Am J Transl Res 2025;17(10):7858-7867
www.ajtr.org /ISSN:1943-8141/AJTR0165811

Original Article

Valproate sodium-associated acute pancreatitis: a case report and systematic analysis of antiepileptic drug adverse events in FAERS

Lujing Wang[1*], Shuyang Yu[2*], Xiaochun Zhang[3*], Zhiwei Jiang[2], Heiying Jin[3], Guanwen Gong[2]

[1]Taizhou Second People's Hospital Affiliated to Yangzhou University, Taizhou, Jiangsu, China; [2]Department of General Surgery, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China; [3]Department of Colorectal Surgery, The Second Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China. [*]Equal contributors.

Received May 5, 2025; Accepted September 15, 2025; Epub October 15, 2025; Published October 30, 2025

Abstract: Background: Drug-induced pancreatitis (DIP) has been increasingly recognized owing to the increased use of pharmacotherapy; however, valproate sodium (VPA)-associated DIP remains uncommon, particularly in adolescents, though severe and life-threatening cases have been documented in this population. We report an adolescent patient with epilepsy who developed DIP following long-term VPA therapy and further investigate the risk of antiepileptic drug (AED)-related pancreatitis through an analysis of the FDA Adverse Event Reporting System (FAERS) database. Methods: We present a case of an adolescent male with epilepsy who developed DIP after VPA treatment. OpenVigil 2.1 was used to conduct a pharmacovigilance analysis of all AED-related adverse events (AEs) reported to the FAERS up to June 2024. Signal detection was performed using the reporting odds ratio (ROR) and proportional reporting ratio (PRR). Results: Among 136,681 cases from 104 countries, 2237 (1.64%) were associated with acute pancreatitis (AP), including 918 serious cases. All evaluated AEDs - except brivaracetam - had ROR and PRR values >1, indicating a potential risk of pancreatitis. The highest-risk AEDs were amobarbital, quetiapine, VPA, and carbamazepine. Conclusion: This study reinforces the association between VPA and AP while providing a broader pharmacovigilance assessment of AED-induced pancreatitis. Clinicians should remain vigilant when prescribing AEDs, particularly to high-risk patients, given the potential of serious pancreatic toxicity.

Keywords: Drug-induced pancreatitis, valproate sodium, FAERS, antiepileptic drug, adverse effect

Introduction

Epilepsy is a chronic neurological disorder characterized by a broad spectrum of symptoms, challenging treatment, and significant disability [1]. It often manifests early in life, with frequent relapses, long disease duration, and high rates of comorbidities, including an increased risk of suicide. Valproate sodium (VPA), a widely used broad-spectrum antiepileptic drug (AED), exerts its therapeutic effects by inhibiting gamma-aminobutyric acid (GABA) aminotransferase, leading to elevated GABA levels in the brain [2, 3]. In addition to controlling seizures, VPA has demonstrated efficacy in managing mood disorders, with benefits in both depressive and manic episodes. However, VPA is associated with several adverse effects (AEs). Common side effects include cognitive impairment, somnolence, dizziness, headache, ataxia, and mental apathy, whereas more severe reactions may involve hepatotoxicity, acute hepatic necrosis, and, rarely, hematologic abnormalities such as leukopenia, erythrocytosis, and thrombocytopenia [4-6]. A particularly rare but severe complication is VPA-induced acute pancreatitis (AP) [7].

This case report highlights a rare instance of VPA-induced AP in a patient with epilepsy, with the aim of increasing clinicians' awareness of this uncommon AE and offering recommendations for the rational and safe use of AEDs. In addition to this case report, we conducted an analysis of the US Food and Drug Administration's Adverse Event Reporting System (FAERS) database to further investigate cases of AP following the use of AEDs. FAERS is one of the largest

