European Journal of Clinical Pharmacology (2019) 75:77–85
https://doi.org/10.1007/s00228-018-2550-1

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Presentations to the emergency department with non-medical use of benzodiazepines and Z-drugs: profiling and relation to sales data

C . Lyphout[1,2] · C. Yates[3] · Z. R. Margolin[4] · P. I. Dargan[1,5] · A. M. Dines[1] · F. Heyerdahl[6] · K. E. Hovda[6] · I. Giraudon[7] · B. Bucher-Bartelson[4] · J. L. Green[4,8] · Euro-DEN Research Group · D. M. Wood[1,5]

Received: 19 February 2018 / Accepted: 29 August 2018 / Published online: 22 September 2018

Abstract

Background Non-medical use of benzodiazepines and Z-drugs is common; however, there is limited information available on the extent of harm related to this in Europe, as well as the relationship between misuse and availability.

Aim To describe presentations to the emergency department in Europe related to the recreational use of benzodiazepines and Z-drugs and compare regional differences in these presentations with legal drug sales of benzodiazepines and Z-drugs within each country.

Methods Emergency department presentations with recreational misuse of benzodiazepines and Z-drugs were obtained from the Euro-DEN dataset for the period from October 2013 to September 2015; data extracted included demographics, clinical features, reported coused drugs, and outcome data. Sales figures obtained by QuintilesIMS™ (Atlanta, Georgia) were used to compare regional differences in the proportion of benzodiazepines and Z-drugs in the emergency department presentations and legal drug sales across Europe.

Results Over the 2 years, there were 2119 presentations to the Euro-DEN project associated with recreational use of benzodiazepines and/or Z-drugs (19.3% of all Euro-DEN presentations). Presentations with 25 different benzodiazepines and Z-drugs were registered in all countries, most (1809/2340 registered benzodiazepines and Z-drugs, 77.3%) of which were prescription drugs. In 24.9%, the benzodiazepine was not specified. Where the benzodiazepine/Z-drug was known, the most frequently used benzodiazepines and Z-drugs were respectively clonazepam (29.5% of presentations), diazepam (19.9%), alprazolam (11.7%), and zopiclone (9.4%). The proportions of types of benzodiazepines/Z-drugs related to ED-presentations varied between countries. There was a moderate (Spain, UK, Switzerland) to high (France, Ireland, Norway) positive correlation between ED presentations and sales data (Spearman Row's correlation 0.66–0.80, $p < 0.005$), with higher correlation in countries with higher ED presentation rates.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-018-2550-1) contains supplementary material, which is available to authorized users.

✉ C . Lyphout
cathelijne.lyphout@uzgent.be

C. Yates
christopher.yates@ssib.es

Z. R. Margolin
zachary.margolin@rmpdc.org

P. I. Dargan
paul.dargan@gstt.nhs.uk

A. M. Dines
alison.dines@gstt.nhs.uk

F. Heyerdahl
frihey@ous-hf.no

K. E. Hovda
knuterikhovda@gmail.com

I. Giraudon
isabelle.giraudon@emcdda.europa.eu

B. Bucher-Bartelson
Becki.bucher@gmail.com

J. L. Green
jgreen@inflexxion.com

D. M. Wood
david.wood@gstt.nhs.uk

Extended author information available on the last page of the article

Conclusion Presentations to the emergency department associated with the non-medical use of benzodiazepines and/or Z-drugs are common, with variation in the benzodiazepines and/or Z-drugs between countries. There was a moderate to high correlation with sales data, with higher correlation in countries with higher ED presentation rates. However, this is not the only explanation for the variation in non-medical use and in the harm associated with the non-medical use of benzodiazepines/Z-drugs.

Keywords Acute toxicity · Benzodiazepine · Z-drug · Prescription · Emergency department · Euro-DEN

Introduction

Benzodiazepines are sedative drugs which are classified as Schedule IV drugs under the 1971 United Nations convention on psychotropic substance classification (except for flunitrazepam which falls under Schedule III) [1]. They increase the binding of γ-aminobutyric acid (GABA) primarily at the $GABA_A$-receptor, and to a lesser extent at the $GABA_B$-receptor, which causes a sedative-hypnotic effect [2]. Benzodiazepines are prescribed for short-term treatment of severe insomnia and anxiety [3].

Z-drugs (e.g., zolpidem and zopiclone) are a group of non-benzodiazepine hypnotics that were introduced in the mid to late 1980s as an alternative to the benzodiazepines [4].

