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Characteristics of drug poisonings treated in eleven Spanish emergency departments: Differentiated analysis by sex

Características de las intoxicaciones por drogas atendidas en once servicios de urgencias españoles: Análisis diferenciado por sexo

MIGUEL GALICIA^{*}; DIMA IBRAHIM-ACHI^{**}; ÒSCAR MIRÓ^{*}; AUGUST SUPERVIA^{***}; JORDI PUIGURIGUER^{****}; MARÍA ÁNGELES LECIÑENA^{*****}; M^a JOSÉ VENEGAS DE L'HOTELLERIE^{*****}; BEATRIZ MARTÍN-PÉREZ^{*****}; ANA FERRER^{*****}; GUILLERMO BURILLO-PUTZE^{*****}; EN REPRESENTACIÓN DE LA RED DE ESTUDIO DE DROGAS EN URGENCIAS HOSPITALARIAS EN ESPAÑA (REDURHE).

^{*} Área de Urgencias, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, España.

^{**} Servicio de Urgencias, Hospital Universitario de Canarias, Tenerife, España.

^{***} Servicio de Urgencias y Unidad Funcional de Toxicología, Hospital del Mar, Barcelona, España.

^{****} Servicio de Urgencias y Unidad de Toxicología Clínica, Hospital Son Espases, Palma de Mallorca, España.

^{*****} Servicio de Urgencias, Hospital Can Misses, Ibiza, España.

^{*****} Servicio de Urgencias, Hospital Rey Juan Carlos, Móstoles, España.

^{*****} Servicio de Urgencias, Hospital Río Hortega, Valladolid, España.

^{*****} Unidad de Toxicología Clínica, Hospital Clínico Universitario Lozano Blesa, Zaragoza, España.

^{*****} Departamento de Medicina Física y Farmacología, Universidad de La Laguna, Tenerife, España.

Abstract

In order to identify the sociodemographic, clinical, emergency management and severity differences of drug poisoning treated in Emergency Departments (ED) from a gender perspective, data on patients from 11 Spanish EDs were recorded over 24 months (August 2017-July 2019). The severity of intoxication was compared by sex and was based on the combined adverse event (orotracheal intubation, cardiorespiratory arrest, intensive care hospitalization, and death). We included 4,526 patients (men 75.5%), with a mean age of 33 years. The most frequent drugs were: cocaine (47.8%), cannabis (44.4%) and amphetamines (25.5%). Men consumed more GHB (5.6% vs. 1.9%, $p < .001$) and less benzodiazepines (8.0% vs. 11.1%, $p = .002$) and alcohol (57.2% vs. 61.2%, $p = .028$) than women, with no differences in other types of drugs. Men presented significantly more severe bradycardia (OR = 4.39, 95%CI = 1.03-18.7), chest pain (OR = 1.72, 95%CI = 1.27-2.35) and symptomatic hypertension (OR = 1.56, 95%CI = 1.06-2.30) and less anxiety (OR = 0.74, 95%CI = 0.61-0.89) and vomiting (OR = 0.64, CI95% = 0.51-0.80). Men had more combined adverse events (3.1% vs. 2.0%, $p = .047$) and a greater intubations (1.9% vs. 1.0%, $p = .044$), with no significant differences in the adjusted model (OR = 1.349, 95%CI = 0.827-2.202 and OR = 1.371, 95%CI = 0.700-2.685, respectively). Twelve patients died (0.3%), with no differences according to sex. Drug intoxications attended in the ED differ according to sex. GHB, benzodiazepines and alcohol are more frequently involved in men than women. Cardiovascular symptomatology is more prevalent in men, while anxiety and vomiting are more frequent in women, which cannot be explained by differences in sociodemographic characteristics or the drugs used. There were no differences in the severity of the intoxication episodes.

Keywords: intoxication, drugs, sex, severity, emergency department

Resumen

Con el objetivo de identificar, con perspectiva de género, las diferencias sociodemográficas, clínicas, manejo en urgencias y gravedad de las intoxicaciones por drogas atendidas en Servicios de Urgencias Hospitalarias (SUH), se registraron todos los pacientes atendidos en 11 SUH españoles durante 24 meses (agosto 2017-julio 2019). La gravedad de la intoxicación se basó en el evento adverso combinado (intubación orotraqueal, parada cardiorrespiratoria, hospitalización en intensivos, y muerte), comparándose según el sexo. Cuando se encontraron diferencias significativas en sintomatología o gravedad, los resultados se ajustaron por características sociodemográficas y drogas consumidas. Se incluyeron 4.526 pacientes (hombres 75,5%), con edad media de 33 años. Las drogas más frecuentes fueron cocaína (47,8%), cannabis (44,4%) y anfetaminas (25,5%). Hubo más GHB en hombres (5,6% vs 1,9%, $p < ,001$) y más benzodiazepinas (8,0% vs 11,1%, $p = ,002$) y alcohol (57,2% vs 61,2%, $p = ,028$) en mujeres, sin diferencias en otras de drogas. Los hombres tuvieron significativamente más bradicardia grave (OR = 4,39, IC95% = 1,03-18,7), dolor torácico (OR = 1,72, IC95% = 1,27-2,35) e hipertensión sintomática (OR = 1,56, IC95% = 1,06-2,30) y menos ansiedad (OR = 0,74, IC95% = 0,61-0,89) y vómitos (OR = 0,64, IC95% = 0,51-0,80). Tuvieron también más eventos adversos combinados (3,1% vs 2,0%, $p = ,047$) y más intubaciones (1,9% vs 1,0%, $p = ,044$), pero sin diferencias significativas en el modelo ajustado (OR = 1,349, IC95% = 0,827-2,202 y OR = 1,371, IC95% = 0,700-2,685, respectivamente). Fallecieron 12 pacientes (0,3%), sin diferencias según sexo. Concluimos que existen diferencias según el sexo en las drogas que originan intoxicaciones atendidas en los SUH. Las diferencias en sintomatología cardiovascular (más en hombres) y ansiosa o digestiva (más en mujeres) no se explican por diferencias sociodemográficas o de drogas utilizadas. La gravedad de la intoxicación no se ve influida por el sexo.

