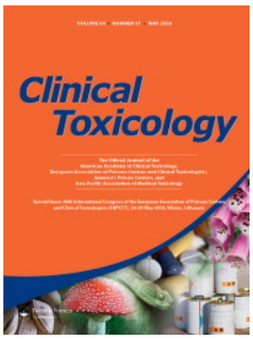

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Relative odds of seizure in emergency department cases of analytically confirmed illicit substance exposure

Shaun L. Greene[a,b], Courtney Weber[c,d,e], Sarah E. Hodgson[a], Jennifer Smith[c,f], Sam Alfred[g,h], David McCutcheon[c,f,i], Viet Tran[j,k,l], Rebekka Syrjanen[a,m] and Katherine Isoardi[n,o]

[a]Victorian Poisons Centre, Austin Health, Melbourne, Australia; [b]Department of Critical Care, University of Melbourne, Melbourne, Australia; [c]Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research, Perth, Western Australia, Australia; [d]East Metropolitan Health Service, Perth, Western Australia, Australia; [e]School of Population and Global Health, The University of Western Australia, Perth, Western Australia, Australia; [f]School of Medicine, The University of Western Australia, Perth, Western Australia, Australia; [g]Emergency Department, Royal Adelaide Hospital, Adelaide, South Australia, Australia; [h]Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia; [i]Emergency Department, Albany Health Campus, Albany, Western Australia, Australia; [j]Tasmanian Emergency Medicine Research Institute, Hobart, Australia; [k]Tasmanian School of Medicine, University of Tasmania, Hobart, Australia; [l]Royal Hobart Hospital, Hobart, Australia; [m]Northern Hospital, Melbourne, Australia; [n]Clinical Toxicology Unit, Princess Alexandra Hospital, Brisbane, Australia; [o]University of Queensland, Brisbane, Australia

ABSTRACT

Introduction: Quantification of risk of seizure from individual illicit substances has traditionally relied on self-reported exposure. This study determined risk of seizure using data from emergency department presentations with analytically confirmed illicit substance exposure.

Methods: Data were extracted from the Emerging Drugs Network of Australia and Emerging Drugs Network of Australia-Victoria illicit substance exposure registries 2020–2025. Cases with analytically confirmed illicit substance exposures were categorised according to reported seizure occurrence. Odds ratios for seizure were calculated for individual drugs using three groups: individual drug including all co-detected substances, individual drug following exclusion of benzodiazepines, anticonvulsants, gabapentinoids, and individual drug following exclusion of benzodiazepines, anticonvulsants, gabapentinoids and gamma-hydroxybutyrate.

Results: Seizure occurrence in all cases ($n=6318$) was 6.7% ($n=425$). Seizure rate increased to 7.1% ($n=196/2748$) when patients co-exposed to an anticonvulsant were excluded, and to 8.1% ($n=143/1665$) with additional exclusion of gamma-hydroxybutyrate. Significantly increased odds of seizure were found for cocaine (odds ratio 3.8, 95% CI 2.5–5.8, $P<0.001$), 3,4-methyledioxymetafetamine (odds ratio 2.5, 95% CI 1.5–3.8, $P<0.001$) and delta-9-tetrahydrocannibinol (odds ratio 2.0, 95% CI 1.3–3.2, $P=0.005$). Gamma-hydroxybutyrate positive cases consistently had decreased odds of seizure (odds ratio 0.58, 95% CI 0.4–0.8, $P=0.001$). Methamphetamine demonstrated a consistent inverse association for seizure across all analytical groups (odds ratio 0.6–0.7), possibly reflective of high background prevalence and residual low-level detections rather than true pharmacological effect. Although positive, odds ratios for seizure for antihistamine, selective serotonin reuptake inhibitor, and ketamine exposures did not reach significance.

Conclusions: In this cohort of analytically confirmed illicit drug exposures, cocaine, 3,4 methylenedioxymethamphetamine and delta-9 tetrahydrocannabinol were strongly associated with increased odds of seizure. Gamma-hydroxybutyrate was associated with decreased seizure odds. These findings underscore the importance of analytical toxicology surveillance in defining outcomes including seizure risk and informing harm-reduction strategies.

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Cocaine; emergency department; illicit drug toxicity; 3,4 methylenedioxymetham-phetamine; methylenedioxymetham-phetamine; seizure

INTERNATIONAL NONPROPRIETARY NAMES
Diacetylmorphine (heroin); chlorphenamine (chlorpheniramine); metamfetamine (methamphetamine); midoamfetamine (methylenedioxymetham-phetamine)

Introduction

Seizures are a potentially life-threatening complication of illicit substance exposure [1] and contribute to morbidity and mortality through aspiration, hypoxia, trauma, and progression to status epilepticus [2–5]. Seizures are associated with a higher rate of intensive care unit admission and hospital length of stay [6]. Although population-based occurrence of illicit substance-induced seizures remains low, the clinical

CONTACT Shaun Greene Shaun.Greene@austin.org.au Victorian Poisons Centre, Austin Health, 145 Studley Road, Heidelberg, Victoria 3084, Australia.
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THE INTERNATIONAL NONPROPRIETARY NAMES: Heroin-diacetylmorphine; chlorpheniramine-chlorphenamine; metamfetamine-methamphetamine.

impact on patients and healthcare systems can be significant [2,7].

