REUE | Original Article

Seizures secondary to illegal drug use treated in hospital Emergency Departments: a multicenter national study

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OBJECTIVES. To estimate the incidence of seizures due to poisoning by street drugs in Spain and to describe the demographic, toxicologic, and clinical characteristics of the events.

METHODS. Prospective multicenter analysis of data from the registry of the Spanish Research Network on Drugs in Hospital Emergency Departments (REDUrHE), a 24-month project in 2017 to 2019 in 11 Spanish hospital emergency departments. The patients were treated for seizures after poisoning due to street drug use.

RESULTS. A total of 243 patients (in 5.4% of the cases registered) had seizures. Seventy-nine percent were men. No statistically significant differences between the sexes were found. A significantly higher incidence of seizures was observed only in the group of patients poisoned by unidentified substances. Patients without seizures had more palpitations (in 17.1% vs in 5.3% of those with seizures), chest pain (9.4% vs 2.1%, respectively), and cerebellar signs and anxiety (26.5% vs 10.7%) (*P*<.001, all comparisons). Patients with seizures differed with respect to need for orotracheal intubation (in 3.3% vs 1.6% of those without seizures; *P*=.038), positive urine tests for drugs (91.8 % vs 75.7%; *P*<.001), and intensive care unit (ICU) admission (5.3% vs 1.8%; *P*<.001). Length of stay in the emergency department and mortality did not differ between patients with and without seizures. The following events were over twice as likely in patients who had seizures: orotracheal intubation, odds ratio (OR), 2.161 (95% CI, 1.025-4.54); use of an unidentified substance, OR, 2.222 (95% CI, 1.457-3.389); and ICU admission, OR, 2.161 (95% CI, 1.025-4.554). Coingestion of alcohol was not related to having seizures: OR, 0.264; 95% CI, 0.097-0.715).

CONCLUSION. A higher risk of seizure was not associated with any particular known street drug, although the risk increased when an unknown substance had been used.

Keywords: Seizures. Poisoning. Street drugs. Emergency health services. Convulsions.

Crisis convulsivas secundarias al consumo de drogas ilegales atendidas en urgencias hospitalarias. Estudio multicéntrico nacional

OBJETIVOS. Conocer la incidencia de crisis convulsivas en las intoxicaciones agudas por drogas en Spain y sus características demográficas, toxicológicas y clínicas.

MATERIAL Y MÉTODO. Análisis de los pacientes del registro REDUrHE, estudio multicéntrico prospectivo de 24 meses de duración (2017-2019) en 11 servicios de urgencias hospitalarios españoles, que convulsionaron (PcC) tras una intoxicación aguda por drogas.

RESULTADOS. Presentaron convulsiones 243 pacientes (5,4%). El 79% eran hombres, sin hallarse diferencias significativas en las variables estudiadas en función del sexo. No se encontraron diferencias en la incidencia de convulsiones con los grupos de drogas, excepto para el grupo de sustancias desconocidas. Los pacientes sin convulsiones presentaban más palpitaciones (17,1% *vs* 5,3%; p < 0,001), dolor torácico (9,4% *vs* 2,1%; p < 0,001), síntomas cerebelosos y ansiedad (26,5% *vs* 10,7%; p < 0,001). Se hallaron diferencias para los pacientes que convulsionaron en cuanto a intubación orotraqueal (3,3% *vs* 1,6%; p = 0,038), determinación de drogas en orina (91,8% *vs* 75,7%; p < 0,001), e ingresos en cuidados intensivos (UCI) (5,3% *vs* 1,8%; p < 0,001). No hubo diferencias en cuanto a estancia en urgencias o fallecimientos. Las variables intubación orotraqueal (OR = 2,161; IC 95% = 1,025-4,554), consumo de sustancia desconocida (OR = 2,222; IC 95% = 1,457-3,389) e ingreso en UCI (OR = 2,161; 95% IC = 1,025-4,554), aumentaban en 2,2 veces su probabilidad en los enfermos que presentaron un cuadro convulsivo. El consumo concomitante de alcohol (OR = 0,264; IC 95% = 0,097-0,715) fue un factor contrario a convulsionar.