https://doi.org/10.62347/EDNS9849

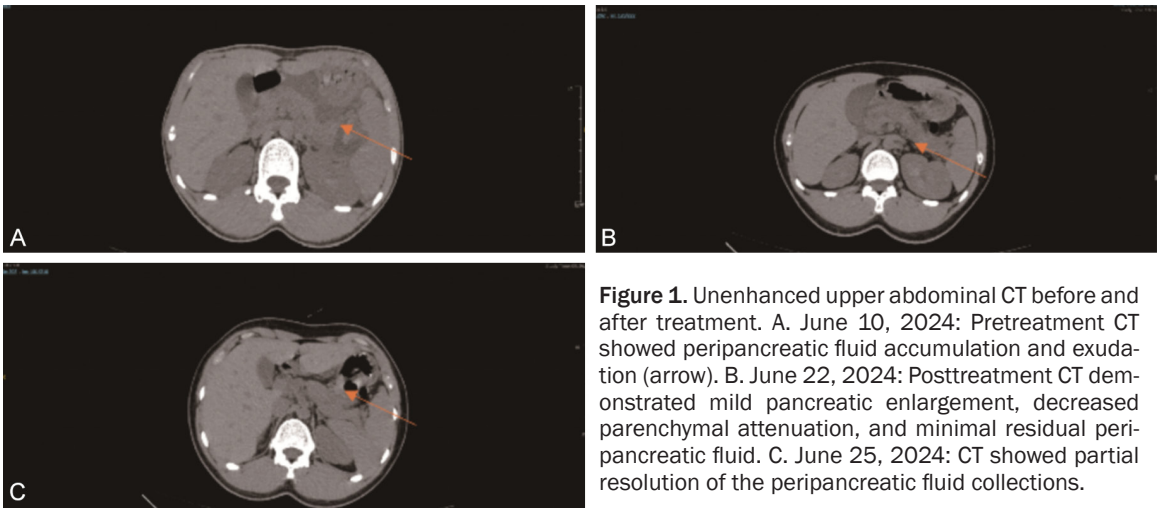

Figure 1. Unenhanced upper abdominal CT before and after treatment. A. June 10, 2024: Pretreatment CT showed peripancreatic fluid accumulation and exudation (arrow). B. June 22, 2024: Posttreatment CT demonstrated mild pancreatic enlargement, decreased parenchymal attenuation, and minimal residual peripancreatic fluid. C. June 25, 2024: CT showed partial resolution of the peripancreatic fluid collections.

databases designed to support the FDA's postmarket safety monitoring program for approved medications [8]. It is publicly accessible and widely used by the FDA, health care systems, clinicians, and pharmaceutical companies to detect and assess potential safety signals [9]. To date, no comprehensive study has utilized the FAERS database to specifically analyze adverse reactions linked to the use of common AEDs causing AP, making this the first such analysis. In this work, we aimed to examine and analyze postmarketing adverse reactions related to AEDs in clinical practice, with a particular focus on VPA. Our goal is to enhance the understanding of the clinical use of VPA by balancing its therapeutic benefits with the potential risks associated with its AEs.

Case presentation

The patient was a 15-year-old male, 166 cm in height and weighing 54 kg, who presented with a one-day history of upper and mid-abdominal pain. He was admitted to our hospital on June 10, 2024. The patient reported sudden onset of abdominal pain without any obvious cause, accompanied by nausea and vomiting. He vomited three times during the night, bringing up gastric contents, but there were no signs of jaundice, fever, or chills. An abdominal CT scan revealed AP with peripancreatic exudation and fluid accumulation in the abdominal and pelvic cavities (**Figure 1A**). Initial laboratory tests revealed a C-reactive protein (CRP) level of 9.36 mg/L (normal range 0.068-8.2 mg/L), a white blood cell (WBC) count of 15.78×10^9/L (normal range 4-11×10^9/L), a red blood cell (RBC) count of 5.55×10^{12}/L (normal range 4.0-5.5×10^{12}/L), a hemoglobin (Hb) level of 178 g/L (normal range 120-160 g/L), and a platelet count (PLT) of 213×10^9/L (normal range 100-300×10^9/L). Biochemical tests revealed an elevated serum amylase level of 1043 U/L (normal range 25-125 U/L).

The patient was admitted with a suspected diagnosis of AP for further evaluation and treatment. At admission, he had intermittent upper abdominal distension and pain, but his bowel movements and flatulence were normal. He had a one-year history of epilepsy and was taking 1000 mg of VPA and 800 mg of quetiapine daily. He had experienced two previous similar episodes of abdominal pain. The patient denied any history of alcohol consumption, gallstone disease, hypertriglyceridemia, hypercalcemia, or other known risk factors for pancreatitis, as well as any significant medical conditions, prior surgeries, food or drug allergies, or a family history of epilepsy. The patient's vital signs were as follows: temperature of 36.3°C, pulse rate of 117 beats per minute, respiratory rate of 16 breaths per minute, and blood pressure of 114/80 mmHg. On physical examination, there was tenderness and rebound tenderness in the upper abdomen but no palpable masses. Additional tests after admission revealed a WBC count of 11.04×10^9/L, a neutrophil percentage of 80.4% (normal range 50-70%), a uric acid level of 468.00 μmol/L (normal range 150-416 μmol/L), a serum amylase level of 832.0 U/L (normal range <122 U/L), and a lipase level of 1107.1 U/L (normal range 0-110

