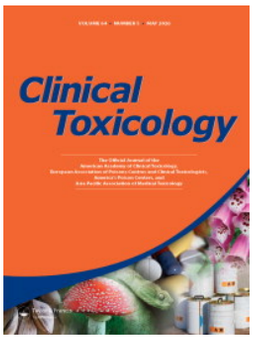

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: www.tandfonline.com/journals/ictx20

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To cite this article: Florian Hauser, Cornelia Reichert, Gerd A. Kullak-Ublick & Alexander Jetter (20 Apr 2026): Acute pharmaceutical poisoning as a cause of seizure events: a database analysis (2011–2023), Clinical Toxicology, DOI: 10.1080/15563650.2026.2643396

To link to this article: https://doi.org/10.1080/15563650.2026.2643396

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2026.2643396

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POISON CENTRE RESEARCH

Acute pharmaceutical poisoning as a cause of seizure events: a database analysis (2011–2023)

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ABSTRACT

Introduction: Supratherapeutic exposures to pharmaceuticals are a considerable cause of seizures, often leading to severe complications. This study aimed to identify the drugs most frequently associated with seizures in overdose and to evaluate their seizure potential, focusing on dosage and age-related differences.

Methods: A retrospective analysis of single-agent pharmaceutical exposures, mostly overdoses, reported to Tox Info Suisse from 1 January 2011 to 31 December 2023 was conducted. Cases with seizures were compared to all cases ("seizure rate") and to all cases involving the same substance ("seizure potential"). The median ingested dose was compared to the maximum approved daily dosage ("relative overdose"), and relative overdose in seizure versus non-seizure cases with the same substance was compared ("seizure overdose ratio").

Results: There were 20,176 single-agent pharmaceutical exposures, with seizures reported in 233 cases (1.2%). Antidepressants were the most frequently implicated drug class (34.3%). Mefenamic acid (15.7%), quetiapine (10%), and bupropion (10%) were most commonly associated with seizures. Cefepime (37.5%) and bupropion (23.7%) showed the highest seizure potentials. Seizures occurred at low relative overdoses for clozapine, chlorprothixene, and trimipramine (1.3×, 2.0×, 2.8×, respectively). Tricyclic antidepressants (notably trimipramine), mefenamic acid, tolperisone, and bupropion exhibited low seizure overdose ratios (1.4, 2.0, 2.1, 2.1, respectively). Age-related seizure rates did not differ significantly between adolescents (1.7%) and adults (1.5%).

Discussion: Besides the established seizure association of antidepressants, this analysis confirmed the high seizure risk of overdoses of mefenamic acid and bupropion. A comparative assessment using relative overdoses and seizure overdose ratios revealed that even mild overdoses of clozapine or chlorprothixene induce seizures. For mefenamic acid, tolperisone and bupropion, seizures occurred at overdoses only about twice those not associated with seizures. Seizures from intravenously administered cefepime were caused by not adapting the posology to decreased kidney function.

Conclusion: Overdoses of mefenamic acid, quetiapine, bupropion, venlafaxine and tramadol, respectively, were most commonly associated with seizures. Cefepime exhibited the highest seizure potential, in patients with impaired renal function. Tricyclic antidepressants (trimipramine, amitriptyline), tolperisone, mefenamic acid and bupropion were associated with seizures at relatively small overdoses compared to respective non-seizure cases.

ARTICLE HISTORY
Received 30 June 2025
Revised 11 February 2026
Accepted 24 February 2026

KEYWORDS
Antidepressants; intoxication; neurotoxicity; overdose; poisoning; relative overdose; seizure; seizure potential

Introduction

Between 1.7% and 14% of acute symptomatic seizures are drug-related [1–3]. Complications, including prolonged hospitalization, intubation, status epilepticus, brain injury, or death, occur in up to 60% of cases [4]. Despite this, epidemiological data on pharmaceutical-induced seizures remain limited.

Previous research found antidepressants were involved in 28.8%–42.4% of pharmaceutical-induced seizures [4–8]. However, these studies included both single-agent and mixed ingestions, complicating conclusions about the specific seizure potential of each drug. Reichert et al. [9] examined single pharmaceutical overdose-induced seizures in the Swiss population from 1997 to 2010, identifying mefenamic acid,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2026.2643396.

citalopram, and trimipramine as the three most common causes of pharmaceutical-related seizures. Bupropion, venlafaxine, citalopram, and mefenamic acid showed the highest seizure incidence relative to all intoxications with these drugs, i.e., seizure potential. A 2018 review by Steinert et al. [10] found seizure risk of therapeutic doses of antidepressants "low to moderate" (seizures in <0.1% of cases). However, due to study heterogeneity, meta-analysis was not possible. Overall, comprehensive epidemiological data concerning drug-related seizures are limited. This is especially evident for recently developed and licensed pharmacological agents.

This study aims to identify pharmaceuticals frequently associated with overdose-associated seizures and their seizure potential, assess age- and dose-related risks, update data up to 2010 previously obtained in Switzerland [9], and describe seizures associated with newly licensed drugs.

