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Early clinical features associated with severe valproic acid poisoning: a toxicology investigators consortium core registry study

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Abstract

Severe acute Valproic Acid (VPA) ingestions may require intensive care, intubation, or Extracorporeal Treatments (ECTRs), but early predictors are poorly defined. In this study we aimed to identify presentation features associated with Intensive Care Unit (ICU)-level care, intubation, and ECTRs after VPA exposure. We analyzed 164 VPA cases reported to the Toxicology Investigators Consortium Core Registry from January 1, 2012, through December 31, 2025. Candidate predictors were selected *a priori* from severe VPA toxicity features. Associations were assessed using Fisher exact tests and Odds Ratios (ORs). Median age was 34.5 years; 144/164 exposures (87.8%) were intentional. ICU-level care occurred in 49/164 cases (29.9%), intubation in 23/164 (14.0%), and ECTRs in 5/164 (3.0%). ICU-level care was associated with respiratory depression (OR 30.0), metabolic acidosis (OR 15.9), hypotension (OR 4.63), central nervous system depression (OR 4.23), and co-ingestion (OR 3.25).

Therapeutic-use cases were less likely to require ICU-level care or intubation. Respiratory depression, metabolic acidosis, hypotension, central nervous system depression, and co-ingestion identify VPA exposures at higher risk for ICU-level care.

Introduction

Valproic Acid (VPA) is a broad-spectrum anticonvulsant widely used in the treatment of generalized and focal seizure disorders. It is also prescribed for mania associated with bipolar disorder, migraine prophylaxis, alcohol withdrawal, neuropathic pain, and other neuropsychiatric indications.[1,2] While anticonvulsant exposures are typically associated with producing mild toxicity involving Central Nervous System (CNS) depression and ataxia, VPA represents one of several exceptions. Among 24,022 exposures reported to the National Poison Data System (NPDS) from 2006-2019, the case fatality rate from VPA was 41.9 per 100,000 exposures.[3]

The anticonvulsant effects of VPA appear to be mediated, in part, through regional increases in CNS Gamma-Aminobutyric Acid (GABA) concentrations via increased synthesis and decreased degradation.[2] The manifestations of VPA toxicity reflect both extension of these therapeutic effects and disruption of intermediary metabolism, particularly mitochondrial fatty acid metabolism and the urea cycle.[2,4,5] VPA is metabolized primarily through glucuronidation, mitochondrial β-oxidation, and cytosolic ω-oxidation. In overdose, and in the setting of relative L-carnitine depletion, mitochondrial transport and β-oxidation may become impaired or overwhelmed, shifting metabolism toward ω-oxidation and increasing formation of toxic metabolites such as 4-en-VPA and related CoA esters.[2,6,7] Valproyl-CoA and related metabolites inhibit N-acetylglutamate synthase, reducing N-acetylglutamate availability and thereby impairing carbamoyl phosphate synthetase I, the first committed step of the urea cycle.[2,8] Reduced carbamoyl phosphate synthetase I activity limits conversion of ammonia and bicarbonate to carbamoyl phosphate, decreases urea cycle flux, and contributes to hyperammonemia. Renal ammonia production may also contribute.[8] In severe cases hyperammonemia may contribute to astrocyte glutamine accumulation, osmotic swelling, and cerebral edema. CNS depression remains the most common consequence of acute overdose and may progress to lethargy, coma, and respiratory depression.[1,9] Other effects in overdose attributable to VPA and its metabolites include pancreatitis, bone marrow suppression, and metabolic derangements.

During therapeutic use, peak VPA concentrations occur within 1-4 hours after ingestion. In overdose, this can be delayed up to 18 hours post-ingestion with a mean of 7.4±3.9 hours.[9] Approximately 15% of patients who ultimately reach toxic (≥ 120 mg/L) levels have low or undetectable concentrations at time of presentation, likely due to ingestion of modified-release preparations.[10] The relationship between serum concentrations and clinical toxicity is logarithmic with saturable albumin binding in overdose resulting in a disproportionate increase in free VPA. Markedly elevated concentrations are consistently associated with severe toxicity; in one case series all patients with VPA concentrations exceeding 850 mg/L were comatose and 63% required endotracheal intubation.[9] Hyperammonemia and toxic metabolite formation, particularly when mitochondrial β-oxidation is impaired and cytosolic ω-oxidation is increased, are thought to contribute to delayed cerebral edema, which may occur 12-96 hours after supratherapeutic ingestion.[5,6,11-13]

