

# DSM-5 in patients seeking their first treatment for alcohol use disorder. Sex differences in the multicenter CohRTA study

## DSM-5 en pacientes que solicitan el primer tratamiento del trastorno por uso de alcohol. Diferencias de sexo en el estudio multicéntrico CohRTA

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### Abstract

**Objective:** We aimed to analyze sex differences in the DSM-5 criteria among patients admitted to their first treatment of alcohol use disorder (AUD). **Methods:** Assessment of AUD was carried out using DSM-5 diagnostic criteria in a multicenter study (CohRTA) within the Spanish Network on Addictive Disorders. Further, baseline questionnaires including socio-demographics, family history, lifetime alcohol consumption and other substance use, as well as clinical and laboratory parameters were obtained during admission. **Results:** 313 patients (74.8%M) were eligible; mean age at first AUD treatment was 48.8 years (standard deviation (SD): 9.9 years). Age at onset of alcohol use was 15.9 years (SD: 3.3 years) and age at starting regular alcohol consumption was 25.6 years (SD: 9.6 years). Almost 69.3% of patients were tobacco smokers and 61% had family history of AUD. Regarding other substance use, 7.7% were current cocaine users and 18.2% were cannabis users. Women started regular alcohol consumption later than men ( $p<.001$ ) and used benzodiazepines more frequently ( $p=.013$ ). According to DSM-5, 89.5% of cases had severe AUD ( $\geq 6$  criteria). In the adjusted analysis (logistic regression), men were more likely to neglect major rules (OR=1.92, 95%CI: 1.06-3.48) and to have hazardous alcohol use (OR=3.00, 95%CI: 1.65-5.46). **Discussion:** DSM-5 detects sex differences in patients seeking their first AUD treatment. Social impairment and risky alcohol use are significantly more frequent in men.

**Key Words:** Alcohol use disorder; DSM-5; Sex differences.

### Resumen

**Objetivo:** Analizar las diferencias de sexo en los criterios diagnósticos del DSM-5 de los pacientes que solicitan un tratamiento para el trastorno por uso de alcohol (TUA) por primera vez. **Métodos:** Pacientes incluidos entre enero 2014 y marzo 2016 en el estudio multicéntrico CohRTA de la Red de Trastornos Adictivos. El diagnóstico del TUA se realizó mediante el DSM-5. Además, se recogieron datos sociodemográficos, sobre el consumo de alcohol y otras sustancias, variables clínicas y una analítica general. **Resultados:** se incluyeron 313 pacientes (74,8% hombres); la edad al inicio del primer tratamiento fue de 48,8 años (desviación estándar (DE): 9,9 años), la edad al inicio del consumo de alcohol de 15,9 años (DE: 3,3 años) y la de inicio del consumo regular de 25,6 años (DE: 9,6 años). Un 69,3% de los pacientes eran fumadores y un 61% tenían antecedentes familiares de TUA. Un 7,7% eran consumidores de cocaína y un 18,2% de cannabis. Las mujeres iniciaron el consumo regular de alcohol más tarde que los hombres ( $p<.001$ ) y usaban benzodiazepinas con mayor frecuencia ( $p=.013$ ). Según el DSM-5, el 89,5% de los pacientes presentaban un TUA grave ( $\geq 6$  criterios). En el análisis ajustado (regresión logística), los hombres tenían mayor probabilidad de presentar el criterio diagnóstico relacionado con el incumplimiento de los deberes fundamentales en el trabajo o en el hogar (OR=1,92, IC95%: 1,06-3,48) y el criterio diagnóstico de consumir alcohol en situaciones de riesgo físico (OR=3,00, IC95%: 1,65-5,46). **Discusión:** El DSM-5 detecta diferencias de sexo en pacientes que solicitan el primer tratamiento del TUA. El deterioro social y el consumo de alcohol de riesgo son significativamente más frecuentes en hombres.