Methods

Data collection

Tox Info Suisse, the Swiss poison information centre, provides 24/7 medical advice by telephone in cases of intoxication or suspicion of intoxication to the public and healthcare professionals. All calls are recorded in an internal database, documenting patient details (age, weight, sex), poisoning circumstances, product or substance identity and quantity, symptoms, and, if already available, further information like laboratory results. All calls from physicians or healthcare institutions are answered by physicians. After these telephone consultations, the treating physicians receive a letter asking for follow-up information. In approximately 70% of these cases, follow-up information is received, which usually includes ingested dose and galenic form, symptoms, poisoning timeline, laboratory results (e.g., from blood or urine samples), clinical parameters, treatments, complications, and outcome. This information is then entered into the database, and the causality between intoxication and symptoms is assessed with modifications, as is recommended in the literature for adverse drug reactions [11,12]. Each case is assessed concerning causality by two toxicological experts. For causality assessment, briefly, the temporal relationship is determined by the reported timing of ingestion versus onset of effects, based on the case history. Cases are classified as "likely related" if they exhibited a clear temporal link between ingestion and clinical effects, no other drugs or conditions explaining the effects were reported (e.g., stimulant or antidepressant co-ingestion, history of alcohol use), and symptoms were consistent with the substance or pharmacodynamically plausible. Cases with additional qualitative or quantitative analytical detection of the substance in body fluids (blood, urine, or both) are classified as "confirmed". In asymptomatic cases, causality cannot be assessed using these criteria. They are included according to the reported substance. Only cases which have been fully assessed and reviewed can be extracted from the database for scientific evaluations using the inclusion criteria mentioned below.

Study design

This retrospective single-centre observational study analysed all cases with follow-up information with exposures towards single pharmaceutical agents reported to Tox Info Suisse between 1 January 2011 and 31 December 2023, with and without symptoms of seizure, or a history of epilepsy.

Inclusion criteria

Cases were extracted from the database using the following criteria. Cases had to have physician-provided follow-up information on clinical effects and outcome. Only cases with administration of a single pharmaceutical agent were included. Cases with a confirmed or likely relationship between exposure and clinical effects were included, as well as asymptomatic cases with a reasonable likelihood of intake. Seizure cases were identified by searching data files for "epileptic", "seizure", or "convulsion". Cases with documented pre-existing epilepsy, multi-substance exposures, concomitant stimulant use or any other factors explaining a seizure were not included.

Ethics approval

Ethical approval was granted by the Cantonal Ethics Committee of Zurich, Switzerland (BASEC-No. 2024-00053). Informed consent was not required per Swiss law (Article 34, Swiss Human Research Act).

Statistics and data analysis

To quantitatively estimate the seizure risk of a pharmaceutical, the following four parameters were calculated: "seizure rate" is the proportion of seizure cases with a given drug compared to all seizure cases, "seizure potential" describes the percentage of cases with seizures of all cases with the same drug. The two

dose-related parameters were "relative overdose" and "seizure overdose ratio". Relative overdose was calculated by dividing the median dose in the respective cases by the maximum approved daily dosage, as published in the official Swiss pharmaceutical database [13]. The seizure overdose ratio was defined as the relative overdose in seizure cases divided by that in non-seizure cases. Confidence intervals (95% CI) for seizure rates were estimated using Wilson's method [14] as recommended in the statistical literature [15,16]. Briefly, this method employs a binomial proportion formula that adjusts for sample size, yielding more precise and reliable results for small sample sizes or extreme proportions than the standard normal approximation. Fisher's exact test was used for binomial comparisons and the Wilcoxon-Mann-Whitney test for dose comparisons. *P* values <0.05 were considered significant. Analysis was conducted using R (version 4.3.3) [17].

Results

During the study period, Tox Info Suisse received an average of 38,942 calls annually (range: 35,576–41,261). The referral population increased from about 7.8 million in 2011 to 8.6 million by the end of the study [18]. Single pharmaceutical exposure cases rose from 8,173 in 2011 to 9,851 in 2023, equating to one single-substance exposure per 954 people in 2011 and one per 873 people in 2023.

Over 13 years, Tox Info Suisse received feedback from the treating physicians or hospitals on 20,176 cases involving single pharmaceutical exposures. Patients' age ranged from one day to 106 years (median age 22.8 years) (Table 1). Females comprised 62.5% of cases ($n=12,595$) and males 37.4% ($n=7,563$) (sex data missing in 0.1% of cases, $n=18$). Cases included accidental exposure ($n=8,867$, 44%), intentional exposure ($n=10,639$, 52.7%), adverse drug effects ($n=439$, 2.2%), and other reasons ($n=231$, 1.1%). Intentional exposures were mainly due to suicidal behaviour ($n=8,366$, 41.5% of all cases), abuse ($n=658$, 3.3%), and other reasons ($n=1,615$, 8.0%). These causes included iatrogenic exposures or unknown origins. Analytical confirmation of the involved drug was available in 12.3% ($n=2,489$) of all cases with feedback.

Table 1. Age distribution of cases with and without seizures and seizure rates.

