Neurotoxicology 73 (2019) 183–187

Contents lists available at ScienceDirect

Neurotoxicology

journal homepage: www.elsevier.com/locate/neuro

Full Length Article

Seizures as a complication of recreational drug use: Analysis of the Euro-DEN Plus data-set

Caitlin E. Wolfe[a,*], David M. Wood[a,b], Alison Dines[a], Benjamin P. Whatley[c], Christopher Yates[d], Fridtjof Heyerdahl[e], Knut Erik Hovda[e], Isabelle Giraudon[f], Paul I. Dargan[a,b], Euro-DEN Research Group[1]

[a] Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, London, UK
[b] Clinical Toxicology, Faculty of Life Sciences and Medicine, King's College London, London, UK
[c] Clinical and Experimental Epilepsy, Queen Square Institute of Neurology, University College London, London, UK
[d] Emergency Department and Clinical Toxicology Unit, Hospital Universitari Son Espases, Mallorca, Spain
[e] The Norwegian CBRNe Centre of Medicine, Oslo University Hospital, Oslo, Norway
[f] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal

ARTICLE INFO

Keywords:
Seizure
Recreational drug
New psychoactive substances
Acute toxicity
Synthetic cannabinoid

ABSTRACT

Seizures are a recognized and potentially serious complication of recreational drug use. This study examined a large international data set of presentations to Emergency Departments with acute recreational drug toxicity, the European Drug Emergencies Plus (Euro-DEN Plus) Network, to compare presentations with and without seizures and estimate incidence and associated drugs. Amongst 23,947 presentations between January 2014 and December 2017, there were 1013 (4.2%) with reported seizures. Clinical and demographic features were similar between individuals who had a seizure and those who did not, although rates of coma, cardiac arrest, intubation, intensive care admission, and death were significantly higher in those with seizures. There was a significant association between specific drugs and a higher seizure incidence, including fentanyl (odds ratio 2.63, 95% confidence interval 1.20–5.80), and synthetic cannabinoids (OR 2.90, 95% CI 2.19–3.84). Other drugs were associated with a lower seizure incidence, including 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). This substantiates observations that the synthetic cannabinoids as a group of novel psychoactive substances are clinically different in consequence of intoxication than cannabis, and that individuals who suffer a seizure in the context of recreational drug intoxication are likely to have worse outcomes overall. Utilising this information of what substances have a greater risk of seizures, could provide tailored harm reduction and education strategies to users to reduce the risk of seizures and their associated complications.

1. Introduction

Seizures are an important and potentially severe clinical consequence in toxicology and can be caused by a variety of potential toxins including classical recreational drugs and new psychoactive substances (NPS), pharmaceutical medicines, and other exposures (Reichert et al., 2014; Sharma and Hoffman, 2011). Although multiple substances are known to promote seizure activity, the incidence and risk associated with specific substances is difficult to quantify and estimates vary widely. Various studies have identified that between 6 and 47% of patients presenting with a first seizure are likely to have had a toxic or metabolic cause (Sharma and Hoffman, 2011). It can be difficult to recognise a seizure as being secondary to a toxin in the acute care setting, and screening is infrequently done to detect undisclosed

* Corresponding author.
E-mail address: caitlin.wolfe@gstt.nhs.uk (C.E. Wolfe).

[1] Euro-DEN Research Group (Corporate Author): Kurt Anseeuw, Robertas Badaras, Jeffrey Bonnici, Miran Brvar, Blazena Caganova, Alessandro Ceschi, Florian Eyer, Miguel Galicia, Stefanie Geith, Johan Gillebeert, Damjan Grenc, Ketevan Gorozia, Karim Jaffal, Gesche Jürgens, Piotr Maciej Kabata, Iarlaith Kennedy, Jutta Konstari, Soso Kutubidze, Gabija Laubner, Evangelia Liakoni, Matthias E Liechti, Cathelijne Lyphout, Bruno Mégarbane, Òscar Miró, Adrian Moughty, Laura Müller, Niall O'Connor, Raido Paasma, Juan Ortega Perez, Marius Perminas, Per Sverre Persett, Kristiina Põld, Jordi Puiguriguer, Julia Radenkova-Saeva, Jan Rulisek, Yasmin Schmid, Irene Scholz, Radhika Sopirala, Jonas Surkus, Ibolya Toth, Odd Martin Vallersnes, Federico Vigorita, Wojciech Waldman, W Stephen Waring, Sergej Zacharov.

https://doi.org/10.1016/j.neuro.2019.04.003
Received 25 January 2019; Received in revised form 4 April 2019; Accepted 4 April 2019
Available online 08 April 2019
0161-813X/

use of a substance known to cause seizures. Furthermore, seizures may also be provoked by withdrawal from chronic use of a substance, which may no longer itself be obvious at the time of presentation.

