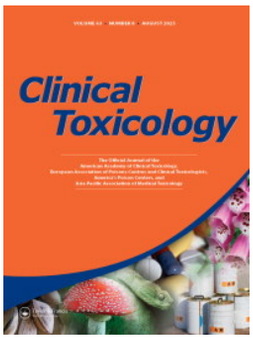

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CLINICAL RESEARCH



# Toxicological seizures: characteristics, outcomes and recurrence

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**ABSTRACT**

**Introduction:** Seizures are a marker of severe toxicity following overdose. Research characterising toxicological seizures is limited. We aim to study toxicological seizures, causative agents, and recurrence.

**Methods:** This is a retrospective observational series of patients with seizure after drug overdose, presenting to three Australian clinical toxicology units between 1 January 2014 and 31 December 2022. Patients were identified from the database of each unit, and data were supplemented by the patient's medical record. Follow-up data were extracted in June 2024.

**Results:** Over the nine-year period, there were 38,493 presentations to the three toxicology units. A seizure occurred in 284 presentations (275 patients). The median age was 29 years (IQR: 21–39 years; range: 15–86 years), and there were 150 males (55%). A previous seizure disorder was documented in 29/275 (11%) patients. In 82 (30%) presentations, more than one proconvulsant drug was taken. In 202 single proconvulsant exposures, the most common agents were tramadol (18/202, 9%), 3,4-methylenedioxymetamfetamine (15/202, 7%), and quetiapine (15/202, 7%). The highest seizure rate, considering total presentations for each agent, was for synthetic cannabinoid receptor agonists (9/43, 21%), tramadol (18/524, 3.4%), cocaine (14/516, 2.2%), and propranolol (8/427, 1.9%). A single seizure occurred in 169 (60%) cases, while status epilepticus occurred in 62 (22%). The median seizure duration was 1 min (IQR:1–3 min). The median time to the first seizure was 2.5 h (IQR: 1.0–7.1 h). Seizures occurred within 12 h for immediate-release preparations and within 24 h for slow-release preparations. Follow-up occurred in 221/275 (80%) patients. Seizure recurrence occurred in 45/221 (20%) patients. In eight patients (4%), a new diagnosis of epilepsy was established.

**Discussion:** Both seizure recurrence and a subsequent diagnosis of epilepsy occurred more frequently than expected. A toxicological seizure may herald a propensity for future seizures and epilepsy.

**Conclusions:** In this series, toxicological seizures were most common after tramadol, 3,4-methylenedioxymetamfetamine, quetiapine and cocaine. Seizure recurrence was common, with 4% of patients later diagnosed with epilepsy, supporting toxicological seizures being investigated, managed and followed up as rigorously as unprovoked first seizures.

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Epilepsy; overdose; poisoning; seizure; status epilepticus

## Introduction

Seizure is a potentially life-threatening brain dysfunction that occurs in a provoked or unprovoked fashion [1]. Seizures are associated with complications such as aspiration, musculoskeletal injury and hypoxic brain injury [2–5]. Approximately, 6% of new seizures are attributable to a drug or toxin [6]. Toxicological seizures are a marker of severe toxicity [7] and predict a more complicated clinical course [2,4,5,8].

Seizures are often treated as a homogenous group irrespective of their underlying cause, and it remains unclear whether toxicological seizures should be treated differently from seizures from other causes, such as epilepsy or structural lesions. Furthermore, there is limited research that describes follow-up in this population and whether any patients are then given a formal diagnosis of epilepsy after a first episode toxicological seizure. Typically, after a first seizure, it is recommended patients are referred for an electroencephalogram (EEG) and brain magnetic resonance imaging (MRI), alongside restrictions on driving and certain high-risk activities [1]. These routine assessments allow risk stratification for seizure recurrence, risk of epilepsy and subsequent

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clinical and occupational prognostication [9]. There is currently a lack of clarity on whether a first toxicological seizure results in an increased risk of seizure recurrence and if patients require a full panel of first seizure investigation and follow-up. It is possible without ongoing drug exposure, the risk of further seizure is sufficiently low that standard investigations and follow-up may not be required.

We aim to investigate the frequency and severity of toxicological seizures, the causative agents, complications and recurrence.