Options for antidotal care and enhanced elimination in patients with VPA toxicity include levocarnitine (*i.e.*, L-carnitine),[7] arginine,[8] carbapenems,[14] Multiple-Dose Activated Charcoal (MDAC),[15] whole bowel irrigation,[16] and Extracorporeal Treatments (ECTRs) such as intermittent hHemodialysis (HD).[17] While published guidelines assist in clinical decision-making regarding the use of antidotes and ECTRs, they are based on relatively low-quality evidence. Furthermore, there is a paucity of evidence to guide appropriate resource utilization with respect to admission and disposition of VPA-toxic patients to the Intensive Care Unit (ICU).

The objective of this study was to identify clinical features associated with the requirement for ICU-level care, endotracheal intubation, use of ECTRs for toxin removal, and mortality in VPA exposure cases reported to the Toxicology Investigators Consortium (ToxIC) Core Registry from 2012 through 2025. HD/CRRT for renal failure was not included as ECTR for analysis purposes.

Materials and Methods

Study design and setting

This was a secondary analysis of de-identified VPA cases from the ToxIC Core Registry, a multicenter database of cases receiving bedside medical toxicology consultation.[18] The analyzed data contained VPA cases reported from January 1, 2012, through December 31, 2025.

Patient population

The ToxIC Core Registry includes patients of all ages. All VPA cases reported in the dataset were eligible for inclusion. The final cohort comprised 164 cases. This study was reviewed by the ToxIC Research Committee, and the ToxIC Core Registry was reviewed by the WIRB-Copernicus Group Institutional Review Board (IRB) and each participating site's IRB.

Variables

The primary outcome was the predictive value of *a priori* selected variables for ICU admission. These variables were consistent with previously described features of severe VPA toxicity, which would be feasibly available at presentation and/or early in the patient's emergency department course. These variables were age, biological sex, self-harm intent, therapeutic-use intent, any co-ingestion, antipsychotic co-ingestion class, sedative-hypnotic co-ingestion class, antidepressant co-ingestion class, alcohol co-ingestion class, coma/CNS depression, respiratory depression, hypotension, metabolic acidosis, and elevated anion gap. Because the dataset does not capture the sequence of treatments, later management variables such as intubation, vasopressors, L-carnitine treatment, and hemodialysis were not included in the primary ICU predictor set. Secondary outcomes were the use of ECTRs, endotracheal intubation, and mortality.

Statistical analysis

Descriptive statistics were calculated for the entire cohort. Continuous age was summarized with median and interquartile range because of non-normal distribution and compared using the Mann-Whitney U test. Categorical variables were compared with Fisher exact testing. Odds Ratios (ORs) were calculated using Haldane-corrected contingency tables to accommodate sparse cell counts. Statistical significance was defined as $p \leq 0.05$. All statistical analyses were performed using IBM SPSS Statistics Version 31.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of study subjects

The cohort included 164 cases of VPA exposure. Median age was 34.5 years (IQR 19.3-50.0). Most patients were adults aged 19-65 years (116/164, 70.7%; Table 1). Sex was male in 89/164 cases

(54.3%). Race/ethnicity was available in 143 cases; of those, 91/143 (63.6%) were coded as non-Hispanic White.

Most encounters were intentional exposures (144/164, 87.8%) while unintentional exposures accounted for 15/164 (9.1%). Among the 132 intentional pharmaceutical cases with a coded intent subtype, 80/132 (60.6%) were classified as self-harm and 34/132 (25.8%) as therapeutic use. Expressed over the full cohort, attempted self-harm was present in 80/164 cases (48.8%), therapeutic use in 34/164 (20.7%), and pharmaceutical misuse without self-harm in 5/164 (3.0%). Exposure type was acute in 64/164 cases (39.0%), acute-on-chronic in 52/164 (31.7%), chronic in 39/164 (23.8%), and unknown in 8/164 (4.9%).