Palabras clave: intoxicación, drogas, sexo, gravedad, urgencias hospitalarias

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■ Send correspondence to:

Dr. Guillermo Burillo-Putze. Departamento de Medicina Física y Farmacología. Facultad de Ciencias de la Salud. Carretera La Cuesta-Taco, s/n, La Laguna, 38320 Tenerife, España. Email: gburillo@telefonica.net

According to the national surveys carried out in Spain (Delegación del Gobierno para Plan Nacional sobre Drogas) in both the general population (EDADES survey, 2021) and specific groups (ESTUDES survey on drug use in secondary education, 2020), the prevalence of drug use is stable or rising. Between the ages of 15 and 64, 37.5% of the population has tried cannabis, 10.9% cocaine and 3.1% sedative-hypnotics at some time (in 2017 these percentages were 35.2%, 10% and 3%, respectively). Furthermore, 10.5% had used cannabis and 2.5% cocaine in the last 12 months, with men more often being users of cannabis and cocaine, and women more frequently taking sedative-hypnotics (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2021).

The situation in the rest of Europe is similar. Of the 96 million European citizens aged between 15 and 64 years, 29% have used an illegal drug in their lifetime (cannabis 27%, amphetamines 8%, cocaine 5%) or in the last year (cannabis 7.6%, amphetamines 1.4%, cocaine 1.3%) (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2020), and among students aged 15-18 years, 18% have used cannabis at some point and 5% some other type of illegal drug (ESPAD Group, 2020). As is the case among the Spanish population, drug use among the general population is predominantly male (EMCDDA, 2020; ESPAD Group, 2020).

Adverse reactions after drug use are a frequent cause of admission to hospital emergency departments (EDs), in some cases comprising up to 1% of all visits (Fernández Egido, García Herrero, Romero García & Marquina Santos, 2008; Puiguiriguer et al., 2013). The ED is often the only contact drug users have with the health system. For this reason, EDs provide an excellent opportunity to observe the drugs being used, new patterns of use, new clinical pictures derived from them, or the illicit use of some of these substances (Burillo-Putze, López-Hernández, Expósito-Rodríguez & Dueñas-Laita, 2013; Burillo-Putze & Matos Castro, 2018; Fernández Alonso, Óscar Quintela, Ayuso Tejedor, Santiago-Sáez & González Armengol, 2019; Hegazi et al., 2017; Perelló et al., 2018).

The creation of a network of EDs where incidences secondary to drug use can be collected makes it possible to increase knowledge regarding the clinical characteristics of these intoxications treated in Spanish EDs. The present study investigated sex differences in the characteristics of drug poisoning, based on a sample from 11 Spanish EDs, both in sociodemographic terms and with regard to the type of drug involved, symptoms presented by the patient, clinical management in the emergency department, and episode severity.

Method

This is a prospective, descriptive, observational study of patients treated for symptoms resulting from the consumption of drugs of abuse in the EDs of eleven Spanish hospitals spread across six autonomous communities, members of the REDUrHE group (research network on drugs in Spanish hospital emergency departments), over a 24-month period (August 2017-July 2019). Hospitals were chosen on a convenience basis to participate in the network, based on their previous history and interest in studying intoxicated patients during emergency care. The inclusion criteria for patients were being treated in ED for symptoms derived from the use of substances of abuse, and that this use was not for the purpose of suicide.

Sociodemographic variables collected were as follows: age, sex, mode of transport to the ED (ambulance or own means), location of the ED (area with a high incidence of recreational tourism -Palma de Mallorca, Tenerife, Ibiza-, large city -Barcelona and Móstoles-, or not mainly tourist city -Zaragoza, Valladolid, Burgos and Salamanca-), and day (work or holiday) and time (morning-early afternoon: 8:00-16:00; afternoon-evening: 16:00-24:00; night: 0:00-8:00) when the patient appeared in the ED. As clinical variables, the following were collected: vital signs (heart rate, blood pressure, respiratory rate and temperature) and symptoms (anxiety, vomiting, headache, hallucinations, agitation/aggressiveness, psychosis, seizures, cerebellar symptoms, palpitations, chest pain, arrhythmias). Decreased consciousness was defined as a score between 9 and 14 points on the Glasgow Coma Scale, with coma defined as ≤ 8 . Finally, patient management details were noted (treatment received and destination at discharge from the ED).

Drug use was determined by clinical history or toxicological analysis by means of urine drug testing using enzyme immunoassay. This is the technique usually available in EDs and allows fast screening for various drugs (usually cannabis, cocaine, heroin, methadone, morphine, MDMA amphetamines and benzodiazepines), achieving an accurate diagnosis for these drugs. However, it should be borne in mind that certain groups of drugs, including gamma-hydroxybutyrate (GHB) and new psychoactive drugs, require more sophisticated techniques and that many EDs base the diagnosis of intoxication by them on the patient's clinical history and symptomatology. The drugs were grouped following a mixed criterion (chemical structure, pharmacodynamics and potential use in medicine). Patients who came to the ED purely with alcohol intoxication, having consumed no other drugs, were excluded.

Any combination of the following adverse events (AE) was considered the primary indicator of severity: need for orotracheal intubation, cardiorespiratory arrest, admission

to intensive care and death. Considered individually, each of these events was a secondary indicator of severity.

The following sociodemographic aspects were compared by sex: drug typology, symptoms, ED management and severity. In addition, regarding the type of drug involved, prevalence according to patient sex is also presented in detail by age group (< 20 years, 20-39 years, 40-59 years, ≥ 60 years). Quantitative variables were expressed as means (standard deviation (SD)) and groups were compared using Student's t or Mann-Whitney U tests, and qualitative variables as absolute numbers and percentages. Comparison between groups was by chi-square or Fisher's exact tests. The magnitude of association was calculated using logistic regression and expressed as an odds ratio (OR) with its 95% confidence interval (95% CI), first in crude form and, when statistical significance was present, adjusted for age, co-ingestion of ethanol and the drugs consumed. Statistical significance was considered when $p < .05$ or if the 95% CI estimations of OR excluded the value 1. The SPSS package version 25.0 for Windows was used for the statistical analysis. The study was approved by the Research Ethics Committee of the Hospital Universitario de Canarias (Tenerife), reference 2016_71.

