



Mood Disorders and Severity of Addiction in Alcohol-Dependent Patients Could Be Mediated by Sex Differences

Raul F. Palma-Álvarez^{1,2}, Laia Rodríguez-Cintas^{1,2}, Alfonso C. Abad¹, Marta Sorribes¹, Elena Ros-Cucurull^{1,2}, María Robles-Martínez³, Lara Grau-López^{1,2}, Lourdes Aguilar⁴ and Carlos Roncero^{4*}

¹Addiction and Dual Diagnosis Unit, Department of Psychiatry, Vall d'Hebron University Hospital–Public Health Agency, Barcelona (ASPB), CIBERSAM, Barcelona, Spain, ²Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, ³Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain, ⁴Psychiatry Service, Salamanca University Health Care Complex, Institute of Biomedicine, University of Salamanca, Salamanca, Spain

OPEN ACCESS

Edited by:

Marc N. Potenza,
Yale University, United States

Reviewed by:

Carolina Haass-Koffler,
Brown University, United States
Kai Müller,
Johannes Gutenberg
University Mainz, Germany

*Correspondence:

Carlos Roncero
roncero@saludcastillayleon.es

Specialty section:

This article was submitted to
Addictive Disorders,
a section of the journal
Frontiers in Psychiatry

Received: 17 September 2018

Accepted: 01 May 2019

Published: 31 May 2019

Citation:

Palma-Álvarez RF,
Rodríguez-Cintas L, Abad AC,
Sorribes M, Ros-Cucurull E,
Robles-Martínez M, Grau-López L,
Aguilar L and Roncero C (2019)
Mood Disorders and Severity of
Addiction In Alcohol-Dependent
Patients Could Be Mediated
by Sex Differences.
Front. Psychiatry 10:343.
doi: 10.3389/fpsy.2019.00343

Background: Alcohol dependence is highly prevalent in the general population; some differences in alcohol use and dependence between women and men have been described, including outcomes and ranging from biological to social variables. This study aims to compare the severity of alcohol dependence with clinical and psychopathological characteristics between sexes.

Methods: A cross-sectional descriptive study was conducted in alcohol-dependent outpatients; the recruitment period was 7 years. The assessment of these patients was carried out by obtaining sociodemographic characteristics and using the Semi-structured Clinical Interview for Axis I and II (SCID-I and SCID-II), European version of the Addiction Severity Index (EuropASI), Beck Depression Inventory (BDI), and State–Trait Anxiety Inventory (STAI) scales. Variables were compared and analyzed.

Results: The sample was composed of 178 patients (74.2% males and 25.8% females) with a mean age of 46.52 ± 9.86 . No sociodemographic differences were found between men and women. Females had a higher rate of suicide attempts and depression symptoms at the treatment onset. When results of EuropASI were compared, females had worse psychological and employment results than males. According to consumption variables, males had an earlier onset of alcohol use, had more regular alcohol use, and develop alcohol dependence earlier than females.

Conclusions: According to results, there are sex-dependent differences (severity and other variables such as mood or suicide) in alcohol dependence. Thus, this may implicate the need of future specific research and treatment programs based on the specific necessities of each sex.

Keywords: alcohol, dependence, depression, suicide attempts, severity, sex differences, gender

INTRODUCTION

Alcohol dependence is a worldwide problem highly prevalent and associated with high morbidity and mortality (1–3). A total of 63.5 million people around the world had alcohol dependence in 2015 (3), and globally, the age-standardized rate for alcohol dependence is 843.2 per 100,000 people (3). For Western Europe, alcohol dependence seems to be higher, the rate being approximately 880.7 per 100,000 people (3). In Spain, 5% of the population aged between 15 and 64 years have a risk consumption of alcohol (4). It is important to highlight that the prevalence of high-risk drinking is higher in men than in women (5), and in Europe, this sex difference is also presented, reporting that 5.4% of men are alcohol-dependent as opposed to 1.5% of women (6). Additionally, alcohol consumption among women is increasing and sex differences are becoming increasingly close, especially in the younger groups (7–10).

Sex could be a modulating factor for several issues in mental and addictive disorders (11–13). Specifically in alcohol dependence, men have early onset of alcohol use, have higher craving levels, and consume more alcohol than women (5, 14, 15), but in contrast, women have a lower tolerance even with an equal alcohol blood level (16). Furthermore, women have more psychiatric comorbidity associated with alcohol consumption (17, 18), more medical and neurological problems related to consumption and dependence (7, 12, 19), and higher mortality rates (2, 19, 20). Although women start consuming the substance later, they become dependent faster than men (7). In the light of the foregoing, this is related to the *telescope effect*, which refers to a faster course of the addictive disorder among women (7, 21–23). It has been postulated that biological differences could support this hypothesis (9, 13, 17, 23). The telescope effect has also been described in alcohol-dependent patients with polydrug abuse (15, 24).