Patient disposition and medical toxicology consultation

Overall, 104 of 164 patients (63.4%) received care beyond the emergency department. 49/164 patients (29.9%) received ICU-level care, 63/164 (38.4%) were managed on a hospital floor, 5/164 (3.0%) in an observation unit, and 1/164 (0.6%) on an inpatient psychiatric service.

Medical Toxicology (MT) was involved as a consult service in 141 cases (86.0%) and as the attending service in 23 (14.0%). MT evaluation occurred in the emergency department in 82 cases (50.0%), on the hospital floor in 57 (34.8%), in the ICU in 47 (28.7%), and in an observation unit in 4 (2.4%). Referrals to MT originated most frequently from the emergency department (96/164, 58.5%) or the admitting service (39/164, 23.8%). Additional referrals came from outside hospital transfers (17/164, 10.4%), another hospital service (5/164, 3.0%), self-referral (5/164, 3.0%), and the poison center (1/164, 0.6%).

Prevalence of clinical abnormalities

Among clinical manifestations, which affected a median of one organ system (IQR 1-2), neurologic effects predominated, occurring in 129 of 164 cases (78.7%), and were characterized mainly by coma/CNS depression in 104/164 cases (63.4%; Table 2). Other neurologic findings were less common, including delirium/toxic psychosis in 13/164 cases (7.9%), agitation in 12/164 (7.3%), seizures in 10/164 (6.1%), hyperreflexia/myoclonus/clonus/tremor in 9/164 (5.5%), weakness/paralysis in 4/164 (2.4%), hallucinations in 2/164 (1.2%), and extrapyramidal symptoms (EPS)/dystonia/rigidity in 1/164 (0.6%).

Major vital-sign abnormalities were documented in 20 of 164 cases (12.2%); the most frequent was hypotension in 11/164 cases (6.7%). Tachycardia, with pulse of 120 beats/min or more, occurred in 6/164 cases (3.7%) and all had a heart rate exceeding 140 beats/minute. Bradypnea occurred in 3/164 cases (1.8%), bradycardia in 2/164 (1.2%), and severe hypertension in 1/164 (0.6%). No cases of hyperthermia were reported.

Pulmonary effects were present in 21 of 164 cases (12.8%), almost entirely due to respiratory depression, which was recorded in 19/164 cases (11.6%). Endotracheal intubation/ventilatory management was required in 23 of 164 cases (14.0%).

Metabolic effects were present in 11 of 164 cases (6.7%). Metabolic acidosis was recorded in 7/164 cases (4.3%), elevated anion gap in 4/164 (2.4%), and hypoglycemia in 4/164 (2.4%). No cases of an elevated osmol gap were recorded. Hyperammonemia was not captured as a structured ToxIC registry variable. On review of optional free-text clinical comments, elevated ammonia or hyperammonemia was documented in 11/164 cases (6.7%).

Cardiovascular effects were present in 11 of 164 cases (6.7%), driven primarily by prolonged QTc interval (greater than 500 milliseconds [msec]) in 11/164 cases (6.7%). A prolonged QRS interval (greater than 120 msec) occurred in 2/164 cases (1.2%). No cases were coded as ventricular dysrhythmia, advanced Atrio-Ventricular (AV) block, or myocardial injury/infarction.

Hematologic effects occurred in 8 of 164 cases (4.9%). Thrombocytopenia, defined as a platelet count less than 100×10^9/L, occurred in 7/164 cases (4.3%). Significant coagulopathy was present in 3/164 cases (1.8%), while pancytopenia and hemolysis each occurred in 1/164 case (0.6%).

Renal/musculoskeletal effects occurred in 7 of 164 cases (4.3%), including rhabdomyolysis in 4/164 cases (2.4%) and acute kidney injury in 3/164 (1.8%). Gastrointestinal/hepatic effects were uncommon overall, occurring in 4 of 164 cases (2.4%). Pancreatitis was recorded in 2/164 cases (1.2%). Marked hepatotoxicity (ALT > 1000 IU/L) occurred in 1/164 case (0.6%) with a co-ingestion of acetaminophen. GI bleeding occurred in 1/164 case (0.6%). No cases of corrosive injury or intestinal ischemia were reported.