Any seizure, toxin related or not, is associated with an increased risk of other complications. These include status epilepticus, cardiac arrhythmia and other ECG changes, aspiration pneumonitis, anoxic brain injury, rhabdomyolysis, hyperthermia and mortality (Thundiyil et al., 2011). One study demonstrated that 18% of 204 reviewed cases of status epilepticus were caused by ethanol or drug overdose, with a mortality rate exceeding 20% (DeLorenzo et al., 1996), although other series have demonstrated lower mortality for toxin induced seizures over other causes (Towne et al., 1994).

Furthermore, a seizure that is demonstrably related to a toxic exposure has implications for management. For instance, a computerized tomography scan or other imaging of the brain may not be required for an isolated first seizure if a plausible toxic cause is known. Knowledge of the mechanism of seizure promotion can also predict the difficulty in controlling seizures, and guide choices between next steps in management (Sharma and Hoffman, 2011; Tetrault and O'Connor, 2008), For example, although benzodiazepines are the mainstay of treatment for most seizures, pyridoxine may be required for gamma-aminobutyric acid (GABA) depleting toxins such as isoniazid, and common second line agents like phenytoin are less efficacious against many drug-induced seizures (Shah and Eddleston, 2010; Wills and Erickson, 2005).

The pathophysiology of toxin related seizures is proposed to have four main mechanisms: i) activity at both *N*-methyl-D-aspartate (NMDA) and GABA receptors; ii) alteration of neuronal resting potential by disturbing ion movements; iii) antagonism of adenosine; and/or iv) alteration in biogenic amine and acetylcholine function (Wills and Erickson, 2005; Sharma and Hoffman, 2011). The first of these mechanisms is likely to have the greatest clinical relevance for commonly implicated toxins, and creates over excitation by decreasing the baseline inhibitory tone. Ethanol in chronic use, for instance, provokes compensatory increases in NMDA proteins and decreased GABA function, altering the balance in favour of excitatory glutamate transmission and decreasing inhibitory tone (Nagy, 2008). This can produce seizures in susceptible patients within 6–48 h of cessation of intake (Leach et al., 2012; Tetrault and O'Connor, 2008). Other substances, such as amphetamine-type stimulants and cocaine lower seizure threshold by enhancing monoamine neurotransmission (Leach et al., 2012; Sanchez-Ramos, 2015), or contribute to sensitization of brain tissue to spread of a generated stimulus (Wills and Erickson, 2005). Toxin related seizures may also be provoked by indirect means, including anoxic injury in highly sedating overdoses that produce respiratory failure, haemorrhagic/ischemic stroke from increases in blood pressure and/or cerebral artery vasospasm, brain trauma secondary to falls or injury, or severe metabolic and biochemical derangement such as hyponatremia (Sanchez-Ramos, 2015).

NPS and recreational drugs that have been associated with seizures include stimulants such as cocaine, amphetamine and mephedrone, along with some opioids that have serotonergic activity such as fentanyl and tramadol; prescription drugs most commonly associated with seizures include antidepressants, particularly tricylic antidepressants and anti-psychotics (Reichert et al., 2014; Rickli et al., 2018; Sharma and Hoffman, 2011; Wills and Erickson, 2005).

Few studies to date have attempted to use toxicology surveillance data on toxic exposures to derive a better understanding of which substances are resulting in seizures and associated clinical outcomes. One such study, conducted in 2011 in California in a regional poison control centre demonstrated an overall complication rate of 60% in 138 drug-related seizure presentations, with fewer complications in unintentional overdoses rather than those taken with suicidal or recreational intent (Thundiyil et al., 2011). The most commonly ingested pharmacological categories were anti-depressants (33.9%), stimulants (14.9%) and anticholinergics (9.9%), and the most common single drug was bupropion (14.9%). Another study of single-agent pharmaceutical ingestions reported to a poison centre in Switzerland identified 313 seizures in a series of 15,411 presentations, again demonstrated that anti-depressants were associated with seizure in single-agent overdoses (Reichert et al., 2014). None of these studies specifically examined recreational use, or emergency department presentations.