**Palabras clave:** Trastorno por uso de alcohol; DSM-5; Diferencias de sexo.

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**A**lcohol use is widespread in Western society, with high levels of alcohol abuse and dependence. In Western Europe, abuse of alcohol and other substances is more prevalent among men than women (European Monitoring Centre for Drugs and Drug Addiction, 2015; Observatorio Español de las Drogas y las Toxicomanías, 2011; Teesson et al., 2010). However, population data indicate that the prevalence of alcohol use among men and women may be similar at ages between 15 and 35 (Observatorio Español de las Drogas y las Adicciones, 2017). This closing of the gender gap suggests that problems related to excessive alcohol use may be increasingly frequent in women.

In the USA, risky alcohol use and alcohol use disorder (AUD) in women increased by 60% and 80%, respectively, between the periods 2001-2002 and 2012-2013 (Grant et al., 2017). In addition, the increase in emergency treatments related to alcohol abuse involving women has been greater than among men (White, Slater, Ng, Hingson & Breslow, 2018). Some studies show that women are less likely to seek AUD treatment than men, develop an alcohol dependence syndrome more quickly, and take longer to receive an AUD diagnosis (Bravo, Gual, Lligoña & Colom, 2013; Johnson, Richter, Kleber, McLellan & Carise, 2005; Rehm, Manthey, Struzzo, Gual & Wojnar, 2015), all of which could contribute to a worse prognosis of the disorder in women.

There is considerable clinical variability in the detrimental effects of alcohol on health, which may be due to multiple biopsychosocial factors. Among the biological factors, the different metabolization of ethanol in men and women stands out (Crabb, Matsumoto, Chang & You, 2004). This is caused by the gastric alcohol dehydrogenase enzyme being less active in women, meaning that for the same amount of alcohol ingested, women will have a higher concentration of ethanol (Lieber, 2000; Mezey, 2000). In fact, it is well known that women are more vulnerable to organic injury caused by alcohol (Lieber, 2000). Drinking alcohol to excess can also impact the plasma levels of sex hormones, which in turn are important mediators of the immune response to different pathogens (Bouman, Heineman & Faas, 2005; Mezey, 2000). Moreover, there are several hypotheses regarding the greater genetic susceptibility of women to alcohol use (Bravo et al., 2013; Wodarz et al., 2003).

In terms of psychosocial and work-related aspects, women have been shown to be more vulnerable and to display greater risks of suffering detrimental health effects (Djindjic, Jovanovic, Djindjic, Jovanovic & Jovanovic, 2012; Hallman, Burell, Setterlind, Odén & Lisspers, 2001). The increasing role of women in society and at work may have made them more likely to drink alcohol. Furthermore, marital status, maternity, and/or partner substance use have been associated with an increased risk of alcohol use among women (Brñez Horta, 2001). However, other

authors do not believe that the social and work-related changes affecting women are sufficient on their own to explain the convergence of alcohol use patterns (White et al., 2015).

DSM-5 is a diagnostic classification of mental disorders established by the American Psychiatric Association (American Psychiatric Association, 2013). Regarding substance use disorder, changes with regard to DSM-IV include combining abuse and dependence in a single diagnostic criterion, adding persistent craving as a new criterion and scaling the severity of the disorder in three categories (Bartoli, Carrà, Crocamo & Clerici, 2015; Hasin et al., 2013). According to DSM-5, an AUD is indicated if in the last 12 months a person reports at least two of the 11 established symptomatic criteria. The severity of the disorder is then determined by the number of criteria involved. It is important to determine the severity of AUD because patients with moderate or severe disorder can benefit from intensive treatment (Edelman & Fiellin, 2016). A multinational study using DSM-5 shows that the prevalence of AUD in adults differs between countries (Slade et al., 2016). In Spain, it is estimated that up to 5% of the general adult population could meet AUD diagnostic criteria according to Alcohol Use Disorder Identification Test (AUDIT) (Observatorio Español de las Drogas y las Adicciones, 2017). However, clinical data when using DSM-5 as a diagnostic tool are still scarce.

The multicentre cohort study within the Spanish Network on Addictive Disorders (Red de Trastornos Adictivos), CohRTA, focuses on patients who seek AUD treatment for the first time. An analysis of cases during first treatment of the disorder provides us with current clinical characteristics and avoids the selection of chronic patients, who have had multiple prior treatments. The principal aim of this study was to use DSM-5 to describe sex differences among those seeking first-time AUD treatment.