Deepening more on alcohol consumption and mental health issues, it has been described that alcohol-dependent women have more psychiatric comorbidity and tend to present a higher prevalence of anxiety and depressive symptoms and other mood disorders (18, 25–28). Depression may be an important factor during the approaching of alcohol use disorder because it could be a predictor factor related to treatment outcome, as it may be associated with craving and alcohol relapse (29–31). Also, lower baseline level in depression is associated with better treatment compliance (32) and better therapy response (33). Besides, depression is frequently associated with suicidal behavior in patients with substance use disorders (34). A recent meta-analysis on more than 400,000 participants reported a strong association between alcohol use disorder and suicidal behavior (35), and if it is analyzed as sex differences, women with alcohol use disorder have more suicidal attempts than men (36).

Finally, it has been described that there are sex differences in the difficulty of access to the clinical resources specialized in addictions between men and women (27, 37). These differences are due to several factors, such as social stigma, feelings of shame, denial, fear of losing their children, lack of specialized resources, and lower purchasing power (38, 39). These conditions could have overestimated the higher prevalence among men and would mean that the groups of women studied were more serious because of the fact that they seek treatment in a more advanced

stage of the disorder. On the other hand, it is affirmed that women utilize and adhere to specialized resources in alcohol addiction and they achieve better outcomes overall (14, 36, 40). They also react positively to the consumption information (16). Thus, it would be helpful to thoroughly analyze the clinical differences due to the presence of mixed results in previous studies and the progressive changes observed in consumption patterns by sex. Furthermore, studies on this issue have been scarcely developed in Spain populations, especially if it is taking into account that not all studies have been performed with large samples and with validated scales and measures.

This study aims to compare the clinical and psychopathological features and the addiction severity according to sex in Spanish alcohol-dependent patients. It is hypothesized that sex differences in severity and in clinical and sociodemographic features will be found.

METHODS

This descriptive study was developed by the Addiction and Dual Diagnosis Unit of the Department of Psychiatry of Vall d'Hebron University Hospital of Barcelona between March 2007 and July 2014. The study was approved by Ethical Committee of Vall d'Hebron University Hospital according to the Declaration of Helsinki.

Participants

Those subjects who were seeking for a new substance use disorder treatment at the Addiction and Dual Diagnosis Unit were invited to participate. The inclusion criteria were as follows: being over 18 years old, being in outpatient treatment for alcohol dependence, and having signed the informed consent form that was approved by the ethics committee of the hospital. The exclusion criteria were as follows: having a current dependence to other substances (excluding nicotine) and inability of the patient to participate in the evaluation process (because of intoxication, current serious psychiatric or somatic problems, and cognitive impairment or language barrier) at the time of the interviews. Patients did not receive financial compensation for their participation.

Procedures

The patients had one psychiatrist visit and four psychological evaluation visits carried out by trained psychologists. Sociodemographic data, clinical information, and addiction variables were collected during the psychiatrist's visit, while data related to addiction severity, presence of axis I and axis II mental disorders, depressive symptoms, anxiety symptoms, and suicidal behavior were collected during the psychologists' visits.

Evaluation Instruments

- *Sociodemographic and clinical questionnaire*: An *ad hoc* questionnaire that assesses sociodemographic variables, including age, marital status, education, employment, clinical relevant variables.

- *European version of the Addiction Severity Index (EuropASI)*: Semi-structured interview, which measures the severity of addiction in different areas: medical, employment, alcohol consumption, use of other drugs, legal problems, family and social relationships, and psychological state. Scores range from 0 to 1; higher scores indicate higher severity (41).
- *Semi-structured Clinical Interview for Axis I and II (SCID-I and SCID-II)*: These interviews were performed for evolution of Axis I and II disorders from the *Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV)* (42, 43).
- *Beck Depression Inventory (BDI)*: Self-administered questionnaire that measures the severity of current depressive symptoms (44).
- *State-Trait Anxiety Inventory (STAI)*: Self-administered questionnaire that measures the current anxiety symptoms of the patient (45).

Data Analysis

A descriptive analysis was conducted. In order to compare mean values between men and women, Student's *t* test for quantitative variables and chi-square test for categorical variables were used. Adjustment of the results by Bonferroni correction was performed. A logistic regression analysis with forward selection

was conducted using sex as dependent variable. Statistically significant variables obtained after bivariate analysis were chosen as independent variables. The statistical program used was the SPSS version 20.

