24.27 (.064)	21.22/ 24.24 **(.009)**	21.67/ 23.55 (.121)
Executive function						
FAS Direct score correct	26.95/ 35.17 **(.002)**	28.1/ 29.97 (.433)	26.10/ 29.97 (.080)	27.34/ 34.14 **(.006)**	26.15/ 34.33 **(.001)**	27.08/ 33.14 **(.013)**
FAS Perseveration errors	0.95/ 1.09 (.669)	1.02/ 0.92 (.718)	0.87/ 1.03 (.539)	0.96/ 1.04 (.781)	0.97/ 1.00 (.917)	0.93/ 1.10 (.554)
FAS Intrusion errors	0.54/ 0.56 (.914)	0.66/ 0.36 (.132)	0.6/ 0.52 (.754)	0.63/ 0.23 **(.028)**	0.68/ 0.27 **(.040)**	0.60/ 0.41 (.389)
FAS Derivation errors	0.50/ 0.43 (.716)	0.63/ 0.26 **(.012)**	0.53/ 0.46 (.708)	0.54/ 0.27 (.078)	0.45/ 0.54 (.600)	0.49/ 0.48 (.984)
ANIMALS Direct Score	17.69/ 19.09 (.388)	17.47/ 18.87 (.259)	16.20/ 18.77 (.044)	17.86/ 18.54 (.643)	17.48/ 19.09 (.235)	17.51/ 19.24 (.224)
SCWT prop correct	0.91/ 0.94 (.290)	0.91/ 0.93 (.272)	0.88/ 0.93 (.09)	0.91/ 0.95 **(.028)**	0.90/ 0.95 **(.003)**	0.90/ 0.96 **(.003)**
SCWT mean RTCC	2457.02/ 2258.21 (.516)	2478.23/ 2306.07 (.555)	3084.08/ 2127.67 **(.017)**	2566.24/ 1856.99 **(.006)**	2599.58/ 2024.70 **(.025)**	2606.32/ 1928.69 **(.008)**
SCWT mean RTCI	3007.75/ 2358.03 (.108)	2965.73/ 2691.38 (.520)	3789.90/ 2466.79 (.033)	3069.78/ 2105.75 **(.010)**	3211.12/ 2135.85 **(.003)**	3147.22/ 2146.19 **(.007)**
SCWT mean RTCCO	2587.36/ 2421.61 (.613)	2544.4/ 2557.91 (.966)	3116.27/ 2310.18 **(.037)**	2690.01/ 2045.47 **(.016)**	2744.17/ 2148.71 **(.021)**	2717.81/ 2132.02 **(.025)**
SCWT PROPCC	732.55/ 808.19 (.714)	763.58/ 727.82 (.862)	586.71/818.67 (.325)	690.26/ 963.46 (.244)	610.36/ 1037.04 **(.045)**	660.82/ 970.63 (.138)
SCWT PROPCI	0.87/ 089 (.710)	0.86/ 0.89 (.566)	0.79/ 0.91 **(.022)**	0.85/ 0.94 **(.016)**	0.83/ 0.95 **(< .001)**	0.84/ 0.95 **(.001)**
SCWT PROPCCO	0.91/ 0.93 (.607)	0.91/ 0.93 (.421)	0.91/ 0.92 (.672)	0.92/ 0.92 (.978)	0.91/ 0.93 (.604)	0.91/ 0.93 (.598)
SCWT mean RT	1798.98/ 1404.21 (.39)	1756.64/ 1633.46 (.763)	2595.75/ 1334.43 **(.012)**	1929.7/ 916.86 **(.009)**	2077.36/ 950.2 **(.002)**	2015.43/ 948.48 **(.005)**
WCST Completed categories	3.24/ 3.65 (.415)	3.45/ 3.15 (.493)	2.67/ 3.62 **(.030)**	3.25/ 3.64 (.488)	3.10/ 3.82 (.121)	3.17/ 3.76 (.221)
WCST Correct	68.85/ 72.69 (.137)	68.45/ 71.74 (.205)	69.33/ 68.89 (.852)	68.10/ 75.54 **(.008)**	68.03/ 73.21 **(.031)**	67.78/ 74.55 **(.005)**