Age (years)	All cases *n* (%)	Cases with seizures *n* (%)	Seizure rate %	95% CI
0–4	4,233 (21.0)	6 (2.6)	0.1	0.1%–0.3%
5–9	769 (3.8)	1 (0.4)	0.1	0.1%–0.6%
10–14	858 (4.3)	13 (5.6)	1.5	0.9%–2.6%
15–19	2,895 (14.4)	48 (20.6)	1.7	1.3%–2.2%
20–106	11,293 (56.0)	165 (70.8)	1.5	1.3%–1.7%
Not reported	128 (0.6)	0	0	
Total	20,176	233	1.2	1.1%–1.4%

Seizures occurred in 233 cases (Figure 1), with patients aged 1-89 years (median age 27.5 years) (Table 1). The overall seizure rate was 1.2% (233 out of 20,176). Females represented 66.9% ($n=156$) and males 33.1% ($n=77$) of seizure cases. Poisoning circumstances were unintentional exposure ($n=28$, 12.0%), intentional exposure ($n=188$, 80.7%), adverse drug effects ($n=11$, 4.7%), and other reasons ($n=6$, 2.6%). Analytical confirmation of the involved drug was available in 18.5% ($n=43$) of seizure cases.

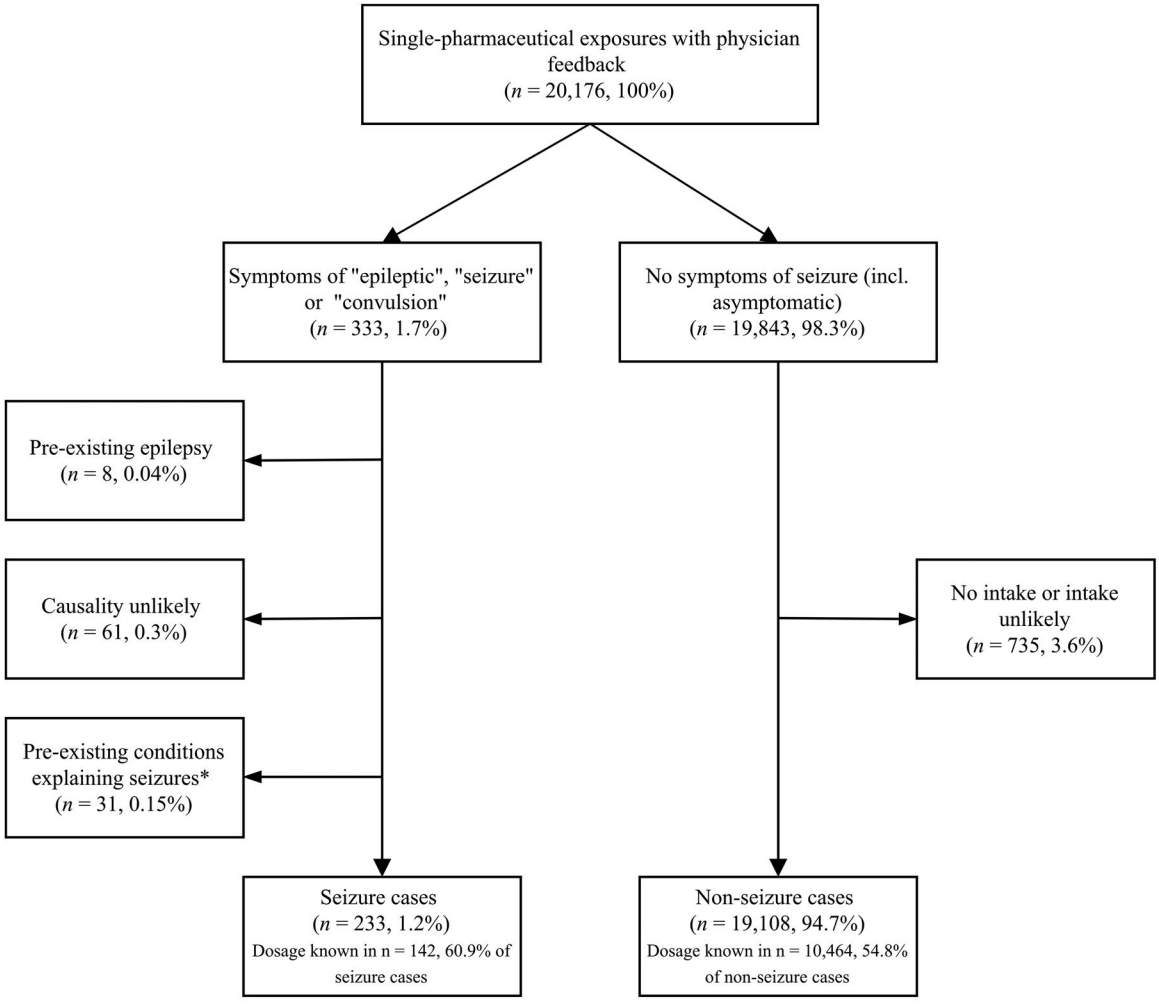
In these 233 seizure cases, 52 distinct drugs were involved. Twenty-two of these drugs were linked to three or more seizure cases (Figure 2). The most common drugs were mefenamic acid (36 cases, 15.7%), quetiapine and bupropion (23 cases each, 10.0% each). Other notable drugs included venlafaxine (13 cases, 5.7%), tramadol (11 cases, 4.8%), diphenhydramine (11 cases, 4.8%), trimipramine (nine cases, 3.9%), clozapine (seven cases, 3.0%), dextromethorphan (seven cases, 3.0%), citalopram (seven cases, 3.0%), and chlorprothixene (seven cases, 3.0%). Twenty-two drugs accounted for 83.3% ($n=194$) of all drug-related seizures (Figure 2).