Results

The study included 4,526 patients (men: 3,418, 75.5%; women: 1,108, 24.5%) with a mean age of 33 (11) years, the men being older (33 vs 31 years, $p < .001$). Cases by centre are detailed in Figure 1. Patients most frequently sought treatment during night hours (35.3%), although men attended the ED more in the morning-early afternoon hours (30.7% vs 27.2%) and women came more frequently at night (34.4% vs 38.2%; $p = .032$). Men were overrepresented in large cities (27.9%), while women predominated in the EDs in areas of greater leisure tourism (55.1%, $p < .001$), such as the Balearic and Canary Islands.

Patients consuming two or more drugs (mean 1.52 substances) comprised 39.4% (1,785), and 58.2% (2,282 cases) had also drunk alcohol, a fact that was more frequent in women (61.2% vs 57.2%, $p = .028$). The most commonly used drugs were cocaine (47.8%), cannabis (44.4%), amphetamines (25.5%), benzodiazepines (8.8%), opiates (7.3%), GHB (4.7%) and ketamine (3.8%). In 254 cases (5.6%) the substance involved could not be identified. Men consumed more GHB (5.6% vs 1.9%, $p < .001$) and women more benzodiazepines (8.0% vs 11.1%, $p = .002$), with no differences in other drugs. Other sociodemographic

Figure 1
Flowchart of patient inclusion

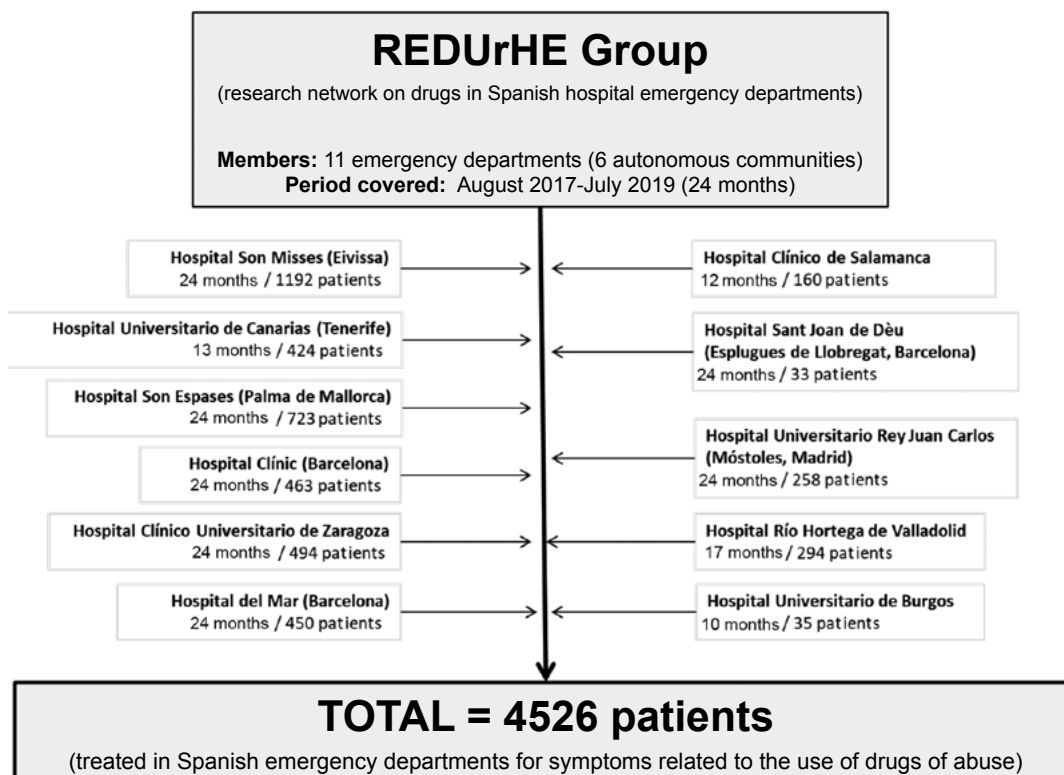
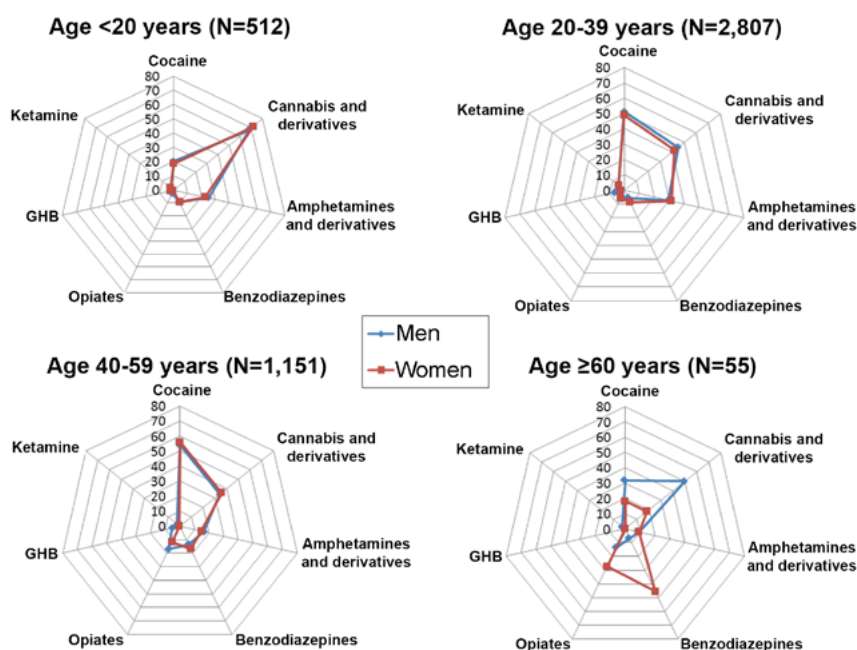