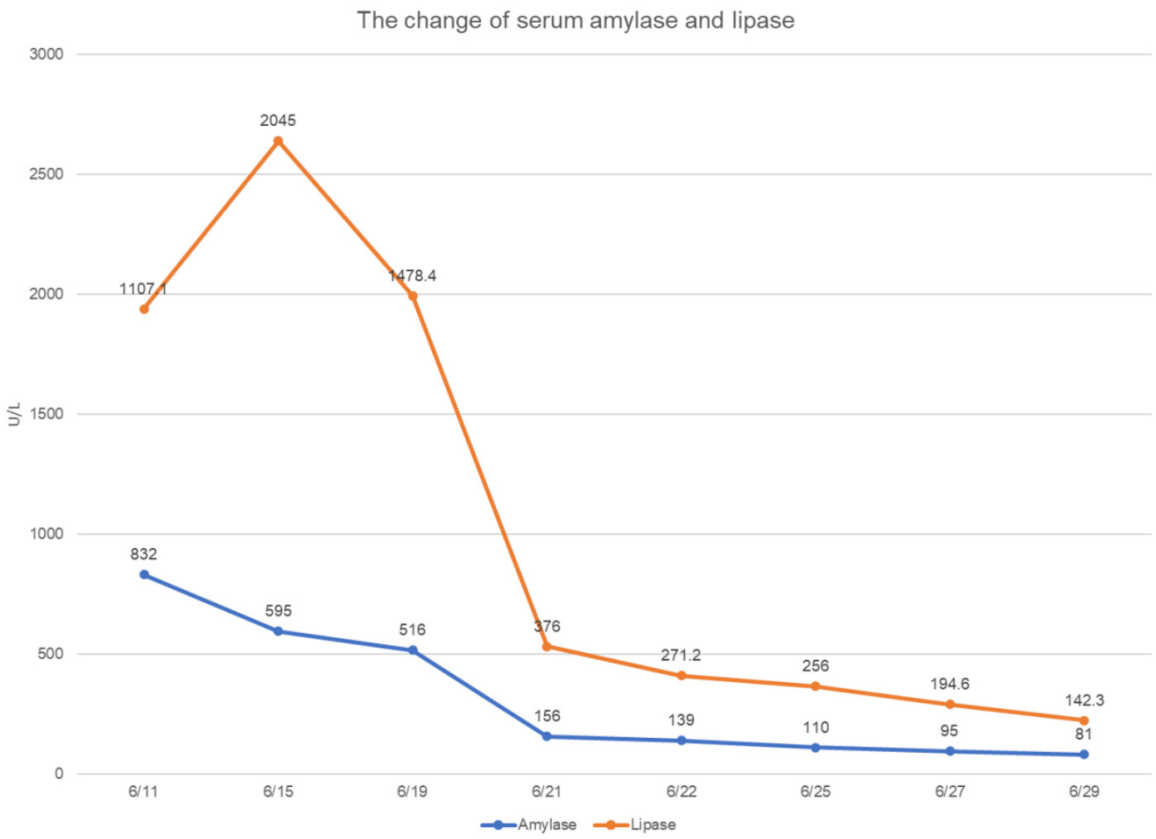

Figure 2. The change of serum amylase and lipase.

U/L). On the basis of the patient's medication history, VPA-induced AP was suspected.

VPA was discontinued, and the patient received symptomatic treatment, including 75 mg of intravenous ranitidine daily for gastric mucosal protection, pain management, hepatoprotective therapy, fluid resuscitation, fasting, and water restriction. A nasojejunal feeding tube was placed, and enteral nutritional support was provided. After treatment, an unenhanced CT scan of the upper abdomen on June 22, 2024 revealed mild pancreatic enlargement with small peripancreatic fluid collections (**Figure 1B**). A follow-up scan on June 25, 2024, revealed only slight pancreatic swelling (**Figure 1C**). Biochemical tests revealed a serum amylase level of 81 U/L and a lipase level of 142.3 U/L, with no significant abnormalities in the complete blood count. The changes in serum amylase and lipase levels during the patient's hospitalization are shown in **Figure 2**. The patient's symptoms improved, and he was discharged in stable condition. Follow-up in the outpatient clinic revealed no recurrence of symptoms to date.

FAERS database analysis of AP induced by AEDs

Data collection

The data for this study were sourced from the FAERS, one of the most comprehensive spontaneous reporting system databases available. The FDA releases FAERS data quarterly, and for this study, we utilized reports submitted up to the second quarter of 2024 [10]. The AEDs analyzed included VPA, carbamazepine, clobazam, oxcarbazepine, lorazepam, ethosuximide, quetiapine, brivaracetam, acetazolamide and amobarbital. Initially, all cases of adverse reactions to AEDs were identified from the FAERS database using the Standardized MedDRA Query (SMQ) with the code 20000006. From this dataset, we extracted cases in which AEDs were implicated in the development of AP. Several key variables, including patient age, sex, reporting country, reporter type, and outcomes, were collected [11]. SAEs were defined as instances in which the treatment led to hospitalization, death, disability, or other life-threatening conditions.

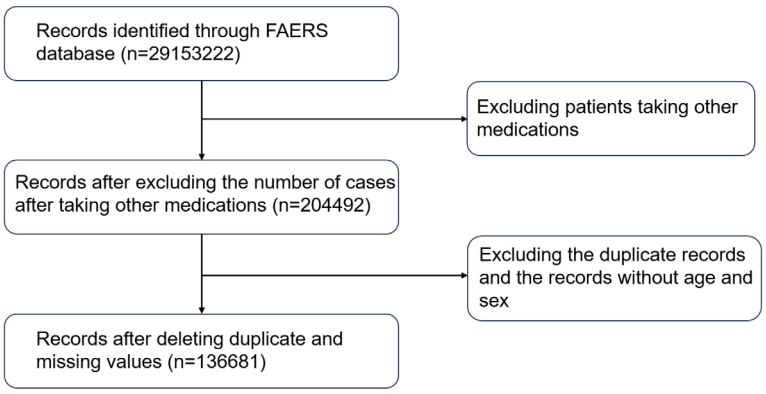

Figure 3. Flowchart of the study.