RESULTS

From an initial sample of 844 patients under alcohol dependence treatment, the subgroup of patients with other substance dependence (except nicotine) was excluded in order to obtain a more homogeneous sample. A total of 325 patients were selected, and from this group, only 178 patients completed the evaluation process (74.2% men vs. 25.8% women; see **Figure 1**). The mean age at the first contact in our unit was 46.52 ± 9.86 . Previously, we ensured that there were no significant differences between sexes regarding the antecedent of previous treatments in other clinical centers. In our sample, women seek treatment at an age equal to or greater than men.

It is observed that women present more depressive symptoms (measured with BDI) at the beginning of the treatment. No differences were found on nicotine use. Regarding the other sociodemographic and clinical variables, no differences were found between men and women (**Table 1**).

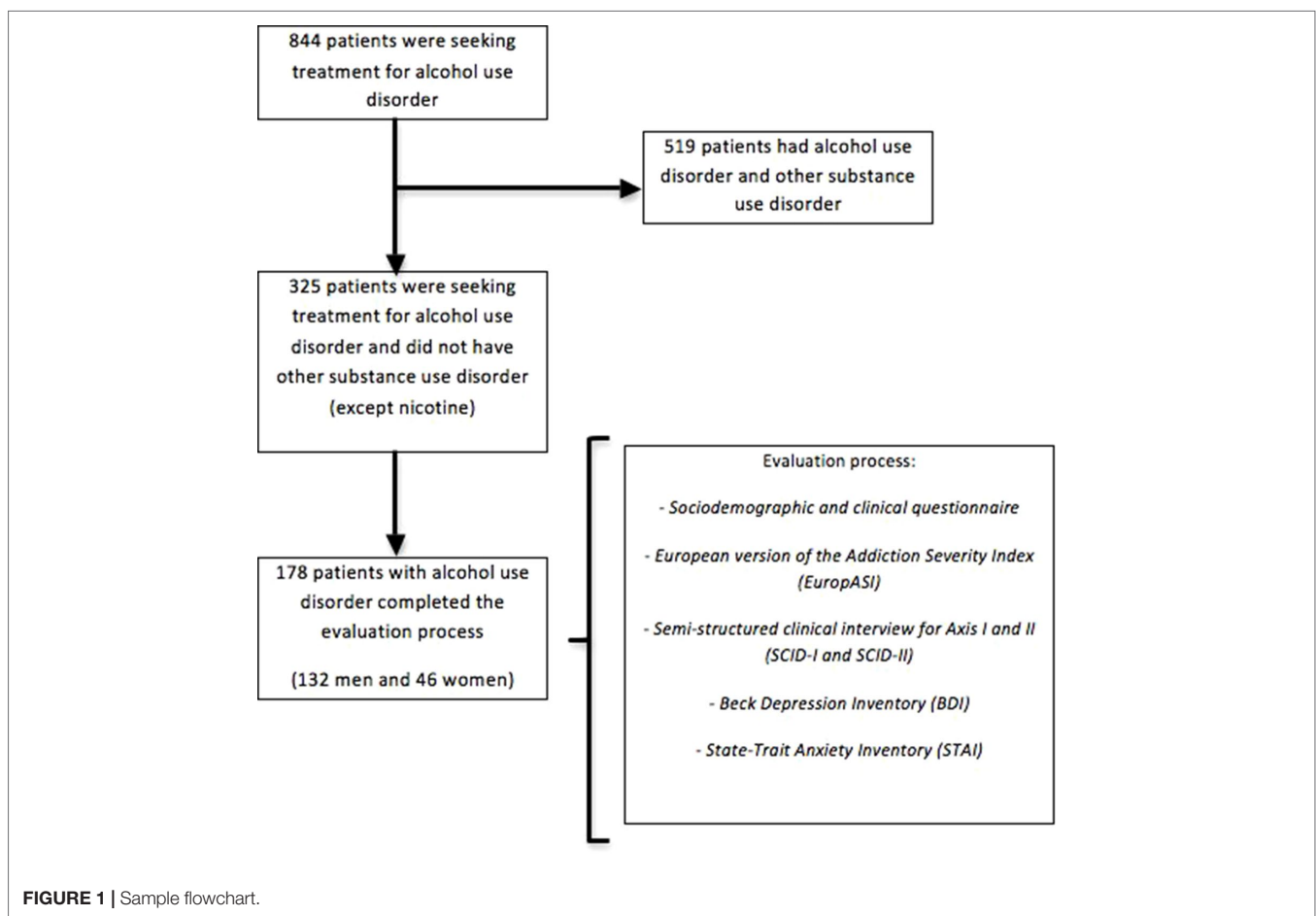


TABLE 1 | Demographic, clinical, and psychiatric variables and diagnoses of the sample.

