

Analysis of Arrhythmia Risk Associated with Antiepileptic Monotherapy and Combination Therapy

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Abstract

Background and Objectives: Drug-related cardiotoxicity, including arrhythmia, is a significant concern in drug safety monitoring. Patients with epilepsy who use antiepileptic drugs (AEDs) long-term may have an increased risk of cardiovascular events. This study aims to evaluate the reporting of arrhythmia adverse events associated with AEDs using spontaneous reporting system data and to investigate differences in signals between monotherapy and combination therapy regimens.

Methods: A pharmacovigilance study was conducted using FAERS data from the first quarter of 2013 to the second quarter of 2023. Adverse events (AEs) related to arrhythmias were identified using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries. The Reporting Odds Ratio (ROR) algorithm was employed to detect signals of arrhythmia-related AEs associated with 21 AEDs. Both monotherapy and combination therapy were analyzed, with adjustments for age, gender, indications, and concomitant medications. Additive and multiplicative models were used to assess drug-drug interactions (DDIs). Logistic regression analysis was performed to evaluate the impact of arrhythmias on mortality.

Results: A total of 1,766,899 adverse reaction reports for AED-treated patients were analyzed. Among the 21 AEDs, 19 were associated with arrhythmias, with 11 showing significant signals for arrhythmia, primarily in the form of bradyarrhythmias. The strongest signals were observed for LEV (cROR = 8.96, 95% CI: 8.64–9.29) and TGB (cROR = 5.66, 95% CI: 1.82–17.62). After adjusting for age, sex, indications, and concomitant medications, 10 drugs retained positive signals. LEV and VPA emerged as newly identified risk factors for arrhythmias. In combination therapy, 166 two-drug combination therapies revealed that 14 of them exhibited significant interaction signals, particularly in combinations based on LEV or CBZ, which showed a higher number of signals. The highest interaction signals were observed in LEV+ETX (additive model = 0.0512, multiplicative model = 6.5658) and TGB+GBP (additive model = 0.0233, multiplicative model = 4.5470). Logistic regression analysis indicated that advanced age, male, and combination therapy were risk factors for arrhythmia-related mortality. The highest mortality rates were observed in combination therapies involving VPA+GBP (58.46%), TPM+CBZ (50.00%), and LEC+CZP (21.28%).

Conclusions: Comprehensive research has indicated a possible connection between antiepileptic medications and cardiac arrhythmias, which could result in significant negative effects, whether these drugs are used alone or

in combination. This underscores the importance of vigilant monitoring and personalized treatment for patients receiving antiepileptic drugs in clinical settings.

Keywords: Drug-induced cardiotoxicity, Antiepileptic drugs (AEDs), Arrhythmias, Pharmacovigilance, FAERS database, Drug-drug interactions (DDIs), Combination therapy.

Introduction

Given the increasing prevalence of long-term pharmacotherapy in patients with chronic conditions, drug-accumulative cardiotoxicity is emerging as a significant clinical concern. Individuals diagnosed with epilepsy exhibit a six-fold heightened risk of experiencing sudden cardiac death or cardiac arrest in comparison to those without the condition^[1, 2]. Furthermore, they face a five-fold increased likelihood of myocardial infarction, a four-fold elevated risk of ischaemic heart disease, and a two- to three-fold increase in all-cause mortality^[3, 4]. Additionally, the risk of ventricular arrhythmias is nearly doubled, and there is a significantly greater risk of developing atrial fibrillation and heart failure^[5, 6]. This elevated risk is not only attributable to the potential for epileptic seizures but is also compounded by the cardiac burden associated with long-term use of antiepileptic drugs (AEDs)^[5]. Among the various cardiotoxic effects linked to AEDs, arrhythmias are particularly prominent. Research indicates that certain AEDs, such as phenytoin (PHT) and phenobarbital (PHB), can induce arrhythmias by influencing the heart's fast delayed rectifier potassium current (IKr)^[7]. Furthermore, the cardiotoxicity of carbamazepine (CBZ) and lacosamide (LCM) is documented in the FDA specification. Despite the existence of cardiac risk warnings for some AEDs, significant gaps remain in the available evidence, particularly concerning the overall incidence of AED-induced arrhythmias, the dose-response relationship, and the synergistic toxic effects of drug combinations.