Z-drugs are chemically distinct from benzodiazepines but share their clinical effects via a similar mode of action. There appears to be a differential binding of Z-drugs to the various $GABA_A$ receptor isoforms, resulting in a potent sedative and hypnotic effect with minimal anxiolytic and anti-epileptic efficacy [5]. Among them, only zolpidem is classified as a Schedule IV drug [6]. Zolpidem is a short-acting non-benzodiazepine compound of the imidazopyridine class that binds to $GABA_A$ receptors at the same location as benzodiazepines. Zopiclone is a cyclopyrrolone and has a similar mode of action [5]. Zaleplon was withdrawn from the European market in 2015 [7, 8].

The growing non-medical use of prescription drugs is a global health concern [4]. Non-medical use can be defined as the use of prescription drugs, whether obtained by prescription or otherwise, other than in the manner or for the reasons or time period prescribed or recommended by a doctor/pharmacist, or by a person for whom the drug was not prescribed [9]. Non-medical use is also sometime referred to as recreational use or misuse—we will use the term non-medical use in this paper.

Non-medical use of benzodiazepines and Z-drugs have been described in the medical literature since the 1990s; however, there is limited data on the extent of non-medical use of benzodiazepines and/or Z-drugs [10–13]. An online questionnaire of 1500 UK respondents published in 2014 reported a life-time prevalence of non-medical use of 7.7% for benzodiazepines and/or Z-drugs; almost one third (31%) of those reporting non-medical use reported "to get high" as the reason for this [14]. In a recent study of 296 HIV-positive patients in San Francisco, 25.3% reported non-medical use of benzodiazepines [15]. Non-medical use of benzodiazepines is common in up to 51–70% of heroin users and also in patients on methadone and/or buprenorphine substation therapy [2, 16]. Although benzodiazepines are prescribed to high-risk drug users for legitimate therapeutic purposes (treatment of insomnia, anxiety), there are concerns relating to unintended health consequences associated with the use of benzodiazepine for longer periods (e.g., more than 2 to 3 weeks), polydrug use, and use that is not in accordance with prescribing guidelines [16]. High-risk opioid users typically misuse benzodiazepines to self-medicate or to increase the effects of opioids [17].

Availability of drugs is a crucial factor for the non-medical use of all types of psychotropic substances [18–21]. A web-based survey conducted in UK found that the most common source for non-medical use of benzodiazepines and Z-drugs was a prescription from a health professional (55.2%) [14]. Other sources included friends and/or family (39.7%), bought from the Internet (26.7%), street dealers (19.8%), or obtained from abroad (11.2%). The American National Center on Addiction and Substance Abuse (CASA) reports that physicians perceived the three main mechanisms of diversion to be (i) patient doctor-shopping, (ii) patient deception or manipulation of doctors, and (iii) forged or altered prescriptions. This aligns with Kapil's finding that the main source of benzodiazepines or Z-drugs for non-medical use is prescription from a health professional [22].

Different sources of information, such as prescription data and sales data, may indicate the availability of benzodiazepines and/or Z-drugs for non-medical use, but are not always readily accessible. The illegal market for benzodiazepines or Z-drugs, and especially the novel benzodiazepines, is difficult to map so indirect indicators are required (e.g., drug seizures). To our knowledge, the relationship between ED presentations related to non-medical use of benzodiazepines and/or Z-drugs and the national sales data of these substances has not been discussed in the literature.

In this paper, (i) for the whole Euro-DEN dataset over the indicated period, we describe acute drug toxicity presentations where benzodiazepines or Z-drugs are involved and compare them with acute drug toxicity presentations where these drugs are not involved, and (ii) for the countries where benzodiazepines or Z-drugs sales data are available, we combine data on presentations associated with the non-medical use of benzodiazepines and Z-drugs to the respective emergency department (ED) with national drug sales data.

Methods

Euro-DEN emergency department presentations

The European Drug Emergencies Network (Euro-DEN) has been collecting data on presentations to sentinel EDs across Europe with acute recreational drug toxicity since October 2013 [23]. The initial network, which collected data from October 2013 to September 2014, consisted of 16 sentinel centers from 10 European countries: Denmark (Copenhagen Oct 2014–Jun 2015, Roskilde July 2015–Sept 2015), Estonia (Tallinn, Pärnu), France (Paris), Germany (Munich), Ireland (Dublin and Drogheda), Norway (two centers in Oslo), Poland (Gdansk), Spain (Barcelona, Palma de Mallorca), Switzerland (Basel), and UK (York and two centers in London) [23, 24]. Subsequently, the network has expanded to 31 centers in 21 countries and is now known as "Euro-DEN Plus." The methodology for data collection, utilization of a minimum dataset for data collection, and the inclusion criteria for cases in the Euro-DEN/Euro-DEN Plus project has been previously described and are available in the online supplement [23, 24].