## Methods

### Study design and setting

This is a retrospective observational series of adult (>15 years) patients presenting to three Australian toxicology units (Princess Alexandra Hospital, Calvary Mater Newcastle Hospital and Prince of Wales Hospital) with one or more seizures following acute drug poisoning. The three toxicology units are staffed by clinical toxicologists who manage all poisoned patients presenting to their respective hospitals. All patients with poisoning or suspected poisoning that present to the emergency department are reviewed by or discussed with the respective toxicology unit. Of note, drug and alcohol withdrawal is not managed by clinical toxicology. If the poisoned patient requires admission, they are then admitted under the respective clinical toxicology unit and reviewed daily by the clinical toxicology team until discharge. The clinical toxicology unit is the primary treating team, irrespective of admission location within the hospital, be it the short stay treatment area, medical ward or intensive care unit. The Princess Alexandra Hospital is a tertiary hospital in Brisbane, Queensland, with approximately 70,000 emergency department presentations and 1,600 toxicology unit admissions annually. The Calvary Mater Newcastle is a metropolitan hospital in Newcastle, New South Wales, with approximately 40,000 emergency department presentations and 900 toxicology unit admissions annually. The Prince of Wales Hospital is a tertiary hospital in Sydney, New South Wales, with approximately 53,000 emergency department presentations and 400 toxicology unit admissions annually. Each unit prospectively collects its own data on all toxicological presentations using a separate purpose-built relational database. The occurrence of seizure is a predefined data element collected in all three databases. The data are entered by trained research or medical staff. The use of de-identified data from the database and patient medical records for observational research has been granted by the respective local area human ethics committee of each unit (HREC/14/QPAH/308, HREC/05/03/09/3.11, HREC/12/184: LNR/12/POW/355).

### Selection of participants

Patients were identified by searching the database of each unit for all patients presenting between 1 January 2014 and 31 December 2022 in whom a seizure was reported following a drug overdose. Patients were excluded if the seizure was not witnessed (requiring the seizure to have been observed by either an ambulance officer, hospital staff member or bystander), if on review, the presentation was not associated with a toxicological exposure, or when the attending physician diagnosed the event as a psychogenic non-epileptic seizure.

### Data collection

The following data were extracted from the toxicology databases: baseline demographics (age, sex) and details of drug exposure (drug, preparation, dose, intent, co-ingestions). The medical record was used to supplement data on the presence of a pre-existing seizure disorder, seizure characteristics (duration, number of seizures, timing of seizure, anti-epileptic drug administration, status epilepticus), traumatic injury, death, and seizure recurrence. Patients with missing data were excluded from analysis. There is a centralised electronic patient medical record at two sites and a paper record at one site. Status epilepticus was defined as continuous seizure activity lasting more than 5 min and/or multiple seizures without recovery between, consistent with the Neurocritical Care Society guidelines [10].

Follow-up of patients was achieved, when possible, via the medical records. Follow-up data were extracted up until completion of data collection in June 2024. The duration of follow-up varied from 18 months to 9 years, depending on when the patient first presented. Electronic medical record linkage enabled patient representation and public outpatient appointments to the same or different hospitals within each catchment to be reviewed to determine if the patient had further seizures following their presentation. At the site with a paper medical record, follow-up data were extracted from the paper record. The cause of any further seizures was noted. The formal diagnosis of epilepsy was extracted from the medical record. The diagnostic pathways varied with patients referred to general medical clinics or neurology. If available, confirmatory EEG or MRI were reviewed.

Drugs implicated in the toxicological seizure were identified as those with known proconvulsant properties, with further confirmation on review of each case by a senior clinical toxicologist (KH). Seizures due to hypoglycaemia or hypoxia following overdose were considered separately. Multiple proconvulsant drug exposures were included in the total data set but excluded in the analysis of dose and time post-ingestion to seizure, where single proconvulsant exposures were used to ensure clarity of association of the implicated pro-convulsant drug.

### *Data analysis*

Descriptive statistics were used with medians, interquartile ranges (IQR) and ranges describing continuous data. Dichotomous data are presented as frequencies and proportions. All analyses were performed, and Figures were made using GraphPad Prism for Mac Version 10.1.1.