This study aimed to utilize clinical presentations, reported to the Euro-DEN Plus network, with acute recreational drug and NPS toxicity to identify the recreational substances most commonly implicated in seizures, the relative risk conferred by their use and determine the clinical and demographic differences between presentations with a seizure and those without.

2. Methods

The European Drug Emergencies Plus Network (Euro-DEN Plus) collates cases of acute recreational drug and NPS toxicity related presentations to 32 Emergency Departments (sentinel centres) in 21 countries across Europe (Wood et al., 2014). Data collected includes demographic data, reported substances used prior to the presentation, clinical features and signs/physiological parameters and outcome measurements (survival and overall length of stay). The Euro-DEN Plus database was retrospectively interrogated to identify all cases between 1 January 2014 and 31 December 2017 inclusive were examined. Substances are named by self-report, and in general are not analytically confirmed or excluded in a laboratory setting. All data were anonymised, and were handled throughout in compliance with relevant national privacy legislation and ethical approvals in each sentinel centre.

A seizure was defined as any type of generalized tonic-clonic, myoclonic, partial or focal seizure that occurred once or more within the patient's presentation. Inclusion criteria was the documentation of the presence or absence of a seizure; cases with unknown or unreported seizure status were excluded. Those with and without seizures were then compared with regard to: demographic data (age, gender), presenting parameters (arrival by ambulance versus other, as well as initial temperature, heart rate, blood pressure, and Glasgow Coma Scale (GCS)), number of substances taken, ethanol co-ingestion, individual drugs by name, classes of drugs, outcomes (arrhythmia, intubation, and death in hospital), and disposition from the emergency department. Vital signs were compared to the normal range definitions used by the Royal College of Emergency Medicine (The College of Emergency Medicine, 2014). Only GCS values reported numerically were included (not the "alert, verbal, pain, unresponsive" system, where used instead). All parameters were found to be non-normally distributed, and Mann-Whitney *U* tests were performed throughout. Data was cleaned of any clear errors or non-physiologically possible values by identifying outliers. To achieve adequate sample size for results, drugs were only included for analysis if present at least 10 times within the database (as a single agent or in combination). These calculations were performed in Excel (Microsoft, 2013) and SPSS (v-25, IBM).

Substances were further examined in the whole data including presentations with multiple co-ingestants, as well as in only single substance presentations, to calculate odds ratios for seizure by substance (in comparison to the baseline seizure rate). Substances were again included for analysis if present 10 times in the database. As there were multiple branded and unbranded listings for synthetic cannabinoids in the data set, these were combined to give a single odds ratio. Substances were grouped into pharmacological class and re-analysed for group comparisons; these included benzodiazepines (including zopiclone and zolpidem), hallucinogens (including ketamine, lysergic acid diethylamide (LSD), psilocybins etc.), opioids (including heroin, morphine, fentanyl, tramadol, codeine etc.), and stimulants (including cocaine, amphetamines, mephedrone, cathinones etc.). All other substances were classified as 'other'. These were analysed in MatLab (v-R2018b, Mathworks).

Table 1
Presenting clinical features.

	N	Seizure group Median (IQR)	No seizure group Median (IQR)	p
Temperature	17653	36.5 (36.0–36.9)	36.4 (35.9–36.8)	< 0.001
Heart rate	21779	94 (78–114)	90 (75–106)	< 0.001
Systolic BP	19910	128 (116–140)	125 (113–139)	0.004
Diastolic BP	14724	77 (66–86)	77 (66–87)	0.619
RR	16656	16 (14–20)	16 (14–18)	< 0.001
GCS	14473	14 (8–15)	15 (13–15)	< 0.001

3. Results

A total of 23,947 cases were reviewed, of which 22,919 (95.7%) had data recorded on whether or not a seizure had occurred. Of these, 1013 had a seizure (4.4%), and 21,906 did not (95.6%).

Age was similar but statistically different between the groups, with a median age of 30 years (interquartile range, IQR, 25–39) in the seizure group, and 31 years in the non-seizure group (IQR 24–38, p = 0.003). Gender was not significantly different between the groups, with males representing 79.1% of the seizure group and 76.0% of the no-seizure group (p = 0.07).