In conclusion, to address these knowledge gaps, the present study seeks to detect and evaluate potential safety signals for arrhythmia-related adverse events by performing a

disproportionality analysis of data from the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) database, covering reports from the first quarter of 2013 to the second quarter of 2023. The analysis will explore the association between these safety signals and the use of AEDs, both as monotherapy and in combination regimens. Additionally, the study will investigate other potential influencing factors, temporal characteristics, and outcomes associated with ADEs. The ultimate objective is to provide a comprehensive signal characterization for arrhythmia-related events associated with antiepileptic drugs, thereby offering critical evidence to inform clinical vigilance, guide targeted monitoring of at-risk populations, and support the development of safer medication management strategies for patients with epilepsy.

Methods

Data Sources

The current investigation is a pharmacovigilance study utilizing FAERS database to examine arrhythmic adverse events associated with AEDs. The study encompasses the following categories of AEDs: (i) Barbiturates and their derivatives (methylphenobarbital (MPBT), PHB, and primidone (PR)); (ii) Hydantoins (PHT); (iii) Fatty acid derivatives (sodium valproate (VPA), vigabatrin (VGB), and tiagabine (TGB)); (iv) Succinimides (ethosuximide (ETX)); (v) Benzodiazepines (clonazepam (CZP)); (vi) Iminostilbenes (CBZ and oxcarbazepine (OXA)); and (vii) Other antiepileptic drugs (lamotrigine (LTG), topiramate (TPM), gabapentin (GBP), levetiracetam (LEV), perampanel (PER), zonisamide (ZNS), pregabalin (PGB), fenfluramine (FFA), beclamide, and LCM). These drugs served as keywords to extract

relevant data from the FAERS database, covering the period from the first quarter of 2013 to the second quarter of 2023, with a focus on cases involving suspected use of AEDs. Adverse events (AEs) reported in FAERS were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs). Standardized MedDRA queries (SMQs), which group MedDRA terms related to specific medical conditions or areas of interest, were employed in this study. A narrow search was conducted for 'Cardiac arrhythmias' (SMQ code: 20000049), yielding results that included bradycardia (SMQ code: 20000053), tachycardia (SMQ code: 20000054), and nonspecific arrhythmias (SMQ code: 20000162). To address uncertainties in the search results, the classification was further validated with input from cardiology experts, resulting in the retention of 77 preferred terms (PTs), the complete list of which is provided in Table S1. This validation process ensured that the PTs analyzed were clinically relevant arrhythmic adverse reactions.

Data Processing Procedures

Deduplication of AED reports from the FAERS database was performed, with the detailed screening process illustrated in Figure 1. Reports exhibiting identical values across the domains of sex, age, country, date of event, adverse reaction, drug, and indication were classified as duplicates. The remaining reports underwent additional screening to exclude cases of cardiac-related adverse events reported in the INDI form, based on specific criteria. Furthermore, AED treatment strategies were screened based on adverse event reports, retaining those pertaining to monotherapy and combination therapy for AEDs. Following these deduplication and screening steps, a total of 1,766,899 adverse reaction reports for AED-treated patients were compiled for further analysis.

statistical analysis

The initial focus of our study was on primary suspect drugs (PS), including TGB, LCM, PHB, CBZ, PHT, ZNS, VPA, LTG, TPM, CZP, PR, OXA, PER, GBP, FFA, PGB, and VGB, as

identified in the standardized drug catalog. We mapped the primary IDs of target drugs across various subfiles and collected and managed AE reports, which included clinical features such as patient demographics (gender, age, and reporter), reporting time, and final patient outcomes. The Reporting Odds Ratio (ROR) algorithm was employed to identify associations between arrhythmia events and target drugs, with signal detection conducted using ROR 95% confidence intervals (CIs), Proportional Reporting Ratios (PRR), and chi-square (χ^2) statistics, calculated from a fourfold table illustrating potential associations between drugs and events (Table 1). A positive signal for detection was defined as a number of cases ≥ 3 , ROR 95% CI > 1 , PRR ≥ 2 , $\chi^2 \geq 4$, and $P < 0.05$ ^[8]. Signal refinement was achieved through specific adjustments to account for potential confounding factors within the database, including age, gender, indication, and concomitant medications, followed by logistic regression analysis.