WCST Error	48.31/ 41.52 (.185)	46.71/ 46.85 (.976)	53.4/ 43.96 **(.048)**	49.14/ 38.23 **(.029)**	51.09/ 37.85 **(.004)**	50.14/ 38.38 **(.011)**
WCST SUMPE	6.19/ 5.26 (.214)	6.35/ 5.38 (.226)	6.60/ 5.72 (.417)	6.38/ 4.54 **(.036)**	6.12/ 5.70 (.644)	6.21/ 5.41 (.413)
WCST PE	19.43/ 20.88 (.761)	21.34/ 17.25 (.255)	17.49/ 20.72 (.421)	19.9/ 19.26 (.879)	17.64/ 24.12 (.125)	19.08/ 21.46 (.554)
WCST PR	7.58/ 6.82 (.481)	7.89/ 6.64 (.210)	7.44/ 7.39 (.970)	7.72/ 6.27 (.209)	7.27/ 7.69 (.700)	7.46/ 7.26 (.862)
WCST SFMS	1.35/ 1.48 (.670)	1.22/ 1.61 (.162)	1.6/ 1.28 (.289)	1.29/ 1.68 (.265)	1.31/ 1.51 (.503)	1.26/ 1.65 (.212)
WCST TRIAL FIRST	29.26/ 31.74 (.716)	29.08/ 31 (.755)	28.03/ 30.58 (.660)	30.62/ 26.95 (.597)	30.62/ 28.18 (.677)	30.61/ 27.86 (.657)
WSCT CI	21.30/ 27.15 (.126)	23.08/ 21.93 (.737)	24.44/ 21.87 (.511)	23.01/ 21.27 (.672)	22.61/ 22.68 (.983)	22.64/ 22.61 (.993)
WCST FI	33.57/ 26.26 (.081)	32.84/ 30.41 (.549)	36.64/ 29.91 (.111)	33.38/ 26.61 (.113)	34.79/ 25.95 (.023)	34.07/ 26.53 (.052)
WSCT NI	29.57/ 22.34 (.219)	28.96/ 26.27 (.616)	35.37/ 24.77 (.110)	29.44/ 22.47 (.227)	30.60/ 22.26 (.106)	28.63/ 26.16 (.656)
WSCT C2	12.19/ 15.31 (.464)	12.60/ 13.38 (.838)	8.64/ 14.7 (.112)	13.85/ 9.50 (.186)	1.23/ 14.28 (.595)	13.32/ 11.87 (.689)
WSCT DIFFC1F1	-12.27/ 0.89 **(.014)**	-9.76/ -8.49 (.811)	-12.20/ -8.03 (.446)	-10.37/ -5.34 (.373)	-12.18/ -3.27 (.071)	-11.42/ -3.92 (.158)
WSCT DIFFF1N1	4.59/ 3.92 (.922)	4.62/ 4.15 (.947)	1.27/ 5.78 (.597)	4.52/ 4.14 (.959)	4.80/ 3.70 (.873)	6.08/ 0.37 (.409)
IGT Total	1734.61/ 2200 (.080)	1816.93/ 1878.20 (.773)	1688.33/ 1904.93 (.336)	1874.50/ 1720.45 (.503)	1765.44/ 1995.45 (.318)	1807.64/ 1922.41 (.631)
IGT CA	46.65/ 52.96 (.156)	47.42/ 49.15 (.641)	44.97/ 49.41 (.295)	48.40/ 46.95 (.700)	46.97/ 50.39 (.401)	47.68/ 49.10 (.728)
IGT CDA	53.35/ 47.04 (.156)	52.58/ 50.85 (.641)	55.03/ 50.59 (.295)	51.59/ 53.04 (.700)	53.03/ 49.61 (.401)	52.32/ 50.90 (.728)
IGT NET 5 AD	9.68/ 11.13 (.261)	9.93/ 10.13 (.855)	9.93/ 10.04 (.925)	9.95/ 10.23 (.798)	9.63/ 10.79 (.304)	9.67/ 10.86 (.292)
IGT NET 5 DIS	10.40/ 8.87 (.236)	10.16/ 9.87 (.783)	10.07/ 10.04 (.983)	10.13/ 9.77 (.745)	10.45/ 9.21 (.268)	10.42/ 9.14 (.259)