There were statistically significant differences in terms of higher median temperature, heart rate, systolic blood pressure, and respiratory rate, and lower GCS in the seizure group (see Table 1). Despite medians being similar, the groups differed in terms of proportion of individuals with abnormal vital signs, with higher percentages of individuals in the seizure group having abnormal vitals at presentation. In the seizure group 40.6% were tachycardic at presentation (heart rate greater than 100 beats per minute), while only 30.8% of the no seizure group were tachycardic (p < 0.001). The same was true for hyperthermia (temperature > 38 °C), where 3.4% versus 1.9% were hyperthermic at arrival (p = 0.002). However hypopnea (respiratory rate less than 10 per minute) was equally likely in either group, at 5.6% in both; as was either hypertension (systolic blood pressure greater than 180 mmHg, in 0.9% of those who seized and 1.3% of those who didn't) or hypotension (systolic blood pressure less than 100 mmHg, in 6.3% versus 7.2%).

The group with seizures was more likely to come to hospital by ambulance, with 88.0% presenting by ambulance compared to 70.5% of the no-seizure group (odds ratio 3.24, 95% confidence interval 2.64–3.98, p < 0.001). The seizure group was more likely to present obtunded, with a GCS of less than or equal to 8 (OR 3.34, p < 0.001, 95% CI 2.82–3.96). They were also more likely to present in cardiac arrest, as 1.1% of the seizure group presented in arrest versus 0.5% of the no-seizure group (OR 2.16, p = 0.001, 95% CI 1.16–4.02).

There were 433 unique substances listed in the database, of which 84 met the inclusion criterion of 10 or more presentations. The number of substances used was similar between the two groups, with a median (IQR) number used per presentation of 1 (1–2) in the seizure group, and in the no-seizure group of 1 (1–2). Both benzodiazepines and opioids were more commonly used in the non-seizure group (benzodiazepines: used in 6.3% of seizure presentations and 13.2% of seizure free presentations, p = 0.002; opioids: used in 15.5% and 22.0% respectively, p = 0.002). Conversely, synthetic cannabinoids (used in 4.8% and 1.8%, p = 0.002), stimulants (used in 40.9% and 33.2%, p = 0.002), and gamma-hydroxybutyrate (GHB); used in 11.7% and 8.9%, p = 0.002) were all more frequently present in the seizure group. There was no significant difference in rates of use of cannabis (used in 10.9% and 11.8%, p = 0.37), or hallucinogens (used in 2.3% in both, p = 0.92).

When individual drugs (taken alone or in any combination) were examined by univariate analysis for significant associations with seizure likelihood, several reached statistical significance (see Table 2 for the complete list of significantly associated substances). Of these, the most relevant were fentanyl (OR 3.11, 95% CI 1.91–5.04), the synthetic cannabinoids (OR 2.92, 95% CI 2.29–3.73), and tramadol (OR 2.87, 95% CI 1.57–5.26), as these compounds all differed from the trend of their broader pharmacologic class.

Table 2
Substances with significant associations with seizure frequency, in any presentation; 3-MMC refers to 3-methylmethcathinone, and MDMA to 3,4-Methylenedioxymethamphetamine.

Substance	N ingestions	N seizures	OR (95% CI)	p
3-MMC	25	4	4.13 (1.42–12.06)	0.023
Fentanyl	158	19	3.11 (1.91–5.04)	< 0.001
Synthetic cannabinoids	695	77	2.92 (2.29–3.73)	< 0.001
Tramadol	107	11	2.87 (1.57–5.26)	0.002
MDMA	2013	137	1.8 (1.49–2.16)	< 0.001
GHB	3140	170	1.35 (1.14–1.63)	< 0.001
Cocaine	4460	221	1.27 (1.09–1.48)	0.002
Heroin	5159	126	0.51 (0.42–0.62)	< 0.001
Diazepam	792	15	0.42 (0.25–0.71)	< 0.001
Alprazolam	519	6	0.25 (0.11–0.57)	< 0.001
Clonazepam	1212	13	0.23 (0.13–0.39)	< 0.001
Oxazepam	202	0	–	0.002