## Methodology

This is a cross-sectional study of patients seeking first treatment of AUD in public primary or hospital care centers. As of December 2017, nine centers in four autonomous communities (Cataluña, Castilla y León, Islas Baleares and Madrid) participated in the study: Hospital del Mar, Hospital Clínic de Barcelona, Hospital Universitari de Bellvitge, Hospital Universitari Germans Trias i Pujol, Centro Municipal de Atención a las Drogodependencias de Badalona (Centro Delta), Hospital Clínico de Salamanca, Alcohólicos Rehabilitados de Valladolid, Hospital Universitario 12 de Octubre and Hospital Universitari Son Espases.

The study was approved by the Clinical Research Ethics Committee (CREC) of the coordinating center (Hospital Universitari Germans Trias i Pujol) and by the CREC

of each participating center. CohRTA patients signed informed consent, which included the transfer of data and biological samples. The methods used in this study comply with the ethical standards for medical research and the principles of good clinical practice established in the Declaration of Helsinki.

The baseline questionnaire included sociodemographic characteristics, family history of the disorder, variables related to alcohol use (age of onset, age of onset of regular consumption, amount, total cumulative time of abstinence up to the beginning of the first AUD treatment, number of alcohol poisonings requiring emergency department attention) and to the use of other substances (tobacco, cannabis, amphetamine, benzodiazepine, opioid use in the last month, history of parenteral drug use); also included for analysis were general blood parameters including blood count (hemoglobin), coagulation (prothrombin time) and biochemistry (sodium, potassium, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], total cholesterol, albumin, total bilirubin, urea and creatinine). Likewise, blood samples were collected and stored in the Red de Trastornos Adictivos biobank (Universidad Miguel Hernández, Alicante). Further details of the study protocol are available (Sanvisens et al., 2018).

AUD diagnosis using DSM-5 involves 11 criteria and assesses four major areas: 1) Impaired control over substance use (higher than expected amounts, longer than expected duration, unsuccessful attempts to quit drinking, spending a great deal of time on alcohol use activities, persistent desire to drink), 2) Social impairment (neglect of major work or home rules, reduction or giving up of social activities, problems in the social sphere), 3) Risky drinking (in situations involving physical risk, despite having drink-related physical and/or psychological problems) and, 4) Pharmacological criteria (substance tolerance and withdrawal).

The severity of the disorder is measured on a three-point scale: 1) mild (2-3 diagnostic criteria), 2) moderate (4-5 criteria), and 3) severe ( $\geq 6$  criteria).

Between January 2014 and March 2016, 369 patients met the criteria for inclusion in the CohRTA study. For this study, 56 patients were excluded because they did not meet all the DSM-5 criteria. However, age on first admission for treatment ( $p = .60$ ), sex ( $p = .36$ ) and age of onset of alcohol use ( $p = .51$ ) were similar among the 313 patients who entered the study analysis and the 56 patients excluded.

### Statistical analysis

Descriptive data analysis showed the relative frequencies of the categorical variables and the means  $\pm$  standard deviations (SD) of the continuous variables. Bivariate analyses were performed to establish sex differences using chi-square and Fisher tests for the comparison of categorical variables and Student's t-tests to determine differences in means.

Multivariate analysis was performed using logistic regression models with each DSM-5 diagnostic criterion as a dependent variable. Independent variables included were those with statistically significant differences between men and women in the univariate analysis.

Values of  $p < .05$  were considered statistically significant. Statistical analysis was performed with Stata software (version 11.0, College Station, Texas, USA).

## Results

A total of 313 patients (74.8% men) were included, with a mean age  $\pm$  SD at the beginning of the first treatment of  $48.8 \pm 9.9$  years. The mean onset age was  $15.9 \pm 3.3$  years and regular drinking started at  $25.6 \pm 9.6$  years. Smokers made up 69.3% of the sample and 61% had a family history of AUD. Regarding other substances, 7.7% of the patients were cocaine users and 18.2% used cannabis.