DEMOGRAPHIC VARIABLES					
	N = 178	Men (n = 132)	Women (n = 46)	t	p
	Mean ± SD	Mean ± SD	Mean ± SD		
AGE	46.52 ± 9.86	45.84 ± 9.73	48.48 ± 10.09	1.57	0.119
CIVIL STATUS	%	%	%	χ^2	<i>p</i>
Single	26.19	29.13	17.07	4.98	0.173
Married/partnered	34.52	33.07	39.02		
Separated/divorced	37.5	37	39.02		
Widow	1.78	0.79	4.88		
LIVING WITH	%	%	%	χ^2	<i>p</i>
Partner and children	14.81	14.52	15.79	12.69	0.123
Partner	14.81	11.29	26.31		
Children	7.41	3.23	21.05		
Parents	14.81	24.2	10.53		
Family	9.88	9.68	10.53		
Friends	1.23	1.61	–		
Alone	22.22	24.19	15.79		
Protected environment	6.17	8.06	–		
Unstable	2.47	3.23	–		
ACADEMIC LEVEL	%	%	%	χ^2	<i>p</i>
Primary (or lower)	43.6	45.9	36.6	1.083	0.364
Secondary (or upper)	56.4	54.1	63.4		
EMPLOYMENT	%	%	%	χ^2	<i>p</i>
Active	27.22	30.71	16.67	3.141	0.076
CLINICAL VARIABLES					
	%	%	%	χ^2	<i>p</i>
Psychiatric history	51.92	52.5	50	0.046	0.830
Nicotine use	76.3	79.2	67.7	1.593	0.222
Psychotic symptoms	18.5	22.7	7.3	4.696	0.034
Suicide attempts	19.1	12.7	34.6	5.721	0.035
	%	%	%	χ^2	<i>p</i>
Medical history	59.4	59.2	60	1.254	0.534
Infectious Dis.	6.3	7	4.4	1.656	0.647
Cardiological Dis.	12.6	15.5	4.4	4.55	0.208
Hepatic Dis.	21.4	20.2	25	2.477	0.479
BDI	16.4	14.65	20.54	2.844	0.006*
STAI-E	58.19	58.11	58.47	0.059	0.953
SCID I (111/39)	%	%	%	χ^2	<i>p</i>
Mood Disorder	30.7	26.4	42.5	3.592	0.072
Anxiety Disorder	17.1	14.3	25	2.386	0.144
SCID II	%	%	%	χ^2	<i>p</i>
Personality Disorder	19.2	20.7	15	0.620	0.492

*Significant with Bonferroni.
All the significant results are in bold.

TABLE 2 | Alcohol consumption chronologic features.

	N = 178		Men (n = 132)		Women (n = 46)		t	p
	Mean	SD	Mean	SD	Mean	SD		
Alcohol consumption in the last 6 months, Standard Drinks (SD)/day	13.14	13.30	14.5	14	8.83	9.84	2.61	0.011*
Alcohol last month, SD/day	8.90	10.53	9.87	11.27	6.18	7.57	2.25	0.027
Age of first contact	16.06	5.42	15.37	4.294	18.12	7.55	2.94	0.004*
Age at onset of regular consumption	24.97	10.36	22.57	8.543	31.95	12.02	4.73	0.000*
Years of regular consumption	19.66	13.8	20.96	13.19	16.25	14.98	1.602	0.112
Years from the first contact to the onset of dependence	8.87	8.6	7.44	7.66	13.05	9.89	3.384	0.000*
	%		%		%		χ^2	<i>p</i>
Abuse of other substance (DSM-IV)	19.5		22.5		11.6		2.345	0.174

*Significant with Bonferroni.
All the significant results are in bold.

TABLE 3 | EuropASI subareas in the evaluation of the severity of addiction.

	N = 178		Men (n = 132)		Women (n = 46)		t	p
	Mean	SD	Mean	SD	Mean	SD		
Medical	0.31	0.35	0.29	0.35	0.39	0.37	1.74	0.084
Employment	0.53	0.33	0.49	0.33	0.63	0.3	2.46	0.015*
Alcohol	0.37	0.31	0.37	0.31	0.36	0.31	0.31	0.761
Drugs	0.09	0.23	0.1	0.25	0.04	0.11	2.3	0.023*
Legal	0.06	0.17	0.07	0.17	0.04	0.15	0.78	0.437
Familiar/Social	0.29	0.28	0.27	0.28	0.34	0.28	1.41	0.159
Psychological	0.33	0.23	0.3	0.23	0.4	0.21	2.47	0.015*

*Significant with Bonferroni.

All the significant results are in bold.