Note. SDU = 0 patients who have consumed 0 standard drink unit per day in the last month; SDU ≤ 2 patients who have consumed 2 or less standard drink unit per day in the last month; patients with a GGT (gamma-glutamyl transferase) equal or lesser value than 50; patients with a MCV (mean corpuscular volume) equal or lesser value than 88; OCDS: Obsessive Compulsive Drinking Scale; OCDS OBSESSIVE ≤ 5 patients with a score less than or equal to 5 in the obsessive subscale of the OCDS; OCDS COMPULSIVE ≤5 patients with a score less than or equal to 5 in the compulsive subscale of the OCDS; OCDS TOTAL ≤ 10 patients with a score less than or equal to 10 in the total subscale of the OCDS. SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

can be seen that there is an improvement in the different cognitive domains (significant for anterograde memory, divided attention, and interference resistance). This trend towards improvement has been found in other follow-up studies (Ros-Cucurull et al., 2018). In this regard, Wollenweber et al. (2014) found that the cognitive impairments primarily affected frontal-executive functions, while memory was relatively spared, and concluded that cognitive deficits tend to improve with abstinence.

The difficulty seems to lie in determining the time it takes these improvements to occur for each domain (Pelletier, Nalpas, Alarcon, Rigole & Perney, 2016). In our present study, after 6 months of treatment, all functions improved, some more remarkably, such as anterograde memory, working memory, and resistance to interference, but none of the cognitive functions reached the level found in the controls.

Kopera et al. (2012) found differences in neurocognitive performance between short-term abstinent (less than one year) and long-term abstinent (longer than a year) individuals. The first group made more errors on both attention and working memory tests than healthy controls and patients with longer durations of abstinence. This is consistent with our results which also showed that, after 6 months of treatment, compared with controls, patients continue to show impairment in attention, both sustained (d2 test) and divided and resistance to interference (Stroop test), and also in working memory (Digit symbol). In addition, we found impairment in other cognitive domains such as processing speed, memory, abstract reasoning, and verbal fluency.

There are neuroimaging data proving that short-term sobriety – 6 weeks in this case – may be sufficient to observe some brain-volume recovery, but does not result in equivalent brain volumes for recovering chronic alcoholics and healthy controls (Zahr & Pfefferbaum, 2017). If the neuroimaging findings reflect cognitive functioning, this would indicate that there is at least a partial improvement in these functions, but they do not reach the level of healthy people. This assumption is consistent with our results, where "intermediate" results were found at 6 months.

In summary, in our study, we see a general trend toward cognitive improvement after 6 months of follow-up, but this trend in not homogenous for all cognitive variables. Anterograde memory, working memory, and interference resistance improve faster, and the others improve more slowly.

An association between substance-use disorders (SUDs), including alcohol, and impulsivity has been stablished in many studies (Carmona-Perera et al., 2019; Körner, Schmidt & Soyka, 2015; Leeman, Hoff, Krishnan-Sarin, Patock-Peckham & Potenza, 2014; Patton et al., 1995; Verdejo-García, Rivas-Pérez, Vilar-López & Pérez-García, 2007). In this regard, in our previous paper, we found this same result, showing higher impulsivity in the patient group than in the control group. However, 6 months after starting treatment, no within-group differences were observed in patients. This could just mean that the treatment time was less than necessary to detect changes in this aspect or that the relation between alcohol use disorder and impulsivity is bidirectional (Kaiser, Bonsu, Charnigo, Milich & Lynam, 2016), i.e., not only does alcohol use cause impulsivity, but impulsivity can also lead to alcohol use. Körner et al. (2015) found higher impulsivity scores on the BIS-11 in alcohol abstainers (between 2 weeks and 38 years) than in healthy individuals.

In our study, we observed that a reduction in alcohol use or abstinence is related to a reduction in impulsivity, and the three subscales of the OCDS reflect a decrease in the intensity of addiction.