In the general blood parameters, mean hemoglobin was  $13.9 \pm 2.5$  g/dL, total cholesterol was  $209 \pm 49$  mg/dL, and mean albumin was  $39.8 \pm 8.8$  g/L. AST was  $> 40$  U/L in 46% of patients, ALT  $> 40$  U/L in 32.8%, and GGT  $> 50$  U/L in 67.2%. Tables 1 and 2 show the socio-demographic characteristics, the results of the general blood parameters and the characteristics of alcohol and other substance use at the beginning of the treatment.

Women started regular alcohol consumption later (6 years on average) ( $p < .001$ ) and had a higher prevalence of benzodiazepine use ( $p = .013$ ) than men (Table 2).

Overall, the most prevalent DSM-5 criteria were: drinking alcohol in higher amounts or for longer periods than expected (97.1%), continuing to drink despite physical or psychological problems caused or exacerbated by alcohol (91.4%) and showing signs of tolerance to the substance (85.9%). In 73.5% of cases, signs or symptoms of alcohol withdrawal were present, and 78.3% showed a persistent craving to drink.

Severe AUD was found in 89.5% of the cases ( $\geq 6$  DSM-5 criteria), with 9.3% presenting moderate (4-5 criteria) and 1.3% mild (2-3 criteria) AUD; no sex differences were observed ( $p = .487$ ).

Table 3 shows the sex differences for the DSM-5 criteria. Men had higher prevalence of withdrawal criteria ( $p = .038$ ), drinking in situations of physical risk ( $p < .001$ ), failing to fulfill major rules at work or at home ( $p = .001$ ) and giving up or reducing social, professional or leisure activities ( $p = .064$ ) than women.

Figure 1 shows the probability of men presenting DSM-5 diagnostic criteria with respect to women, adjusting for the age of onset of regular drinking, benzodiazepine consumption and employment. Logistic regression analysis indicates that men were up to 3 times more likely than women to use alcohol in situations involving physical risk (OR = 3.00, CI

Table 1. Sociodemographic and analytical characteristics of 313 patients admitted to AUD treatment.

	Total N=313 n (%)	Men N=234 n (%)	Women N=79 n (%)	p value
Age, mean $\pm$ SD	48.8 $\pm$ 9.9	48.6 $\pm$ 10.1	49.1 $\pm$ 9.1	.726
Born in Spain	299 (95.5)	225 (96.1)	74 (93.7)	.356
<b>Educational level (n=303)</b>				
Does not know how to read or write	5 (1.7)	4 (1.8)	1 (1.3)	.710
Primary education	65 (21.4)	51 (22.6)	14 (18.2)	
Secondary education	181 (59.7)	135 (59.7)	46 (59.7)	
University student	52 (17.2)	36 (15.9)	16 (20.8)	
<b>Marital status (n=309)</b>				
Single	77 (25.0)	61 (26.3)	16 (20.7)	.328
Married or domestic partner	132 (42.7)	101 (43.5)	31 (40.3)	
Widowed, separated or divorced	100 (32.3)	70 (30.2)	30 (39.0)	
<b>Employment (n=309)</b>				
Working	144 (46.6)	113 (48.6)	31 (40.3)	<b>&lt;.001</b>
Unemployed, permanent disability, pensioner	155 (50.2)	117 (50.5)	38 (49.3)	
Students/Home/Other tasks	10 (3.2)	2 (0.9)	8 (10.4)	
<b>Cohabitation (n=308)</b>				
Living alone	53 (17.2)	40 (17.3)	13 (16.9)	.198
With partner and/or children	169 (54.9)	120 (51.9)	49 (63.6)	
With family of origin	70 (22.7)	59 (25.6)	11 (14.3)	
Other situations	16 (5.2)	12 (5.2)	4 (5.2)	
General analysis at the beginning of AUD treatment			<i>mean <math>\pm</math> SD</i>	
Hemoglobin (g/dL) (n=298)	13.9 $\pm$ 2.5	14.5 $\pm$ 2.4	12.7 $\pm$ 2.3	<b>.010</b>
Prothrombin time (INR) (n=277)	1.0 $\pm$ 0.2	1.0 $\pm$ 0.2	1.0 $\pm$ 0.1	.436
Total cholesterol (mg/dL) (n=279)	209 $\pm$ 49	204 $\pm$ 45	219 $\pm$ 56	.255
Albumin (g/L) (n=279)	39.8 $\pm$ 8.8	41.3 $\pm$ 7.4	36.8 $\pm$ 10.7	.073
Total bilirubin (mg/dL) (n=279)	0.9 $\pm$ 0.7	0.9 $\pm$ 0.6	0.8 $\pm$ 0.8	.665
Sodium (mEq/L) (n=298)	139 $\pm$ 3.2	139 $\pm$ 3.4	139 $\pm$ 2.6	.607
Potassium (mEq/L) (n=298)	4.4 $\pm$ 0.4	4.4 $\pm$ 0.5	4.4 $\pm$ 0.3	.876
AST (U/L) (n=279)	59.4 $\pm$ 50.5	61.2 $\pm$ 50.0	55.4 $\pm$ 53.0	.710
ALT (U/L) (n=279)	42.6 $\pm$ 31.9	46.3 $\pm$ 33.5	34.5 $\pm$ 27.0	.185
GGT (U/L) (n=279)	245 $\pm$ 504	305 $\pm$ 594	116 $\pm$ 141	.157
Urea (mg/dL) (n=298)	22.6 $\pm$ 9.4	24.4 $\pm$ 9.3	18.6 $\pm$ 8.5	<b>.028</b>
Creatinine (mg/dL) (n=298)	0.7 $\pm$ 0.2	0.8 $\pm$ 0.2	0.6 $\pm$ 0.1	<b>.002</b>