CONCLUSIONES. El riesgo de convulsión no se asocia con ningún grupo de drogas en particular, aunque este aumenta en el caso de no conocer la sustancia consumida.

Palabras clave: Convulsiones. Intoxicación. Drogas. Urgencias. Convulsiones.

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Introduction

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), approximately 83 million (28.9%) European adults have used illicit drugs at least once in their lifetime.[1] In Spain, according to the Spanish Observatory on Drugs and Addictions, 22.5% of the population aged 15–64 years report having used hypnotics–sedatives with or without a medical prescription, 37.5% cannabis, and 11.2% cocaine.[2] Additionally, the Spanish Early Warning System (SEAT) detected the presence of 122 new NPS (novel psychoactive substances) over the past 7 years.[2]

Between 0.1% and 3.5% of patients who present to emergency departments (EDs) do so because of acute intoxications (AI). Most AIs are managed in the ED either due to their potential initial severity, the need for psychiatric evaluation in cases of self-harm intent, the need for several hours of clinical observation, or the need for hospital admission. Furthermore, EDs are often the only point of contact that drug users have with the health care system.[3]

Focusing on Spanish EDs, according to the Spanish Hospital Emergency Drug Study Network (REDUrHE), the substances most frequently involved in intoxicated patients treated in EDs are cocaine (47.8%), cannabis (44.4%), and amphetamines and derivatives (25.5%). Multiple drug use is present in 40% of cases, and concomitant ethanol use in 58.2%.[4]

The clinical relevance of AIs due to illicit drugs lies in their neuropsychiatric and cardiovascular toxicity. Among their potential risks, they may cause severe conditions such as hyperthermia, disseminated intravascular coagulation, acute renal failure, and seizures.[5] Although multiple substances are known to induce seizure activity, up to 13.4% of patients who experience a first seizure present one of toxic origin.[6]

Publications on seizures due to drug use are scarce. Given the potential morbidity and mortality associated with AI-related seizures, the aim of this study was to determine the incidence of seizures in AIs due to drugs in Spain and to identify the toxicological, sociodemographic, and clinical factors associated with them, including a gender-based perspective.

Materials and methods

We conducted a substudy of the REDUrHE registry, analyzing patients who presented seizures (PS) vs the remaining ED visits due to drug use—patients without seizures (PWS). REDUrHE is a prospective multicenter registry involving 11 EDs from regional and reference hospitals in 6 Spanish autonomous communities. Data were collected over a 2-year period (08/2017–07/2019), yielding a final sample of 4,487 patients.[4,7,8]

Inclusion criteria were recent drug use as the reason for consultation, signs or symptoms indicative of recent drug use, and a positive toxicological test result, provided that in the latter case there were symptoms compatible with adverse effects of drug use.

Demographic variables included hospital, date and time of ED care, patient age and sex, and whether arrival to the ED occurred via ambulance. Toxicological variables included the types of substances involved and concomitant use of alcohol (based on history or ethanol level) and other substances of abuse. Intoxications caused exclusively by ethanol ingestion were excluded. Substances were determined using the health history and, when possible, toxicology analysis via urine drug testing. The patient's final disposition after ED evaluation was recorded, distinguishing discharge (medical or voluntary), admission (to the intensive care unit [ICU], psychiatry, or medical ward), or death. The duration of hospital stay in hours was also recorded.

Quantitative variables were expressed as median and interquartile range (IQR) and analyzed using the Mann–Whitney U test for independent samples. Qualitative variables were expressed as absolute and percentage values and compared using the chi-square test, except in cases with < 5 observations, where Fisher's exact test was used. Statistical significance was defined as $P < .05$ or a 95% confidence interval (CI) for an odds ratio (OR) not including 1. Statistical analysis was performed using SPSS v.28.0.1 (IBM, Armonk, New York, USA).