The Euro-DEN Plus project database was searched to identify cases involving the self-reported recreational use (non-medical use) of benzodiazepines and/or Z-drugs, with or without co-used other recreational drugs, new psychoactive substances and/or alcohol, between October 2013 and September 2015; only the original 16 sentinel centers were included as they had complete data collection for the 2-year period. Based on the underlying Euro-DEN methodology, benzodiazepines/Z-drugs are only recorded in the Euro-DEN database if an individual presents to participating acute care facilities with symptoms and/or signs consistent with acute recreational drug toxicity and directly related to recreational (non-medical) use of one or more benzodiazepine/Z-drug.

The following data were extracted from identified cases: (i) demographics, (ii) reported co-used drugs (including classical, established recreational drugs, new psychoactive substances, non-medical use of other prescription medicines and/or alcohol), (iii) clinical features prior to and/or during admission to hospital, and (iv) outcome data (overall length of stay following presentation to the ED, disposition from the ED and deaths). Additional analyses were undertaken for presentations involving use of benzodiazepines or Z-drugs without concomitant use of alcohol or drugs, presentations involving poly-drug use, use with or without alcohol, and per country.

Data were calculated in Excel® and presented as percentages or median (interquartile range, IQR) and p values. Benzodiazepine derivatives were categorized as benzodiazepines for the purpose of this paper.

Drug utilization data

Drug utilization data were obtained from IQVIA™ (Danbury, CT, USA) and were available from the beginning of 2011 through 2015 for 7/10 countries: France, Germany, Ireland, Norway, Spain, Switzerland, and UK. Data were not available for Denmark, Poland, or Estonia. Drug utilization-based rates provide an assessment of the use of prescription drugs adjusted for differences in drug volumes. This approach adjusts for the bias towards endorsements of widely prescribed or more readily available medications. Various measures of drug utilization are obtainable, depending on the country and can include total sales (reported in local currency), number of standard units sold, number of prescriptions dispensed, number of dosage units dispensed or total milligrams dispensed. To enable comparison, we used the number of standard units sold from the manufacturer to various channels (i.e., pharmacies, hospitals, supermarkets, online retailers, dispensing doctors, home care, and industry clinics). A standard unit for a tablet is the number of tablets sold, while for a patch, a standard unit is the number of patches sold, and for liquids, 5 ml is a standard unit.

Subgroups and comparators

Sales data for 17 benzodiazepines and 2 Z-drugs were analyzed and compared to benzodiazepines and Z-drugs encountered in the Euro-DEN dataset. The reported benzodiazepines and Z-drugs in the Euro-DEN dataset and available comparators in the IMS data are listed in the online supplement.

Statistical methods

Drug utilization-based rates were calculated as the number of Euro-DEN presentations for a particular drug in each country divided by the total standard units sold for that drug in that country. If more than one benzodiazepine or Z-drug was recorded in a presentation, this presentation was counted for each drug. A drug utilization rate of 0 indicates that there were no presentations for that particular drug. Drug utilization-based rates were scaled per 100,000 standard units sold.

Spearman correlation coefficients were calculated to quantify the strength of the monotonic relationship between the number of Euro-DEN presentations and the number of standard units sold. In addition, Spearman correlation coefficients were calculated between the percentage of Euro-DEN ED presentations for a given drug and the percentage of standard units available for that drug. The percentage of Euro-DEN presentations was calculated by enumerating the total cases reported for each respective drug and then dividing each drug by the total cases per country. P values were assessed to determine if the correlation value is statistically significantly different from 0.

All statistical procedures were performed using SAS® version 9.4 (SAS Institute Inc., Cary, North Carolina). All plotting procedures were performed using R Studio.

Results

Over the 2 years, there were 10,957 Euro-DEN presentations with acute recreational drug toxicity, of which the non-medical use of benzodiazepines and/or Z-drugs were reported in 2119 (19.3%) presentations. Benzodiazepines were used in 1943 (17.7%) presentations and Z-drugs were used in 245 presentations (2.2%), and there were 89 (0.8%) presentations where both benzodiazepines and Z-drugs were used. Five hundred twenty-four (24.7%) presentations involved lone-use (without use of other illicit drugs) of benzodiazepines or Z-drugs when alcohol is not taken into account; of these, 114 cases (5.4%) presented as lone-use of benzodiazepines or Z-drugs without alcohol use. In 293 (13.8%) cases with lone benzodiazepine or Z-drugs use, alcohol was used; in the 117 residual cases (5.5%), alcohol use was not recorded. Of the 2119 presentations, benzodiazepines or Z-drugs were combined with other drugs in 1595 cases (75.3%).