95%: 1.65-5.46), and also more likely to neglect major rules (OR = 1.92, CI 95%: 1.06-3.48).

## Discussion

This study shows that women with AUD start regular drinking later than men. However, the age at which they seek admission for treatment of the disorder for the first time is similar to that of men, which suggests that excessive alcohol use could develop into AUD more quickly among women. In this multicenter study, first AUD treatment is sought late (at the age of almost 50 for both men and women) and occurs several decades after the start of

regular drinking, thus increasing the likelihood of presenting greater morbidity when treatment is first sought. Several studies describe a marked delay between AUD diagnosis and therapy (Chapman, Slade, Hunt & Teesson, 2015; Teesson et al., 2010). However, a recent study in Australia analyzing predictors of delay did not observe sex differences (Chapman et al., 2015). On the other hand, it has been reported that women are less likely to seek treatment for the disorder, although they are more compliant once they have initiated it (Bravo et al., 2013; Rehm et al., 2015). In any case, only a minority of people with AUD seek treatment of the disorder at some stage during their lifetime

Table 2. Characteristics of alcohol and substance use of 313 patients with AUD.

	Total N=313 n (%)	Men N=234 n (%)	Women N=79 n (%)	p value
Age of onset of alcohol use, <i>mean ± SD</i>	15.9 ± 3.3	15.7 ± 3.1	16.7 ± 3.8	<b>.016</b>
Age of onset of regular drinking, <i>mean ± SD</i>	25.6 ± 9.6	24.0 ± 8.6	30.5 ± 11.0	<b>&lt;.001</b>
Alcohol use (g/day), <i>mean ± SD</i>	134.8 ± 80.6	138.7 ± 86.2	123.1 ± 60.2	.316
Total cumulative time of alcohol abstinence (years), (n = 307), <i>mean ± SD</i>	2.1 ± 3.4	2.1 ± 3.4	2.2 ± 3.7	.843
Family history of AUD (n = 307)	188 (61.0)	138 (60.3)	50 (64.1)	.548
<b>Lifetime number of alcohol poisonings (n = 304)</b>				
None	132 (43.4)	98 (43.4)	34 (43.6)	.977
1-5	159 (52.3)	118 (52.2)	41 (52.6)	
>5	13 (4.3)	10 (4.4)	3 (3.8)	
<b>Tobacco smoker</b>				
Yes	217 (69.3)	157 (67.1)	60 (75.9)	.137
No	62 (19.8)	47 (20.1)	15 (19.0)	
Ex-smoker	34 (10.9)	30 (12.8)	4 (5.1)	
<b>Consumption in the last month:</b>				
Cocaine	24 (7.7)	18 (7.7)	6 (7.6)	.978
Cannabis/marijuana (n=312)	57 (18.2)	47 (20.2)	10 (12.7)	.135
Amphetamines	6 (1.9)	5 (2.4)	1 (1.3)	.625
Benzodiazepines	18 (5.7)	9 (3.8)	9 (11.4)	<b>.013</b>
Opiates	1 (0.3)	1 (0.4)	0 (0)	.561
History of parenteral drug use (n=311)	9 (2.9)	6 (2.6)	3 (3.8)	.579

Table 3. Sex differences in the diagnostic criteria and severity of AUD according to DSM-5 in 313 patients admitted to treatment for the first time.