Our data suggest that when patients reduce their alcohol intake and craving as measured with the OCDS, SDU, and biological variables, there is a significant improvement in their cognitive skills, mainly working memory, interference resistance, cognitive flexibility, abstract reasoning, and verbal fluency. In parallel to this cognitive improvement, as expected, we also found a reduction in impulsivity. Thus, it becomes quite clear that patients need to reduce their alcohol intake in order to improve their cognitive performance and reduce their impulsivity.

The OCDS provides us with a useful tool to measure the different aspects of craving (Anton, 2000; Connor, Jack, Feeney & Young, 2008). Our findings show significantly lower scores on the three subscales after 6 months of treatment, reflecting decreases in obsessive thoughts about alcohol and compulsive drinking behaviour.

As we hypothesized, the SDUs consumed daily during the last month, which is a marker of recent use, together the parameters that measure the negative effects of alcohol abuse on blood tests (GOT, GPT, GGT and MCV), had decreased significantly after 6 months of cessation treatment (Giuffredi, Gennaro, Montanari, Barilli & Vescovi, 2003; Harada, Agarwal, Goedde & Miyake, 1985).

It is recommended that all patients at risk of alcohol-related brain damage be evaluated once they have completed at least one week of abstinence to detect the patients most affected and therefore at a higher risk of not responding correctly to treatment (Hayes, Demirkol, Ridley, Withall & Draper, 2016). Our data support this statement. After 6 months of follow-up, there was a significant association between reporting more alcohol addiction with the OCDS and more alcohol intake through SDUs and biological variables and worse baseline performance on the following cognitive functions: working memory, interference resistance, and abstract reasoning. Therefore, patients with worse cognitive performance at baseline made less improvement in drinking reduction,

which is why they need to be detected so that they can receive extra care.

In summary, after 6 months of treatment, anterograde memory, working memory, and resistance to interference significantly improved in patients. However, we still found the effects of alcohol-related brain damage with the rest of the cognitive assessment tools. Our research also shows that the OCDS has predictive utility over time to determine the association between alcohol use and cognitive function. The OCDS is more significantly associated with the cognitive function results than the analytical parameters (GGT and MCV) and the SUD, which were less sensitive for determining this association. This makes the OCDS a good tool in clinical practice. On the other hand, our data shows a trend toward a small but significant cognitive improvement related to a reduction in alcohol use and impulsivity. Executive function, verbal fluency, and working memory are the cognitive functions most significantly influenced by reduction in alcohol use and impulsivity.

All of this leads us to conclude that cognitive impairment can be considered a prognostic factor in outpatients with moderate to severe AUD. Our study shows that cognitive disorders associated with AUD influence the outcomes of outpatient alcohol dishabituation, and this fact is important for daily practice.

Limitations

The present study has limitations that should be noted. The final sample is heterogeneous due to the fact that not all patients achieved abstinence. Estimation of premorbid IQ was not determined, which could influence performance and recovery in neuropsychological tests. Neuropsychological tests give rise to practice effects when used several times in a row. These might partially account for the cognitive improvement between the baseline and the follow-up assessment. Experienced clinicians determined that patients had no symptoms of intoxication prior to evaluation, but no other monitoring methods such as urinalysis or breathalyser were used. Our results show that there is a tendency for cognitive function to improve in different domains but, despite the longitudinal design of this study, it is probable that such improvement continues beyond 6 months of treatment, as reported by Stavro et al. (2013) and Bartels et al. (2006). Thus, it would be interesting to perform another longer-term evaluation. Despite the longitudinal design of this study, it does not establish a relationship between impulsivity measured with the BIS-11 and alcohol use disorder due to the bi-directionality between the two parameters. It must be taken into account that the inclusion and exclusion criteria used in this study meant that patients with low severity AUD were excluded, and the conclusions of this study are therefore applicable only to patients with moderate to serious AUD. Finally, a larger sample size would have provided stronger confirmation of the results obtained.

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Conflict of interests

All authors declare a lack of conflicts of interest regarding the subject matter or materials discussed in the manuscript.