The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki for research involving human subjects. The REDUrHE registry was approved by the Ethics Committee of Hospital Universitario de Canarias (Canary Islands, Spain), reference 2016-71. The requirement for informed consent was waived because this epidemiological study fulfilled the objectives of the Government Delegation for the National Drug Plan in its research project calls and used an anonymized database. The project was funded by the Government Delegation for the National Drug Plan, Ministry of Health, reference 2016/072.

Results

A total of 5.4% of patients (243 cases) presented seizures in the ED, of whom 192 (79%) were men and 51 (21%) women. PS had a mean age of 33 years vs 32 years in PWS, with no statistically significant differences.

No significant differences were found regarding seizure incidence among the different drug groups or with polydrug use. A significant association was observed between seizures and exposure to unknown substances, and conversely, a lower likelihood of seizures was associated with concomitant use of drugs and alcohol (Table 1).

Regarding vital signs on arrival, no significant differences were found between patients with and without seizures except for respiratory rate ($P = .04$) (Table 2).

With respect to initial clinical presentation, significant differences were observed between PS and PWS, with seizures being less frequent in patients presenting with palpitations (5.3% PS vs 17.1% PWS; $P < .001$), chest pain (2.1% PS vs 9.4% PWS; $P < .001$), cerebellar symptoms, and anxiety (10.7% PS vs 26.5% PWS; $P < .001$) (Table 3).

A total of 21% of PS did not receive treatment. Significant differences were found in orotracheal intubation (OTI)

Table 1. Drug groups consumed and presence of seizures

	Total cases n (%)	Patients with seizures n (%)	Patients without seizures n (%)	*P*
Co-ingestion of multiple drugs	1,766 (39.4)	94 (38.7)	1,672 (39.4)	.82
Concomitant ethanol use	257 (5.7)	4 (1.6)	253 (6.0)	**.005**
Drugs involved in the intoxication				
Cocaine and derivatives	2,150 (47.9)	116 (47.7)	2,034 (47.99)	.95
Cannabis and derivatives	1,985 (44.2)	105 (43.2)	1,880 (44.3)	.74
Amphetamines and derivatives	1,145 (25.5)	60 (24.7)	1,085 (25.6)	.76
Benzodiazepines	385 (8.6)	14 (5.8)	371 (8.7)	.1
Opioids	331 (7.4)	14 (5.8)	317 (7.5)	.33
Gamma-hydroxybutyrate and derivatives	212 (4.7)	16 (6.6)	196 (4.6)	.16
Ketamine	174 (3.9)	4 (18.6)	170 (4.0)	.064
Unknown substance	253 (5.6)	27 (11.1)	226 (5.3)	**< .001**
LSD and other hallucinogens	31 (0.7)	1 (0.4)	30 (0.7)	.58
NPS	14 (0.3)	2 (0.8)	12 (0.3)	.14

LSD: lysergic acid diethylamide; NPS: novel psychoactive substances.

(3.3% PS vs 1.6% PWS; *P* = .038) and in the performance of urine drug testing (91.8% PS vs 75.7% PWS; *P* < .001). Patients who experienced seizures were also more frequently admitted to the ICU (5.3% PS vs 1.8% PWS; *P* < .001). No differences were observed in ED length of stay or mortality (Table 3).

After the descriptive analysis, variables with statistical significance were evaluated for strength of association. OTI (OR, 2.161; 95% CI, 1.025–4.554), consumption of unknown substances (OR, 2.222; 95% CI, 1.457–3.389), and ICU admission (OR, 2.161; 95% CI, 1.025–4.554) increased the likelihood of seizure presentation by approximately 2.2-fold. Conversely, concomitant alcohol use (OR, 0.264; 95% CI, 0.097–0.715), agitation (OR, 0.434; 95% CI, 0.307–0.616), palpitations (OR, 0.274; 95% CI, 0.156–0.481), chest pain (OR, 0.205; 95% CI, 0.084–0.500), and anxiety (OR, 0.332; 95% CI, 0.220–0.502) were characteristics associated with a lower likelihood of seizures (Figure 1).