	Total N=313 n (%)	Men N=234 n (%)	Women N=79 n (%)	p value
<b>DSM-5</b>				
<b>Impaired control</b>				
Greater amounts/extended time	304 (97.1)	229 (97.9)	75 (94.9)	.178
Amounts greater than expected	301 (96.2)	227 (97.1)	74 (93.7)	.182
Longer than expected	281 (89.8)	211 (90.2)	70 (88.6)	.692
Unsuccessful attempts to abandon/control use	262 (83.7)	196 (83.8)	66 (83.5)	.964
Spending a lot of time on alcohol use activity	183 (58.5)	137 (58.6)	46 (58.2)	.960
Craving	245 (78.3)	181 (77.3)	64 (88.0)	.495
<b>Social impairment</b>				
Neglect of major rules	196 (62.6)	129 (55.1)	27 (34.2)	<b>.001</b>
Reduction or giving up of social activities	143 (45.7)	114 (48.7)	29 (36.7)	.064
Problems in the social sphere	231 (73.8)	176 (75.2)	55 (69.6)	.328
<b>Risky consumption</b>				
Physical risk	196 (62.6)	165 (70.5)	31 (39.2)	<b>&lt;.001</b>
Physical/psychological problems	286 (91.4)	213 (91.0)	73 (92.4)	.706
<b>Pharmacological criteria</b>				
Withdrawal	230 (73.5)	179 (76.5)	51 (64.6)	<b>.038</b>
Two or more symptoms	222 (70.9)	171 (73.1)	51 (64.6)	.149
Drinking to relieve symptoms	166 (53.0)	131 (56.0)	35 (44.3)	.072
Substance tolerance	269 (85.9)	204 (87.2)	65 (82.3)	.279
Need for greater quantities	259 (82.7)	195 (83.3)	64 (81.0)	.637
Reduced effect	236 (75.4)	182 (77.8)	54 (68.3)	.093
<b>Severity</b>				
Number of criteria, <i>mean ± SD</i>	10.1 ± 2.4	10.4 ± 2.4	9.3 ± 2.3	<b>.001</b>
Mild (2-3 criteria)	4 (1.3)	2 (0.8)	2 (2.5)	.487
Moderate (4-5 criteria)	29 (9.3)	21 (9.0)	8 (10.1)	
Severe (≥6 criteria)	280 (89.4)	211 (90.2)	69 (87.4)	

(Dawson, Goldstein & Grant, 2012; Edlund, Booth & Han, 2012; Rehm et al., 2015).

In the univariate analysis, women show a higher prevalence of benzodiazepine use than men. This finding coincides with data from the Spanish Observatory on Drugs in its 2017 survey on alcohol and drug use in the general

population (Observatorio Español de las Drogas y las Adicciones, 2017). The design of this cross-sectional study does not allow us to establish whether the higher prevalence of benzodiazepine use by women is due to psychiatric comorbidity or other concurrent symptoms, such as alcohol with-