Methods

For this study, three FAERS tables ("DEMO", "DRUG", "REAC", and "OUTC") were used for analysis. Demographic and AE data related to VPA and other AEDs were analyzed using OpenVigil 2.1. Duplicated demographic data were removed according to FAERS recommendations to ensure accuracy.

Data acquisition

Data analysis was conducted using IBM SPSS V.26.0 and StataCorp Stata 12.0 software. Normally distributed data are expressed as the mean (SD), whereas nonnormally distributed data are presented as the median (Q1, Q3). In this study, we mainly used frequency methods for signal mining, including the ROR and PRR [12]. The ROR reflects the odds of an AE occurring with a specific drug compared with the odds of the same event occurring with all other drugs. The PRR compares the proportion of reports of a specific adverse drug reaction (ADR) for a particular drug to the proportion of the same ADR for all other drugs [13]. It is another measure of disproportionality used to detect signals. A p value <0.05 was considered to indicate statistical significance.

Results

As shown in **Figure 3**, after excluding duplicate records and those missing age and sex data, a total of 136,681 patients were included in the analysis up to June 2024. The median age of the included patients was 44 years (interquartile range: 27-61 years). Males represented a greater proportion of patients taking VPA (51.64%) and amobarbital (54.24%). Patients using acetazolamide were generally older, with a median age of 56 years (interquartile range: 32-72 years), followed by those taking lorazepam (52 years (35-67)). In contrast, patients taking clobazam were younger, with a median age of 26 years (9-48). Further details are provided in **Table 1**.

Among the 136,681 reports, 2,237 cases (1.64%) were associated with AP. These cases originated from 104 countries, including the United States (1580 cases), France (156 cases), Canada (48 cases), the United Kingdom (34 cases), and Japan (30 cases), among others. A total of 918 patients were classified as having SAEs, which included hospitalization (756 patients, 33.80%), disability (26 patients, 1.16%), life-threatening outcomes (53 patients, 2.37%) and death (83 patients, 3.71%). **Tables 2** and **3** present the clinical features of AP events associated with AEDs.

Table 4 includes the number of AP cases associated with each AED, along with the corresponding RORs, PRRs, and their respective 95% confidence intervals (CIs). With the exception of brivaracetam, all the other AEDs presented ROR and PRR values greater than 1. The ROR and PRR values in descending order are as follows: amobarbital: ROR: 116.729 (95% CI: 268.371-107.940); PRR: 107.94 (95% CI: 47.062-247.567); quetiapine: ROR: 56.869 (95% CI: 54.041-59.845); PRR: 54.883 (95% CI: 52.155-57.753); VPA: ROR: 11.196 (95% CI: 9.643-13.000); PRR: 11.117 (95% CI: 9.575-12.908); carbamazepine: ROR: 5.024 (95% CI: 4.335-5.822); PRR: 5.010 (95% CI: 4.323-5.806); clobazam: ROR: 4.790 (95% CI: 3.497-6.561); PRR: 4.777 (95% CI: 3.487-6.544); oxcarbazepine: ROR: 4.714 (95% CI: 3.625-6.131); PRR: 4.702 (95% CI: 3.616-6.115); lorazepam: ROR: 3.465 (95% CI: 2.872-4.180); PRR: 3.459 (95% CI: 2.867-4.173); ethosuximide: ROR: 2.468 (95% CI: 0.795-7.660); PRR: 2.465 (95% CI: 0.794-7.653); acetazolamide: ROR: 2.014 (95% CI: 0.838-4.843); PRR: 2.013 (95% CI: 0.837-4.839); brivaracetam: ROR: 0.879 (95% CI: 0.283-2.726); PRR: 0.879 (95% CI: 0.283-2.762).

Table 1. Demographic characteristics of individuals taking AEDs within the FAERS database

	N	Male	Female	Age
Total	136681	59790 (43.74%)	76891 (56.26%)	44 (27, 61)
valproate sodium	15684	8100 (13.55%)	7584 (9.86%)	40 (22,58)
Carbamazepine	34134	15374 (25.71%)	18760 (24.40%)	42 (25,60)
Clobazam	4564	2259 (3.78%)	2305 (3.00%)	26 (9, 48)
Oxcarbazepine	9258	4103 (6.86%)	5155 (6.70%)	38 (18, 55)
Lorazepam	30349	11981 (20.04%)	18368 (23.89%)	52 (35, 67)
Ethosuximide	1015	398 (0.67%)	617 (0.80%)	10 (7, 19)
Quetiapine	37392	15716 (26.29%)	21676 (28.19%)	45 (31, 60)
Brivaracetam	1705	788 (1.32%)	917 (1.19%)	37 (23, 53)
Acetazolamide	2521	1039 (1.74%)	1482 (1.93%)	56 (32, 72)
Amobarbital	59	32 (0.05%)	27 (0.04%)	43 (27, 55)

Normal distribution (mean + standard deviation); Non-normal distribution (median (Q1, Q3)).