Table 1
Sociodemographic characteristics and drugs detected in the patients included in the present study and comparison by patient sex

	Total N=4526 n (%)	Missing data n (%)	Men N=3418 n (%)	Women N=1108 n (%)	P
Sociodemographic characteristics					
Age (years) (mean (SD))	32.6 (11.1)	5 (0.1)	33.1 (11.3)	31.1 (11.3)	< .001
Brought to ED by ambulance	2566 (58.9)	167 (3.7)	1952 (57.1)	614 (55.4)	.075
Location of ED		0			< .001
Area of leisure tourism	2339 (51.7)		1728 (50.6)	611 (55.1)	
Large city	1204 (26.6)		954 (27.9)	250 (22.6)	
Non-tourist city	983 (21.7)		736 (21.5)	247 (22.3)	
Attended ED on a holiday	2218 (49.0)	0	1675 (49.0)	543 (49.0)	.999
Time of attending ED		0			.032
Night (0:00-8:00)	1598 (35.3)		1175 (34.4)	423 (38.2)	
Morning - early afternoon (8:00-16:00)	1349 (29.8)		1048 (30.7)	301 (27.2)	
Late afternoon - evening(16:00-24:00)	1579 (34.9)		1195 (35.0)	384 (34.7)	
Substances identified					
Co-ingestion of alcohol	2282 (58.2)	606 (13.4)	1681 (57.2)	601 (61.2)	.028
Co-ingestion of multiple drugs	1785 (39.4)	0	1369 (40.1)	416 (37.5)	.138
Number of drugs consumed (mean (SD))	1.52 (0.73)	0	1.53 (0.73)	1.48 (0.71)	.06
Drugs involved					
Cocaine and derivatives	2164 (47.8)	0	1660 (48.6)	504 (45.5)	.075
Cannabis and derivatives	2011 (44.4)	0	1514 (44.3)	497 (44.9)	.744
Amphetamines and derivatives	1156 (25.5)	0	868 (25.4)	288 (26.0)	.692
Benzodiazepines	397 (8.8)	0	274 (8.0)	123 (11.1)	.002
Opiates	331 (7.3)	0	200 (7.6)	71 (6.4)	.183
Gamma-hydroxybutyrate and derivatives	212 (4.7)	0	191 (5.6)	21 (1.9)	< .001
Ketamine	174 (3.8)	0	135 (3.9)	39 (3.5)	.518
Psychotropic drugs (not included in other groups)	64 (1.4)	0	46 (1.3)	18 (1.6)	.495
LSD and other hallucinogenic substances	31 (0.7)	0	25 (0.7)	6 (0.5)	.505
New psychoactive drugs (not included in other groups)	14 (0.3)	0	11 (0.3)	3 (0.3)	.790
Other substances (not included in other groups)	57 (1.3)	0	48 (1.4)	9 (0.8)	.125
Unknown substance	254 (5.6)	0	192 (5.6)	62 (5.6)	.978

Note. SD: standard deviation. LSD: lysergic acid diethylamide.

Figure 2
Prevalence in men and women of the main drugs identified as a cause of intoxication, by age group (axes values indicate the percentage to which each drug was present)



characteristics and drugs present are detailed in Table 1. In addition, it was observed that while in the age groups below 60 years the prevalence of the main types of drugs is very similar in men and women, this diverges in patients aged 60 and over: here, cocaine and cannabis are more commonly used by men, while benzodiazepines and opiates are more frequent in women (Figure 2).

Among symptoms, psychomotor agitation (1,338 patients, 29.8%) and anxiety (1,152 patients, 25.6%) predominated, although as shown in Table 2, there was also a high percentage of patients with decreased consciousness or coma (816 cases -18.8%-, and 278 cases -6.4%-, respectively). When comparing the symptoms between sexes, a significant increase in chest pain, symptomatic hypertension, coma and

severe bradycardia (< 50 bpm) was observed in men, and a greater presence of anxiety and vomiting in women. Systolic blood pressure and temperature on arrival were higher in men (Table 2). In the adjusted analysis, men were observed to have significantly more chest pain (OR = 1.72, 95% CI = 1.27-2.35), more symptomatic hypertension (OR = 1.56, 95% CI = 1.06 - 2.30) and more severe bradycardia (OR = 4.39, 95% CI = 1.03-18.7), and presented less anxiety (OR = 0.74, 95% CI = 0.61-0.89) and vomiting (OR = 0.64, 95% CI = 0.51-0.80), with no differences in the remaining variables analyzed (Figure 3).

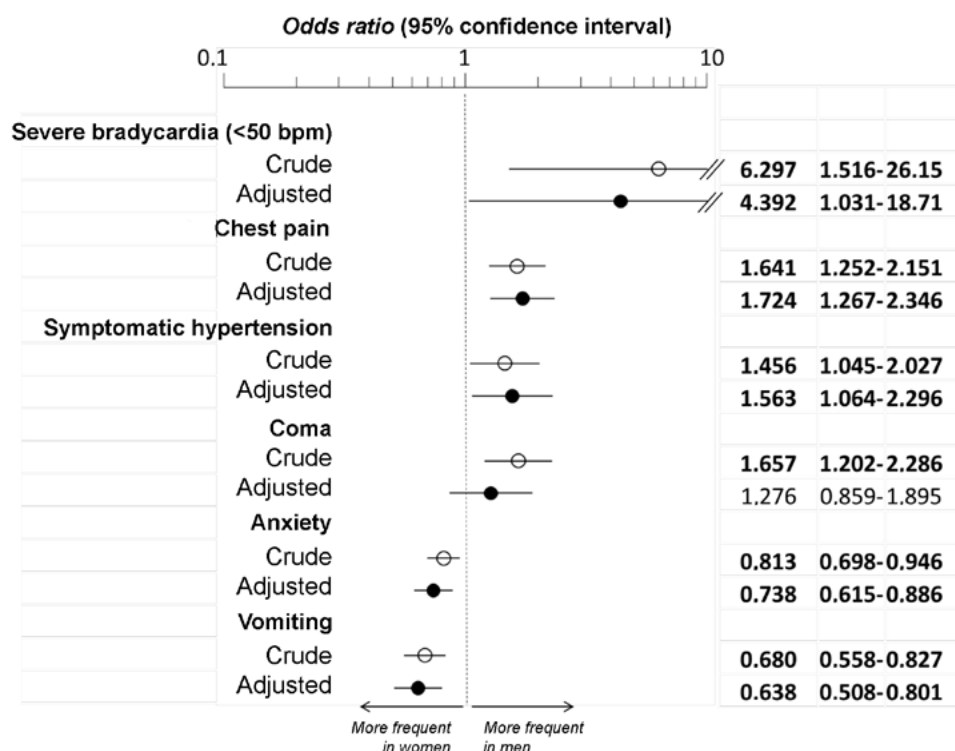
Treatment for intoxication was given to 76.1% of the patients received, in particular anxiolytics and sedatives, which were used more in men (34.6% vs 30.9%, p = .023).