In the sex-stratified analysis, no significant differences were found (Table 4).

Discussion

Based on the largest Spanish series of acute care episodes for illicit drug intoxications attended in EDs, with 4,487 cases collected over 2 years, this substudy on their association with seizures provides relevant information. The report of the National Drug Plan, "Hospital Emergency Indicator in Users of Psychoactive Substances 1987–2017," with 4,293 episodes from 15 centers across 17 autonomous communities, in addition to being retrospective, does not analyze this clinical complication of drug intoxication, which, as we have determined, affects at least 5.4% of these patients.[9] The Euro-DEN network, in a study including 23,947 patients from 32 EDs in 21 European countries, reported 1,013 (4.2%) patients presenting seizures—a similar incidence to ours.[10] Of note, both Euro-DEN and REDUrHE use the same study methodology; our work is essentially a Spanish-level replication of the European model, making the data fully comparable.[5,11]

Classically, seizure onset has been associated with certain drugs such as phencyclidine, inhalants, cocaine, and psychostimulants.[12] In the Euro-DEN network analysis of substances involved in seizures, a significant association was found with fentanyl (OR, 2.63; 95% CI, 1.20–5.80) and synthetic cannabinoids (OR, 2.90; 95% CI, 2.19–3.84). Oth-

Table 3. Comparison of clinical and care characteristics between patients with and without seizures

	Total cases n (%)	Patients with seizures n (%)	Patients without seizures n (%)	*P*
Clinical findings				
Palpitations	739 (16.5)	13 (5.3)	726 (17.1)	**< .001**
Agitation/Aggression	1,336 (29.8)	39 (16.0)	1,297 (30.6)	**< .001**
Cerebellar symptoms	9 (0.2)	9 (4.0)	0 (0.0)	**< .001**
Vomiting	536 (11.9)	23 (9.5)	513 (12.1)	.22
Hyperthermia	1 (0.0)	1 (0.0)	0 (0.0)	.81
Headache	181 (4.0)	12 (4.8)	169 (4.0)	.46
Chest pain	398 (9.0)	5 (2.1)	393 (9.4)	**< .001**
Anxiety	1,151 (25.7)	26 (10.7)	1,125 (26.5)	**< .001**
Hypertension	242 (5.5)	16 (6.7)	226 (5.4)	.39
Hypotension	93 (2.1)	4 (1.7)	89 (2.1)	.63
Level of consciousness				
Coma	255 (5.7)	21 (8.6)	234 (5.5)	.12
Sedated	82 (1.8)	3 (1.2)	79 (1.9)	.12
Somnolent	500 (11.1)	20 (8.2)	480 (11.3)	.12
Alert	3,260 (72.7)	174 (71.6)	3,086 (72.7)	.12
Not recorded	390 (8.7)	25 (10.3)	365 (8.6)	.12
Treatment				
Yes	3,365 (75.1)	192 (79.0)	3,173 (74.9)	.14
No	1,117 (24.9)	51 (21.0)	1,066 (25.1)	.14
Type of treatment				
Sedation	1,507 (33.7)	93 (38.4)	1,414 (33.4)	.1
Antidote	351 (7.8)	14 (5.8)	337 (8.0)	.21
Naloxone	243 (5.4)	9 (3.7)	234 (5.5)	.22
Flumazenil	229 (5.1)	10 (4.1)	219 (5.2)	.4
Cardiopulmonary resuscitation	11 (0.2)	0 (0.0)	11 (0.3)	.4
Intubation	74 (1.7)	8 (3.3)	66 (1.6)	**.038**
Admission				
Medical ward	572 (12.8)	37 (15.2)	535(12.7)	.24
Intensive care unit	88 (2)	13 (5.3)	75 (1.8)	**< .001**
Outcomes				
Deaths	12	1 (0.4)	11 (0.3)	.65
Length of stay (hours), median (IQR)	15.1 (7.8)	16.71 (6.86)	12.49 (5.3)	.21