Table 2. Demographic characteristics of AEDs-related AP up to June 2024

	N	Male	Female	Age
Total	2237	1043 (46.62%)	1194 (53.38%)	43 (33, 51)
valproate sodium	175	129 (5.77%)	46 (2.06%)	37 (18, 57)
Carbamazepine	179	88 (3.93%)	91 (4.07%)	39 (23, 59)
Clobazam	39	18 (0.80%)	21 (0.94%)	30 (18, 34)
Oxcarbazepine	56	27 (1.21%)	29 (1.30%)	23 (14, 45)
Lorazepam	110	44 (1.97%)	66 (2.95%)	47 (44, 52)
Ethosuximide	3	2 (0.09%)	1 (0.04%)	-
Quetiapine	1661	728 (32.54%)	933 (41.71%)	44 (32, 50)
Brivaracetam	3	2 (0.09%)	1 (0.04%)	-
Acetazolamide	5	0 (0.00%)	5 (0.22%)	23.2±20.62
Amobarbital	6	5 (0.22%)	1 (0.04%)	23 (23, 35.75)

Discussion

To the best of our knowledge, this is the first extensive pharmacovigilance study to use FAERS data mining to examine the relationship between AEDs and AP. AP is characterized by sudden abdominal pain resulting from the abnormal activation of pancreatic enzymes, leading to localized inflammation of the pancreas and surrounding organs and potentially resulting in organ dysfunction [14, 15]. Common etiologies include gallstones, alcohol consumption, and hypertriglyceridemia; however, DIP remains relatively infrequent [16]. DIP refers to pancreatic injury caused either by the drug's metabolism or as a hypersensitivity reaction of the body to the drug [17].

High-risk groups for DIP include children, elderly individuals, women, patients with HIV, individuals with inflammatory bowel disease, those receiving immunosuppressive therapy, and patients using multiple medications concurrently [18, 19]. The specific pathogenesis of DIP is not fully understood but may involve several mechanisms: 1. Direct toxic effect: Certain drugs may cause coagulative necrosis and hemorrhagic damage to pancreatic tissue, leading to dysfunction and the accumulation of toxic metabolites [20]. 2. Allergic reaction: Drugs can induce congestion and edema in the pancreas, which releases histamine and other inflammatory mediators, activating pancreatic enzymes [21]. 3. Idiosyncratic reactions: Unpredictable responses to drugs may lead to pancreatitis in susceptible individuals [22]. 4. Biliary obstruction: Some medications may increase pressure within the biliary tract, surpassing that of the pancreatic duct, resulting in bile reflux and subsequent activation of pancreatic enzymes [23]. 5. Drug side effects: Certain drugs can lead to hyperlipidemia, which increases the viscosity of

Table 3. Basic data and outcomes of AEDs-related AP up to June 2024

	AEDs-related AP
Gender	
Female	1194 (53.38%)
Male	1043 (46.62%)
Age	
<20	190 (8.49%)
20-50	1466 (65.53%)
50-80	563 (25.17%)
>80	18 (0.80%)
Reported countries	
USA	1580 (70.63%)
France	156 (6.97%)
Canada	48 (2.15%)
United Kingdom	34 (1.52%)
Japan	20 (0.89%)
Grmany	20 (0.89%)
Spain	19 (0.85%)
Poland	17 (0.76%)
Others	343 (15.33%)
Reporter Type	
Consumer	738 (32.99%)
Healthcare Professional	907 (40.55%)
Unknown	592 (26.46%)
Outcomes	
Hospitalization	756 (33.80%)
Disability	26 (1.16%)
Life-threatening	53 (2.37%)
Death	83 (3.71%)
Non-Serious	11 (0.49%)
Required Intervention	11 (0.49%)
Other Outcomes	1297 (57.98%)

pancreatic secretions and contributes to the development of pancreatitis [24].

Numerous clinical drugs have been implicated in causing DIP, and the latency period from initial drug intake to the onset of pancreatitis symptoms can vary significantly, complicating early diagnosis. The diagnostic criteria for DIP include the following: 1. adherence to the diagnostic criteria for AP; 2. onset of AP during the course of medication treatment; 3. exclusion of other potential causes of AP; 4. resolution or alleviation of symptoms upon discontinuation of the medication; 5. a positive provocation test [25, 26].