The remaining 39 seizure cases were linked to 30 other drugs (Supplementary Table 1). Antidepressant drugs were implicated in 80 seizures (34.3%), followed by antipsychotics (46 cases, 19.8%) and non-steroidal anti-inflammatory drugs (38 cases, 16.3%) (Table 2, detailed data in Supplementary Table 2).

The intravenously administered antibiotic cefepime exhibited the highest seizure potential, with 37.5% of cases involving seizures (three of eight cases) (Figure 3). High seizure potentials were also observed for bupropion (23.7%, 23 of 97 cases), mefenamic acid (14.8%, 36 of 243 cases), venlafaxine (8.7%, 13 of 149 cases), and pipamperone (7.7%, four of 52 cases). Further drugs with a relevant seizure potential included baclofen (7.1%, three of 42 cases), tolperisone (6.8%, four of 59 cases), tramadol (6.1%, 11 of 181 cases), trimipramine (5.7%, nine of 157 cases), and citalopram (5.6%, seven of 125 cases) (Figure 3).

Seizures were reported after exposures towards only three drugs approved after 2010 [19]: insulin detemir, insulin degludec, and crizotinib. Each was associated with one seizure case, precluding a reliable seizure potential calculation. Both insulin-related seizures followed suicidal administration, while the crizotinib case represented an adverse drug reaction. Dosage in all three cases was unknown.

Figure 4 shows the multiple of the maximum approved daily dosage [13] (relative overdose) in cases



***Excluded cases, reasons for exclusion and pharmaceuticals involved:**

1) **Co-Ingestion of stimulants or (other) antidepressants (*n* = 12)**: diphenhydramine (3), quetiapine (2), fluoxetine (2), tramadol (1), sertraline (1), bupropion (1), promazine (1), fluvoxamine (1)

2) **Alcohol and drug abuse (*n* = 8)**: venlafaxine (1), tramadol (1), tolperisone (1), bupropion (1), trimipramine (1), diphenhydramine (1), alkylamines (1), quetiapine (1)

3) **Drug abuse (*n* = 6)**: quetiapine (3), sertraline (1), mirtazapine (1), pipamperone (1)

4) **Alcohol abuse (*n* = 3)**: ethanol (1), lamotrigine (1), insulin (human) (1)

5) **Combination drug (*n* = 2)**: Makatussin ® (dihydrocodeine, diphenhydramine, ethanol) (1), Rudocain forte ® (articaine, epinephrine) (1)

Figure 1. Flowchart of case inclusion and exclusion.

with and without seizures, for cases with medications associated with 3 or more seizures. For clarity, this Figure shows up to 15-fold overdoses over the maximum licensed daily dose (full graph in Supplementary Figure 1). Tramadol and mefenamic acid, alongside neuroleptics (clozapine, pipamperone, chlorprothixene), were linked to seizures closer to their therapeutic dosages than selective serotonin reuptake inhibitors (e.g., sertraline, citalopram, escitalopram) and serotonin-noradrenaline reuptake inhibitors (e.g., duloxetine).

Table 3 shows ranges and medians of ingested doses for the six drugs most frequently associated with seizures. Dosage information was available for 60.9% of seizure cases (*n* = 142) and 54.8% of all cases