However, when drugs were examined for single drug presentations, the results were slightly different. For instance, 3-MMC was the most strongly associated overall, but had no significant association in the single drug presentations, of which there were only 9 cases (and one seizure). Benzodiazepines as a class represented 924 single drug ingestions (OR 0.45 for seizure, 95% CI 0.29–0.71, p = 0.002), and opioids (including fentanyl) comprised 3288 single ingestions (OR 0.54, 95% CI 0.43–0.68, p < 0.001). The remainder of the classes had no significant association with seizure frequency. Conversely, fentanyl itself remained significantly associated with an increased risk of seizure (OR 2.63, 95% CI 1.20–5.80), as did the synthetic cannabinoids (OR 2.90, 95% CI 2.19–3.84). Heroin (OR 0.46, 95% CI 0.35–0.61) and clonazepam (OR 0.22, 95% CI 0.06–0.91) remained statistically associated with decreased likelihood of seizure, while the other benzodiazepines and opioids had a non-significant trend towards the same. Cannabis also achieved significance in its association with decreased seizure frequency in the single drug ingestion group (OR 0.65, 0.50–0.86). See Table 3 for the list of all substances with statistically significant associations.

More individuals in the seizure group had an arrhythmia recorded (2.8%) than in the no seizure group (1.2%; OR 2.38, 95% CI 1.56–3.56, p < 0.001). There was also a strong association between seizure and intubation rate, with 13.8% of the individuals in the seizure group having been intubated during the presentation, compared with 2.8% of the no seizure group (OR 5.56, 95% CI 4.56–6.77, p < 0.001).

Disposition from the emergency department was also different between the groups, with only 40.7% of the seizure group being medically discharged from the department compared to 58.8% of the no seizure group (OR 0.48, 95% CI 0.42–0.55, p < 0.001). The seizure group were more likely to be admitted to hospital overall, 21.1% versus 18.2% (OR 1.53, 95% CI 1.30–1.80, p < 0.001) and much more likely to be admitted to critical care, 19.6% versus 5.5% (OR 4.22, 95% CI 3.58–4.99, p < 0.001). Length of stay was correspondingly longer in the seizure group, with a median length of stay of 7 h and 30 min (IQR 3 h 16 min–21 h 55 min) compared to 4 h and 40 min in the no seizure group (IQR 2 h 31 min–9 h 27 min; p < 0.001).

There was also a greater proportion of deaths in the seizure group, in which 9 individuals died (0.9% of the group) while 86 individuals in the no seizure group died (0.4%; OR 2.27, 95% CI 1.14–4.53, p = 0.002). Of the deaths in the seizure group, three had ingested cocaine alone, one each a single ingestion of MDMA, GHB and methadone, two were polysubstance ingestions (one with cocaine and MDMA; one with amphetamine, methylone, and 3,4-methylenedioxy-*N*-

Table 3
Substances with significant association with seizure frequency, in single drug presentations.

Substance	Single N (% of total ingestions of substance)	Seizures N (% of seizures with this substance)	OR (95% CI)	p
Fentanyl	68 (43%)	7 (32%)	2.63 (1.20–5.80)	0.024
Synthetic cannabinoids	529(76%)	59 (76%)	2.94 (2.08–4.17)	< 0.001
MDMA	907 (45%)	59 (43%)	1.65 (1.25–2.18)	< 0.001
GHB	1506 (49%)	92 (54%)	1.45 (1.16–1.82)	0.002
Heroin	2517 (49%)	57 (45%)	0.46 (0.35–0.61)	< 0.001
Clonazepam	191 (16%)	2 (15%)	0.22 (0.06–0.91)	0.013
Cannabis	1952 (49%)	61 (38%)	0.65 (0.50–0.86)	0.002

ethylamphetamine), and one was an ingestion of an unknown substance.

4. Discussion

This study examined factors associated with seizures in a large, international data set of presentations to the Emergency Department with acute recreational drug toxicity. It confirmed that several drugs that are anecdotally related to seizure frequency in clinical practice are statistically associated with increased seizure frequency in this cohort of patients. We also found that in this data set there was very little clinically relevant difference in terms of presenting vital signs, demographic characteristics, or numbers of substances taken between the group who had a seizure during their presentation and those who did not. Biologically plausible trends were present, with some reaching significance, including more cases of hyperthermia at presentation in the seizure group as would be expected given the association of serotonin syndrome both with true seizures and the propensity for the neuromuscular excitation of the syndrome to be misjudged as a seizure (Sharma and Hoffman, 2011; Koury et al., 2015). There were, however, significant differences between the groups in terms of other key clinical outcomes, including a higher rate of intubation, arrhythmia, admission to intensive care, and death.