Table 2
Characteristics of the emergency care episode of the patients included in the present study and comparison patient sex

	Total N=4526 n (%)	Missing data n (%)	Men N=3418 n (%)	Women N=1108 n (%)	P
Symptoms					
Agitation / Aggressive behaviour	1338 (29.8)	33 (0.7)	1028 (30.3)	310 (28.1)	.149
Anxiety	1152 (25.6)	33 (0.7)	835 (24.6)	317 (28.7)	.008
Decreased consciousness	816 (18.8)	183 (4.0)	622 (19.0)	194 (18.1)	.504
Palpitations	740 (16.5)	35 (0.8)	574 (17.0)	166 (15.0)	.133
Vomiting	536 (11.9)	33 (0.7)	368 (10.9)	168 (15.2)	< .001
Psychotic symptoms	429 (9.6)	34 (0.8)	340 (10.0)	89 (8.1)	.051
Chest pain	398 (9.0)	84 (1.9)	330 (9.8)	68 (6.2)	< .001
Hallucinations	352 (7.8)	36 (0.8)	272 (8.0)	80 (7.2)	.393
Seizures	243 (5.4)	34 (0.8)	192 (5.7)	51 (4.6)	.179
Symptomatic hypertension	242 (5.0)	116 (2.6)	197 (5.9)	45 (4.1)	.026
Headache	181 (4.0)	34 (0.8)	130 (3.8)	51 (4.6)	.251
Arrhythmias	123 (2.8)	164 (3.6)	91 (2.8)	32 (3.0)	.729
Symptomatic hypotension	93 (2.1)	119 (2.6)	72 (2.2)	21 (1.9)	.648
Coma	278 (6.4)	183 (4.0)	231 (7.1)	47 (4.4)	.002
Cerebellar symptomatology	9 (0.2)	51 (1.1)	6 (0.2)	3 (0.3)	.543
Vital signs in ED					
Systolic blood pressure (mmHg) (mean (SD))	126 (20)	558 (12.3)	128 (20)	122 (19)	< .001
Severe hypotension (< 80 mmHg)	22 (0.6)		19 (0.6)	3 (0.3)	.228
Severe hypertension (> 200 mmHg)	10 (0.3)		8 (0.3)	1 (0.2)	.730
Heart rate (bpm) (mean (SD))	94 (24)	529 (11.7)	94 (24)	95 (23)	.283
Severe bradycardia (< 50 bpm)	40 (1.0)		38 (1.3)	2 (0.2)	.004
Severe tachycardia (> 150 bpm)	66 (1.7)		50 (1.7)	16 (1.6)	.932
Respiratory rate (bpm) (mean (SD))	19 (6)	3684 (81.4)	19 (6)	18 (5)	.175
Severe tachypnea (> 30 bpm)	29 (3.4)		24 (3.6)	5 (2.8)	.611
Severe bradycardia (< 10 bpm)	13 (1.5)		11 (1.7)	2 (1.1)	.615
Temperature (°C) (mean (SD))	36.2 (0.8)	1584 (35.0)	36.2 (0.8)	36.1 (0.8)	.021
Severe hypothermia (< 35 °C)	100 (3.4)		74 (3.4)	26 (3.5)	.868
Severe hyperthermia (< 40 °C)	5 (0.2)		4 (0.2)	1 (0.1)	1.000
ED management					
Administration of any kind of treatment (including fluid therapy)	3412 (76.1)	43 (1.0)	2579 (76.3)	833 (75.5)	.556
Administration of anxiolytics/sedatives	1511 (34.2)	43 (1.0)	1170 (34.6)	341 (30.9)	.023
Administration of antidotes	351 (7.8)	40 (0.9)	278 (8.2)	73 (6.6)	.084
Naloxone	243 (5.4)		199 (5.9)	44 (4.0)	.015
Flumazenil	229 (5.1)		174 (5.1)	55 (5.0)	.829
Determination of toxicological analysis	3473 (76.7)	0	2610 (76.4)	863 (77.9)	.296
Direct discharge from the ED without hospitalization	3908 (87.1)	33 (0.7)	2943 (87.0)	441 (13.0)	.704
Time spent in the emergency room until discharge (in hours) (median (IQR))	5.2 (3.1-9.5)	140 (3.1)	5.3 (3.1-9.7)	5.1 (2.9-8.9)	.124

Note. SD: standard deviation. IQR: interquartile range.

Figure 3
Crude and adjusted analyses of the differential symptoms between men and women consulting EDs for intoxication by drugs of abuse



Note. Values in bold are statistically significant ($p < 0.05$). As covariates in the adjusted model, all statistically significant symptoms in the crude analysis were forced-entry, as were age, ethanol co-ingestion, and each of the drugs analyzed in the present study.