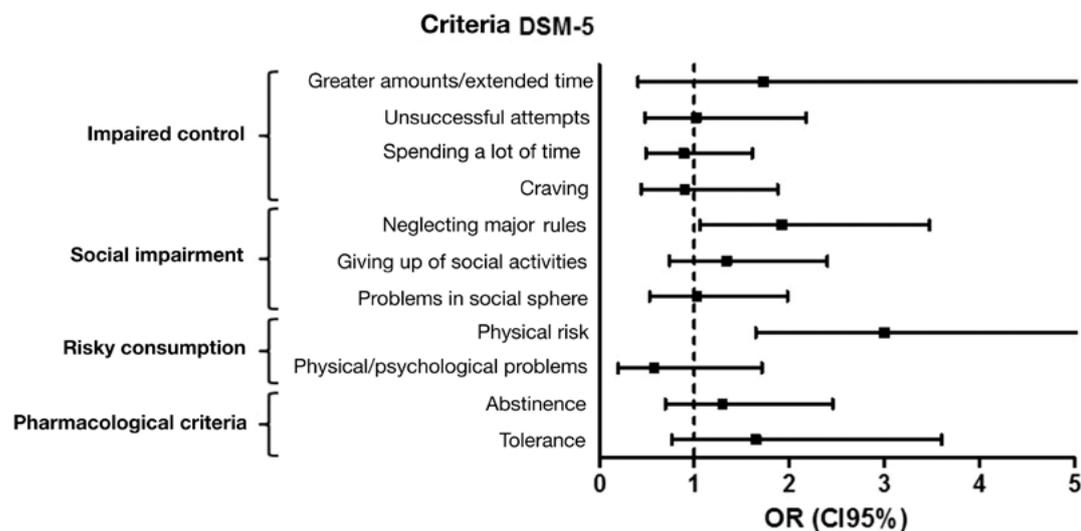


Figure 1. Adjusted probability \* (logistic regression) of men admitted to AUD treatment for the first time presenting DSM-5 diagnostic criteria compared to women

Note. \* Adjusted for age of onset of regular alcohol consumption, benzodiazepine use and employment status

drawal syndrome which is treated with this family of drugs (Mirijello et al., 2015; Saitz, 2005).

Another sex difference observed in the univariate analysis is in the employment situation. An analysis of possible causes suggests that these differences are mainly due to the fact that some of the women with an AUD report housework as their employment (data not shown).

With reference to DSM-5, the prevalence of severe AUD was high in this series of cases admitted for treatment of the disorder, with no differences between men and women. However, sex differences in this study are detected by DSM-5 in certain diagnostic areas such as social deterioration and alcohol use in situations of risk, more likely in men. These differences may be due to multiple factors, associated with lifestyle or with other reasons; it is known, for example, that men are exposed to situations of risk more frequently than women in relation to alcohol abuse (Schwartz & Davaran, 2013; White, Hingson, Pan & Yi, 2011). It is interesting to note that when DSM-5 is used to detect AUD in the general population, the same conclusions are drawn: recurrent alcohol use in situations involving physical risk and social impairment are always more prevalent in men (Caetano, Gruenewald, Vaeth & Canino, 2018). In fact, there is a lot of scientific evidence of sex differences in some physiological and psychosocial neural

processes in relation to AUD (Kelly, Ostrowski & Wilson, 1999; Nolen-Hoeksema & Hilt, 2006).

On the other hand, some genetic factors may influence the behavioral aspects of AUD and can be divided into two major groups: the genetic neurotransmission modifiers, such as the genes that encode the GABA receptor, and the genetic modifiers of ethanol metabolism, in particular, the polymorphisms of the enzymes involved (Anstee, Daly & Day, 2015). It would thus be interesting to have more studies showing the genetic and environmental interaction in AUD (Salvatore, Cho & Dick, 2017).

This study has several limitations which must be mentioned. First, given the cross-sectional design, we cannot draw conclusions about the causality of the DSM-5 diagnostic criteria. Second, there may be some bias in patient selection towards cases with severe AUD attended in public centers, most of them hospitals, compared to those treated for the first time in primary care centers, who may be younger and with lower comorbidity. Finally, it has been argued that DSM-5 has some limitations as a diagnostic tool, among them its heterogeneous diagnostic criteria and an approach which is excessively strict when analyzing the severity of the disorder as it does not distinguish between alcohol abuse and dependence, nor determine the severity of these conditions (Helzer, van den Brink & Guth, 2006; Lane & Sher, 2015; Muthén, 2006). Neverthe-

less, the strength of this multicenter study lies in the fact that it includes other variables which complement DSM-5 (e.g., polydrug use), allowing us to better characterize the disorder. The results presented here reveal the need to advance the diagnosis of AUD and encourage treatment at the earliest stages of the disease.

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## Conflicts of interest

None.

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