Most published data on illicit substance related seizures derive from retrospective case series or self-reported exposures. The European Drug Emergencies Network Plus (Euro-DEN Plus) project provided the first large-scale international toxicosurveillance dataset examining seizures within acute illicit substance hospital presentations, and identified synthetic cannabinoid receptor agonists, tramadol, cocaine, and 3,4-methylenedioxymethamphetamine as leading precipitants of seizures [3]. Of note, gamma-hydroxybutyrate, a gamma-aminobutyric acid B receptor (GABA-B) agonist, was reported to have a statistically significant positive association with seizures. In Australia, McCulloch et al. (2025) described 284 toxicological seizures across three tertiary clinical toxicology units, reporting that 20 percent of patients had recurrent seizures and four percent later developed epilepsy [4]. Synthetic cannabinoid receptor agonists, cocaine and 3,4-methylenedioxymethamphetamine were identified as having the highest seizure rates amongst illicit substances. McCutcheon et al. (2023) reported a seizure rate of 6.2% in a cohort of patients presenting to Western Australian emergency department [8]. Although informative, the two largest of these studies relied on self-report or clinical identification of drug exposure, potentially limiting accurate risk quantification [3,4].

Recent toxicosurveillance initiatives, including the Emerging Drugs Network of Australia and the Emerging Drugs Network of Australia Victoria, have established a prospective, multi-jurisdictional framework enabling analytical confirmation of illicit substance exposures within Australian Emergency Departments [9,10]. We utilised these two datasets to calculate odds ratios of seizure for common illicit substances and to assess whether statistical associations persisted after excluding anticonvulsant co-exposures.

Methods

Study dataset

The Emerging Drugs Network of Australia and the Emerging Drugs Network of Australia-Victoria are separate prospective clinical studies utilising comprehensive analysis of blood samples obtained from a purposive sample of individuals presenting to selected Australian emergency departments with reported or suspected illicit substance related toxicity. Emerging Drugs Network of Australia collects data across five states from 12 emergency departments, while Emerging Drugs Network of Australia-Victoria collects data from 18 metropolitan and regional emergency departments within the state of Victoria [9,10]. Under ethics committee approved waivers of consent, de-identified clinical and analytical data are collated within secure registries (Emerging Drugs Network of Australia Clinical Registry South Metropolitan Health Service HREC RGS0000003673, Emerging Drugs Network of Australia Victoria Clinical Registry, HREC/66506/Austin-2020). Full study methodologies have been published in detail elsewhere [9,10]. The registry captures analytically detected substances but does not always permit definitive differentiation between prior consumption and medications administered therapeutically in the pre-hospital or emergency department setting. Where documentation clearly indicated iatrogenic administration, this was considered during interpretation; however, some misclassification may remain. In particular, benzodiazepine detection could reflect antecedent use, mixed use, or iatrogenic administration in the pre-hospital or emergency department setting; these categories cannot be reliably distinguished using qualitative results alone.

Analytical methodology

Blood samples obtained from cases at the time of emergency department presentation undergo comprehensive toxicological analysis at six state forensic toxicology laboratories (ChemCentre, Victorian Institute of Forensic Medicine, Coronial and Public Health Sciences, Queensland Pathology Forensic and Scientific Services Queensland, Forensic Science South Australia, Forensic Science Service Tasmania). Analysis uses state-specific methods to screen for common pharmaceutical, illicit and novel substances, but typically includes LC-MS/MS and LC-QOTF screening instruments. Samples are subsequently analysed using untargeted screening via liquid chromatography quadrupole-time-of-flight mass spectrometry (LC-QTOF-MS) using the crowd-sourced HighResNPS.com database [11]. Ethanol is only routinely measured as part of the comprehensive screen within South Australia, and at the attending physician's discretion at each study hospital within other states.

Case selection and primary study groups

All Emerging Drugs Network of Australia and Emerging Drugs Network of Australia-Victoria registry cases presenting between 1 July 2020 and 31 December 2024 were reviewed for eligibility. Cases with missing or "unknown" seizure data, or incomplete toxicological data, were excluded (Figure 1). To examine potential confounding effects of co-exposure to seizure

suppressing illicit substances or pharmaceuticals, and to provide increased evidence for biological plausibility, three groups were defined for each illicit substance analysis based on analytical results of toxicological analysis (Figure 2). Group 1 comprised each specific illicit substance including all co-detections. Group 2 and Group 3 both comprised each specific illicit substance but excluded anticonvulsants (a detailed list of pharmaceuticals and illicit substances comprising this group is available in Supplementary Table 1). Group 2 and Group 3 differed by the inclusion or exclusion of gamma-hydroxybutyrate. Gamma-hydroxybutyrate is a GABA-B receptor agonist producing central nervous system depression and theoretical seizure supressing activity [12], however gamma-hydroxybutyrate has previously been reported as positively associated with seizures [3]. To further define the association of gamma-hydroxybutyrate with seizures, Group 2 included cases with positive gamma-hydroxybutyrate co-detection and Group 3 excluded cases with positive gamma-hydroxybutyrate co-detections (Figure 2).