Table 2. Clinical vital signs at admission according to the presence or absence of seizures

	Missing data n (%)	Patients with seizures		Patients without seizures		*P*
		Mean (SD)	95% CI	Mean (SD)	95% CI	
Heart rate	497 (11)	92.5 (23.3)	95.55-89.51	94.3 (23.9)	95.13-93.6	.79
Systolic blood pressure	526 (11.7)	126.6 (18.4)	129.06-124.24	126.4 (14.9)	127.09-125.8	.22
Diastolic blood pressure	530 (11.8)	75.9 (14.3)	77.21-76.26	76.8 (14.9)	77.27-76.31	.31
Respiratory rate	839 (81.3)	18 (4.9)	19.19-16.84	18.7 (5.7)	19.17-18.36	**.04**
Temperature	1,550 (34.5)	36.2 (0.89)	36.338-36.07	36.1 (0.77)	36.2-36.150	.33

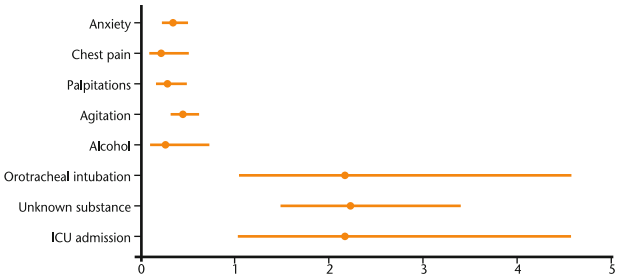

Figure 1. Odds ratios and 95% confidence intervals for variables associated with seizure presentation.

er drugs were associated with a lower seizure incidence rate, such as heroin (OR, 0.46; 95% CI, 0.35–0.61), clonazepam (OR, 0.22; 95% CI, 0.06–0.91), and cannabis (OR, 0.65; 95% CI, 0.50–0.86). In our study, we only found associations for "unknown substance" (OR, 2.222; 95% CI, 1.457–3.389) and concomitant ingestion of ethanol (OR, 0.264; 95% CI, 0.097–0.715), the latter more associated with the non-seizure group.

Regarding synthetic cannabinoids, Havenon *et al.* already warned in 2011 about the increased seizure risk of these substances, which, because they are not detected by the standard hospital toxicology tests, may go unnoticed in the etiological diagnosis of seizures, as occurs with other NPS.[3,13] Moreover, because phytocannabinoids have so far been associated with a lower seizure risk, clinicians may not thoroughly investigate their use during history taking.[14] It remains to be seen whether the increased potency of THC in contemporary cannabis could contribute to higher seizure risk, especially in cases of acute cerebrovascular disease associated with its use.[15,16] In our study, we could not differentiate between phytocannabinoids and synthetic cannabinoids, or find a causal relationship between cannabis and seizures ($P = .82$).

Regarding cocaine use, studies from the 1990s reported seizure rates up to 22% following its consumption. Neither Euro-DEN nor our study found such an association. Although seizures can occur with cocaine, given its psychostimulant nature, the current risk of pure seizures—without associated ischemic or hemorrhagic cerebral or cardiac events—appears low.[10] Majlesi *et al.* retrospectively studied 1.5 million emergency visits over 4 years in New Jersey, analyzing 12,579 seizure episodes. Although cocaine was detectable in 549 patients, only 43 had consumed it within 48 hours, yielding a seizure incidence rate of 0.3% for acute cocaine use, with 60.5% showing co-ingestion of other drugs and 16.3% having a seizure history.[17] Since dose, purity, and cutting agents were unknown, the reasons for this decreased seizure incidence rate remain unclear.