To evaluate the synergistic effects of AEDs in the context of arrhythmias, both PS and non-PS drugs were incorporated into the analysis. Cases were identified to assess the incidence of arrhythmias in patients undergoing combined treatment with two AEDs. Reports of patients not receiving AED treatment served as the reference group, while those receiving combined treatment with two AEDs constituted the index group. A case/non-case differentiation analysis was performed to compare the index and reference groups, calculated as crude ROR and 95% CI (Figure 3). To assess the consistency and reliability of drug interactions, both additive and multiplicative models were employed for reanalysis. The multiplicative model posits that the risk associated with drugs multiplies with the background risk, whereas the additive model suggests that the risk associated with drugs adds to the background risk. A value exceeding 0 (interaction term) indicates a positive interaction in the additive model, while a value greater than 1 indicates a positive interaction in the multiplicative model. Thus, a value > 0 (additive model) or > 1 (multiplicative model) signifies a positive interaction^[9]. Additionally, we gathered

management and clinical features of reported arrhythmias, encompassing patient characteristics (gender, age, and reporter), reporting time, and final patient outcomes.

To investigate the relationship between arrhythmia and the risk of death, this study employed a logistic regression model. The outcome variable was broadly defined as "death," encompassing cases in the FAERS database where any arrhythmia-related adverse event was reported and the outcome was fatal. The exposure variable was the occurrence of any arrhythmia-related adverse event. The model was adjusted for age, sex, and medication regimen (monotherapy versus combination therapy). To account for competing risks, the nine most frequent non-arrhythmia adverse events reported in death cases were also included as covariates. After establishing that arrhythmia is a significant risk factor for death overall, we conducted subgroup analyses based on arrhythmia subtypes. Data management and analysis were conducted utilizing Microsoft Office Excel, R version 4.1.3, and IBM SPSS software.

Results.

Demographic description of reported arrhythmias associated with monotherapy with AEDs

Among the 21 AEDs, a total of 19 AEDs detected 15,084 reports of arrhythmias. S.1 presents the demographic descriptions of arrhythmia reports with the suspected drug of interest as the target drug. According to the results, the age group of 18-64 years had the highest number of cases, with a median age of 47.00 years for all participants. There were slight differences in age distribution among individual drugs. For example, the age distribution of PR was highest in the 65 and over age group (n=65, 42.21%); VGB (n=26, 83.87%) and ETX (n=5, 100.00%) had the highest proportion in the 0-17 age group. Female patients (n=5880, 52.10%) outnumbered male patients (n=4325, 38.32%) in the total population. There was a significant amount of missing information related to adverse event

reporters, with the majority being unknown. The most common known reporters were doctors (n=3778, 33.47%). Detailed demographic data are shown in Table S2. This study further analyzed the occurrence time of arrhythmia caused by AEDs. Reports with incomplete or unavailable occurrence time were excluded. The analysis focused on the suspected primary drug as the target drug. Overall, adverse events of arrhythmia associated with AEDs occurred within a concentrated period of 100 days or less, with a median range of 0-73 days. The median occurrence time for CZP was on the first day of medication (Figure 2, B).

Analysis of signals and risk factors for arrhythmias due to monotherapy with AEDs

We extracted 21 AEDs, among which 19 had cases of arrhythmia. Table 1 presents the results of the disproportionality analysis of arrhythmia events associated with these drugs. 11 AEDs had significant signals for arrhythmia, with their crude ROR (cROR) (95% confidence interval) ranked from strongest to weakest as follows: LEV, 8.96 (95%CI, 8.64 ~ 9.29); TGB, 5.66 (95%CI, 1.82 ~ 17.62); LCM, 3.04 (95%CI, 2.83 ~ 3.28); PHB, 2.88 (95%CI, 1.63 ~ 5.08); CBZ, 1.57 (95%CI, 1.44 ~ 1.71); PHT, 1.56 (95%CI, 1.47 ~ 1.65); ZNS, 1.88 (95%CI, 1.41 ~ 2.51); VPA, 1.53 (95%CI, 1.48 ~ 1.59); LTG, 1.26 (95%CI, 1.21 ~ 1.30); TPM, 1.21 (95%CI, 1.10 ~ 1.33); CZP, 1.18 (95%CI, 1.08 ~ 1.28). Among these 11 drugs, LEV and VPA did not mention arrhythmia-related adverse events in the instructions, which represents newly discovered drug warning signals, and the cROR of LEV was significantly high. When the main endpoint reports were divided into three groups, it was found that the signals were mainly concentrated in bradyarrhythmia, tachyarrhythmia and nonspecific cardiac arrhythmia, with few positive signals. Except for TGB [5.66 (95% CI, 1.82 ~ 17.62)] which is mainly associated with tachyarrhythmia, LCM [6.49 (95% CI, 5.91 ~ 7.13)] had the strongest signal in bradyarrhythmia (Figure 2, A). The detailed information on the arrhythmia subtypes with AEDs as the primary suspected drugs can be found in Table S3.