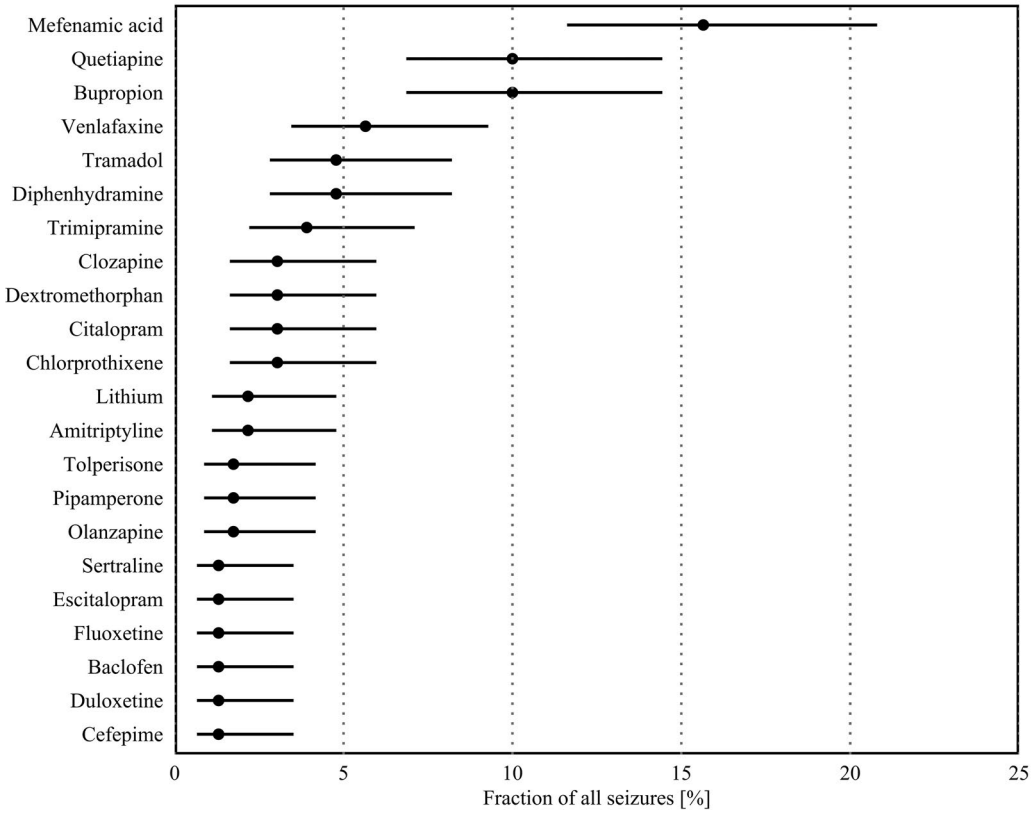


Figure 2. Pharmaceutical drugs associated with three or more cases of seizures. Lines correspond to 95% confidence intervals.

Table 2. Seizure rates in different drug classes.

Drug	Number of seizures	Seizures as % of all seizures
Antidepressants	**80**	**34.3%**
Bupropion	23	9.9%
Selective serotonin reuptake inhibitors	17	7.3%
Serotonin noradrenaline reuptake inhibitors	16	6.9%
Tricyclic antidepressants	16	6.9%
Lithium	5	2.2%
Deanxit (melitracen + flupentixol)	1	0.4%
Mirtazapine	1	0.4%
Maprotiline	1	0.4%
Antipsychotics	**46**	**19.7%**
Quetiapine	23	9.9%
Chlorprothixene	7	3.0%
Clozapine	7	3.0%
Pipamperone	4	1.7%
Olanzapine	4	1.7%
Risperidone	1	0.4%
Non-steroidal anti-inflammatory drugs	**38**	**16.3%**
Mefenamic acid	36	15.5%
Ibuprofen	2	0.9%

The table indicates the absolute number of seizures and the percentage in relation to all 233 cases with pharmaceuticals-associated seizures.

($n = 10{,}464$) (67.5% ($n = 117$) and 73.3% ($n = 1{,}300$), respectively, for the six drugs most frequently associated with seizures). The median ingested doses and relative overdoses were significantly higher in the seizure group compared to the non-seizure group for all six agents (Wilcoxon-Mann-Whitney test) (extended list in Supplementary Table 3). Besides tramadol, mefenamic acid, and trimipramine, relative overdoses linked to seizures were notably low for certain neuroleptics (clozapine (1.3x), chlorprothixene (2.0x), pipamperone (4.4x)) and the muscle relaxant tolperisone (5.3x) (Figure 4 and Supplementary Table 3). Within the drugs most frequently associated with seizures, trimipramine, mefenamic acid, tolperisone, amitriptyline and bupropion had low seizure overdose ratios, that is, were associated with seizures at lower relative overdose compared to non-seizure cases (1.4-fold, 2.0-fold, 2.1-fold, 2.1-fold and 2.1-fold, respectively) than escitalopram (7.0-fold) or quetiapine (8-fold).

Seizures primarily occurred in adolescents (15–19 years, 20.6% of cases, $n = 48$) and adults (20 years and older, $n = 165$, 70.8%; Table 1). The difference in seizure rates between adolescents (1.7%) and adults (1.5%) was numerically, but not statistically significant (Fisher's exact test). No obvious age-related differences in seizure rates were observed for the six drugs with the highest seizure incidences (Supplementary material, comparison of seizure rates between adolescents and adults). Seizures in infants (0–4 years, $n = 6$) and young children (5–9 years, $n = 1$) were rare at <1% (Supplementary Table 4).