A prior investigation revealed that the mortality rate of DIP was 15.4% for juvenile patients and 21.4% for adults [27]. In this case, after other potential causes were excluded, the patient's AP episode was most likely attributable to VPA. The patient, a male adolescent with a history of epilepsy, had been taking VPA for one year without episodes of overeating and presented with normal blood glucose and cholesterol levels. Most studies suggest that the risk of VPA-induced DIP is influenced by factors such as patient age, duration of medication use, and dosage of the medication.

In this study, we performed a retrospective analysis of all cases reported in the FAERS database concerning AEDs associated with AP. Both preliminary and sensitivity analyses were conducted to assess the correlation between commonly used AEDs and AP. Our results indicate that, with the exception of brivaracetam, all the other AEDs had RORs and PRRs greater than 1, indicating a significant association with AP. Multiple mechanisms are thought to underlie AED-induced acute pancreatitis. One of the most widely accepted theories is an immune-mediated hypersensitivity reaction, in which the immune system exhibits an exaggerated response to AEDs [28, 29]. This hypersensitivity can cause inflammation in several organs, including the pancreas. The release of proinflammatory cytokines and other inflammatory mediators is believed to be a key factor in triggering pancreatic inflammation, ultimately leading to AP. Notably, this type of hypersensitivity reaction can occur without warning and is not necessarily dose dependent. In addition to immune responses, direct pancreatic toxicity is also considered a potential cause. AEDs or their metabolites may accumulate in the pancreas, exerting toxic effects on pancreatic cells and resulting in cellular damage and inflammation. Oxidative stress is another proposed mechanism by which the metabolism of AEDs produces reactive oxygen species, leading to oxidative damage in pancreatic tissue and exacerbating inflammation and tissue injury [30]. Finally, biliary complications may contribute to AED-induced AP [31]. Some studies suggest that AEDs may increase biliary pressure, causing reflux of bile into the pancreas [32, 33]. This reflux can lead to the premature activation of pancreatic enzymes within the pancreas, triggering inflammation and AP. In summary, AED-induced acute pancreatitis likely results from a combination of mechanisms, including immune-mediated hypersensitivity reactions, di-

Table 4. The association of AP with AEDs

Drugs	Number of AP reports	Number of non-AP reports	Number of AP reports with other drugs	Number of non-AP reports with other drugs	ROR (95% CI)	PRR (95% CI)
valproate sodium	175	22365	20344	29110338	11.196 (9.643-13.000)	11.117 (9.575-12.908)
Carbamazepine	179	50942	20340	29081761	5.024 (4.335-5.822)	5.010 (4.323-5.806)
Clobazam	39	11578	20480	29121125	4.790 (3.497-6.561)	4.777 (3.487-6.544)
Oxcarbazepine	56	16901	20463	29115802	4.714 (3.625-6.131)	4.702 (3.616-6.115)
Lorazepam	110	45248	20409	29087455	3.465 (2.872-4.180)	3.459 (2.867-4.173)
Ethosuximide	3	1726	20516	29130977	2.468 (0.795-7.660)	2.465 (0.794-7.653)
Quetiapine	1661	45051	18858	29087652	56.869 (54.041-59.845)	54.883 (52.155-57.753)
Brivaracetam	3	4847	20516	29127856	0.879 (0.283-2.726)	0.879 (0.283-2.762)
Acetazolamide	5	3525	20514	29129178	2.014 (0.838-4.843)	2.013 (0.837-4.839)
Amobarbital	6	73	20513	29132630	116.729 (268.371-107.940)	107.94 (47.062-247.567)

rect toxicity, oxidative stress, and potential biliary obstruction. Further research is needed to fully understand the underlying pathophysiology and to identify patients at greater risk for developing this rare but serious condition.

As a second-generation AED, brivaracetam offers several advantages in the treatment of epilepsy, particularly for partial-onset seizures in adults and adolescents [34]. First, brivaracetam exerts its effect by binding to synaptic vesicle protein 2A (SV2A), a protein involved in neurotransmitter release. Compared with levetiracetam, another commonly used AED, brivaracetam has a greater affinity for SV2A. This enhanced selectivity results in better seizure control with fewer off-target effects, thereby reducing side effects [35, 36]. Moreover, brivaracetam has linear pharmacokinetics, meaning that its plasma levels are predictable and stable across different doses [37]. This feature simplifies dose adjustments without causing significant variability, thereby enhancing patient safety and facilitating management. Additionally, unlike many older AEDs, brivaracetam is metabolized primarily via hydrolysis and does not significantly induce or inhibit cytochrome P450 enzymes [38]. This minimizes the potential for drug interactions, making brivaracetam a safer option for patients undergoing polytherapy.

Although AEDs are widely used in clinical settings, a comprehensive evaluation of the association between AEDs and AP is currently lacking in the scientific literature. Clinical case reports have historically been one of the earliest means of identifying adverse drug events. Leveraging the extensive dataset from the FAERS, our study provides a detailed exploration of the risk of AP associated with AED therapy, offering valuable evidence for clinical reference.