Demographics and admission characteristics

The majority of presentations were in males (1528; 72.1%); presentations involving benzodiazepine and/or Z-drugs use were older (mean ± SD age 36.1 ± 10.9 years) than presentations without benzodiazepines or Z-drugs (31.6 ± 10.4 years; $p < 0.001$) [25].

Outcome

Median length of stay was 5 h and 46 min (IQR 3 h 16 m–12 h 16 m) in the 2119 presentations involving non-medical use of benzodiazepines and/or Z-drugs; there were no significant differences in length of stay in the different subgroups. Over half (55.2%) of presentations in the overall benzodiazepine and/or Z-drug group were medically discharged from the ED and 20.2% self-discharged from the ED. Admission occurred in 24.3%, of which 4.3% (92 cases) were admitted to critical care. In the Euro-DEN presentations without benzodiazepine or Z-drug use, the admission rate to critical care was 6.1%. The admission rate to critical care in the overall Euro-DEN group was 5.7%.

Clinical features

Anxiety (12.3%) and agitation or aggression (10.5%) were the most common clinical features in the benzodiazepine and/or Z-drug presentations without co-ingestants, but were still less frequent than in the whole Euro-DEN cohort (Table 1). Lowest GCS (Glasgow Coma Scale) was similar throughout groups as shown in Table 1. Hypotension was more frequent in the subgroup taking multiple benzodiazepines and/or Z-drugs without other drugs (12.1%; 7 cases).

Flumazenil was administered in 81 cases (3.8%) of all ED presentations related to benzodiazepines and/or Z-drugs regardless of co-ingestants; of these, 10 (12.5%) cases presented with

Table 1 Clinical features of benzodiazepine and/or Z-drug use (with and without co-ingestants, regardless alcohol) compared to the Euro-DEN presentations without benzodiazepines

Clinical features	Benzodiazepine and/or Z-drug without co-ingestants ($n = 524$)	Benzodiazepine and/or Z-drug regardless co-ingestants ($n = 1597$)	Euro-DEN presentations without benzodiazepine and/or Z-drug ($n = 8866$)	Euro-DEN presentations where flumazenil was administered ($n = 81$)	P value (pure vs. without benzodiazepines)
Agitation/aggression	10.5%	17.3%	26.6%	12.5%	< 0.001
Anxiety	12.3%	10.2%	19.7%	10.0%	< 0.001
Vomiting	1.8%	3.9%	9.2%	2.5%	< 0.001
Palpitations	0.9%	1.9%	8.6%	1.3%	< 0.001
Chest pain	0.0%	2.3%	7.3%	1.3%	< 0.001
Hallucinations	4.4%	3.0%	7.0%	0.0%	< 0.001
Psychosis	3.5%	4.1%	6.2%	1.3%	< 0.001
Hypotension	3.5%	6.2%	4.5%	13.8%	0.917
Headache	4.4%	3.0%	4.0%	1.3%	0.083
Hypertension	2.6%	1.6%	4.0%	6.3%	0.001
Seizures	0.9%	1.6%	3.8%	3.8%	0.001
Cerebellar features	0.9%	1.3%	1.7%	1.3%	0.170
Hyperthermia	0.0%	1.2%	1.3%	2.5%	0.050
Arrhythmias	1.8%	0.6%	1.2%	1.3%	0.284
Lowest GCS[a]	13.1	13.1	12.2	5.8	

[a] Lowest GCS is the lowest Glasgow Coma Score (on 15) which was documented throughout the admission

agitation and aggression. In the ED presentations with benzodiazepines and/or Z-drugs without co-ingestants, flumazenil was given in nine cases (1.7%); of these, two (2.2%) presented with agitation and aggression. The mean for lowest GCS in the group where flumazenil was administered was 6/15, which was significantly lower than in the benzodiazepine, and/or Z-drug presentations where flumazenil was not administered ($p < 0.001$). Clinical features were less pronounced when flumazenil was administered, except for hypotension (13.8%), hypertension (6.3%), and seizures (3.8%).

Nine patients (0.4%) with non-medical benzodiazepine and/or Z-drugs use had a cardiac arrest either pre-hospital or during the hospital admission. Five of these patients (0.2%) died, of which four had used other recreational drugs. One patient died in ED, and four were admitted to critical care and subsequently died. In four out of five patients, the used benzodiazepine or Z-drug remained unspecified. Three of those patients had also used one or more opioids, and one of them also used amphetamines. In one patient, oxazepam was involved, together with baclofen.