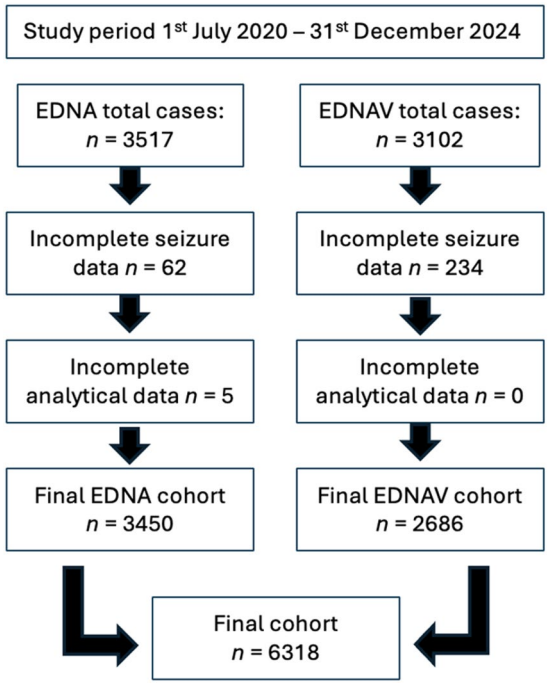

Figure 1. Strobe flow diagram illustrating the derivation of final study cohort. EDNA: Emerging Dugs Network of Australia and EDNAV: Emerging Drugs Network of Australia Victoria

Lone exposure to any illicit substance as defined by analytical detection was rare in both datasets, precluding the calculation of odds ratios for seizures in mono-intoxication cases for any illicit substance. Generation of relative odds ratios of seizure for known proconvulsants was undertaken to provide context to the interpretation of illicit substance relative odds ratios.

Quantitative (concentration) data was available for a minority of analytes; therefore, primary analysis was classified as positive for any qualitative positive detection. Illicit substances were considered "detected" if the parent substance or metabolite specific to that substance was detected. Metabolites considered as indicating exposure to a parent substance are listed in Supplementary Table 2. Pharmaceutical drugs administered therapeutically to manage acute intoxication

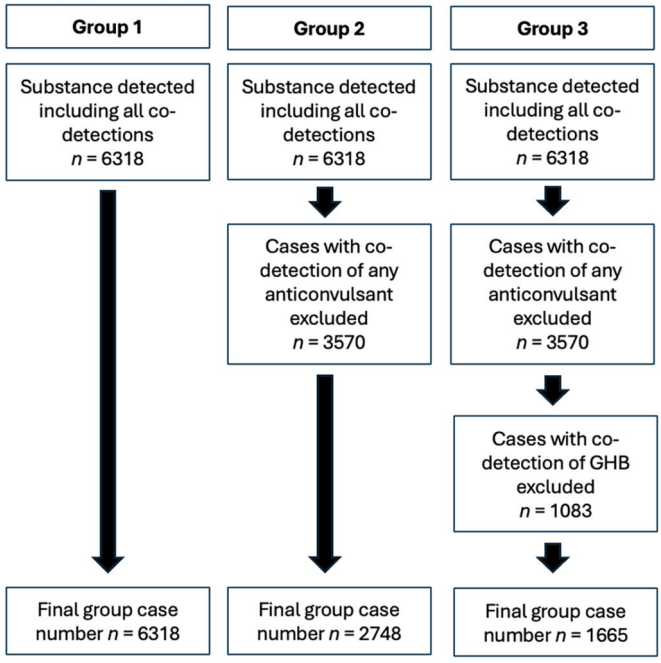

Figure 2. Analysis groups (GHB: gamma-hydroxybutyrate).

and/or a seizure were excluded from odds ratio calculations.

Seizure occurrence

Seizure occurrence was based on the clinician observation. Seizures reportedly occurring prior to contact with a health care provider were included if the attending clinician documented seizure positivity based on reported events. Electroencephalograms were not routinely obtained in most cases and EEG results were not utilised in this study. Seizures were coded as 0 = none, 1 = single, 2 = multiple, or 3 = status epilepticus (recurrent generalised seizures without recovery of consciousness between seizures); values ≥1 were defined as seizure positive. Patients with an established history of seizure disorder were not automatically excluded, however co-detection of an anticonvulsant excluded those cases from analysis within the group adjusted for possible seizure supressing pharmaceuticals.