Therapies administered

Non-pharmacologic supportive care was documented in 56/164 cases (34.1%), most commonly with Intravenous (IV) fluid resuscitation (47/164, 28.7%) and intubation/ventilatory management (23/164, 14.0%).

Pharmacologic supportive therapy was used in 35/164 cases (21.3%), most commonly with benzodiazepines (24/164, 14.6%), followed by anticonvulsants and vasopressors (7/164 each, 4.3%), antipsychotics (5/164, 3.0%), and bronchodilators (2/164, 1.2%). Decontamination was performed in 21/164 cases (12.8%). All patients who received decontamination received activated charcoal (21/164, 12.8%), and one also underwent gastric lavage (1/164, 0.6%). Whole bowel irrigation was not recorded. The registry does not include a dedicated structured field for endoscopic decontamination; however, no endoscopy or pharmacobezoar formation was documented in optional free-text comments. Enhanced elimination strategies were uncommon (10/164, 6.1%), including toxin-directed hemodialysis in 5/164 (3.0%), Continuous Renal Replacement Therapy (CRRT) in 2/164 (1.2%), MDAC in 2/164 (1.2%), and urinary alkalinization in 1/164 (0.6%). One patient received both hemodialysis and CRRT.

Antidotal care and/or other toxin-directed therapy was documented in 65/164 cases (39.6%), primarily with IV L-carnitine administration (52/164, 31.7%). Other VPA-targeted therapies included use of meropenem in 3/164 (1.8%) cases. N-acetylcysteine was administered in 4/164 (2.4%) cases, two of which had an acetaminophen co-ingestion. Naloxone was administered in three cases; none had a coded opioid co-ingestant, suggesting possible empiric use for undifferentiated CNS or respiratory depression. Sodium bicarbonate was administered in 3/164 (1.8%) cases for QRS prolongation or acidemia; co-ingestants included olanzapine/quetiapine, quetiapine/clonazepam, and doxepin, respectively.

Primary outcome

Admission to an ICU was most strongly associated with respiratory depression (17/19 *vs*. 32/145; OR 30.0 [95% CI 6.59–136.81]; $p < 0.001$) and metabolic acidosis (6/7 *vs*. 43/157; OR 15.9 [1.86–136.00]; $p = 0.003$; Table 3). Coma/CNS depression was also strongly associated with ICU-level care (41/104 *vs*. 8/60; OR 4.23 [1.82–9.82]; $p < 0.001$), as was hypotension (7/11 *vs*. 42/153; OR 4.63 [1.29–16.61]; $p = 0.018$).

Among exposure features, the presence of any co-ingestion (35/85 *vs*. 14/79; OR 3.25 [1.58–6.68]; $p = 0.001$), an antipsychotic co-ingestion class (15/33 *vs*. 34/131; OR 2.38 [1.08–5.23]; $p = 0.035$), sedative-hypnotic co-ingestion class (11/22 *vs*. 38/142; OR 2.74 [1.10–6.83]; $p = 0.043$), and self-harm intent (30/80 vs. 19/84; OR 2.05 [1.04–4.06]; $p = 0.042$) were associated with ICU-level care.

Cases coded as therapeutic use were less likely to receive ICU-level care (4/34 *vs*. 45/130; OR 0.25 [0.08–0.76]; p = 0.011). Age and biological sex were not associated with ICU-level care. Median age was 32 years (IQR 19.8-51.8) among ICU-level-care cases and 35.5 years (IQR 18.8-49.0) among non-ICU cases (p = 0.873).

Secondary outcomes

In the secondary outcome analysis of endotracheal intubation, respiratory depression (12/19 *vs*. 11/145; OR 20.9 [6.84–63.79]; p < 0.001), metabolic acidosis (5/7 *vs*. 18/157; OR 19.3 [3.49–106.93]; p < 0.001), and hypotension (7/11 *vs*. 16/153; OR 15.0 [3.95–56.84]; p < 0.001) were the strongest associations. Coma/CNS depression was also associated with intubation (20/104 *vs*. 3/60; OR 4.52 [1.28–15.94]; p = 0.011). Therapeutic-use cases were less likely to be intubated (1/34 *vs*. 22/130; OR 0.15 [0.02–1.15]; p = 0.049).