Regarding vital signs, Euro-DEN reported statistically significant differences in median temperature ($P < .001$), heart rate ($P < .001$), systolic blood pressure ($P = .004$), respiratory rate (RR) ($P < .001$), and level of consciousness ($P < .001$).[10] We only found significant differences in RR, which was more associated with the PWS group ($P = .043$). This finding must be interpreted cautiously because RR was recorded in only 19% of patients—a common problem in emergency settings.[18]

Regarding clinical management, Euro-DEN found a strong association between seizures and intubation: 13.8% of patients with seizures were intubated vs 2.8% without seizures (OR, 5.56; 95% CI, 4.56–6.77; $P < .001$).[10] We found similar results, with an association between OTI and the PS group (3.3% vs 1.6%; OR, 2.161; 95% CI, 1.025–4.554). The use of flumazenil in 4% of PS also calls attention, given its pro-convulsant properties;[19] however, due to the study design, we were unable to determine whether seizures were a consequence of its use.

This study has several limitations. First, the sample may not be representative of certain areas, since participation was voluntary and nationwide coverage was not homogeneous. This implies that local differences in drug types (and adulterants) circulating in each hospital's referral area may have influenced the results. Second, some substances may not have been identified, as the diagnosis was based mainly on health history and, in some cases, urine enzyme immunoassay testing. Regarding NPS, their low detection may reflect limited clinician awareness and the lack of hospital-level detection kits. For example, we could not detect novel benzodiazepines such as etizolam, substances that could influence seizure or intubation rates. Third, the purpose of drug use was not investigated, so suicidal intent, chemsex use, or drug-facilitated assault cannot be ruled out. Fourth, there was no external supervision of case reporting, as data were locally collected by principal investigators. Nonetheless, interpretative bias is likely low because the events considered were highly objective. Finally, although this is a large series, the low num-

Table 4. Sex-based analysis

	Total cases	Seizures				*P*
		Men		Women		
		Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Chest pain	398	4 (2.1)	326 (10.3)	1 (2)	67 (6.5)	.2
Palpitations	739	11 (5.7)	563 (17.6)	2 (3.9)	163 (15.5)	.27
Anxiety	1151	17 (8.9)	818 (25.6)	9 (17.6)	307 (29.2)	.33
Agitation	1336	34 (17.7)	99 (31.1)	5 (9.8)	305 (29.0)	**.43**
Alcohol	257	4 (2.1)	169 (5.3)	0 (0)	84 (7.6)	.26
Unknown substance	253	22 (11.5)	169 (5.3)	5 (9.8)	57 (5.4)	2.22
Intubation	74	8 (4.2)	55 (1.7)	0 (0)	11 (1)	2.16
ICU admission	88	9 (4.7)	62 (2)	4 (7.8)	13 (1.2)	3.13

ICU: intensive care unit.

ber of cases involving certain drugs or adverse events may have resulted in beta error.

In any case, there is little literature addressing the direct relationship between AIs due to drugs and secondary seizures in Spain. The only indirect references we identified are the prospective multicenter studies by Fernández-Alonso *et al.*, reporting toxic seizure incidences ranging from 8.3%[20] to 13.4%, although these studies did not provide further detail on the substances involved.[6]

In conclusion, we did not find a direct association between seizures and specific drug groups, although seizure risk was highest when the substance consumed was unknown—highlighting the potential need for more precise toxicological analytical methods.[21] We also found no gender-based differences in seizure episodes. Furthermore, since 6 out of every 100 patients treated present seizures, at least those involving unknown substances should be placed in ED areas allowing close monitoring and immediate access to advanced life-support techniques.

Future studies on seizures due to intoxications should include samples with broader territorial representation, access to at least qualitative analytical data, and improved detection of NPS.[2]

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ADDENDUM

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