TABLE 4 | Logistic regression analysis.

	Wald	p	OR	IC 95%
Suicide attempts	4.903	0.027	15.500	1.370–17.538
BDI	8.779	0.003	1.055	1.018–1.093
Age at onset of regular consumption	9.568	0.002	1.077	1.027–1.128
Employment	4.823	0.028	3.458	1.143–10.463
Psychological	5.109	0.024	5.941	1.267–27.855

All the significant results are in bold.

By comparing the variables related to the characteristics of consumption, men start drinking earlier, consume alcohol regularly, and develop dependence earlier than women. When the amount is observed, men consume more Standard Drinks per day (1 SD = 10 g of alcohol in Spain) in the past 6 months (Table 2).

It is observed that alcohol-dependent women had more problems in the areas related to employment status and psychological state, which were measured by the EuropASI score (Table 3). However, alcohol-dependent men showed more problems in the area of other drug consumption (throughout life).

Finally, multivariate analysis is depicted in Table 4. There were statistically significant sex-dependent differences associated with suicide attempts, EuropASI (*Psychological* and *Employment* areas), age at onset of regular consumption, and BDI.

DISCUSSION

The obtained results show the existence of sex-related differences in alcohol consumption in the Spanish population. Alcohol-dependent women who sought treatment in our center presented a later drinking onset and consumed less amounts of alcohol than men. However, they tended to seek treatment in our unit later than men and had more depressive symptoms. These results are in line with previous research in other countries. In many recent studies, it has been described that there is an increasing prevalence of alcohol dependence among women (8–10), and they have a more severe alcohol use disorder (2, 11, 12, 19).

Regarding clinical variables, sex differences are observed. It was found that women who sought treatment for alcohol dependence presented more depressive symptoms at the beginning of the treatment, which had been previously described

in other countries (26, 29, 46, 47). It has been described that depressive symptoms in alcohol-dependent women are related to a greater craving (which can lead to a relapse), and this issue has not been observed in the male sex (30, 31, 47, 48). Therefore, depression becomes an important and critical issue during the approaching for alcohol use disorder, not only for its prevalence but also because depression levels are associated with some treatment outcomes (32, 33). Furthermore, depression and suicidal behavior are closely related; in the current sample, suicide behavior was significant at multivariate analysis. This is in line with some authors that have described that women with alcohol dependence are at higher risk for unplanned or planned attempts (49). Therefore, alcohol dependence is an important risk factor for suicidal behavior, and this concern should always be evaluated for an adequate and integral management (35, 36). Differences in relation to the presence of psychotic symptoms between men and women are suggested, which would be consistent with previous studies that evaluate both the presence of alcohol-induced psychotic symptoms and delirium tremens (50, 51), but these results are nonsignificant when Bonferroni correction was performed.

Although men consumed, in general, larger amounts of alcohol and began consumption earlier than women, taking into account the results of the EuropASI scale, it could be suggested that alcohol dependence was more serious in women because they had higher severity in two of the seven areas measured by the EuropASI scale (*Employment* and *Psychological* areas) and less severity in one of the seven areas (*Drugs* area), showing no differences in the other areas. It is also observed that the employment area in EuropASI was more affected in women. The improvement of economic and work conditions in women could be associated with an increased consumption of alcohol in women. Recent studies have found that changes in economic and work conditions could be contributing to the convergence in sex differences (8). Scores in the *Psychological* area were worse in women; this could be related to the depressive symptoms in this group. This finding is similar to other research that described that the *Psychological* area in EuropASI is worse in women in several settings, such as outpatient centers and therapeutic communities (22, 52). Thus, analyzing all the results, in the current sample, there seems to exist a certain degree of

telescope effect, in line with other research in similar samples in other countries (7, 21, 23).

This study should be analyzed regarding its limitations. Thus, the transversal nature and the incomplete representation of all the alcohol-dependent patients become an important issue (participants who do not seek treatment or patients with mixed dependences). Furthermore, we did not analyze differences regarding nicotine use, as this substance could be related to psychopathology and sex differences. It is also possible that the men who seek treatment tend to minimize or deny their depressive symptoms. Finally, the recruitment period (2007–2014) could generate outdated information; however, these data could contribute to understand this issue in Spanish populations with alcohol use disorder and allow to compare future research on this issue. On the other hand, the study was conducted in a large homogeneous sample of patients who are only alcohol-dependent in an outpatient treatment center. Consequently, the results are representative of the clinical activity in a real clinical setting.