Age, sex, alcohol co-ingestion, and antidepressant co-ingestion class were not clearly associated with intubation. Any co-ingestion (16/85 *vs*. 7/79; OR 2.39 [0.92–6.15]; p = 0.075), antipsychotic co-ingestion class (8/33 *vs*. 15/131; OR 2.47 [0.95–6.47]; p = 0.088), sedative-hypnotic co-ingestion class (6/22 *vs*. 17/142; OR 2.76 [0.95–8.01]; p = 0.091), and elevated anion gap (2/4 *vs*. 21/160; OR 6.62 [0.88–49.55]; p = 0.095) showed nonsignificant trends.

Hemodialysis and mortality

A total of 5/164 patients underwent HD for toxin removal. Among the prespecified variables, hypotension was the clearest association (3/11 *vs*. 2/153; OR 28.3 [4.13–194.15]; p = 0.002). Age trended higher among dialyzed patients (median, 51 *vs*. 34 years), but this difference was not statistically significant (p = 0.294). Respiratory depression, coma/CNS depression, metabolic acidosis, elevated anion gap, self-harm intent, therapeutic, co-ingestions, and sex were not clearly associated with HD in this sparse sample.

In an exploratory analysis of severe-course markers, HD was associated with intubation (4/23 *vs*. 1/141; OR 29.5 [3.13–277.72]; p = 0.001), vasopressor use (2/7 *vs*. 3/157; OR 20.5 [2.78–151.52]; p = 0.015), and L-carnitine treatment (4/48 *vs*. 1/116; OR 10.5 [1.14–96.14]; p = 0.026). No documented deaths occurred.

Discussion

In this cohort of VPA-poisoned patients, the strongest physiologic predictors of ICU admission were respiratory depression and metabolic acidosis, followed by coma/CNS depression and hypotension. Exposure characteristics also showed moderate predictive value with intentional ingestions, any co-ingestion, and co-ingested antipsychotics or sedative-hypnotics conferring greater odds of requiring critical care. Adverse events associated with chronic, therapeutic VPA use were less commonly admitted to the ICU or intubated. This pattern is consistent with the previously described spectrum of severe VPA poisoning requiring critical care and/or ECTRs.[9,17]

L-carnitine was the most frequently recorded antidotal or toxin-directed therapy in this cohort, administered intravenously in 52/164 cases (31.7%). Its use is biologically plausible because VPA toxicity may impair mitochondrial fatty acid transport and β-oxidation while favoring ω-oxidation and toxic metabolite formation.[7] However, the clinical efficacy of L-carnitine in acute VPA overdose remains uncertain. A recent retrospective single center cohort study of 69 ICU patients with acute VPA poisoning using toxicokinetic modeling and concentration/effect analyses and found no significant contribution of L-carnitine to enhanced VPA elimination, accelerated blood lactate normalization, or prevention of organ dysfunction.[19] Because treatment timing, dose, duration, indication, and serial ammonia or VPA concentrations were not systematically captured, our data cannot assess the efficacy of L-carnitine.

Anticonvulsants represent one of the top four categories of ingestions with an increasing number of serious outcomes. United States Poison Center data showed VPA accounted for the most fatalities among anticonvulsants, the majority of which involved intentional, acute-on-chronic ingestions.[3] Massive VPA overdoses of ≥ 400 mg/kg typically result in severe toxicity.[1] CNS depression is the most common finding in VPA overdose which can progress to coma and, less commonly, seizures; this may occur with or without cerebral edema and/or hyperammonemia which are often present in fatal cases.[2,3] Respiratory depression is common in severe overdoses; endotracheal intubation is required in more than 60% of patients with a serum VPA concentration ≥ 450 mg/L.[20] Hypotension occurs in 3% of patients overall but may affect 25% of patients with severe toxicity, defined as a serum VPA concentration of ≥ 850 mg/L.[9,21] An elevated anion gap, with or without a metabolic acidosis, is specific for severity with a 26% incidence in patients with a VPA concentration ≥ 450 mg/L and is thought to be due to the accumulation of VPA, a small organic fatty acid.[20,22,23] Other metabolic abnormalities noted more commonly in severe poisoning include hypernatremia, a direct effect of the

sodium content in most VPA formulations (e.g. 3.47 mmol sodium per gram of divalproex sodium), and hypocalcemia of an unclear etiology.[20,24,25]