Within the Euro-DEN cohort, the most frequently used benzodiazepines and Z-drugs were clonazepam (625, 29.5% of 2119 presentations), diazepam (421, 19.9%), alprazolam (248, 11.7%), and zopiclone (200, 9.4%). There were 23 different benzodiazepines and 2 types of Z-drugs among the 2119 presentations involving a benzodiazepine and/or Z-drug.

Most (1809, 77.3%) of the 2339 reported benzodiazepines or Z-drugs were prescription drugs; in 527 (22.5%), the type of benzodiazepine was unspecified and in 3 presentations involved the use of a new psychoactive substance (NPS) benzodiazepine: 2-chlorodiazepam in 1 case and clonazolam in 2 cases.

The three most common benzodiazepines or Z-drugs for each country are displayed in Fig. 1 together with the proportion of cases that involved an unspecified benzodiazepine.

In the 1595 presentations in which benzodiazepines and/or Z-drugs were used with other recreational drugs, the most frequent co-used drugs were heroin (672, 42.1%), cannabis (281, 17.6%), amphetamine (261, 16.4%), methadone (224, 14.0%), and cocaine (181, 11.3%) with similar proportions of co-ingestants in the subgroups with only benzodiazepines or Z-drugs, or without alcohol.

Analytical confirmation was not mandatory; however, in those where analytical confirmation was done, 88% of the samples were positive for benzodiazepines or Z-drugs.

Drug utilization data

There was a moderate (Spain, UK, Switzerland) to high (France, Ireland, Norway) positive correlation between ED presentations and sales data as shown in Table 2. In the Euro-DEN ED dataset from Germany, only 3.9% of benzodiazepines/Z-drugs were named, reflected by a non-significant result.

In France, Germany, and Switzerland, diazepam had the highest presentation rate per 100,000 units sold, while in Spain and UK, alprazolam had the highest presentation rate per 100,000 units sold. For Ireland, this was zopiclone and for Norway, flurazepam. Diazepam (9/10 countries), alprazolam (7/10 countries), clonazepam, and zopiclone (both 5/10 countries) make up most top three's in ED presentations in the European countries involved in Euro-DEN. Many of the benzodiazepines and Z-drug were only encountered in one or a few Euro-DEN countries, as shown in Table 3.

The rate of Euro-DEN presentations for alprazolam, clonazepam, flunitrazepam, and flurazepam in Norway was 10- to 100-fold greater than the rates of the most frequent benzodiazepines or Z-drugs in the other countries.

Discussion

Non-medical use of benzodiazepines and Z-drugs was involved in almost one fifth of all acute recreational drug toxicity presentations to the ED in this large European series. Almost a quarter of these presentations were lone benzodiazepine and/or Z-drug use, suggesting that acute toxicity related to the non-medical use of benzodiazepines and/or Z-drugs alone is common. The most common co-ingestants are a reflection of the most used recreational drugs encountered in the overall Euro-DEN group, with the most frequent co-used drug being heroin (42.1%) [24]. Another Euro-DEN analysis found that 191 out of 662 heroin users (28.9%) combined their heroin use with benzodiazepines, a greater proportion than in the overall Euro-DEN cohort (19.4%) [26]. The combination of the depressant effect of benzodiazepines and heroin may yield a higher risk of complications. A tendency for stimulant users to self-medicate with benzodiazepines and/or Z-drugs was not commonly seen in this large cohort. No specific frequent combinations of recreational drugs were found in the benzodiazepines and/or Z-drug population. Four out of the five fatal cases involved multiple drugs, and it is difficult to define the contribution of the benzodiazepines or Z-drug in these cases. Most deaths occurred days after admission.

Benzodiazepine and Z-drug involvement in acute drug toxicity presentations vary between countries. Euro-DEN centers in some countries exhibit a clear prominence of certain benzodiazepines, for example alprazolam in Spain (65.7% of all acute drug toxicity presentations where a benzodiazepine or a Z-drug is involved), diazepam in UK (71.0%), and clonazepam in Norway (54.5%). Euro-DEN centers in other countries, like France, had greater diversity in the benzodiazepines and Z-drugs seen in Euro-DEN presentations. Certain benzodiazepines were unique for one or two countries (e.g., midazolam in Switzerland). For some Euro-DEN countries (Germany, Estonia), most benzodiazepine presentations were