Statistical analysis

Overall data and groups were described using descriptive statistics including median and interquartile range for non-normally distributed data. Seizure occurrence was compared between exposure and non-exposure groups using 2×2 contingency analysis with Fisher's exact test to calculate odds ratios, 95% confidence intervals, and *P*-values. For each analyte, the referent (non-exposed) group comprised all other cases within the study cohort in which that specific substance was not detected, irrespective of the presence of other drugs. Thus, odds ratios compare seizure occurrence in cases with a given analyte detected versus all remaining presentations without detection of that analyte. Analyses were conducted in GraphPad Prism v10.1.1 and Microsoft Excel (V2502). Given the predominance of polydrug exposures and qualitative detection, reported odds ratios describe associations between detection and seizure occurrence and do not establish causation for individual substances.

To ensure stable estimates and avoid low-frequency bias, we a priori restricted primary odds ratio analyses to substances detected in 100 or greater cases overall and with five or greater seizure events among exposed and five or greater seizure events among unexposed cases. Substances detected in 20–99 of cases, or with a seizure number of less than five, are presented in Supplementary Table 2. Illicit substances detected in less than 20 cases were not included in the study.

Results

Study cohort and baseline demographic characteristics

A total of 7244 cases were included within the two study registries between 1st July 2020 and 31st December 2024. Following exclusion of records with incomplete clinical or analytical data ($n = 858$), 6318 cases (Group 1) were eligible for inclusion in the current analysis (Figure 1). Seizures were reported in 6.7% of cases ($n = 425/6318$). Following exclusion of cases with co-detection of benzodiazepines, gabapentinoids or anticonvulsants, 2748 cases remained (Group 2) and 7.1% ($n = 196$) had reported seizures (Table 1). Following further exclusion of gamma-hydroxybutyrate cases, 1665 cases remained (Group 3) with 8.6% having reported seizures ($n = 143/1665$).

Median age in the overall cohort (Group 1) was 32 years (interquartile range 25–42 years), 31 years (interquartile range 25–40 years) in the group with exclusion of benzodiazepines, gabapentinoids or anticonvulsants (Group 2) and 31 years (interquartile range 23–40 years) in the group with additional exclusion of gamma-hydroxybutyrate (Group 3). Patients identified as male in 65% in the first group, 64% of the second group, and 66% in the third group. Absolute seizure frequencies in exposed and non-exposed groups for each substance are provided in Supplementary Table 3 to aid interpretation of the reported odds ratios.

Odds ratios for seizures in cases with all co-detections included (group 1)

Six illicit substances and four pharmaceuticals met the predefined thresholds for calculating odds ratios. Seizures occurred in 6.7% (Table 1). Seizures occurred in 11.6% of cocaine-positive cases compared to 6.3% of all other cases in which cocaine was not detected corresponding with an odds ratio of 1.97, $P < 0.001$. Seizures occurred in 10.4% of 3,4-methylenedioxymethamphetamine-positive cases compared to 6.7% of cases without 3,4-methylenedioxymethamphetamine detection, corresponding with an odds ratio of 1.69, $P = 0.008$. Delta-9 tetrahydrocannabinol, ketamine, tramadol, selective serotonin reuptake inhibitors, and antihistamines were not significantly associated with seizures. Metamfetamine (odds ratio 0.63, $P < 0.001$) and gamma-hydroxybutyrate (odds ratio 0.60, $P < 0.001$) were inversely associated with seizures (Figure 3). Synthetic cannabinoid receptor agonists were only detected in 31 cases and have been reported in Supplementary Table 2.

Table 1. Reported seizure percentage for illicit substances and pharmaceuticals in all three analytical groups (MDMA:3, 4-methylenedioxymethamphetamine, THC: Delta-9 tetrahydrocannabinol, SSRI: Selective serotonin reuptake inhibitor, GHB: Gamma-hydroxybutyrate).

	Group 1 all detections		Group 2 anticonvulsants excluded		Group 3 anticonvulsants and GHB excluded	
Illicit or pharmaceutical	Cases exposed *n*	Reported seizure *n* (%)	Cases exposed (*n*)	Reported seizure *n* (%)	Cases exposed (*n*)	Reported seizure *n* (%)
Entire group	6318	425 (6.7)	2748	196 (7.1)	1665	143 (8.6)
Cocaine	550	64 (11.6)	235	34 (14.5)	170	36 (21.2)
MDMA	481	50 (10.4)	248	31 (12.5)	192	30 (15.6)
Ketamine	362	31 (8.6)	156	14 (8.8)	113	11 (9.7)
Tramadol	141	12 (8.5)	–	–	–	–
THC	766	63 (8.2)	299	29 (9.7)	184	25 (13.6)
SSRIs	613	44 (7.2)	249	26 (10.4)	183	19 (10.4)
Antihistamines	365	25 (6.8)	–	–	–	–
Heroin	495	33 (6.6)	152	10 (6.6)	139	9 (6.5)
Desvenlafaxine	188	11 (5.9)	–	–	–	–
Metamfetamine	4270	243 (5.7)	1885	106 (5.6)	365	25 (6.8)
GHB	2123	102 (4.8)	1104	52 (4.7)	–	–