## Results

Over the nine-year period, there were 38,493 presentations to the three toxicology units. There were 313 presentations with seizure. Twenty-nine presentations were excluded: 23 seizure events were not witnessed, five were psychogenic non-epileptic seizures, and one was an alcohol withdrawal seizure and not related to poisoning. This left 284 of 38,493 (0.7%) presentations in 275 patients in whom a seizure occurred. The median age was 29 years (IQR: 21–39 years; range: 15–86 years), and there were 150 males (55%). Twenty-nine patients (29/275, 11%) had a formal diagnosis of epilepsy prior to presentation. Deliberate self-poisoning accounted for 152 of 284 (54%) presentations, 118 (42%) were recreational drug exposures, seven (2%) were unintentional, six (2%) were unknown, and one (<1%) was an occupational exposure.

Overall, quetiapine was the most common drug taken in 41 (14%) presentations, followed by tramadol in 29 (10%), pregabalin in 27 (10%) and 3,4-methylenedioxymetamfetamine in 27 (10%). Seizures were associated with hypoxia or hypoglycaemia following an overdose in 18 patients (6%). Eleven (4%) presentations had hypoxic seizures following either an opioid or carbon monoxide overdose, while seven (2%) presentations involved hypoglycaemic seizures following insulin overdose. Multiple proconvulsant agents were taken in 82 (30%) presentations.

In 202 presentations, a single proconvulsant drug was taken (Table 1). Tramadol was the most common single agent taken in 18 of 202 (9%) presentations, followed by 3,4-methylenedioxymetamfetamine in 15 (7%), quetiapine in 15 (7%), cocaine in 14 (7%), pregabalin in 11 (5%) and metamfetamine in 10 (5%) presentations.

The seizure rate, considering total presentations for each agent over the period, was highest for synthetic cannabinoid receptor agonists (9/43, 21%), followed by tramadol (18/524, 3.4%), cocaine (14/516, 2.2%) and propranolol (8/427, 1.9%) (Table 1).

A single seizure occurred in 169 (60%) presentations, two seizures occurred in 56 (20%) presentations, and 59 (20%) involved three or more seizures. In the 237 of 284 presentations for which the duration of seizure was recorded, the median duration of seizure was 1 min (IQR: 1–3 min). In 119 (42%) presentations, a benzodiazepine was used to terminate the seizure.

**Table 1.** Details of 202 single proconvulsant agent overdoses with toxicological seizure.

| Proconvulsant agent | Presentations with toxicological seizure | | All presentations and seizure rate |
|---|---|---|---|
| | *n* (%) | Median (IQR) dose, mg | *n* (%) |
| Tramadol | 18 (9) | 1,800 (350–12,800) | 524 (3.4) |
| 3,4-Methylenedioxymetamfetamine | 15 (7) | | 1,355 (1.1) |
| Quetiapine | 15 (7) | 9,363 (650–24,000) | 3,550 (0.4) |
| Cocaine | 14 (7) | | 627 (2.2) |
| Pregabalin | 11 (5) | 1,800 (600–4,200) | 699 (1.5) |
| Metamfetamine | 10 (5) | | 5,412 (0.2) |
| Synthetic cannabinoid receptor agonist | 9 (4) | | 43 (20.9) |
| Amitriptyline | 8 (4) | 1,250 (850–5,000) | 751 (1.1) |
| Propranolol | 8 (4) | 4,000 (3,200–5,360) | 427 (1.9) |
| Venlafaxine | 7 (3) | 3,900 (3,150–7,800) | 866 (0.8) |
| Unknown | 5 | | |
| Others[†] | 67 (33) | | |
| Hypoxic seizure* | 8 (4) | | |
| Hypoglycaemic seizure[#] | 7 (3) | | |

[†]Other implicated drugs included 25I-NBOMe (2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine), alprazolam, amfetamines, aspirin, baclofen, chlorpromazine, citalopram, clozapine, dextromethorphan, dothiepin, doxepin, doxylamine, escitalopram, fluoxetine, fluvoxamine, gamma-hydroxybutyric acid, hallucinogens, halogenated hydrocarbon, hydrocarbons, isoniazid, kratom, lamotrigine, lithium, lysergic acid diethylamide, cannabis, mefenamic acid, methylphenidate, naloxone, orphenadrine, oxybutynin, promethazine, psilocybin, sertraline.
*Agents implicated in seizure secondary to hypoxia: buprenorphine, carbon monoxide, diacetylmorphine (heroin), pethidine, methadone.
[#]Agents implicated in seizure secondary to hypoglycaemia: insulin (aspart, glargine).