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Back to content-based validity

De regreso a la validez basada en el contenido

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The development and validation of self-reported measuring instruments as a way of quantifying addictive behaviors is currently common practice. These instruments in articles about addiction, however, are dominated by methods involving structural equations and, therefore, evidence based on internal structure (Mezquita, Camacho, Suso-Ribera, Ortet & Ibáñez, 2018; Mezquita, Ruiz-Valero, Martínez-Gómez, Ibáñez & Ortet-Fabregat, 2019). This is the case even though it is known that there are other sources of evidence, such as test consequence, relationships with other variables, content and response processes, which are considered to contribute methodological rigor when researching addiction (Fonseca, 2017). The purpose of this letter to the editor is thus to examine the importance of content-based validity in the development and/or adaptation of measurement instruments in the study of addiction.

Suppose you wanted to create a scale to measure addiction to love and an item is worded: "I experience anguish when my partner is not with me", with a factorial load of greater than .30; despite this, the item may not capture a behavior representative of the universe of behaviors of the construct in question (Cohen & Swerdik, 2001). To test this, the researcher needs the judgment and assessment of an expert, someone who can be considered as such because of his or her extensive experience and recognition in the field (Escobar-Pérez & Cuervo-Martínez, 2008).

The procedure by which the logic is reviewed or by which the representativeness and relevance of the test contents in the interpretation of the test scores is analyzed, is called *content-based validity* (American Psychological Association [APA], American Educational Research Association [AERA], and National Council on Measurement in Education [NCME], 2014). Such a review of the representativeness or relevance of the construct can prevent the covariation of erroneous theoretical information (Haynes, Richard & Kubany, 1995), thus avoiding irrelevant construct variance (APA, AERA & NCME, 2014), which is important because measurement instruments should rely not only on factor models, but also on theoretical argumentation which can show whether an item is representative of a particular domain or not (Bonifay, Lane & Reise, 2017).

Given the above, the author of this letter would like to offer readers an expert rater grid, which can be requested in its entirety and free of charge (see an excerpt in Appendix A). This grid is based on APA, AERA and NCME (2014) guidelines concerning the relevance (degree to which the item is important and should be included in the measurement of the construct) and representativeness (degree to which the item represents the construct to be measured); in addition, a clarity criterion is incorporated (the degree to which the item is clear and understandable).

Once the raters' answers have been obtained, they can be quantified by Aiken's *V*, a coefficient which is simple to calculate and easy to interpret, as expressed below (Penfield & Giacobbi, 2004):

$$V = \frac{\bar{X} - l}{k}$$

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Where $\bar{X}$ is the mean expert rating, l is the lowest possible score and k is the difference between the highest and lowest score on the rating scale. Values of V close to 1 indicate perfect agreement between the raters. A minimum cut-off point of .70 is required (Napitupulu, Syafrullah, Rahim, Amar & Sucahyo, 2018). Likewise, at present, confidence intervals (CI) can be established for Aiken's V, the mathematical expression of which is presented below (Penfield & Giacobbi, 2004):

$$L = \frac{2nkV + z^2 - z\sqrt{4nkV(1-V) + z^2}}{2(nk + z^2)}$$

$$U = \frac{2nkV + z^2 + z\sqrt{4nkV(1-V) + z^2}}{2(nk + z^2)}$$

Where L is the lower limit and U the upper limit, n is the number of raters, k is the difference between the highest and lowest scores on the scale; V is the value of Aiken's V; and z is the standard distribution chosen, so 90%, 95% and 99% confidence corresponds to it 1.65, 1.96 and 2.58 respectively.

For the interpretation of CIs, it is recommended that the value of the lower limit ≥ .70 (Charter, 2003), although it is known that CI size depends to a large extent on the increase of sample size (Penfield & Giacobbi, 2004). If you would like to calculate Aiken's V with its respective CIs, you can request an Excel® spreadsheet at no cost from the author of this letter or use the following codes in the statistical program R:

```
####AIKEN'S V#####
x = 1.90 # arithmetic mean of expert ratings
l = 0 # lowest
s = 3 # highest value
k = s-l # range
v = (x-l)/k ## Aiken's v equation
v
####CONFIDENCE INTERVALS#####
Z = 1.96 # value of z at 95%
N = 10 # number of raters
IC1 = (((2*v*N*K)+(Z^2)))
IC2 = Z*(sqrt((4*N*K*v)*(1-v)+(Z^2)))
IC3 = 2*((N*K)+(Z^2))
INFIC = (IC1- IC2)/IC3
SUPIC = (IC1+IC2)/IC3
INFIC
SUPIC
```