VPA induced pancreatitis is most common in patients ≤ 16 years old receiving therapeutic dosing for weeks to months,[26] however its occurrence in acute overdose is well documented.[11,21] In this cohort, the incidence of pancreatitis is potentially underestimated given the case definition for the registry (lipase >1000 IU/L) but nonetheless occurred in 2/164 (1.2%). Hepatotoxicity is distinctly uncommon in acute VPA overdose but well reported in chronic use. The mechanism is multifactorial and thought to be related to the metabolite 2-propyl-4-pentenoic acid, glutathione depletion, and inhibition of fatty acid oxidation and carnitine transport.[27] We report an incidence of 1/164 (0.6%) in this cohort, with the patient also having co-ingested acetaminophen which more than likely contributed to the aminotransferase elevation.

Myelosuppression, with a predilection for megakaryocytes, is reported in acute and chronic VPA exposures and was evident from these data with thrombocytopenia being the most commonly reported hematologic effect.[28] Leukopenia is also well reported, albeit less commonly, but cannot be assessed with these data as it is not captured in the ToxIC registry.[29] Pancytopenia is distinctly uncommon but does occur.[30] In these data one patient was pancytopenic in the context of a VPA ingestion, without co-ingestions, albeit in the context of critical illness with respiratory depression, coma, and a metabolic acidosis.

Extrapolating the data from this registry-based cohort to clinical practice is difficult given the time-agnostic nature of recorded observed effects, however, suggest the prognostic utility of several variables after a suspected VPA exposure. Intentional co-ingestion of other xenobiotics, especially antipsychotics and sedative-hypnotics, suggest an increased odds of later ICU admission. The presence of metabolic acidosis is easily ascertained with a chemistry panel and, in locations without readily available serum VPA concentrations, may serve as an early marker of severity. These data would also suggest that unintentional exposures and/or exposures related to therapeutic use confer a lower risk of serious outcomes, including the need for ICU-level care and endotracheal intubation. The variables predictive of the need for toxin-directed ECTRs, including hypotension and/or vasopressor use (*i.e.*, shock) and respiratory depression requiring endotracheal intubation, were consistent with the Extracorporeal Treatments In Poisoning (EXTRIP) workgroup guidelines.[17]

Ultimately these data are exploratory and hypothesis-generating, suggesting the need for prospective studies that capture exposure data and serial VPA concentrations together with precise timing of airway

management, vasopressors, antidotal therapy, and ECTRs. A more precise time course will allow better prediction of treatment thresholds and early disposition to an ICU-level setting.

Limitations

This study has several limitations. This registry analysis is based on clinical documentation by treating medical toxicology physicians, and therefore vulnerable to missing data, variable ascertainment, and misclassification. The small number of HD cases and the complete absence of documented deaths limit statistical power and precludes multivariable modeling. The HD results are best interpreted as descriptive associations rather than definitive predictors. ToxIC is a consultation-based registry and may overrepresent more serious poisonings compared to poison center-only or general emergency department populations. Clinical variables and outcomes were reported in a time-agnostic manner, confounding any causality inferences that could be made. Treatment fields documented that an intervention occurred but did not capture the treating clinician's indication, the timing of therapy relative to clinical deterioration, or whether the therapy was directed at VPA versus a co-ingestant. The registry did not systematically capture VPA formulation, including immediate-release, delayed-release, enteric-coated, or extended-release products. Serial VPA concentrations and timing of peak concentration were also unavailable. As a result, we could not assess delayed absorption, prolonged toxicity attributable to formulation, whether formulation complicated gastrointestinal decontamination, whether pharmacobezoar formation was considered, or whether endoscopic decontamination was considered but not performed. Laboratory abnormalities were incompletely detailed (e.g. the presence of dysnatremias) and presented as nominal data, limiting the robustness of the statistical analysis that could otherwise have been performed. Similarly, ammonia concentrations were not systematically captured as structured data and were only available when entered in optional free-text fields. Therefore, the true prevalence, severity, timing, and prognostic value of hyperammonemia could not be determined from this dataset. ICU-level care may have been misclassified in earlier years of the registry, as variables available from 2012–2021 were not uniformly designed to capture the patient's highest level of care during hospitalization. As a result, some patients who later required ICU care may not have been identified as such, which could bias ICU estimates toward underascertainment. Lastly, treatment associations such as intubation, vasopressor use, and L-carnitine use are susceptible to confounding by indication.