The time of first seizure was recorded in 278 of 284 presentations, with the median time to first seizure being 2.5 h (IQR: 1.0–7.1h). This time was similar among common drug types (Figure 1). Seizures occurred within 12 h for all immediate-release preparations but were delayed for up to 24 h for slow-release formulations (Figure 1).

Traumatic injuries occurred in 17 (6%) and ranged from minor soft tissue injuries, minor fracture, shoulder dislocation, vertebral fractures, and one patient with traumatic subdural haemorrhage secondary to a fall during seizure. Endotracheal intubation occurred in 104 (37%) presentations; however, only in seven (2%) was this for seizure termination.

Most presentations (166, 58%) were managed in the emergency department or short-stay unit, while 110 (39%) were admitted to the intensive care unit, and eight (3%) were admitted to a medical ward. The median hospital length of stay was 25 h (IQR: 11–63 h). There were nine (3%) deaths. Three people with hypoglycaemic seizures after insulin overdose were palliated in an intensive care unit between 4.5 and 15 days after presentation due to severe encephalopathy from hypoglycaemia. One patient who developed progressive respiratory failure and aspiration pneumonitis after an opiate overdose in the context of malignancy was palliated and died 2.5 days after the initial seizure event. A further patient died from a hypoxic brain injury after an opiate overdose, with an MRI demonstrating severe hypoxic brain injury. Brain death occurred in one patient with a single, prolonged seizure and pre-hospital cardiac arrest with prolonged downtime after an unknown drug exposure. Two patients suffered recurrent seizures in the emergency department and then refractory cardiac arrest and death. One after a dothiepin, olanzapine and chlorpromazine overdose and another following a large quetiapine overdose. Recurrent, early seizures complicated a venlafaxine and pregabalin overdose in one patient who was palliated in the intensive care unit 20 days after presentation, with a severe brain injury and an MRI demonstrating leukoencephalopathy.

### *Status epilepticus*

Status epilepticus occurred in 62 (22%) presentations (Table 2), most commonly after quetiapine overdose (10/62, 16%). In six of 62 patients with status epilepticus, there was an existing diagnosis of epilepsy. In 45 presentations with status epilepticus, a benzodiazepine, most commonly midazolam, was given as first-line therapy for seizure termination. The median midazolam dose for seizure termination was 5 mg (range 1–20 mg). Intravenous diazepam in doses of 5 and 15 mg was given to two patients. In those patients for whom a benzodiazepine was not used as first-line therapy, three were given levetiracetam: one