The comparison of the risk of seizures with different drugs in multiple and single drug ingestions is a potentially useful one, despite being unable to analytically verify the true number of compounds taken. The presentations with multiple drugs ingested are an accurate reflection of real world practice among recreational drug users presenting to the Emergency Department with acute drug toxicity (in the dataset as a whole 36.8% of presentations presented with stated polydrug use). We have shown in this study that that several drugs are associated with increased seizure risk in the data set as a whole, generally those with biological or historic plausibility of a causal association including stimulants, synthetic cannabinoids, GHB and fentanyl. In numerous presentations, multiple potentially pro-convulsant drugs were taken. However, the analysis of those presentations in which only a single drug was declared confirmed that most of these associations remain significant, in particular for synthetic cannabinoids, fentanyl, GHB, and MDMA.

Furthermore, as would be expected, multiple drugs from the benzodiazepine and opioid classes are associated with a lower incidence of seizures; important exceptions to this are fentanyl and tramadol which are opioids with an increased risk of seizures. There are numerous reports in the anaesthetic literature of fentanyl causing seizures in the peri-operative period, although later studies did not demonstrate any cortical seizure activity on simultaneous electroencephalography (Holen, 1984; Safwat and Daniel, 1983; Scott and Sainquist, 1985; Webb, 1990). Fentanyl has also been implicated in numerous case reports/series in contributing to serotonin syndrome, and has been shown to have direct pharmacological activity on the serotonin system which is likely at least in part to explain the association with seizures in those with acute fentanyl toxicity (Koury et al., 2015; Rickli et al., 2018). It is also possible that the potency of fentanyl contributed to more severe toxicity, including greater respiratory depression and subsequent seizure than other opioids, although this was not directly examined in our data-set.

Synthetic cannabinoids were strongly associated with seizure, while cannabis use alone was associated with lower incidence of seizures. This corroborates the growing body of evidence that these drugs behave completely differently from cannabis, despite the enduring association by name (Havenon et al., 2011). The structure of these synthetic ligands for the endocannabinoid receptors differ markedly from cannabis, and are potent central nervous system depressants with additional stimulant like properties (Adams et al., 2017; Lovett et al., 2015). Indeed, agitation, delirium, psychosis and cardiotoxicity are significantly more likely in synthetic cannabinoid usage than cannabis (Adams et al., 2017; Hill et al., 2016; Lovett et al., 2015; Zaurova et al., 2016).

The most significant limitation of the study is the self-reported nature of the drug(s) involved in the presentations, with no information recorded about the quantity, order, or timing of the drugs taken. This particularly may complicate our attempted distinction between multiple and single drug presentations. However, a study of the Euro-DEN data set from 2013 to 2015 demonstrated high concordance between self-reported drug use and analytically detected compounds (Liakoni et al., 2018). Further, in presentations with multiple drugs used by a single individual, it is not possible to quantify the relative doses consumed, and therefore to determine which is likely responsible for any clinical consequences, including seizures. Whilst this information may be available from users, the amount used is often reported in terms of number of tablets and/or amount of powder/liquid used; given the variability in purity and content of recreational drugs and NPS used, analysis of this information may not be helpful as users are unable to report a “true dose used”. The usual limitations of a retrospective analysis of data that collected without this express purpose also limit our post hoc conclusions; however a standardised purpose designed database is used to collect the Euro-DEN Plus data. A further limitation is that that analysis was not blinded to the seizure status of the presentations.

Given the rate of seizures demonstrated in this case series, with around 4% of presentations involving a seizure, at a European level this would equate to many thousands of individuals presenting with recreational drug and NPS related seizures per year. Not only will these presentations be associated with high utilisation and cost of pre-hospital and hospital services and resources, there is the potential that they will lead to significant individual and population level morbidity and mortality. Utilising this information of what substances have a greater risk of seizures could provide tailored harm reduction and education strategies to users to reduce the risk of seizures and their associated complications. Furthermore, we encourage clinicians to consider substance use early in their approach to the patient with an unexplained seizure, particularly given the high morbidity.

Funding sources

The Euro-DEN project has received financial support from the DPIP/ISEC Programme of the European Union (2013–2015) and the Euro-

DEN Plus project has received financial support from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) from 2015 onwards.

MEL and YSL received funding from the Swiss Centre of Applied human Toxicology (SCAHT).

AC and LM received funding from the Scientific Research Advisory Board of the Ente Ospedaliero Cantonale (ABREOC).