Conclusions

In this ToxIC Core Registry analysis of VPA cases the presence of respiratory depression, coma/CNS depression, metabolic acidosis, and hypotension were associated with ICU-level care and endotracheal intubation. Intentional ingestions, as well as those co-ingesting anti-psychotics and sedative-hypnotics, also had a higher likelihood of ICU admission. Hemodialysis was uncommon and was associated with intubation, hypotension, vasopressor use, and L-carnitine treatment.

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Table 1. Demographics and exposure characteristics.

Characteristic	**Value (n/N [%])**
Demographics[*†]	
Age, median (IQR), y	34.5 (19.3–50.0)
Age group, ≤12 y	10/164 (6.1)
Age group, 13–18 y	29/164 (17.7)
Age group, 19–65 y	116/164 (70.7)
Age group, >65 y	8/164 (4.9)
Male sex	89/164 (54.3)
Female sex	74/164 (45.1)
Transgender/non-binary	1/164 (0.6)
Race/ethnicity available	143/164 (87.2)

Non-Hispanic White	91/143 (63.6)
Black/African American	25/143 (17.5)
Hispanic	9/143 (6.3)
Asian	9/143 (6.3)
Exposure characteristics[§]	
Intentional exposure	144/164 (87.8)
Unintentional exposure	15/164 (9.1)
Other coded reasons for encounter[‡]	5/164 (3.0)
Acute exposure	64/164 (39.0)
Acute-on-chronic exposure	52/164 (31.7)
Chronic exposure	39/164 (23.8)
Unknown exposure type	8/164 (4.9)
Any co-ingestant	85/164 (51.8)
Intent subtype among intentional pharmaceutical cases[¶]	
Self-harm intent	80/132 (60.6)
Therapeutic use	34/132 (25.8)
Unknown intent	13/132 (9.8)
Misuse[††]	5/132 (3.8)

IQR, Interquartile range; y, years; [*]1 missing/uncoded age; [†]Race/ethnicity was available for 143/164 cases; [‡]Other coded reasons were organ system dysfunction (n = 2), unintentional non-pharmaceutical exposure (n = 1), interpretation of toxicology laboratory data (n = 1), and intentional non-pharmaceutical exposure (n = 1); [§]1 missing/uncoded exposure type; [¶]Available/subtype coded for 132/144 intentional exposures; [††]Use of another person's prescription medication or taking any prescription medication in doses greater than prescribed (unrelated to self-harm).

Table 2. Incidence of clinical findings by organ system.

Organ system / category	Overall affected, n/N (%)	Specific findings, n/N (%)
Neurologic	129/164 (78.7)	Coma/CNS depression 104/164 (63.4%
		Delirium/toxic psychosis 13/164 (7.9)
		Agitation 12/164 (7.3)
		Seizures 10/164 (6.1)
		Hyperreflexia/myoclonus/clonus/tremor 9/164 (5.5)
		Weakness/paralysis 4/164 (2.4)
		Hallucinations 2/164 (1.2)
		EPS/dystonia/rigidity 1/164 (0.6)
Major vital-sign abnormalities	20/164 (12.2)	Hypotension 11/164 (6.7)
		Tachycardia ≥120 bpm 6/164 (3.7)
		Bradypnea 3/164 (1.8)
		Bradycardia 2/164 (1.2)
		Severe hypertension 1/164 (0.6)
		Hyperthermia 0/164 (0)
Pulmonary	21/164 (12.8)	Respiratory depression 19/164 (11.6)
		Acute lung injury/ARDS 2/164 (1.2)
		Aspiration pneumonitis 2/164 (1.2)
		Asthma/RADS 1/164 (0.6)
Metabolic	11/164 (6.7)	Metabolic acidosis 7/164 (4.3)
		Elevated anion gap 4/164 (2.4)
		Hypoglycemia 4/164 (2.4)
Cardiovascular	11/164 (6.7)	QTc >500 msec 11/164 (6.7)
		QRS >120 msec 2/164 (1.2)