Table 3
Markers of severity of the episode of care of patients attended for drug intoxication in the Emergency Department and comparison according to the sex of the patient

	Total N=4526 n (%)	Missing data n (%)	Men N=3418 n (%)	Women N=1108 n (%)	p	Crude OR in men (95% CI)	Adjusted OR in men (95% CI)
Primary marker of severity							
Combined adverse events	128 (2.9)	50 (1.1)	106 (3.1)	22 (2.0)	.047	1.595 (1.002-2.537)	1.349 (0.827-2.202)
Secondary marker of severity							
Initial cardiorespiratory arrest	11 (0.2)	0	8 (0.2)	3 (0.3)	.829	0.864 (0.229-3.264)	0.702 (0.177-2.777)
Need for intubation	75 (1.7)	39 (0.9)	64 (1.9)	11 (1.0)	.044	1.917 (1.007-3.647)	1.371 (0.700-2.685)
Admission to intensive care	90 (2.0)	33 (0.7)	73 (2.2)	17 (1.5)	.204	1.410 (0.828-2.400)	1.298 (0.740-2.275)
Death	12 (0.3)	0	10 (0.3)	2 (0.2)	.528	1.623 (0.355-7.419)	1.084 (0.230-5.099)

Note. OR: odds ratio. CI: confidence interval.

Antidotes were used in 351 patients (7.8%), with more naloxone being used in men (5.9% vs 4%, $p = .015$) and with no differences in the use of flumazenil. Toxins were detected in 3,473 cases (76.7%), with the toxins involved in the remaining cases being taken from the anamnesis data of the patient or their companions with a clinical picture (except in 254 cases in which a specific type of drug could not be determined given that no analytical toxicological history was made or no clinical history pointing to a particular source was available). There were no differences in terms of the percentage of men and women in whom

toxicological confirmation was obtained. After their stay in the ED, (mean stay 5.4 hours), 87.1% of the patients (3,945) were discharged home (Table 2).

Combined adverse events were observed in 128 patients (2.9%), more frequently in men (3.1% vs 2.0%, $p = .047$) (Table 3). Among the AE considered individually, the need for intubation was the only difference by sex, being higher in men (1.9% vs 1.0%, $p = .044$). In the adjusted analysis, statistical significance disappeared in both cases (OR = 1.349, 95% CI = 0.827-2.202, and OR = 1.371, 95% CI = 0.700-2.685, respectively). Twelve patients (0.3%) died,

without sex differences (0.3% vs 0.2%, $p = .528$). Among the 12 deceased patients, cocaine was present in 8 cases (67%), amphetamine derivatives in 3 (25%), cannabis or derivatives in 3 (25%), GHB in 1 (8%) and new psychoactive drugs (cathinone) at 1 (8%). In 6 cases (50%), co-ingestion of ethanol was also present.

Discussion

Several absolute epidemiological data worthy of comment were found in the present study. First, in line with other published research on drug poisoning treated in EDs (Dines et al., 2015; Galicia et al., 2012; Miró et al., 2021), this phenomenon was more frequently observed in men than in women (with a 3:1 ratio in the present series). In addition, the relationship between drug use and recreational activity was also confirmed, being more frequent in tourist areas, on holidays and at night. Finally, it is noteworthy that the proportion of sexes among those treated varies depending on whether the ED was located in more touristy areas (in which women are overrepresented in relation to the expected proportion) or in large metropolises (where men are overrepresented). Drug use patterns are related to local, socioeconomic or cultural characteristics, which make it possible to identify differences between countries or regions. Thus, previous studies have shown that Spaniards, for example, consume more cocaine and fewer opiates and NPS (novel psychoactive substances) than citizens of the British Isles or regions of central and northern Europe (Miró et al., 2018).

Regarding the drugs involved in ED care, men used more cocaine, opiates, GHB and ketamine, and women more benzodiazepines, although the differences were only significant for GHB (more in men) and benzodiazepines (more in women). In relation to this last finding, we must consider the possibility that the greater prevalence of benzodiazepines in women is due to an increase in cases of use with suicidal ideation (and not exclusively to recreational purpose use), or that it is more easily within reach as the proportion of women receiving treatment with benzodiazepines prescribed by a doctor is higher. Although the principal investigators of each centre were advised that cases in which it was clear that substance users had a clear suicidal purpose were to be excluded, this possibility could not be consistently ruled out given the way in which the information was recorded as the etiology of intoxication was not prospectively collected. The fact that a higher prevalence was observed in patients aged 60 or over could suggest this bias, although the number of patients corresponding to this age group was minimal (55 of the total of 4,526) and its influence on the global comparison was therefore very small. Finally, it is striking that ethanol co-intake was clearly higher among women (61.2% vs 57.2%, $p = .028$). We have not found similar

references in the literature in this regard, nor indeed was such a difference between the sexes found in a European study that included more than 17,000 patients (Miró et al., 2021).

Regarding clinical manifestations, the most frequent were those of a hyperadrenergic nature (agitation, aggressiveness, anxiety), possibly due to the predominance of cocaine and amphetamines among the drugs used (Galicia, Nogué, Sanjurjo & Miró, 2008; Galicia, Nogué, Sanjurjo & Miró, 2010; Nosedá et al., 2021). However, there were different prevalences depending on sex in some specific clinical manifestations, even after controlling for the sociodemographic differences and the type of drugs consumed by each sex. Thus, men were observed to have a higher likelihood of presenting cardiovascular symptoms: chest pain, symptomatic hypertension and severe bradycardia. We do not know if this is related to more previous cardiovascular comorbidities in men (known or hidden), since comorbidity was not collected in the study. On the other hand, anxiety and vomiting were more frequent in women. It cannot be ruled out that these differences in clinical expression may be linked to an increased susceptibility to certain manifestations linked to sex. Earlier studies have shown, for instance, that women have a 1.5-1.7 times higher risk than men of presenting adverse reactions in relation to the use of medical drugs (Anderson, 2008; Rademaker, 2001).