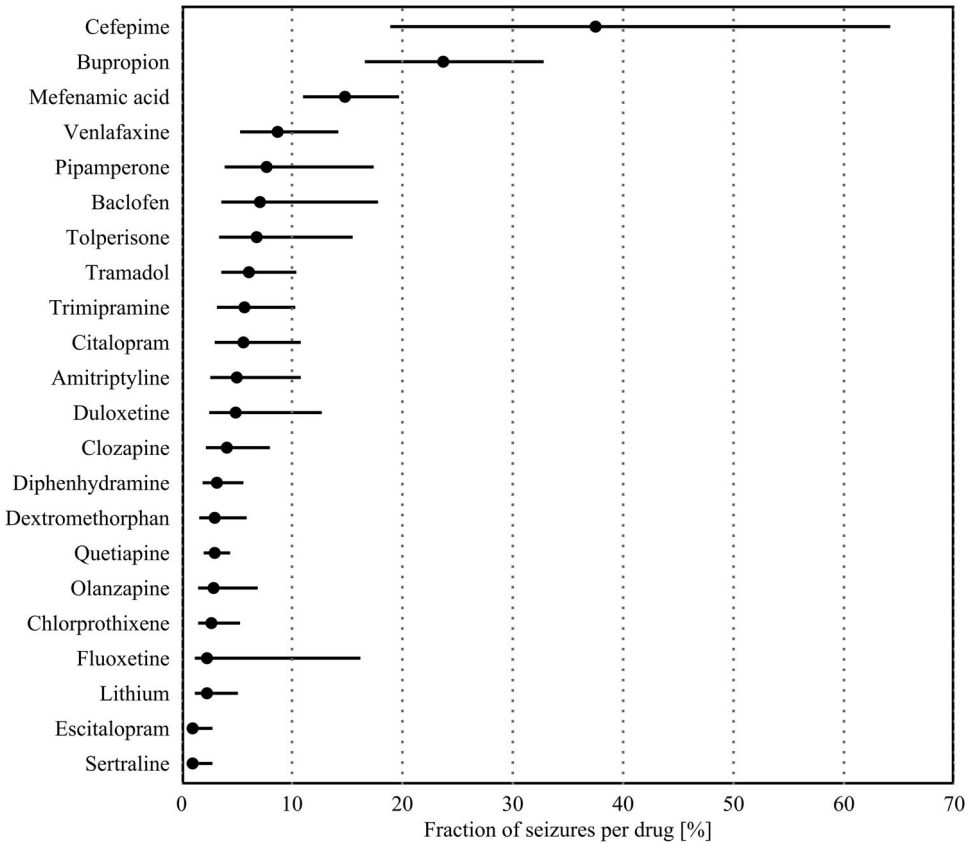


Figure 3. Seizure potential of pharmaceuticals in overdose. Lines correspond to 95% confidence intervals.

Discussion

Drugs involved

Antidepressants were the drug class most frequently associated with seizures (34.3%), consistent with the prior Tox Info Suisse study (43.5%) from 1997 to 2010 [9]. Steinert and colleagues [10] found overdose seizure rates for antidepressants from 0.1% to 37%. Older studies showed similar rates (28.8%–42.5%) [4–8,20], but lacked controls for multi-agent intoxications or pre-existing conditions like epilepsy. By excluding predisposing factors and drug-drug interactions where known, this study increases the plausibility of an association between drugs and seizures.

In accordance with the prior Tox Info Suisse study [9] and other work [4,10,21–24], mefenamic acid, venlafaxine and tramadol were among the drugs most commonly associated with seizures. Seizure cases associated with quetiapine rose from 3.2% [9] to 10.0% in this study. Similarly, bupropion cases accounted for only 1.9% in the previous study [9], while they rose to 10% in this analysis. Both quetiapine and bupropion are described to cause seizures in the literature [4,10,20,25–27]. In contrast, seizures associated with citalopram (10.9% to 3.0%) and trimipramine (8.6% to 3.9%) decreased substantially [9]. These observations may be attributed to altered prescribing practices [28,29].

Among drugs licensed after 2010 [19], only insulin detemir, insulin degludec, and crizotinib were linked to one seizure case each. While insulin overdose reportedly can cause seizures [30], no data exists so far for these insulin analogues. Hitherto, crizotinib has not been associated with an established seizure risk, unlike other anaplastic lymphoma kinase (ALK) inhibitors (e.g., ceritinib) [31].

Seizure potential and relative overdose

Drugs frequently implicated in seizure cases may reflect a higher seizure potential, more frequent exposures, or both. Most prior studies lacked data on non-seizure cases, precluding comparative analysis [4–8,23].

This study identified cefepime with the highest seizure potential (37.5%, three of eight exposures), consistent with prior reports (7%–40%) [32–35]. Unlike all other drugs investigated, cefepime is only given intravenously in hospitalized, critically ill patients. All cefepime-associated seizures occurred in intensive care patients and were linked to unadjusted dosing for kidney impairment.