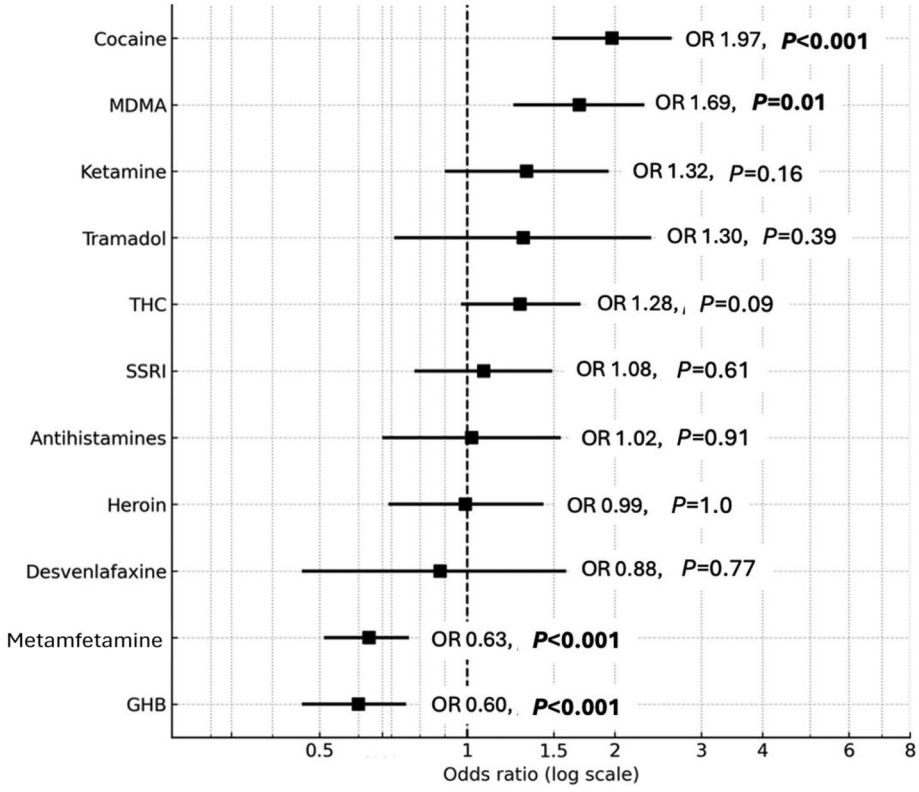

Figure 3. Forest plot of odds ratios for seizures for illicit substances and pharmaceuticals with all co-detections included (MDMA: 3,4 methylenedioxymethamphetamine, THC: Delta-9 tetrahydrocannabinol, SSRI: Selective serotonin reuptake inhibitors).

Odds ratios for seizures in cases with exclusion of co-detected benzodiazepines, anticonvulsants and gabapentinoids (group 2)

A total of 2748 cases remained following exclusion of cases with co-detection of seizure supressing illicit or pharmaceutical substances. Seizures were reported in 7.1% ($n=196$). Eight illicit substances and pharmaceuticals met the predefined thresholds for analysis. Seizures occurred in 14.5% of cocaine-positive cases compared to 6.0% of cases without cocaine detection, corresponding with an odds ratio of 2.66, $P<0.001$. Seizures occurred in 12.5% of 3,4 methylenedioxymethamphetamine -positive cases compared to 6.0% of cases without 3,4-methylenedioxymetamfetamine detection, corresponding with an odds ratio of 2.19, $P=0.0004$. Seizures occurred in 9.7% of delta-9-tetrahydrocannabinol-positive cases compared to 6.3% of delta-9-tetrahydrocannabinol-negative cases (odds ratio 1.59, $P=0.04$). Selective serotonin reuptake inhibitors and ketamine demonstrated

non-significant positive associations, while heroin showed no association. Metamfetamine (odds ratio 0.64; $P=0.003$) and gamma-hydroxybutyrate (odds ratio 0.58; $P=0.001$) remained inversely associated with seizures (Table 1 and Figure 4).