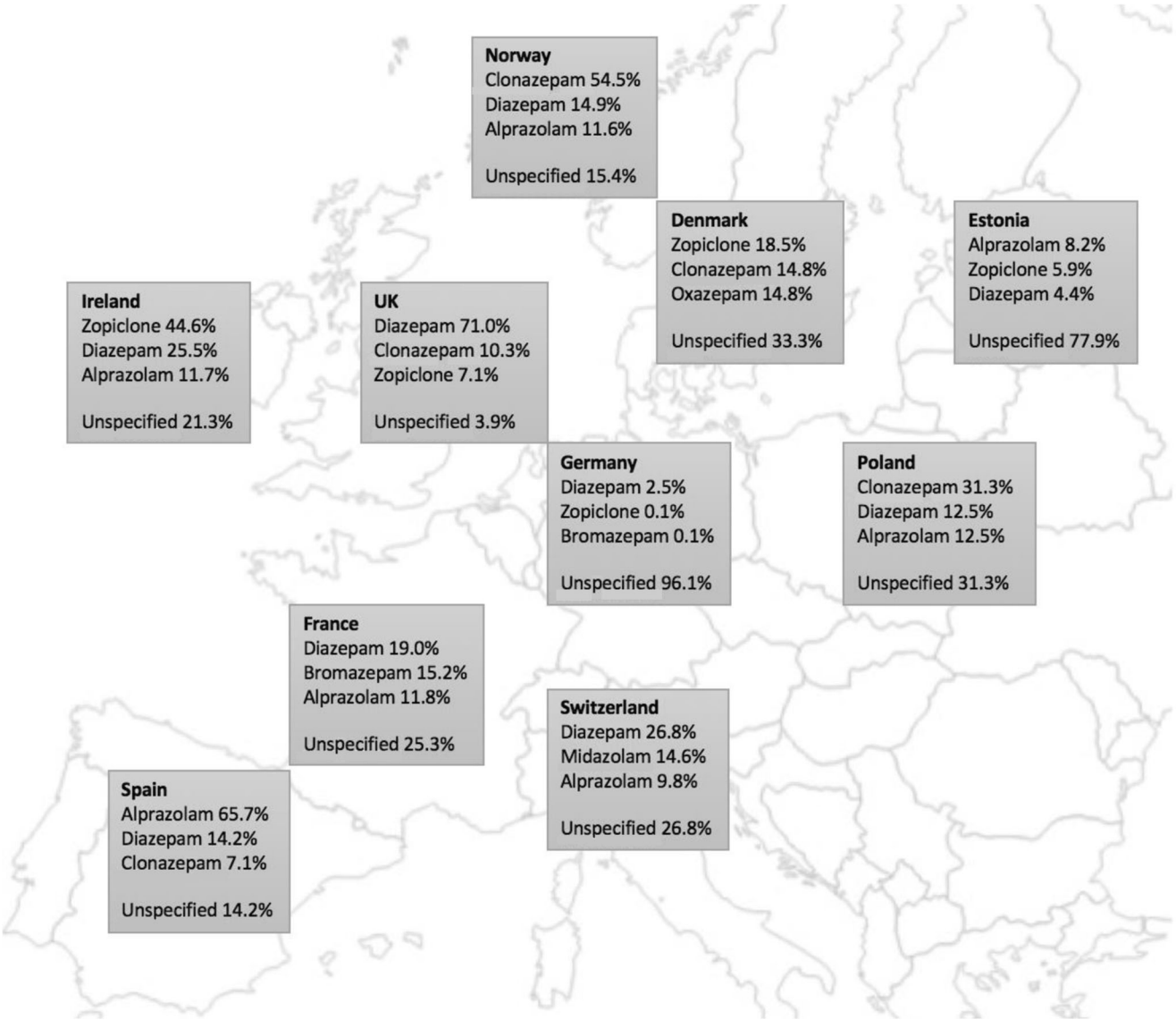

Fig. 1 Top three benzodiazepines and/or Z-drugs leading to ED presentations per country

documented as unknown benzodiazepines or Z-drugs, making it very difficult to comment on their pattern.

We have shown that overall, there was a moderate to high positive correlation between ED presentation data and sales data in the seven European countries for which paired data was available. The absolute benzodiazepine or Z-drug ED presentation counts for Spain, Switzerland, and the UK are all under 200, compared to France, Ireland, and Norway with more than 200 presentations (see Table 3). The standard units range in the millions and billions depending on the country. These higher counts would facilitate a moderate to high correlation value.