The current results provide new information that has been scarcely explored in large samples in Spanish populations with alcohol use disorder. The increased presence of depressive symptoms and the greater severity of addiction make women a particularly vulnerable group. Thus, as other authors recommended, it could be suggested that it is necessary to consider the special clinical characteristics of women when planning the treatments (7, 53, 54). Furthermore, regarding the results of this study, it seems to be advisable that the implementations of programs to detect depressive symptoms and to prevent suicide, especially in alcohol-dependent women, are needed.

REFERENCES

- Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. *JAMA* (2018) 320:815–24. doi: 10.1001/jama.2018.11406
- Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Alcohol use disorder and mortality across the lifespan: a longitudinal cohort and co-relative analysis. *JAMA Psychiatry* (2016) 73:575–81. doi: 10.1001/jamapsychiatry.2016.0360
- Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction* (2018) 113(10):1905–26. [In Press] doi: 10.1111/add.14234
- Observatorio Español de la Droga y Toxicomanías (2017). Encuesta sobre Alcohol y Drogas en Población General en España (EDADES 2015). Madrid: Delegación del Gobierno para el Plan Nacional sobre Drogas. Available on: http://www.pnsd.msssi.gob.es/profesionales/sistemasInformacion/informesEstadisticas/pdf/INFORME_2015.pdf (accessed September 1, 2018).
- Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: contemporary knowledge and future research considerations. *Drug Alcohol Depend* (2015) 156:1–13. doi: 10.1016/j.drugalcdep.2015.08.023
- Rehm J, Shield KD, Gmel G, Rehm MX, Frick U. Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol* (2013) 23:89–97. doi: 10.1016/j.euroneuro.2012.08.001
- Ait-Daoud N, Blevins D, Khanna S, Sharma S, Holstege CP. Women and addiction. *Psychiatr Clin North Am* (2017) 40:285–97. doi: 10.1016/j.psc.2017.01.005
- Keyes KM, Li G, Hasin DS. Birth cohort effects and gender differences in alcohol epidemiology: a review and synthesis. *Alcohol Clin Exp Res* (2011) 35:2101–12. doi: 10.1111/j.1530-0277.2011.01562.x

ETHICS STATEMENT

The research was approved by Ethical Committee of Vall d'Hebron University Hospital according to Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

CR and LG-L designed the study. RP-A, LR-C, AA, MR-M, and ER-C collected the sample. LR-C, MS, and MR-M performed psychological evaluation. RP-A, LR-C, LG-L, and LA conducted the analyses and prepared the data. AA, MS, MR-M, ER-C, and LA performed the literature review. RP-A, AA, ER-C, and LA wrote the initial version of this manuscript. All authors edited, read, and approved the last version of this manuscript.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

We are grateful to our research team for their support, particularly Dr. Ángel Egido, Dr. Nieves Martínez-Luna, Dr. Joan Alvarós, and Dr. Claudia Gutiérrez (psychiatrists); Dr. Constanza Daigre and Dr. Marta Perea (psychologists); Miguel Ángel Cantillo (nurse); and Carmen Simón (social worker). We are also grateful to Ms. Rosa Milne (mental health nurse from the UK) who reviewed the grammar.

- Alati R, Betts KS, Williams GM, Najman JM, Hall WD. Generational increase in young women's drinking: a prospective analysis of mother-daughter dyads. *JAMA Psychiatry* (2014) 71:952–7. doi: 10.1001/jamapsychiatry.2014.513
- Keyes KM, Grant BF, Hasin DS. Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug Alcohol Depend* (2008) 93:21–9. doi: 10.1016/j.drugalcdep.2007.08.017
- Roncero C, Rodríguez-Cintas L, Egido A, Barral C, Pérez-Pazos J, Collazos F, et al. The influence of medical student gender and drug use on the detection of addiction in patients. *J Addict Dis* (2014) 33:277–88. doi: 10.1080/10550887.2014.969600
- Vatsalya V, Liaquat HB, Ghosh K, Mokshagundam SP, McClain CJ. A review on the sex differences in organ and system pathology with alcohol drinking. *Curr Drug Abuse Rev* (2016) 9:87–92. doi: 10.2174/1874473710666170125151410
- Zagni E, Simoni L, Colombo D. Sex and gender differences in central nervous system-related disorders. *Neurosci J* (2016) 2016:2827090. doi: 10.1155/2016/2827090
- Bravo F, Gual A, Lligoña A, Colom J. Gender differences in the long-term outcome of alcohol dependence treatments: an analysis of twenty-year prospective follow up. *Drug Alcohol Rev* (2013) 32:381–8. doi: 10.1111/dar.12023
- Buu A, Dabrowska A, Mygrants M, Puttler LI, Jester JM, Zucker RA. Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes. *J Stud Alcohol Drugs* (2014) 75:850–8. doi: 10.15288/jsad.2014.75.850
- Calafat A, Fernández-Hermida JR, Becoña E, Juan M, Duch M, Fernández del Río E, et al. Blood alcohol level tests in nightlife recreational settings as a preventive tool. *Actas Esp Psiquiatr* (2013) 41:10–6.
- Greenfield SF. Women and alcohol use disorders. *Harv Rev Psychiatry* (2002) 10:76–85. doi: 10.1080/10673220216212