Odds ratios for seizures in cases with exclusion of co-detected benzodiazepines, anticonvulsants, gabapentinoids, and gamma-hydroxybutyrate (group 3)

Seven illicit substances and pharmaceuticals met the predefined thresholds for analysis. Seizures occurred in 8.6% (Table 1). Seizures occurred in 21.2% of cocaine-positive cases compared to 6.5% of cases without cocaine detection, corresponding with an odds ratio of 3.84, $P<0.001$. Seizures occurred in 15.6% of 3,4 methylenedioxymethamphetamine-positive cases compared to 7.0% of cases without 3,4 methylenedioxymethamphetamine detection (odds ratio of 2.46, $P=0.001$). Seizures occurred in 13.6% of delta-9-tetrahydrocannabinol-positive cases compared to 7.3% of delta-9-tetrahydrocannabinol-negative cases (odds ratio 2.01, $P=0.006$). Odds ratios increased in cases of cocaine, 3,4-methylenedioxymethamphetamine, and delta-9-tetrahydrocannabinol exposures without gamma-hydroxybutyrate co-detection, compared to cases with gamma-hydroxybutyrate co-detection. Metamfetamine remained inversely associated with seizures (odds ratio 0.68; 95% confidence interval 0.48–0.96; $P=0.03$) (Table 1 and Figure 5).

Discussion

This study utilised data from two clinical registries prospectively collecting multi-centre data on analytically confirmed acute illicit substance intoxications. The overall seizure rate of 6.7% is higher than previously reported rates from two large European (4.4%) and Australian (4.3%, 6.2%) based studies in drug-related presentations [3,4,8]. This may reflect the purposive sampling approach utilised to select cases for analysis within the clinical registries (cases with severe toxicity are preferentially selected).

Cocaine and 3,4 methylenedioxymethamphetamine were strongly associated with seizures, including in the study groups with co-detection of pharmaceuticals or illicit substances with seizure supressing pharmacological effects. These results align with the Euro-DEN Plus dataset and the recent Australian toxicology unit study by McCulloch et al. [3,4]. Cocaine is a potent sodium-channel blocker that increases cortical

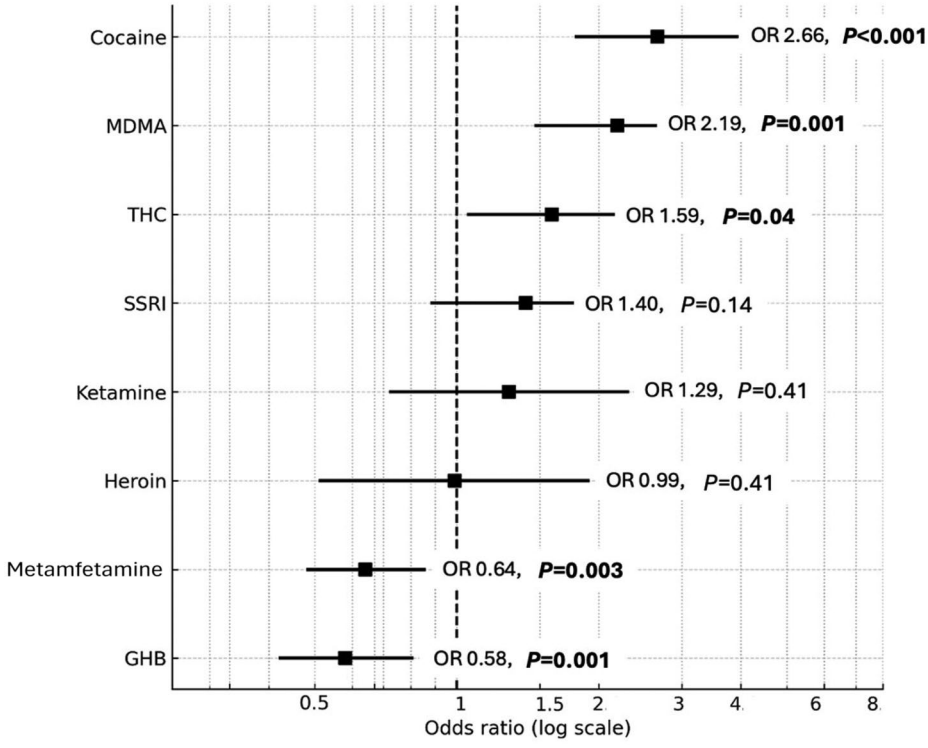

Figure 4. Forest plot of odds ratios for seizures for illicit substances and pharmaceuticals, with cases of seizure suppressing illicit substances or pharmaceuticals excluded (MDMA: 3,4-methyledioxymetafetamine, THC: Delta-9 tetrahydrocannabinol, SSRI: Selective serotonin reuptake inhibitors).