In addition to availability, other factors may contribute to individuals developing acute toxicity and therefore presenting to the ED. Certain benzodiazepines or Z-drugs may have a pharmacokinetic profile has a higher risk for complications

Table 2 Spearman correlation coefficients between percentage of Euro-DEN ED presentations and percentage of standard units sold with *p* value

	France	Germany	Ireland	Spain	Norway	Switzerland	UK
Spearman Correlation	0.80	0.45	0.79	0.67	0.82	0.65	0.60
p value	< 0.001	0.054	< 0.001	0.002	< 0.001	0.002	0.007

Table 3 Euro-DEN ED presentation rates per 100,000 standard units sold

Drug (number[b])	Rate of ED presentations per 100,000 standard units sold						
	France (206)	Germany (6)	Ireland (243)	Spain (65)	Norway (1050)	Switzerland (19)	UK (148)
Alprazolam	0.0045	0	0.1419	0.0115	7.0273	0.0231	0.2382
Bromazepam	0.0119	0.0021	0	0	0	0.0114	0
Chlordiazepoxide	0	0	0.1363	0	0	0	0.0076
Clonazepam	0.0171	0	0.0369	0.0036	8.943	0.0353	0.0296
Diazepam	0.0354	0.0063	0.2688	0.0029	0.6367	0.1745	0.0328
Flunitrazepam	0	0	0	0	9.2234	0	133.3333[†]
Flurazepam	0	0	0.1374	0	23.8095	0	0
Loprazolam	0.0029	0	0	0	0	0	0
Lorazepam	0.002	0	0	0.0005	0	0.0077	0.0019
Lormetazepam	0.0011	0	0	0	0	0	0
Midazolam	0	0	0	0	0	0.0835	0
Nitrazepam	0	0	0	0	0.3351	0	0
Oxazepam	0.0047	0	0	0	0.2424	0.0052	0
Prazepam	0.0065	0	0	0	0	0	0
Temazepam	0	0	0.0237	0	0	0	0.0032
Tetrazepam	145.7726[a]	0	0	0	0	0	0
Zolpidem	0.0087	0	0.0104	0	0.0942	0	0.0033
Zopiclone	0.0117	0.0009	0.511	0	0.0404	0.0341	0.0059

[a] The rates for tetrazepam and flunitrazepam are seemingly high due to a decrease in standard units during the study period, 2013Q3-2015Q3, although cases remained sporadic. Zeros indicate that there were no presentations for a particular drug in the study period

[b] The number of ED presentations related to named benzodiazepine and/or Z-drugs of which sales data are available

(e.g., long half-life, lipophilia) or may have a higher abuse potential ($GABA_A$ receptor binding profile; e.g., zolpidem) [11, 27, 28]. Furthermore, the presentations to the ED may not relate directly to acute toxicity of the benzodiazepine or Z-drug but may be related to a co-ingested drug.

There are many other factors—in addition to availability—that may be important in determining whether a patient presents to the ED after non-medical use of benzodiazepines or Z-drugs; therefore, the ED presentation rate will not be directly related to availability or toxicity risk of the benzodiazepine or Z-drug. The extent to which sales data impacts use of benzodiazepines or Z-drugs, both at an overall population level, but more importantly non-medical use of these drugs, is unclear. For cannabis, an increase in prevalence of non-medical use was noted when cannabis was legalized in certain states in the USA [29]. In an interview-based study on prescription opioids, just over half of the users report buying the drug themselves, the rest was generally obtained via friends or relatives; buying prescription opioids over the internet was very uncommon [14, 30].

As shown in Table 3, the majority of the rates for the benzodiazepines and Z-drugs were < 0.001, as there were no ED presentations with the benzodiazepine or Z-drug recorded. However, it is important to discern instances where the rate was not 0. There is a difference in rates between both different types of benzodiazepines and Z-drugs, and between countries within the same type. Possibly, some benzodiazepines are not as popular in specific countries compared to the three main ones (alprazolam, diazepam, and clonazepam) and are not being (mis)used in every country. "Popular" is being defined as drug availability, which comes down to how many standard units are being sold of these products.

Tetrazepam and flunitrazepam did have rates greater than 100, largely due to the fact that the standard units for these two benzodiazepines have been in decline since 2011. Tetrazepam was suspended by the EMA (European Medicines Agency) in 2013, while flunitrazepam had been taken off the market in many European countries. Since the amount of product (denominator) is decreasing, while the amount of Euro-DEN presentations (numerator) remains constant, the resulting rate is inflated.

Limitations

The Euro-DEN data collection is set up through sentinel centers, with one to three hospitals per country collecting data on all presentations to their center with acute drug toxicity on a voluntary basis. This means that the data is not necessarily

representative of acute drug toxicity presentations throughout the whole country. The data is based on ED presentations which may well be disproportionate to the overall use of recreational drugs, depending on the clinical features leading to ED admission, accessibility, and alternatives for provision of care in the community. Nevertheless, they represent an important marker of the morbidity associated with the use of these drugs. In order to generate representative information on the harms associated with recreational drug use in Europe, data from different sources needs to be collated [31, 32]. Despite this limitation, in light of the limited systematic data available on acute drug toxicity in Europe, the Euro-DEN dataset offers a unique insight into acute drug toxicity presentations in Europe and is currently the most extensive and consistent database on recreational drug use at our disposal [33].