A toxicological analysis was performed in 76% of the cases, without differences between the sexes. It could be considered that this percentage of toxicological tests is adequate since it has been shown that they are not essential for emergency management of intoxicated patients, with some authors suggesting that toxicological tests should be reserved for specific cases (Córdoba et al., 2020). The present study does not show there is a difference in application of this criterion depending on the sex of the patient. However, we believe that the importance of this toxicological determination goes beyond the clinical relevance it may have in, for example, revealing substances that the patient does not know they have consumed (Liakoni et al., 2018). This determination also has an epidemiological role that EDs should not ignore, given their key position when it comes to detecting new patterns of use or the introduction of new drugs on the market (as may be the case of NPS). Samples of these should moreover be kept during the treatment process for later analysis using specific methods since their identification is beyond the immunoassay techniques available in EDs (Fernández Alonso, Quintela Jorge & Santiago Sáez, 2016; Miró & Galicia, 2019; Observatorio Español de las Drogas y las Adicciones, 2020).

In relation to the treatment carried out in the ED, it was found that anxiolytic or sedative drugs were more frequently given to men, a fact that contrasts with their lower

prevalence of anxiety symptoms. This difference may have several explanations: the presence of more pronounced manifestations in men or a greater occurrence of agitation, psychotic symptoms, seizures or even hypertension, where benzodiazepines are used to control symptoms. Men also received more naloxone, which is more to be expected considering that in terms of absolute numbers they consumed more opiates or GHBs and presented more frequently in comatose states in the EDs (Sivilotti, 2016).

Men presented more serious intoxications, given their 59% higher risk of presenting combined AE compared to women. Among the AE, the need for endotracheal intubation was the only one that was significantly increased, with an increased risk of 92% compared to women. The latter is likely related to the increased presence of coma, opiates and GHB (Galicia et al., 2008). However, this greater severity of poisonings in men would be more linked to older age or the type of substances consumed by men. Thus, when adjusting for these factors, the differences decreased (the rise in combined AE decreased to 35% and that of orotracheal intubation to 37%) and lost statistical significance.

This study has limitations. First, despite being a prospective study, some data, in particular vital signs, were not recorded in the medical records. This is a general issue in EDs (Galicia, 2020; Miró et al., 2018; Roset Ferrer et al., 2020). We must highlight the clinical importance of this in general and especially in intoxicated patients, where it is absolutely essential to know and record both the temperature (missing in 35% of the patients in this series, and which allows cases of hyperthermia to be detected) and the respiratory rate (missing in 81%, and which allows bradypnea to be detected in cases of intoxication by GHB or opiates or tachypnea in cases of metabolic acidosis). Second, the diagnosis of the drug involved was based on clinical history and/or analytical identification, so that in some cases it was not possible to identify substances by either the patient or the analysis. As previously indicated, some of the drugs, such as GHB or new psychotropic substances, cannot be identified by immunoassay, the technique most used in EDs, and so these groups may have been underrepresented. It could also happen that the drug indicated by the patient was not actually the one involved, due to the use of other substances such as drug adulterants. Third, the identification of adverse events was made by the investigator of each centre, without external monitoring. The events under consideration are very objective and are probably subject to only small interpretive biases of little relevance. Fourth, despite being a large series, for some drugs, the number of cases with some symptoms or some AE was low, so a beta error may have been incurred by disregarding the existence of statistical significance in the differences found between men and women. Finally, and despite the fact that the participating centres were

distributed across the country, only six autonomous communities were represented, which partially reduces the global vision of the problem in Spain.

In conclusion, this study shows that sex differences exist in drug intoxications treated in ED. There is a greater involvement of GHB in men and of benzodiazepines and alcohol in women. In the case of benzodiazepines, this is very evident in older patients. Cardiovascular symptoms prevail in men and anxiety and vomiting in women, a difference which cannot be attributed to sociodemographic variation or to the drugs used by each of the sexes. Men have more severe AD, which could be related to older age and the type and pattern of drug use, since when adjusting for these differences, the severity of intoxication episodes was not significantly different by sex.

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Conflict of interests

None of the authors of this study has declared a conflict of interest.