18. García-Carretero MA, Novalbos-Ruiz JP, Robles-Martínez M, Jordán-Quintero MA, O'Ferrall-González C. Psychopathological profile and prevalence of dual pathology on patients with alcoholic dependence undergoing outpatient treatment. *Actas Esp Psiquiatr* (2017) 45:1–11.
19. Milic J, Glisic M, Voortman T, Borba LP, Asllanaj E, Rojas LZ, et al. Menopause, ageing, and alcohol use disorders in women. *Maturitas* (2018) 111:100–9. doi: 10.1016/j.maturitas.2018.03.006
20. Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction* (2013) 108:1562–78. doi: 10.1111/add.12231
21. Zilberman M, Tavares H, el-Guebaly N. Gender similarities and differences: the prevalence and course of alcohol- and other substance-related disorders. *J Addict Dis* (2003) 22:61–74. doi: 10.1300/J069v22n04_06
22. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol Depend* (2004) 74:265–72. doi: 10.1016/j.drugalcdep.2004.02.001
23. Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, Mattson ME. Telescoping of landmark events associated with drinking: a gender comparison. *J Stud Alcohol* (1999) 60:252–60. doi: 10.15288/jsa.1999.60.252
24. Lewis B, Hoffman LA, Nixon SJ. Sex differences in drug use among polysubstance users. *Drug Alcohol Depend* (2014) 145:127–33. doi: 10.1016/j.drugalcdep.2014.10.003
25. Miquel L, Roncero C, García-García G, Barral C, Daigre C, Grau-López L, et al. Gender differences in dually diagnosed outpatients. *Subst Abuse* (2013) 34:78–80. doi: 10.1080/08897077.2012.709223
26. Cornelius JR, Jarrett PJ, Thase ME, Fabrega H Jr, Haas GL, Jones-Barlock A, et al. Gender effects on the clinical presentation of alcoholics at a psychiatric hospital. *Compr Psychiatry* (1995) 36:435–40. doi: 10.1016/S0010-440X(95)90251-1
27. Limosin F. Clinical and biological specificities of female alcoholism. *Encephale* (2002) 28:503–9.
28. Conner KR, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol use disorders. *J Subst Abuse Treat* (2009) 37:127–37. doi: 10.1016/j.jsat.2008.11.007
29. Abulseoud OA, Karpyak VM, Schneekloth T, Hall-Flavin DK, Loukianova LL, Geske JR, et al. A retrospective study of gender differences in depressive symptoms and risk of relapse in patients with alcohol dependence. *Am J Addict* (2013) 22:437–42. doi: 10.1111/j.1521-0391.2013.12021.x
30. Luminet O, Cordovil de Sousa Uva M, Fantini C, de Timary P. The association between depression and craving in alcohol dependency is moderated by gender and by alexithymia factors. *Psychiatry Res* (2016) 239:28–38. doi: 10.1016/j.psychres.2016.02.062
31. Zilberman ML, Tavares H, Hodgins DC, el-Guebaly N. The impact of gender, depression, and personality on craving. *J Addict Dis* (2007) 26:79–84. doi: 10.1300/J069v26n01_10
32. Gjestad R, Franck J, Hagtvet KA, Haver B. Level and change in alcohol consumption, depression and dysfunctional attitudes among females treated for alcohol addiction. *Alcohol Alcohol* (2011) 46:292–300. doi: 10.1093/alcal/agr018
33. Merrill JE, Reid AE, Carey MP, Carey KB. Gender and depression moderate response to brief motivational intervention for alcohol misuse among college students. *J Consult Clin Psychol* (2014) 82:984–92. doi: 10.1037/a0037039
34. Rodríguez-Cintas L, Daigre C, Braquehais MD, Palma-Álvarez RF, Grau-López L, Ros-Cucurull E, et al. Factors associated with lifetime suicidal ideation and suicide attempts in outpatients with substance use disorders. *Psychiatry Res* (2018) 262:440–5. doi: 10.1016/j.psychres.2017.09.021
35. Darvishi N, Farhadi M, Haghtalab T, Poorolajal J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. *PLoS One* (2015) 10:e0126870. doi: 10.1371/journal.pone.0126870
36. Arnau MM. Differential features of female alcoholism. *Adicciones* (2010) 22:339–52. doi: 10.20882/adicciones.176
37. Schmidt L, Weisner C. The emergence of problem-drinking women as a special population in need of treatment. *Recent Dev Alcohol* (1995) 12:309–34. doi: 10.1007/0-306-47138-8_20