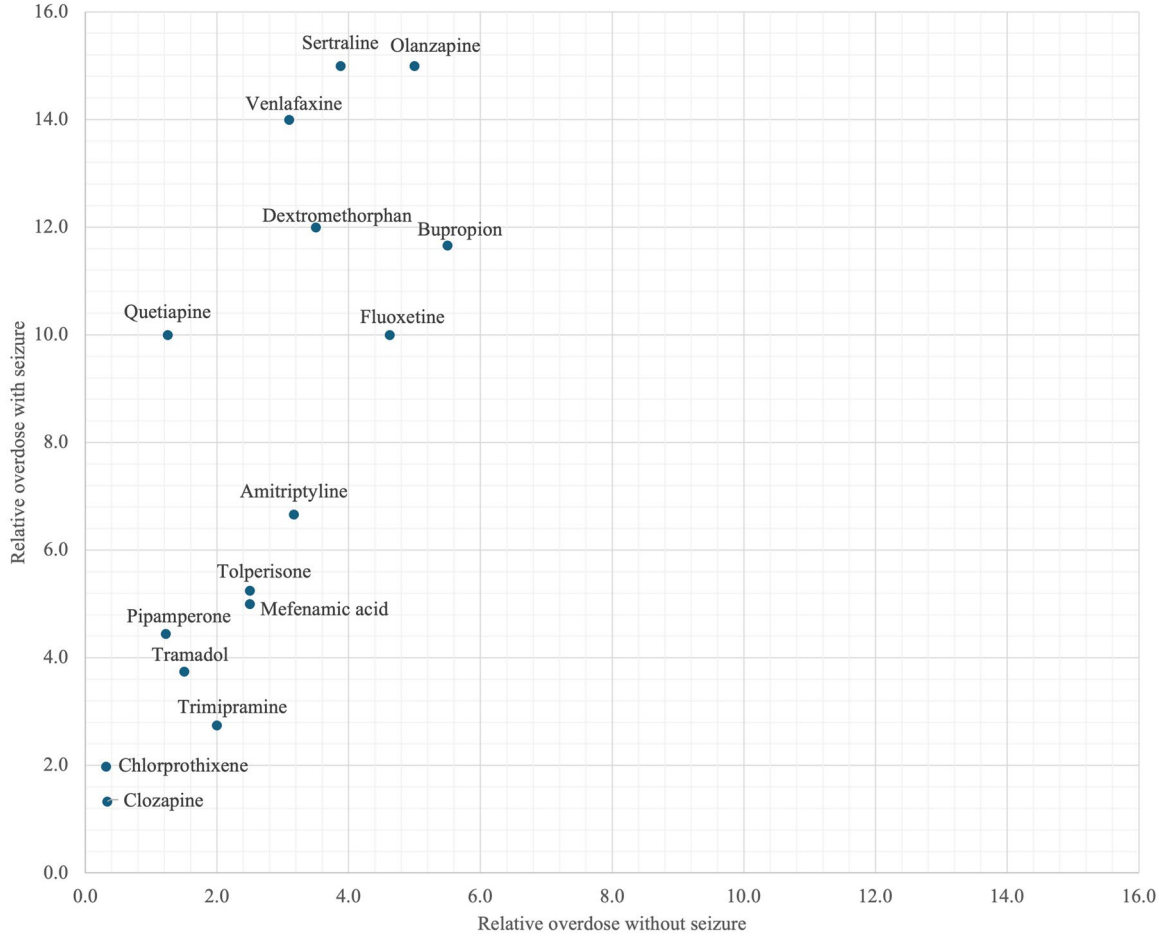


Figure 4. Seizure overdose ratio: Relative overdose in cases without seizures compared to cases with seizures.

Consequently, monitoring kidney function and adjusting dosage is essential to mitigate seizure risk. The earlier Swiss study [9] found no cefepime-related seizures, likely because it was introduced into the Swiss market in 2007 [19], three years before the previous study ended, and limited use at that time.

Bupropion's seizure potential was 23.7%, consistent with prior Swiss data (31.6%) [9] and other overdose studies (19.6%–32%) [20,26,36], while therapeutic doses showed lower rates (0.24%–2.8%) [27,37].

Mefenamic acid's seizure potential (14.8%) aligns with findings from earlier studies (9.1%–28%) [9,38–42]. Venlafaxine and citalopram showed slightly reduced seizure potentials (8.7% and 5.6%) compared to earlier Swiss data (13.7% and 13.1%) [9]. Nevertheless, both remain among the top 10 seizure-causing drugs, consistent with other studies [10,21].

To increase comparability between drugs and to improve visibility of the relationship between dose and seizure risk, multiples of maximum daily doses (relative overdose) in seizure and non-seizure cases and the ratio of these values (seizure overdose ratio) were calculated.

Tramadol and mefenamic acid caused seizures at low relative overdoses (3.8× and 5× of the maximum approved daily dosage, respectively). Notably, seizures occurred following low dosages of certain neuroleptics (that is, clozapine, chlorprothixene, pipamperone) and tolperisone, a finding not observed in other analyses. While seizures have been reported for some of these drugs in overdose [43,44], no prior study has systematically compared relative overdoses as a parameter reflecting dose-adjusted seizure risk.

Furthermore, trimipramine, mefenamic acid, tolperisone, amitriptyline and bupropion had low seizure overdose ratios (1.4, 2.0, 2.1, 2.1, and 2.1), that is, caused seizures at lower relative overdose compared to non-seizure cases, than, for example escitalopram (7.0) or quetiapine (8.0). The seizure overdose ratio adjusts for typical dosage patterns, distinguishing substances with inherently high seizure risk from those associated with seizures only at extreme overdoses. Although this concept facilitates comparisons across substances, seizure overdose ratios remain relative measures that must be interpreted alongside absolute dosages. For most substances, only a few seizure cases

Table 3. Dose ranges, median of ingested doses, relative overdoses and seizure overdose ratios of the six pharmaceuticals most often associated with seizures.