References

- Anderson, G.D. (2008). Gender differences in pharmacological response. *International Review of Neurobiology*, 83, 1–10. doi:10.1016/S0074-7742(08)00001-9.
- Burillo-Putze, G., López-Hernández, A., Expósito-Rodríguez, M. & Dueñas-Laita, A. (2013). Sumisión química, oportunista o premeditada. *Medicina Clínica*, 140, 139. doi:10.1016/j.medcli.2012.05.035.
- Burillo-Putze, G. & Matos Castro, S. (2018). Los servicios de urgencias como atalaya de los patrones de uso de drogas y sus consecuencias clínicas. *Emergencias*, 30, 377–379.
- Córdoba, F., Iglesias Lepine, M. L., García Gibert, L., Gispert, M. À., Moreno, A. & Supervía, A. (2020). Grado de conocimiento de la detección de drogas en orina entre médicos que atienden a pacientes intoxicados. *Emergencias*, 32, 451–452.
- Delegación del Gobierno para el Plan Nacional sobre Drogas. (2021). *Encuesta sobre alcohol y otras drogas en España, EDADES 2019/20*. Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2019-20_Informe_EDADES.pdf.
- Delegación del Gobierno para el Plan Nacional sobre Drogas. (2020). *Encuesta sobre Uso de Drogas en Enseñanzas Secundarias en España (ESTUDES) 1994-2018*. Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/ESTUDES_2018-19_Informe.pdf.
- Dines, A. M., Wood, D. M., Yates, C., Heyerdahl, F., Hovda, K. E., Giraudon, I.,... Euro-DEN Research Group (2015). Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). *Clinical Toxicology*, 53, 893–900. doi:10.3109/15563650.2015.1088157.
- ESPAD Group (2020). *ESPAD Report 2019: Results from the European school survey project on alcohol and other drugs*, Luxembourg: EMCDDA joint publications. Publications office of the European Union.
- European Monitoring Centre for Drugs and Drug Addiction [EMCDDA]. (2020). *European drug report 2020: Trends and developments*. Luxembourg: Publications office of the European Union.
- Fernández Alonso, C., Óscar Quintela, J., Ayuso Tejedor, S., Santiago-Sáez, A. E. & González Armengol, J. J. (2019). Intoxicación aguda por nuevas drogas de abuso en probables casos de sumisión química oportunista o mixta y chemsex en pacientes con VIH atendidos en urgencias. *Emergencias*, 31, 289–290.
- Fernández Alonso, C., Quintela Jorge, O. & Santiago Sáez, A. S. (2016). Identificación de la droga de abuso flakka (α -PVP) como sospecha de sumisión química no probada en urgencias de un hospital terciario. *Medicina Clínica*, 147, 227–228. doi:10.1016/j.medcli.2016.03.028.
- Fernández Egido, C., García Herrero, G., Romero García, R. & Marquina Santos, A. J. (2008). Intoxicaciones agudas en las urgencias extrahospitalarias. *Emergencias*, 20, 328–331.
- Galicia, M. (2020). Efectos adversos agudos en usuarios de drogas sintéticas: Una aproximación a la magnitud del problema en España. *Emergencias*, 32, 7–8.
- Galicia, M., Nogué, S., Casañas, X., Iglesias, M., Puiguriguer, J., Supervía, A.,... Miró, Ò. (2012). Multicenter assessment of the revisit risk for a further drug-related problem in the emergency department in cocaine users (MARRIED-cocaine study). *Clinical Toxicology*, 50, 176–182. doi:10.3109/15563650.2012.658917.
- Galicia, M., Nogué, S., Sanjurjo, E. & Miró, Ò. (2008). Evolución de las consultas urgentes relacionadas con el consumo de cocaína durante el periodo 2002-2007. *Emergencias*, 20, 385–390.
- Galicia, M., Nogué, S., Sanjurjo, E. & Miró, Ò. (2010). Consultas urgentes derivadas del consumo de éxtasis (3,4-metilenodioximetanfetamina) y derivados anfetamínicos: Perfil epidemiológico, clínico y evolutivo. *Revista Clínica Española*, 210, 371–378. doi:10.1016/j.rce.2010.01.013.
- Galicia, M., Nogué, S., To-Figueras, J., Echarte, J. L., Iglesias, M. L. & Miró, Ò. (2008). Intoxicaciones por éxtasis líquido atendidas en servicios de urgencias hospitalarios de la ciudad de Barcelona durante 2 años. *Medicina Clínica*, 130, 254–258. doi:10.1157/13116549.
- Hegazi, A., Lee, M. J., Whittaker, W., Green, S., Simms, R., Cutts, R.,... Pakianathan, M. R. (2017). Chemsex and the city: Sexualised substance use in gay bisexual and other men who have sex with men attending sexual health clinics. *International Journal of STD and AIDS*, 28, 362–366. doi:10.1177/0956462416651229.
- Liakoni, E., Yates, C., Dines, A. M., Dargan, P. I., Heyerdahl, F., Hovda, K. E.,... Euro-DEN Plus Research Group (2018). Acute recreational drug toxicity: Comparison of self-reports and results of immunoassay and additional analytical methods in a multicenter European case series. *Medicine*, 97, e9784. doi:10.1097/MD.0000000000009784.
- Miró, Ò. & Galicia, M. (2019). Sobre las fuentes de conocimiento del consumo de drogas y sus consecuencias. *Revista Española de Salud Pública*, 90, 1-3.
- Miró, Ò., Waring, W. S., Dargan, P. I., Wood, D. M., Dines, A. M., Yates, C.,... Euro-DEN Plus Research Group (2021). Variation of drugs involved in acute drug toxicity presentations based on age and sex: An

- epidemiological approach based on European emergency departments. *Clinical Toxicology*, 59, 896-904. doi:10.1080/15563650.2021.1884693.
- Miró, Ò., Yates, C., Dines, A. M., Wood, D. M., Dargan, P. I., Galán, I.,... Galicia, M. (2018). Comparación de las urgencias atendidas por drogas de abuso en dos servicios de urgencias españoles con las atendidas en tres áreas europeas distintas. *Emergencias*, 30, 385-394.
- Noseda, R., Schmid, Y., Scholz, I., Liakoni, E., Liechti, M. E., Dargan, P. I.,... Euro-DEN Research Group (2021). MDMA-related presentations to the emergency departments of the European Drug Emergencies Network plus (Euro-DEN Plus) over the four-year period 2014-2017. *Clinical Toxicology*, 59, 131-137. doi:10.1080/15563650.2020.1784914.
- Observatorio Español de las Drogas y las Adicciones. (2020). *Informe 2020. Alcohol, tabaco y drogas ilegales en España. Sistemas de alerta temprana. Esquema del sistema español de alerta temprana*. Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasAlerta/pdf/2020_Informe_Alertas.pdf.
- Perelló, R., Aused, M., Saubí, N., Quirós, C., Blanco, J. L., Martínez-Rebollar, M.,... Nogué, S. (2018). Intoxicación aguda por drogas de abuso en el paciente VIH: Papel del chemsex. *Emergencias*, 30, 405-407.
- Puiguirguer, J., Nogué, S., Echarte, J. L., Ferrer, A., Dueñas, A., García, L.,... Burillo-Putze, G. (2013). Mortalidad hospitalaria por intoxicación aguda en España (EXITOX 2012). *Emergencias*, 25, 467-471.
- Rademaker, M. (2001). Do women have more adverse drug reactions? *American Journal of Clinical Dermatology*, 2, 349-351. doi:10.2165/00128071-200102060-00001.
- Roset Ferrer, C., Gomila Muñiz, I., Elorza Guerrero, M. Á., Puiguirguer Ferrando, J., Leciñena Esteban, M. Á., Tuero León, G.,... Barceló Martín, B. (2020). Intoxicaciones por anfetamina y metanfetamina atendidas en los servicios de urgencias: Características clínicas y utilidad de la confirmación analítica. *Emergencias*, 32, 26-32.
- Sivilotti, M. L. A. (2016). Flumazenil, naloxone and the "coma cocktail." *British Journal of Clinical Pharmacology*, 81, 428-436. doi:10.1111/bcp.12731.