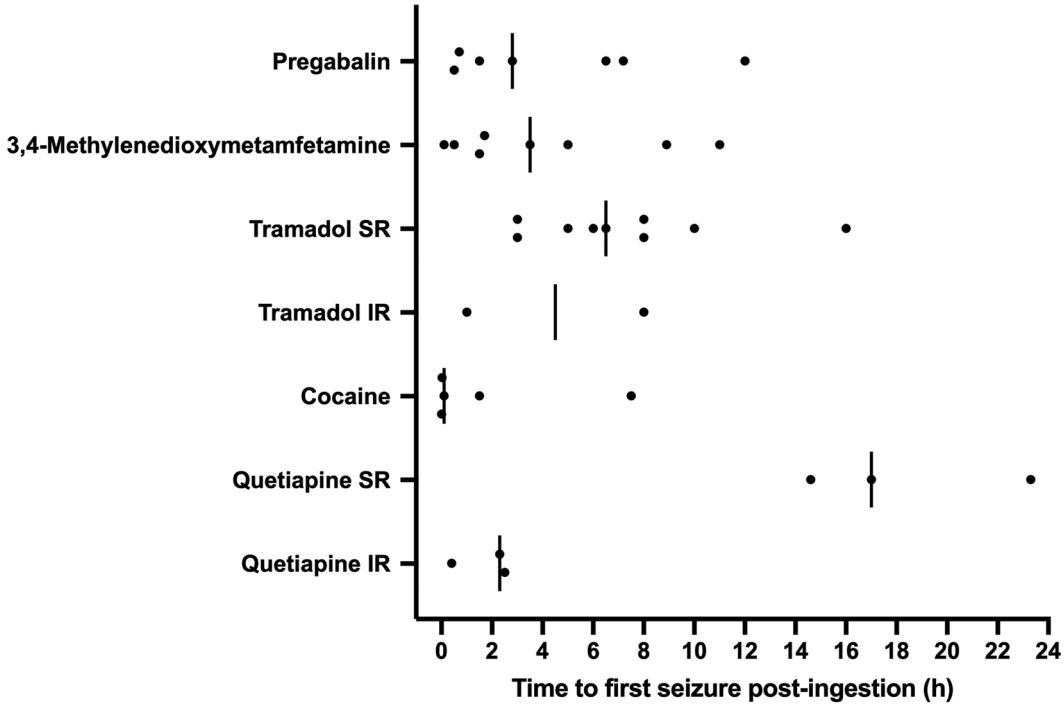


Figure 1. Hours post-overdose until the onset of first seizure in single drug poisoning (immediate-release [IR] and slow-release [SR] where relevant) for the five most common single drug exposures with median marked by a vertical line.

**Table 2.** Characteristics of 62 presentations with status epilepticus following overdose.

| | |
|---|---|
| Age (years), median (range) | 33 (17–85) |
| Pre-existing epilepsy, *n* (%) | 6 (9) |
| Status epilepticus criterion met | |
| Seizure lasting >5 min, *n* (%) | 27 (42) |
| Seizure duration (min), median (range) | 15 (6–90) |
| Multiple seizures without return to baseline, *n* (%) | 39 (61) |
| Implicated drugs (includes single and multi-drug overdoses) | |
| Quetiapine, *n* (%) | 9 (15) |
| 3,4-Methylenedioxymetamfetamine, *n* (%) | 7 (11) |
| Gamma-hydroxybutyric acid, *n* (%) | 6 (10) |
| Amfetamines, *n* (%) | 5 (8) |
| Amitriptyline, *n* (%) | 3 (5) |
| Cocaine, *n* (%) | 3 (5) |
| Lamotrigine, *n* (%) | 3 (5) |
| Metamfetamines, *n* (%) | 3 (5) |
| Synthetic cannabinoid receptor agonist, *n* (%) | 3 (5) |
| Tramadol, *n* (%) | 3 (5) |
| Venlafaxine, *n* (%) | 3 (5) |
| Others, *n* (%)† | 43 (70) |
| Unknown, *n* | 2 |
| Treatment to terminate seizure: | |
| First-line: | |
| Benzodiazepine, *n* (%) | 43 (70) |
| Levetiracetam, *n* (%) | 3 (5) |
| Phenobarbital, *n* (%) | 1 (2) |
| Second-line: | |
| Levetiracetam, *n* (%) | 15 (24) |
| Phenobarbital, *n* (%) | 5 (8) |
| Sodium valproate, *n* (%) | 3 (5) |
| Phenytoin, *n* (%) | 2 (3) |
| Thiopental, *n* (%) | 2 (3) |
| Lacosamide, *n* (%) | 1 (2) |
| Targeted treatments: | |
| Dextrose, *n* (%) | 4 (6) |
| Pyridoxine, *n* (%) | 1 (2) |
| No pharmacological seizure management | 6 (9) |

†Other implicated drugs included: 25I-NBOMe (2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine), atomoxetine, baclofen, benztropine, carbon monoxide, chlorpromazine, clozapine, desvenlafaxine, dothiepin, doxepin, escitalopram, fluvoxamine, halogenated hydrocarbon, hydrocarbons, insulin, ketamine, lacosamide, lithium, morphine, olanzapine, orphenadrine, oxycodone, paroxetine, pethidine, pregabalin, promethazine, propranolol, sodium valproate, topiramate.

after 3,4-methylenedioxymetamfetamine use, one after ketamine and 3,4-methylenedioxymetamfetamine use and one after a quetiapine overdose of 11,100 mg. Phenobarbital was given as first-line treatment in one person after an orphenadrine overdose of 9,000 mg. Two presentations with hypoglycaemia after insulin overdose were treated primarily with dextrose. One presentation with isoniazid poisoning received pyridoxine. Seven patients not given first-line therapies were endotracheally intubated and ventilated for seizure termination. In six, no seizure-terminating therapy was given as seizures were brief and self-limiting; these patients met the criteria for status epilepticus as recovery was not achieved between seizure events. Second-line therapies were given at the discretion of the treating physician. In those with existing epilepsy, two required second-line therapy, and levetiracetam was chosen in both cases.