Drug	Cases[a]	Dose range (g)[b]	Median dose (g)	Maximum approved daily dosage (g)	Relative overdose[c]	Seizure overdose ratio[d]
Mefenamic acid	all ($n=243$)	0.13–150 ($n=172$)	5.0	2	2.5	2.0
	with seizures ($n=36$)	3.0–35.0 ($n=24$)	10.0		5.0	
	without seizures ($n=207$)	0.13–150 ($n=148$)	5.0		2.5	
Quetiapine	all ($n=762$)	0.02–42.9 ($n=579$)	1.2	0.8	1.5	8.0
	with seizures ($n=23$)	2.0–18.0 ($n=13$)	8.0		10.0	
	without seizures ($n=739$)	0.02–42.9 ($n=566$)	1.0		1.3	
Bupropion	all ($n=97$)	0.2–11.3 ($n=67$)	2.1	0.3	7.0	2.1
	with seizures ($n=23$)	0.8–11.3 ($n=16$)	3.5		11.7	
	without seizures ($n=74$)	0.2–11.3 ($n=51$)	1.7		5.5	
Venlafaxine	all ($n=149$)	0.04–22.5 ($n=106$)	1.2	0.375	3.2	4.5
	with seizures ($n=13$)	0.75–18.9 ($n=10$)	5.3		14.0	
	without seizures ($n=136$)	0.04–22.5 ($n=96$)	1.2		3.1	
Tramadol	all ($n=181$)	0.01–6.0 ($n=107$)	1.0	0.4	2.5	2.5
	with seizures ($n=11$)	0.3–4.8 ($n=8$)	1.5		3.8	
	without seizures ($n=170$)	0.01–6.0 ($n=99$)	0.6		1.5	
Diphenhydramine	all ($n=342$)	0.1–7.5 ($n=269$)	0.8	0.05	15.5	2.6
	with seizures ($n=11$)	0.5–7.5 ($n=8$)	2.0		40	
	without seizures ($n=331$)	0.1–7.5 ($n=261$)	0.8		15.5	

[a]Number in brackets indicates total cases.
[b]Number in brackets indicates cases with known dosage.
[c]Relative overdose: Multiple of maximum approved daily dosage.
[d]Seizure overdose ratio: Ratio of multiples of maximum approved daily dosage in seizure versus non-seizure cases.
Due to rounding, the numerical values in this table are approximations and may not yield exact summations or calculations when derived directly from the table.

were reported, and therefore "real" seizure overdose ratios might be different.

Seizure rates and age distribution

Seizures in infants and young children were rare (<1%), consistent with prior studies [9,45], likely due to accidental and therefore smaller ingestions. Seizure rates were similar in adolescents (1.7%) and adults (1.5%). Additionally, no dosage differences were noted between adolescents and adults for the drugs most commonly associated with seizures. The earlier Swiss study showed significantly higher seizure rates in adolescents, but this difference disappeared when excluding mefenamic acid cases [9]. Our results could not replicate prior findings of increased adolescent susceptibility [38,42].

Ingested dose and probability of seizure

As expected, higher drug doses increased seizure risk, consistent with prior research on mefenamic acid [38–42], bupropion [5,10,20,27], venlafaxine [22] and other antidepressants [10,46,47], along with quetiapine [10,25]. This supports the pathophysiological understanding of pharmaceutical-induced seizures through disrupted neurotransmission and neuronal hyperexcitability [48]. However, the concept of seizure overdose ratios revealed large differences in seizure risk between various pharmaceuticals.

Developments in the last 13 years

Quetiapine and bupropion were more frequently involved in seizures, whereas cases with citalopram and tricyclic antidepressants decreased compared to the earlier Swiss study [9]. A new signal was identified for cefepime. Drugs licensed after 2010 [19] were rarely linked to seizures, limiting conclusions on their seizure potential.

Limitations

Limitations inherent to poison centre data [49] include the retrospective design, potential underreporting, reliance on voluntary reporting, and low analytical confirmation rates. Descriptive analysis of retrospective data can elucidate associations but cannot prove causality. Small case numbers for high-seizure-potential drugs (e.g., cefepime) may lead to overestimations. Varying pharmaceutical usage across countries (e.g., mefenamic acid) affects the transferability of the results to other countries. Strict inclusion/exclusion criteria reduce multiple-drug exposures and enhance the accuracy of results by reducing the potential effects of drug interactions, but result in smaller sample sizes. Due to low case numbers, "true" seizure potential and seizure overdose ratios might differ. Future research might consider using total sales of specific substances to provide more robust estimations of seizure potential, thereby reducing reliance on poison centre data.

Conclusion

The analysis confirms antidepressants, particularly bupropion and venlafaxine, as the drug class most commonly associated with seizures. Furthermore, mefenamic acid, quetiapine, and tramadol frequently caused seizures. Drugs licensed after 2010 did not notably contribute to seizures.

Cefepime, which was only administered intravenously in severely ill patients, exhibited the highest seizure potential, highlighting the necessity to adjust dosage in patients with decreasing or impaired renal function. High seizure incidence does not always correlate with high intrinsic potential of the drug to cause seizures (e.g., quetiapine). Some drugs, like tramadol and certain neuroleptics, were associated with seizures at far lower relative overdoses than others (e.g., sertraline). Especially tricyclic antidepressants (trimipramine, amitriptyline), tolperisone, mefenamic acid and bupropion were associated with seizures at low relative overdoses compared to respective non-seizure cases. This emphasizes the importance of close monitoring of patients with overdoses of these substances.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

There was no external funding for this project. Tox Info Suisse supported it through free research funds and data provision.

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Data availability statement

The data supporting these findings are available within the article. Further data are available from the corresponding author, AJ, upon reasonable request.

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