38. Small J, Curran GM, Booth B. Barriers and facilitators for alcohol treatment for women: are there more or less for rural women? *J Subst Abuse Treat* (2010) 39:1–13. doi: 10.1016/j.jsat.2010.03.002
39. Jackson A, Shannon L. Barriers to receiving substance abuse treatment among rural pregnant women in Kentucky. *Matern Child Health J* (2012) 16:1762–70. doi: 10.1007/s10995-011-0923-5
40. DeVito EE, Babuscio TA, Nich C, Ball SA, Carroll KM. Gender differences in clinical outcomes for cocaine dependence: randomized clinical trials of behavioral therapy and disulfiram. *Drug Alcohol Depend* (2014) 145:156–67. doi: 10.1016/j.drugalcdep.2014.10.007
41. Kokkevi A, Hartgers C. European adaptation of a multidimensional assessment instrument for drug and alcohol dependents. *Eur Addict Res* (1995) 1:208–10. doi: 10.1159/000259089
42. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured clinical interview for DSM-IV axis I disorders, clinician version (SCID-CV)*. Washington: American Psychiatric Press, Inc. (1997).
43. First MB, Gibbon M, Spitzer RL, Williams JB, Benjamin LS. *Structured clinical interview for DSM-IV axis II personality disorders (SCID-II)*. Washington: American Psychiatric Press, Inc. (1997).
44. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* (1961) 4:561–71. doi: 10.1001/archpsyc.1961.01710120031004
45. Gaudry E, Vagg P, Spielberger CD. Validation of the state–trait distinction in anxiety research. *Multivariate Behav Res* (1975) 10:331–41. doi: 10.1207/s15327906mbr1003_6
46. Dişsiz M, Beji N, Oskay Ü. The effects of alcohol dependence on the quality of life and sex life of women. *Subst Use Misuse* (2015) 50:1373–82. doi: 10.3109/10826084.2015.1013129
47. Petit G, Luminet O, Cordovil de Sousa Uva M, Monhonnal P, Leclercq S, Spilliaert Q, et al. Gender differences in affects and craving in alcohol-dependence: a study during alcohol detoxification. *Alcohol Clin Exp Res* (2017) 41:421–31. doi: 10.1111/acer.13292
48. Robles-Martínez M, García-Carretero MÁ, Gibert J, Palma-Álvarez RF, Abad AC, Sorribes M, et al. Differences between craving and health-related quality of life in patients with alcohol dependence with or without dual pathology in outpatient treatment: a descriptive study. *Med Clin (Barc)* (2018) 150:49–55. doi: 10.1016/j.medcli.2017.06.005
49. Conner KR, Hesselbrock VM, Meldrum SC, Schuckit MA, Buchholz KK, Gamble SA, et al. Transitions to, and correlates of, suicidal ideation, plans, and unplanned and planned suicide attempts among 3,729 men and women with alcohol dependence. *J Stud Alcohol Drugs* (2007) 68:654–62. doi: 10.15288/jsad.2007.68.654
50. Jordaán GP, Emsley R. Alcohol-induced psychotic disorder: a review. *Metab Brain Dis* (2014) 29:231–43. doi: 10.1007/s11011-013-9457-4
51. Soyka M, Raith L, Steinberg R. Mean age, sex ratio and psychopathology in alcohol psychoses. *Psychopathology* (1988) 21:19–25. doi: 10.1159/000284535
52. De Wilde J, Broekaert E, Rosseel Y, Delespaul P, Soye V. The role of gender differences and other client characteristics in the prevalence of DSM-IV affective disorders among a European therapeutic community population. *Psychiatr Q* (2007) 78:39–51. doi: 10.1007/s11126-006-9025-8
53. Gual A, Sabadini MB. Implementing alcohol disorders treatment throughout the community. *Curr Opin Psychiatry* (2011) 24:203–7. doi: 10.1097/YCO.0b013e3283459256
54. Rolland B, Paille F, Gillet C, Rigaud A, Moirand R, Dano C, et al. Pharmacotherapy for alcohol dependence: the 2015 recommendations of the French Alcohol Society, issued in partnership with the European Federation of Addiction Societies. *CNS Neurosci Ther* (2016) 22:25–37. doi: 10.1111/cns.12489

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Palma-Álvarez, Rodríguez-Cintas, Abad, Sorribes, Ros-Cucurull, Robles-Martínez, Grau-López, Aguilar and Roncero. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.