However, this study is not without limitations. First, the FAERS is a voluntary reporting system, which implies that not all AEs may be documented, potentially leading to incomplete data. Second, the reports submitted to the FAERS may lack completeness or detailed information, which can affect the accuracy of AE analysis. Additionally, FAERS reports generally do not establish a definitive causal relationship between the AE and the drug or device in question. Further epidemiological studies and analyses are needed to ascertain causality. Moreover, our study did not account for variables such as dosage or body weight, which precludes us from evaluating the relationship between dosage and risk. Finally, we focused solely on AED monotherapy and did not consider the potential effects of complex polytherapy involving AEDs.

Conclusion

In this study, we conducted a comprehensive analysis of VPA-induced AP in a teenage patient with epilepsy and utilized the FAERS database to conduct a broader assessment of AED-induced AP. Our findings indicate that, with the exception of brivaracetam, most AEDs are significantly correlated with AP. These results emphasize the necessity of enhancing clinical awareness and conducting further research on the safety of AEDs, particularly the need for an intensified monitoring protocol for pancreatic enzymes during the initial VPA treatment phase in adolescents and considering alternative AEDs for therapeutic drug monitoring in high-risk pediatric populations.

Acknowledgements

This study was performed using the FAERS source that was provided by the FDA. The information, results, and interpretation of the current study do not represent any opinion of the FDA. This study was supported by Jiangsu Province 14th Five-Year Medical Key Discipline: Traditional Chinese Surgery (numbering: ZDXK202251).

Disclosure of conflict of interest

None.

Abbreviations

DIP, Drug-induced pancreatitis; VPA, Valproate sodium; AED, Antiepileptic drug; FAERS, Food and Drug Administration's Adverse Event Reporting System; AE, Adverse effect; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; AP, Acute pancreatitis; SAE, Serious adverse event; GABA, Gamma-aminobutyric acid; FDA, Food and Drug Administration; CT, Computed Tomography; CRP, C-reactive protein; WBC, White blood cell; RBC, Red blood cell; Hb, Hemoglobin; PLT, Platelet count; SMQ, Standardized MedDRA Query; ADR, Adverse drug Reaction; SV2A, Synaptic Vesicle Protein 2A.

Address correspondence to: Dr. Guanwen Gong, Department of General Surgery, Affiliated Hospital of Nanjing University of Chinese Medicine, No. 155 Hanzhong Road, Qinhuai District, Nanjing 210029, Jiangsu, China. Tel: +86-15751868216; ORCID: 0009-0002-5449-5152; E-mail: efy103@njucm.edu.cn