### *Patient follow-up*

Patient follow-up was possible in 221 of 275 (80%) patients (Figure 2). Seizure recurrence occurred in 45 of 221 (20%) patients. The recurrent seizure was identified as toxicological in 15 of 45 (Figure 2). In 20 of 45 patients, the seizure was diagnosed as epileptogenic; 12 of these had pre-existing epilepsy. Eight patients (4%) received a new diagnosis of epilepsy on follow-up.

## Discussion

Seizure remains a rare but important complication of drug overdose. Most toxicological seizures in this series were single, brief and self-limiting. Tramadol was the most common single causative agent. Recurrent

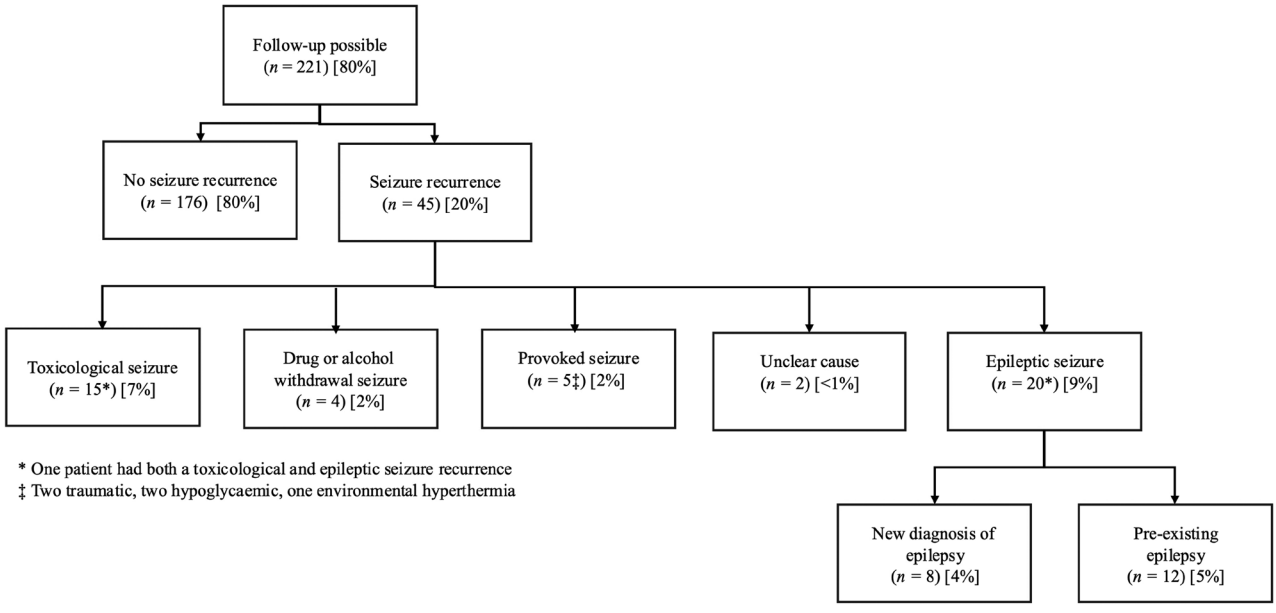


**Figure 2.** Flow diagram of follow-up of seizure recurrence in patients with a toxicological seizure.

seizure was common, occurring in 20% of patients, and 4% of patients eventually received a formal diagnosis of epilepsy.