The information collected in the Euro-DEN project was pre-defined to cover all recreational drug toxicity and was not designed specifically for benzodiazepines and/or Z-drugs. Benzodiazepines and Z-drugs are only captured if there has been non-medical use which directly impacts on the presentation; doses and regular therapeutic use of benzodiazepines and/or Z-drugs are not included in the Euro-DEN collection sheet. The patients are retrospectively included and data collection sheets are completed based on the clinician's notes, which might yield incomplete data.

The Euro-DEN registry relies on self-reporting and may allow inconsistency with the factual ingestion. It is conceivable that many patients actually having consumed benzodiazepines/Z-drugs are not included, because they do not exactly know (and thus do not report) what they have in fact ingested. There was no mandatory analytical confirmation within the registry. False positive and negative results can occur for benzodiazepines /Z-drugs. [27]

Drug utilization-based rates (the number of units sold in a country) provide an assessment of the availability of benzodiazepines and Z-drugs to non-medical users, but are not an exact measure, because the level of diversion outside the appropriate supply chain and the availability of other sources may vary. It will be impossible to get an exact view on all the sources of benzodiazepines and Z-drugs for non-medical use.

National-level drug utilization-based rates may not be representative of regional sales data that would apply to the region of each sentinel center. It is possible that there are local variations in prescription practices or differences in consumption in the populations where the sentinel centers are located; it is also possible that there are additional supplies (such as on the illicit market) not captured by this sales data. However, these rates are the nearest proxy which can be used as denominator data, as neither regional nor individual sales data are available for research purposes.

Furthermore, we did not have sales data for all documented benzodiazepines, or for all countries. Also, the country where the benzodiazepine or Z-drug was sold may not be the same as the country of use. Within the Euro-DEN registry, there is an important variation in the documentation of the type of benzodiazepines or Z-drugs, with a reporting rate varying from 3.9 to 96.1%, although the type is known in 75.2% in the group as a whole.

Conclusion

Non-medical use of benzodiazepines and/or Z-drugs is commonly reported among presentations to the EDs in Europe with acute drug toxicity. The reported involvement of different benzodiazepines/Z-drug related to ED presentations varies considerably between countries. There was a moderate to high correlation between ED presentations related to non-medical use and the country-level data on sales of these drugs.

Triangulation of this information with other data sources on the non-medical use of benzodiazepines, such as prescription data, reasons for non-medical use, and prevalence of non-medical use will enable the design of appropriate interventions to tackle the problem of non-medical use of benzodiazepines and Z-drugs.

Funding information The Euro-DEN Project was funded by the DPIP/ISEC Programme of the European Union; all of the authors had funding from the European Commission through the Euro-DEN project except ML and EL, whose costs were co-funded by the Swiss Centre of Applied Human Toxicology (SCAHT), and BB, JG, ZM, and CL.

Compliance with ethical standards

Conflict of interest PD and DW have received financial and statistical support to undertake population and web monitoring studies on the non-medical use of prescription and non-prescription medicines in the UK and Singapore and travel and honorarium costs to attend and present at the Annual RADARS International Symposium and Scientific Meeting from the RADARS System, Denver Health and Hospital Authority, Denver, US.

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Affiliations

C . Lyphout[1,2] · C. Yates[3] · Z. R. Margolin[4] · P. I. Dargan[1,5] · A. M. Dines[1] · F. Heyerdahl[6] · K. E. Hovda[6] · I. Giraudon[7] · B. Bucher-Bartelson[4] · J. L. Green[4,8] · D. M. Wood[1,5]

1 Clinical Toxicology, Guy's and St Thomas' Hospitals NHS Foundation Trust, and King's Health Partners, London, UK

2 Emergency Department, University Hospital, Ghent, Belgium

3 Emergency Department and Clinical Toxicology Unit, Hospital Universitari Son Espases, Mallorca, Spain

4 Denver Health Rocky Mountain Poison & Drug Center, Denver, USA

5 Faculty of Life Sciences and Medicine, King's College London, London, UK

6 The National CBRNe Centre of Medicine, Department of Acute Medicine, Medical Division, Oslo University Hospital, Oslo, Norway

7 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal

8 Inflexxion, Inc., Waltham, MA, USA