Hematologic	8/164 (4.9)	Thrombocytopenia[a] 7/164 (4.3)
		Pancytopenia 1/164 (0.6)
Renal/musculoskeletal	7/164 (4.3)	Rhabdomyolysis 4/164 (2.4)
		Acute kidney injury 3/164 (1.8)
Gastrointestinal/hepatic	4/164 (2.4)	Pancreatitis[b] 2/164 (1.2)
		Marked hepatotoxicity[c] 1/164 (0.6)

ARDS, Acute respiratory distress syndrome; CNS, Central nervous system; EPS, Extrapyramidal symptoms; RADS, Reactive airways dysfunction syndrome; [a]Defined as a platelet count of less than 100 x 10^9/L; [b]Defined as a serum lipase over 1000 IU/L; [c]Defined as a serum alanine aminotransferase (ALT) of over 1000 IU/L.

Table 3. Predictive value of clinical features.

Outcome (n/N, %)	**Predictor**	**Outcome (+) ‡ Predictor (+)**	**Outcome (+) ‡ Predictor (-)**	**OR† (95% CI)**	***p* value §**
ICU-level care (49/164, 29.9%)	Respiratory depression	17/19	32/145	30.0 (6.59–136.81)	**<0.001****
	Metabolic acidosis	6/7	43/157	15.9 (1.86–136.00)	**0.003****
	Coma/CNS depression	41/104	8/60	4.23 (1.82–9.82)	**<0.001****
	Hypotension	7/11	42/153	4.63 (1.29–16.61)	**0.018***
	Any co-ingestant	35/85	14/79	3.25 (1.58–6.68)	**0.001****
	Antipsychotic co-ingestant	15/33	34/131	2.38 (1.08–5.23)	**0.035***

	Sedative-hypnotic co-ingestant	11/22	38/142	2.74 (1.10–6.83)	**0.043***
	Self-harm intent	30/80	19/84	2.05 (1.04–4.06)	**0.042***
	Therapeutic use	4/34	45/130	0.25 (0.08–0.76)	**0.011***
Endotracheal intubation (23/164, 14.0%)	Respiratory depression	12/19	11/145	20.9 (6.84–63.79)	**<0.001****
	Metabolic acidosis	5/7	18/157	19.3 (3.49–106.93)	**<0.001****
	Hypotension	7/11	16/153	15.0 (3.95–56.84)	**<0.001****
	Coma/CNS depression	20/104	3/60	4.52 (1.28–15.94)	**0.011***
	Therapeutic use	1/34	22/130	0.15 (0.02–1.15)	**0.049***
	Any co-ingestant	16/85	7/79	2.39 (0.92–6.15)	0.075
	Antipsychotic co-ingestant	8/33	15/131	2.47 (0.95–6.47)	0.088
	Sedative-hypnotic co-ingestant	6/22	17/142	2.76 (0.95–8.01)	0.091
	Elevated anion gap	2/4	21/160	6.62 (0.88–49.55)	0.095
ECTR for toxin removal (5/164, 3.0%)	Hypotension	3/11	2/153	28.3 (4.13–194.15)	**0.002****
	Intubation	4/23	1/141	29.5 (3.13–277.72)	**0.001****
	Vasopressor use	2/7	3/157	20.5 (2.78–151.52)	**0.015***

	L-carnitine treatment	4/48	1/116	10.5 (1.14–96.14)	**0.026***

ECTR, Extracorporeal treatment; CI, Confidence interval; CNS, Central nervous system; ICU, Intensive care unit; L-carnitine, Levocarnitine; OR, Odds ratio; ‡ Reported as patient counts (n/N) who had the outcome of interest occur (n) with and without the predictor (N) variable, respectively; † Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from 2x2 contingency tables using the log-odds-ratio (Wald/Woolf) method with a Haldane-Anscombe correction for zero counts, when required; §p values calculated with Fisher exact testing; * Significant at a $p \leq 0.05$; ** Significant at a $p \leq 0.01$

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Informed consent: the ToxIC Core Registry contains deidentified data and does not collect protected health information or other identifying fields; as such the requirement for informed consent was waived

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