References

[1] Pollandt S and Bleck TP. Thermoregulation in epilepsy. Handb Clin Neurol 2018; 157: 737-747.
[2] Pellegrini A, Gloor P and Sherwin AL. Effect of valproate sodium on generalized penicillin epilepsy in the cat. Epilepsia 1978; 19: 351-360.
[3] Shakir RA, Nanda RN, Lambie DG and Johnson RH. Comparative trial of valproate sodium and clonazepam in chronic epilepsy. Arch Neurol 1979; 36: 301-304.
[4] Gogri PY, Bhalerao S and Vuyyuru S. Sodium valproate-induced cataract. BMJ Case Rep 2021; 14: e240997.
[5] Kennedy GM and Lhatoo SD. CNS adverse events associated with antiepileptic drugs. CNS Drugs 2008; 22: 739-760.
[6] Yin Z and Li P. Association of UGT1a6 gene polymorphisms with sodium valproate-induced tremor in patients with epilepsy. Seizure 2024; 120: 56-60.
[7] Murphy MJ, Lyon IW, Taylor JW and Mitts G. Valproic acid associated pancreatitis in an adult. Lancet 1981; 1: 41-42.
[8] Gastaldon C, Raschi E, Kane JM, Barbui C and Schoretsanitis G. Post-marketing safety concerns with esketamine: a disproportionality analysis of spontaneous reports submitted to the FDA adverse event reporting system. Psychother Psychosom 2021; 90: 41-48.
[9] Xiong CY, Yang YM, Zhou Y, He TS, Luo XW, Wang J and Mao CX. Systematic analysis of the adverse effects of commonly used clinical tetracycline drugs based on the FAERS database. Expert Opin Drug Saf 2025: 24: 949-957.
[10] Brown EG. Using MedDRA: implications for risk management. Drug Saf 2004; 27: 591-602.
[11] Cirmi S, El Abd A, Letinier L, Navarra M and Salvo F. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). Cancers (Basel) 2020; 12: 826.
[12] Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A and De Freitas RM. A bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54: 315-321.
[13] Liu M, McPeek Hinz ER, Matheny ME, Denny JC, Schildcrout JS, Miller RA and Xu H. Comparative analysis of pharmacovigilance methods in the detection of adverse drug reactions using electronic medical records. J Am Med Inform Assoc 2013; 20: 420-426.
[14] Ranson JH. Diagnostic standards for acute pancreatitis. World J Surg 1997; 21: 136-142.
[15] Tenner S and Banks PA. Acute pancreatitis: nonsurgical management. World J Surg 1997; 21: 143-148.
[16] Zerem E, Kurtcehajic A, Kunosic S, Zerem Malkočević D and Zerem O. Current trends in acute pancreatitis: diagnostic and therapeutic challenges. World J Gastroenterol 2023; 29: 2747-2763.
[17] Nitsche CJ, Jamieson N, Lerch MM and Mayerle JV. Drug induced pancreatitis. Best Pract Res Clin Gastroenterol 2010; 24: 143-155.
[18] Balani AR and Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. Drug Saf 2008; 31: 823-837.
[19] Bui SK, O'Brien JM and Cunningham EJ. Purtscher retinopathy following drug-induced pancreatitis in an HIV-positive patient. Retina 2001; 21: 542-545.
[20] Weissman S, Aziz M, Perumpail RB, Mehta TI, Patel R and Tabibian JH. Ever-increasing diversity of drug-induced pancreatitis. World J Gastroenterol 2020; 26: 2902-2915.
[21] Alberti-Flor JJ, Hernandez ME, Ferrer JP, Howell S and Jeffers L. Fulminant liver failure and pancreatitis associated with the use of sulfamethoxazole-trimethoprim. Am J Gastroenterol 1989; 84: 1577-1579.
[22] Zaccara G, Franciotta D and Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia 2007; 48: 1223-1244.
[23] Yang J, Ying Y, Jin L, Ying F, Fang J, Chen X, Zhu M and Yang X. Sertraline-induced acute pancreatitis: a case report and literature review. Altern Ther Health Med 2024; 30: 318-321.
[24] Klein SM and Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. J Rheumatol 1983; 10: 512-513.
[25] Trivedi CD and Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005; 39: 709-716.
[26] Wolfe D, Kanji S, Yazdi F, Skidmore B, Moher D and Hutton B. Methods for the early detection of drug-induced pancreatitis: a systematic review of the literature. BMJ Open 2019; 9: e027451.
[27] Wolfe D, Kanji S, Yazdi F, Barbeau P, Rice D, Beck A, Butler C, Esmaeilisaraji L, Skidmore B, Moher D and Hutton B. Drug induced pancreatitis: a systematic review of case reports to determine potential drug associations. PLoS One 2020; 15: e0231883.
[28] Rogozina O, Ruiz-Fernandez C, Martin-Lopez S, Akatbach-Bousaid I, Gonzalez-Munoz M and

Ramirez E. Organ-specific immune-mediated reactions to polyethylene glycol and polysorbate excipients: three case reports. Front Pharmacol 2023; 14: 1293294.
[29] Straumann A, Bauer M, Pichler WJ and Pirovino M. Acute pancreatitis due to pyritinol: an immune-mediated phenomenon. Gastroenterology 1998; 115: 452-454.
[30] Karunakaran U, Elumalai S, Moon JS and Won KC. C-Abl tyrosine kinase inhibition attenuate oxidative stress-induced pancreatic beta-cell dysfunction via glutathione antioxidant system. Transl Res 2022; 249: 74-87.
[31] Radulova-Mauersberger O, Belyaev O, Birgin E, Bosch F, Brunner M, Muller-Debus CF, Wellner UF, Grutzmann R, Keck T, Werner J, Uhl W and Witzigmann H. Indications for surgical and interventional therapy of acute pancreatitis. Zentralbl Chir 2020; 145: 374-382.
[32] Isogai M. Pathophysiology of severe gallstone pancreatitis: a new paradigm. World J Gastroenterol 2024; 30: 614-623.
[33] Schroder H and Goring G. Reactive involvement of the pancreas in biliary tract disorders. Zentralbl Chir 1971; 96: 1614-1620.
[34] Ben-Menachem E, Mameniskiene R, Quarato PP, Klein P, Gamage J, Schiemann J, Johnson ME, Whitesides J, Mcdonough B and Eckhardt K. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies. Neurology 2016; 87: 314-323.
[35] Kasteleijn-Nolst Trenité DG, Genton P, Parain D, Masnou P, Steinhoff BJ, Jacobs T, Pigeolet E, Stockis A and Hirsch E. Evaluation of brivaracetam, a novel SV2a ligand, in the photosensitivity model. Neurology 2007; 69: 1027-1034.
[36] Markham A. Brivaracetam: first global approval. Drugs 2016; 76: 517-522.
[37] Coppola G, Iapadre G, Operto FF and Verrotti A. New developments in the management of partial-onset epilepsy: role of brivaracetam. Drug Des Devel Ther 2017; 11: 643-657.
[38] Stockis A, Watanabe S, Scheen AJ, Tytgat D, Gerin B, Rosa M, Chanteux H and Nicolas JM. Effect of rifampin on the disposition of brivaracetam in human subjects: further insights into brivaracetam hydrolysis. Drug Metab Dispos 2016; 44: 792-799.