In conclusion, the incorporation of evidence based on content in self-reported addiction instruments is relevant for two reasons: (a) the review of item content by expert raters prior to carrying out the statistical analyses will allow construct irrelevant variance to be reduced; (b) reporting that a test is valid merely because it shows evidence of validity based on its internal structure is insufficient; it is necessary to explore more sources of validity, one of them being based on content. Finally, it is hoped that the R codes and the expert rater grid can offer a way of returning to a review of item content and coherence with theoretical postulates, thereby providing better-calibrated scales, questionnaires or tests in addiction research.

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Appendix A

Table 1. *Excerpt from the expert rater grid.*

		Relevance				Representativeness				Clarity				Suggestions
Positive self-esteem* Positive perception of oneself, taking into account one's qualities														
Nº	**Items**													
1	I feel I'm worth as much as others	0	1	2	3	0	1	2	3	0	1	2	3	
3	I think I have some good qualities	0	1	2	3	0	1	2	3	0	1	2	3	
4	I can do things just as well as others can	0	1	2	3	0	1	2	3	0	1	2	3	
6	I have a positive attitude towards myself	0	1	2	3	0	1	2	3	0	1	2	3	
7	I almost always feel good about myself	0	1	2	3	0	1	2	3	0	1	2	3	
Negative self-esteem Negative perception of oneself, tending to see one's bad sides														
Nº	**Items**													
2	I almost always feel like a failure	0	1	2	3	0	1	2	3	0	1	2	3	
5	I feel I haven't got much to be proud of	0	1	2	3	0	1	2	3	0	1	2	3	
8	I would like to have more self-respect	0	1	2	3	0	1	2	3	0	1	2	3	
9	I feel really useless sometimes	0	1	2	3	0	1	2	3	0	1	2	3	
10	I sometimes feel I'm no good for anything	0	1	2	3	0	1	2	3	0	1	2	3	

Note: The response options of the scale range from 1 to 4 as follows: (0) Completely disagree; (1) Disagree; (2) Agree; (3) Completely agree; *: Excerpt from the expert rater grid based on the Rosenberg scale in Spanish by Atienza, Moreno and Balaguer, 2000.

Signature of expert rater

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Smoking cessation treatment attendance among smokers with substance use disorders

Asistencia a un tratamiento para dejar de fumar con personas con trastorno por uso de sustancias

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Attrition rates pose a considerable problem in smoking cessation intervention, especially with hard-to-treat population (Lappan, Brown & Hendricks, 2019; Lien, Bolstad & Bramness, 2021). In this sense, non-attendance to a smoking cessation treatment decreases effectiveness of these interventions (Garey et al., 2020; Martínez-Vispo, López-Durán, Rodríguez-Cano, Senra & Becoña, 2021), and also brings about several resource-related costs (e.g., therapists time, urinalysis, materials) (Brorson, Arnevik, Rand-hendriksen & Duckert, 2013; Cooper, Kline, Baier & Feeny, 2018). All of the above results in a decrease in the cost-effectiveness of smoking cessation treatments in this population (Cooper et al., 2018).

Although multiple researches on dropping out of smoking cessation treatments has been examined in SUD population, to our knowledge, no previous studies have examined specific predictors associated with treatment attendance in this population. Analyzing which factors predict non-attendance is expected to be clinically informative because it will enable to improve the efficacy and cost-effectiveness of existing smoking treatments. Amid this background, this exploratory study sought to examine which baseline variables (i.e., sociodemographic, tobacco, and substance use related variables) were associated with non-attendance to the smoking cessation treatment.

This is a secondary study derived from a parent randomized controlled trial (Aonso-Diego, González-Roz, Krotter, García-Pérez & Secades-Villa, 2021). The eligibility criteria were: being ≥ 18 years old, smoking at least 10 cigarettes per day within the last year, and being enrolled in an outpatient substance use treatment. Participants were excluded if they had severe mental disorders (i.e., active psychotic disorder, or suicidal ideation), current cannabis use, or were receiving any other smoking cessation treatment, either psychological or pharmacological. Out of 101 participants who were assessed in an individual baseline interview, 15 were excluded for not meeting inclusion criteria, and a total of 86 patients were assigned to smoking cessation treatment.