Seizure recurrence and rates of epilepsy diagnosis in this series appear higher following toxicological seizure compared to the general population. The lifetime risk of seizure recurrence after the first seizure is reported to be 3–10% [1,11]. Some suggest the risk should be lower if the first seizure was provoked by a toxicological insult [1]. However, in this series, 20% of patients had seizure recurrence. Some of this is explained by further drug overdose precipitating another toxicological seizure and likely reflects a vulnerable patient cohort. However, the 4% of patients receiving a diagnosis of epilepsy in this series is higher than the general population of a similar age. The cumulative incidence of epilepsy is approximately 1.7% to age 50 and only a 0.25% risk over 10 years for a 30-year-old without prior epilepsy [11]. It is possible a toxicological seizure uncovers an existing seizure propensity or that the drug overdose initiates a neurological insult, increasing the risk of further seizure and epilepsy. These findings support toxicological seizures being investigated, managed and followed up as rigorously as unprovoked first seizures as they may be a sign of future seizure propensity.

The drugs most commonly implicated in seizure in this series were those with a well-known association with seizure. Seizure in tramadol poisoning is well established, with an occurrence as high as 38% in a large meta-analysis [12]. A European series reported seizure after synthetic cannabinoid receptor agonist use in 77 of 695 (11%) patients and seizure after 3,4-methylenedioxymetamfetamine use in 137 of 2013 (7%) patients. Quetiapine was a surprisingly common agent in this series, as it has been infrequently associated with seizures and typically only in large overdoses [13]. Rates of prescribing, use, misuse and overdose of quetiapine have all significantly increased over recent years [14,15]. In a recent Australian series of patients with borderline personality disorder, quetiapine was the pharmaceutical agent most frequently taken in overdose [16]. The high occurrence of quetiapine poisoning resulting in seizure in this series is likely explained by the high number of quetiapine presentations overall, rather than it being highly proconvulsant. This is supported by the low overall seizure rate of 0.4% when considering the total number of presentations ($n = 3{,}550$) after quetiapine overdose.

The drugs with the highest seizure potential differed from those in the North American and European context and likely relate to differences in drug availability and prescribing trends. In particular, bupropion has an established high seizure potential in European and North American series [3,17]. Prescribing of bupropion in Australia is only indicated in the treatment of nicotine dependence [18] and is not represented in the Australian antidepressant prescribing trends [19].

Benzodiazepines are established first-line agents in the treatment of toxicological seizures [6]. Second-line agents are less well described. In this series, levetiracetam was utilized in 18 of 62 (29%) patients with status epilepticus. The use of levetiracetam in toxicological seizures is not clearly established. A small North American retrospective series of 34 patients that had received levetiracetam as a second-line therapy for control of toxicological seizure appeared to be effective; however, there was no comparator arm [20]. This emerging treatment remains an area for future research.

There are a number of limitations to this study, the main one being its retrospective design and the potential inaccuracies in documentation or missing data in the patient's medical record. The method of patient identification may have underidentified patients with early or pre-hospital endotracheal intubation, when there was no known drug exposure. This is anticipated to be a small number of presentations, given that suspected poisonings are also discussed with or reviewed by the clinical toxicology units. Follow-up was reliant on patient presentation to a public hospital or outpatient clinic, and for information regarding seizure recurrence to be documented. Follow-up data were not available in 20% of patients in the series. The follow-up period was shorter for those presentations that occurred later in the study period, which may have led to an underestimate of seizure recurrence and epilepsy rates. Implicated drugs were determined on patient history, and analytical testing of drugs was not performed. The reporting of the timing of the first seizure onset post-overdose was at times limited by a lack of reported time of drug exposure. Due to variability and limitations of records surrounding seizure events, hypoxic events precipitating seizure may have been under-reported. Finally, this is an Australian series, with associated variations in prescribing and drug misuse trends, limiting the generalizability to a global setting.

## Conclusion

Toxicological seizures were largely single, brief, and self-limiting in this series. Seizure recurrence following discharge occurred in 20% of patients, with 4% eventually receiving a diagnosis of epilepsy. This supports toxicological seizures being investigated, managed and

followed up as rigorously as unprovoked first seizures. We would advocate that standard practice of neuroimaging, EEG and outpatient neurology assessment be followed for those presenting with a first episode of toxicological seizure.

## Author contributions

KM, KI and KH conceived the study. KM, IB, AC, KW and BS contributed to data collection. KM and KH analyzed the data. KM and KI drafted the manuscript; all authors contributed to its revision. KM takes responsibility for the paper as a whole.

## Disclosure statement

No potential conflict of interest was reported the authors.

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## Data availability statement

The de-identified data we analyzed are not publicly available, but requests to the corresponding author will be considered case-by-case.

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