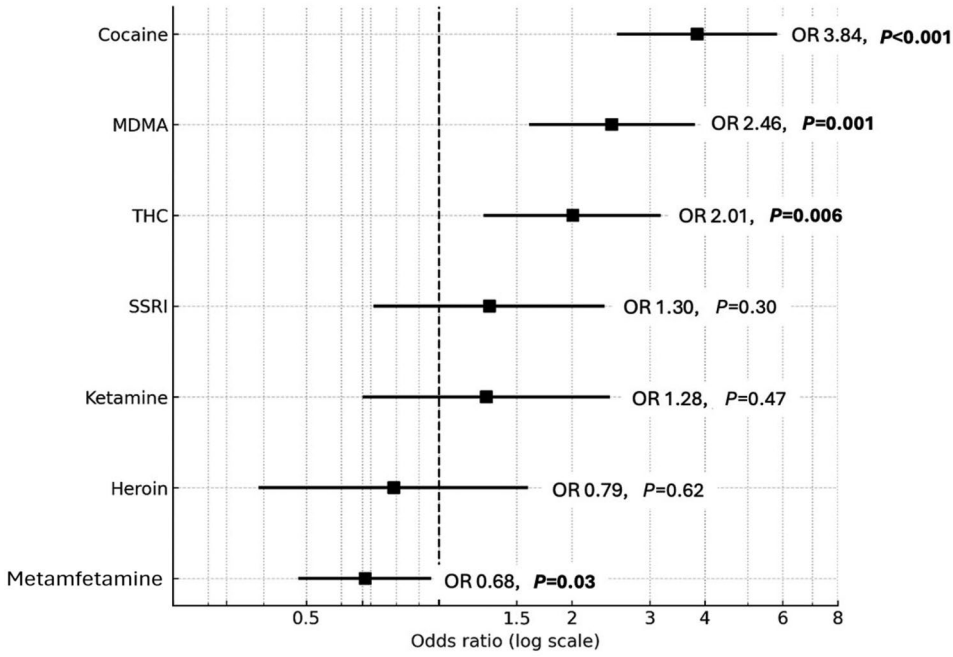

Figure 5. Forest plot of odds ratios for seizures for illicit substances and pharmaceuticals, with cases of seizure suppressing illicit substances or pharmaceuticals including gamma-hydroxybutyrate excluded (MDMA: 3,4-methyledioxymetafetamine, THC: Delta-9 tetrahydrocannabinol, SSRI: Selective serotonin reuptake inhibitors).

excitability and lowers seizure threshold [13]. Cocaine may also reduce seizure threshold through inhibition of acetylcholine esterase [14].

Delta-9-tetrahydrocannabinol was also positively associated with seizure occurrence when sedative co-detections were excluded, an association that, while less well described, has been reported [15]. Proposed mechanisms include CB1 receptor–mediated modulation of GABA and glutamatergic neurotransmission, which may unmask seizure susceptibility in predisposed individuals [16].

Gamma-hydroxybutyrate was associated with significantly lower seizure odds. This finding aligns with gamma-hydroxybutyrate's pharmacological profile as a central nervous system depressant and GABA-B receptor agonist [17]. Gamma-hydroxybutyrate reduces concentrations of the excitatory neurotransmitter glutamate in the central nervous system during acute intoxication [18]. Gamma-hydroxybutyrate withdrawal involves GABA-B and gamma-hydroxybutyrate receptor down regulation, and upregulation of excitatory neurotransmitters including glutamate with an associated increased risk of seizure [19]. It is possible that previous reports of a positive gamma-hydroxybutyrate seizure association [3,4] were related to gamma-hydroxybutyrate withdrawal states or the observation of myoclonic activity during acute intoxication. In our study, all gamma-hydroxybutyrate cases were representative of acute intoxication (positive gamma-hydroxybutyrate serum concentration) rather than a withdrawal state.

The inverse association observed for methamphetamine should be interpreted cautiously. Metamfetamine is widely recognised as capable of precipitating seizures [20]. In our cohort, the negative association most likely reflects confounding by co-exposure patterns and comparator composition, as well as potential treatment and selection effects (e.g., differing clinical phenotypes of metamfetamine-predominant toxicity compared with cocaine/MDMA presentations) [21]. Importantly, our data do not support a conclusion that metamfetamine is protective against seizures, nor do they exclude seizures occurring in individual cases of metamfetamine toxicity. Rather, the findings suggest that within a heterogeneous, polydrug ED cohort, seizures were more strongly associated with other detected substances (notably cocaine and MDMA) than with methamphetamine detection alone.

Previous studies have reported positive associations between seizures and other drug classes, particularly fentanyl and synthetic cannabinoid receptor agonists [3,4]. In the present study, the number of analytically confirmed fentanyl and synthetic cannabinoid receptor agonist detections was small, precluding meaningful inclusion in the primary odds ratio analysis. However, these substances are recognised causes of acute toxicological seizures, and their limited representation in

our study should not be interpreted as evidence of the absence of effect. Data on synthetic cannabinoid receptor agonist-related presentations are included in the supplementary material, where they demonstrate a pattern consistent with previous published findings. Tetrahydrocannabinol was associated with seizures only in groups two and three; given known heterogeneity in cannabinoid effects and the potential for confounding by co-exposures, this finding should be considered hypothesis-generating rather than evidence of direct causation.

Although pregabalin is classified therapeutically as an anticonvulsant, recent studies examining seizures in toxicological presentations have described proconvulsant effects following high-dose or recreational exposures [4,22]. In the present dataset, pregabalin detections were relatively uncommon (6.5% of all cases), and quantitative concentrations were not available. Within our cohort, it is likely that most pregabalin detections represented background therapeutic or recreational exposure rather than acute overdose. For this reason, and because pregabalin is primarily an anticonvulsant drug at usual concentrations, pregabalin was classified as a potential seizure-suppressing medication.