A binary logistic regression analysis was performed with attrition groups as dependent variable. The independent variables introduced were: sociodemographic (i.e., sex, age, employment status, marital status, and educational level), smoking features (i.e., cigarettes per day, years of regular use, nicotine dependence, urine cotinine levels, previous quit attempts, and current motivation to quit), and substance use related characteristics, that is, primary substance use (cocaine, alcohol, opioids, or cannabis), days of substance abstinence, and days on substance use treatment. Treatment condition [(cognitive-behavioral treatment (CBT) or CBT + contingency management (CM)] was also included in the analyses.

Findings indicate that out of 86 participants allocated to treatment groups, 65 (75.58%) patients began the treatment, and the remaining 21 (24.42%) patients did

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Table 1. *Baseline predictors of non-attendance.*

Variables	*B*	*OR*	95%CI	*p*
Age	-.248	.780	.623, .976	.030
Sex (female)	.938	2.554	.550, 11.872	.232
Educational level (< high school)	1.138	3.121	.591, 16.464	.180
Marital status (married)	-.408	.665	.131, 3.382	.623
Employment status (working)	-.185	.831	.130, 5.309	.845
CPD	-.092	.912	.801, 1.039	.165
Years of regular use	.172	1.187	.976, 1.444	.085
Cotinine	.000	1.000	.999, 1.001	.589
FTND	.115	1.122	.721, 1.745	.611
Previous quit attempts	-.039	.962	.526, 1.759	.900
Stage of change				
Contemplation (vs. precontemplation)	.195	1.215	.039, 37.961	.912
Prepare to action (vs. precontemplation)	.026	1.027	.031, 34.218	.988
Primary substance				
Cocaine (vs. opioids)	3.064	21.423	1.194, 384.301	.037
Alcohol (vs. opioids)	1.760	5.810	.267, 126.515	.263
Cannabis (vs. opioids)	.511	1.667	.034, 82.526	.797
Days of substance abstinence	.001	1.001	.999, 1.002	.269
Days on substance use treatment	-.005	.995	.991, .999	.024
Treatment group (CBT)	.279	1.322	.234, 7.465	.754

Note. 'Completers' is the reference category; *OR*: Odds ratio; CI: confidence interval; CPD: cigarettes per day; FTND: Fagerström test for nicotine dependence; CBT: cognitive-behavioral treatment; AUC_{logd}: base-10 logarithmic transformation of the area under the curve.

not start the treatment. Among participants who initiated the treatment, 17 participants (19.76%) dropped out during the treatment, and 48 patients completed the entire treatment (55.81%). Table 1 displays predictors of non-attendance. Results indicated that younger age (OR = .780), cocaine as a primary substance use of treatment (OR = 21.42), and fewer days on substance use treatment (OR = .995), were significantly associated with greater likelihood of non-attendance.

These results suggest that several individuals with SUD did not benefit from smoking cessation treatments and underscore the importance of developing innovative treatment strategies aimed at increasing attendance at smoking cessation treatments in these populations (McCrabb et al., 2019; Naslund et al., 2017). Online treatments could be a useful strategy to this population, especially for young smokers, due to its ease of use at any time and place, the ability to tailor messages to the participants' characteristics (e.g., gender, or psychiatric disorders), few material resources, and the ability to send reminder messages to facilitate adherence (e.g., medication) (Whittaker et al., 2019).

In conclusion, this study provides evidence for understanding non-attendance rates in smokers with SUD assigned to smoking cessation treatment. Findings indicated that younger patients, treated for cocaine use, and with fewer days on substance use treatment, were more likely to not attend the treatment. Future smoking cessation trials with this hard-to-treat population should consider incorporating tailored strategies to improve attendance and retention rates. We hope this information can help guide clinicians to develop and implement interventions for reducing tobacco-related illness among SUD population.

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Conflict of interests

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Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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

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

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

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

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

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

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

PRESENTACIÓN DE LOS TRABAJOS

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

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

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

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