Transparency document

The Transparency document associated with this article can be found in the online version.

References

Adams, A., Banister, S., Irizarry, L., Trecki, J., Schwartz, M., Gerona, R., 2017. "Zombie" outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York. N. Engl. J. Med. 235–242.

DeLorenzo, R.J., Hauser, W.A., Towne, A.R., Boggs, J.G., Pellock, J.M., Penberthy, L., Garnett, L., Fortner, C.A., Ko, D., 1996. A prospective population-based epidemiologic study of status epilepticus in Richmond, Virgina. Neurology 1029–1035.

Havenon, A., Chin, B., Thomas, K., Afra, P., 2011. The secret "spice": an undetectable toxic cause of seizure. Neurohospitalist 182–186.

Hill, S., Najafi, J., Dunn, M., Acheampong, P., Kamour, A., Grundlingh, J., et al., 2016. Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMB-CHMICA. A report from the Identification of Novel psychoActive substances (IONA) study. Clin. Toxicol. 638–643.

Holen, A., 1984. Another case of grand mal seizure after fentanyl administration. Anesthesiology 387.

Koury, B., Tsui, B., Gulur, P., 2015. Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents. Pain Physician 27–30.

Leach, J., Mohanraj, R., Borland, W., 2012. Alcohol and drugs in epilepsy: pathophysiology, presentation, possibilities, and prevention. Epilepsia 48–57.

Liakoni, E., Yates, C., Dines, A.M., Dargan, P.I., Heyerdahl, F., Hovda, K.E., et al., 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, 5.

Lovett, C., Wood, D., Dargan, P., 2015. Pharmacology and toxicology of the synthetic cannabinoid receptor agonists. Reanimation 527–541.

Nagy, J., 2008. Alcohol related changes in regulation of NMDA receptor functions. Curr. Neuropharmacol. 39–54.

Reichert, C., Reichert, P., Monnet-Tschudi, F., Kupferschmidt, H., Ceschi, A., Rauber-Luthy, C., 2014. Seizures after single-agent overdose with pharmaceutical drugs: analysis of cases reported to a poison center. Clin. Toxicol. 52, 629–634.

Rickli, A., Liakoni, E., Hoener, M., Liechti, M.E., 2018. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. Br. J. Pharmacol. 175, 532–543.

Safwat, A., Daniel, D., 1983. Grand mal seizure after fentanyl administration. Anesthesiology 790.

Sanchez-Ramos, J., 2015. Neurologic complications of psychomotor stimulant abuse. Int. Rev. Neurobiol. 131–160.

Scott, J., Sainquist, F., 1985. Seizure-like movements during a fentanyl infusion with absence of seizure activity in a simultaneous EEG recording. Anesthesiology 812–814.

Shah, A., Eddleston, M., 2010.). Should phenytoin or barbiturates be used as second-line anticonvulsant therapy for toxicological seizures? Clin. Toxicol. 800.

Sharma, A., Hoffman, R., 2011. Toxin-related seizures. Emerg. Med. Clin. North Am. 125–139.

Tetrault, J., O'Connor, P., 2008. Substance abuse and withdrawal in the critical care setting. Crit. Care Clin. 767–788.

The College of Emergency Medicine, 2014. Clinical Standards for Emergency Departments. The College of Emergency Medicine, London.

Thundiyil, J., Rowley, F., Papa, L., Olson, K., Kearney, T., 2011. Risk factors for complications of drug-induced seizures. J. Med. Toxicol. 16–23.

Towne, A., Pellock, J., Ko, D., DeLorenzo, R., 1994. Determinants of mortality of status epilepticus. Epilepsia 27–34.

Webb, M., 1990. Seizure-like activity during fentanyl anesthesia. Anesth. Prog. 306–307.

Wills, B., Erickson, T., 2005. Drug and toxin associated seizures. Med. Clin. North Am. 1297–1321.

Wood, D., Heyerdahl, F., Yates, C., Dines, A., Giraudon, I., Hovda, K., Dargan, P., 2014. The European Drug Emergencies Network (Euro-DEN). Clin. Toxicol. 239–241.

Zaurova, M., Hoffman, R., Vlahov, D., Manini, A., 2016. Clinical effects of synthetic cannabinoid receptor agonists compared with marijuana in emergency department patients with acute drug overdose. J. Med. Toxicol. 335–340.