Implications

Illicit substance related seizures are associated with significant emergency department resource allocation [7]. The finding of significantly increased seizure risk following analytically confirmed cases of 3,4 methylenedioxymethamphetamine, cocaine and delta-9-tetrahydrocannabinol exposure may facilitate resource planning for management of illicit substance toxicity in settings such as music festivals where stimulants are commonly used. Findings from this study may aid educational interventions targeting at risk communities and individuals who use illicit substances. Near real-time toxicovigilance data from networks such as Emerging Drugs Network of Australia and Emerging Drugs Network of Australia-Victoria can inform alerts regarding high-potency 3,4-methylenedioxymetamfetamine tablets, adulterated cocaine, or combinations of stimulants that may elevate seizure risk.

Strengths and limitations

This study's major strengths are its use of analytical confirmation of exposures and inclusion of presentations from multiple jurisdictions, enhancing generalisability and avoiding bias from self-reported drug use. The use of predefined inclusion thresholds ensured adequate event counts for stable odds ratio estimation. Exclusion analyses provided biological plausibility by reducing confounding from sedative and anticonvulsant drugs that may mask seizures.

A key limitation is that most presentations involved multiple co-detected substances and the analytical results were primarily qualitative. Accordingly, the observed odds ratios should be interpreted as associations between detection and seizure occurrence rather than attribution of seizure causality to a specific substance. These associations nevertheless remain clinically useful as risk signals within real-world ED presentations, where management decisions are often made in the context of polysubstance exposure.

Other limitations include the inability to adjust for dose, route, or timing of exposure, as quantitative data were available for only a minority of substances. Selection bias may have occurred because the Emerging Drugs Network of Australia and Emerging Drugs Network of Australia-Victoria registries preferentially include more clinically significant presentations. Additionally, some substances with low detection counts were underpowered to detect moderate effects and were therefore reported only as exploratory. Fisher's exact testing does not adjust for covariates, so residual confounding by unmeasured factors cannot be excluded. Individuals with a known seizure disorder were not explicitly excluded from the dataset. However, cases involving an existing seizure disorder that were being actively treated with an anticonvulsant were excluded from analytical groups with anticonvulsants excluded. The analysis was conducted at the case level rather than the individual level, and it is therefore possible that some individuals were represented more than once if they presented on multiple occasions during the study period. This approach was chosen to capture the characteristics of all analytically confirmed presentations, but it introduces the potential for non-independence of observations. Given the large overall sample size and the relatively small proportion of repeat attendances expected within both registries, any resulting bias is likely to be modest but should be considered when interpreting the odds ratios. Some detected substances may have been administered therapeutically in response to agitation or seizures rather than representing non-therapeutic exposure. Although clinical documentation was reviewed where available, definitive differentiation was not possible in all cases, introducing the possibility of indication bias. Specifically, benzodiazepine detection may represent pre-existing use or iatrogenic treatment for agitation or seizures. Information regarding prior epilepsy or

baseline seizure susceptibility was not consistently available. Consequently, some individuals may have been predisposed to seizures independent of the substances detected, which could influence observed associations.

Conclusion

Cocaine, 3,4 methylenedioxymethamphetamine and delta-9-tetrahydrocannabinol were the illicit substances most strongly associated with seizures in this large cohort of analytically confirmed illicit drug exposures. In cases of analytically confirmed acute gamma-hydroxybutyrate intoxication, gamma-hydroxybutyrate had a consistent, statistically significant negative odds ratio for seizure, consistent with its primary pharmacodynamic action of GABA-B receptor agonism. Although metamfetamine demonstrated a consistent negative association across all analytical groups, this is unlikely to represent a protective effect but suggests that within this cohort, seizures were less frequently observed in cases with metamfetamine detection than in cases involving certain other stimulants. Comprehensive toxicological analysis, as utilised in this study, aids clinical management and harm-reduction strategies aimed at reducing morbidity from stimulant and polydrug toxicity.

Disclosure statement

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ORCID

Shaun L. Greene http://orcid.org/0000-0002-7423-2467
Courtney Weber http://orcid.org/0000-0003-1868-153X
Sarah E. Hodgson http://orcid.org/0000-0003-4649-1813
Jennifer Smith http://orcid.org/0000-0002-0398-2121
Sam Alfred http://orcid.org/0000-0002-2226-7887
David McCutcheon http://orcid.org/0000-0001-8034-7749
Viet Tran http://orcid.org/0000-0002-8890-1457
Rebekka Syrjanen http://orcid.org/0000-0002-8109-164X
Katherine Isoardi http://orcid.org/0000-0002-1176-7923

Data availability statement

The data that support the findings of this study are available from the corresponding author (Shaun Greene) upon reasonable request.

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