Next, we stratified the patients and adjusted for age, sex, indications, and concomitant medications (Figure 2, C). The results showed that, compared to the reference group of drugs with no cROR signal, the adjusted ROR was calculated, and 10 drugs showed positive signals, with the signal strength of 9 drugs remaining unchanged, although the signal strength of LEV weakened despite having a signal. The adjusted signal for TGB disappeared. Multivariate analysis indicated that advanced age, indications for psychiatric disorders, and concomitant use of AEDs are risk factors for arrhythmia in patients. In the population receiving AED treatment, the 65 years and older age group was more likely to experience arrhythmia compared to the 18-64 age group at 1.24 (95% CI, 1.18 ~ 1.31); as compared to epilepsy patients, there was a risk of arrhythmia occurrence when the indication is for psychiatric disorders [1.41 (95% CI, 1.31 ~ 1.50)] and for epilepsy with comorbid psychiatric disorders [1.51 (95% CI, 1.30 ~ 1.77)]; the risk of arrhythmia occurrence is higher with concomitant AEDs therapy compared to AED alone, with an odds ratio of 1.04 (95% CI, 1.00 ~ 1.09).

Demographic Description of Reported Arrhythmias Associated with Combination Therapy with AEDs

This study analyzed the combination use of 21 AEDs, with the proportions of single AED use, combination of two AEDs, and combination of three or more AEDs being 62.48%, 11.93%, and 25.59% respectively. In order to investigate the DDIs among AEDs, we further focused on single-drug and two-drug combinations, and identified a total of 166 two-drug combination regimens, among which 20 regimens were found to have DDI signals. Table S4 presents the demographic descriptions of arrhythmia reports for these combinations. The occurrence time of AEs of arrhythmia in AEDs combination therapy follows a similar trend to the suspected primary drug, with the majority occurring within 100 days. Among the combination regimens, there were five regimens where adverse events occurred on the first day of medication, namely

LEV+ETX, OXA+ZNS, PHB+PR, TPM+CBZ, and CBZ+PHB. Only CBZ+PGB and VPA+OXA had longer occurrence times at 431.00 [IQR 126.00 ~ 903.00] and 1552.00 [IQR 388.00 ~ 1862.50] days, indicating a longer time to onset (Figure 3, C).

Analysing signals and risk factors for arrhythmia induced by AED combination therapy

The cROR and DDI analyses were conducted on the two-drug combination regimens for arrhythmia to investigate the impact of concurrent use of AEDs (Figure 3, A). In the cROR analysis, 25 regimens showed positive signals. Further DDI analysis using additive and multiplicative models revealed interaction signals in 14 regimens, ranked in order of strength as follows: LEV+ETX (cROR=8.53, additive model/multiplicative

model=0.0512/6.5658);
TGB+GBP(4.08,0.0233/4.5470);
OXA+ZNS(4.07,0.0228/4.5832);
PHB+PR(3.60,0.0150/2.2514);
PHT+PR(3.49,0.0123/1.8695);
LEV+LCM(2.99,0.0018/1.0364);
PER+LCM(2.39,0.0009/1.4617);
CBZ+PR(2.08,0.0058/1.5887);
LEV+CBZ(1.95,0.0045/1.4337);
CBZ+PGB(1.63,0.0036/1.4546);
TPM+CBZ(1.55,0.0030/1.3770);
LEV+CZP(1.50,0.0017/1.1599);
LTG+PGB(1.49,0.0007/1.1074);
LEV+GBP(1.44,0.0032/1.4425).

In the combination regimens, two-drug combination regimens where LEV or CBZ was one of the baseline drugs were found to have more detected DDI signals leading to arrhythmia. When the main endpoints were divided into three groups (Figure 3, B), among 14 regimens, LEV+ETX, OXA+ZNA, CBZ+PR, LEV+CBZ, and TPM+CBZ, 5 regimens were predominantly associated with tachyarrhythmia, with a significantly enhanced ROR for tachyarrhythmia; PHB+PR, LEV+LCM, PER+LCM, and CBZ+PGB, 4 regimens were predominantly associated with bradyarrhythmia, with no significant difference in ROR for arrhythmia; nonspecific cardiac arrhythmia signals were only

present in OXA+ZNS. Among the original regimens that did not show DDI, it was discovered that 5 treatment regimens presented bradyarrhythmia signals and 1 regimen detected tachyarrhythmia signals. Detailed information on the arrhythmia subtypes with concurrent use of AEDs can be found in Table S5/S6.

Analysis of clinical outcomes of arrhythmias

To assess the impact of AEDs on arrhythmia-related mortality, the occurrence of death was used as the dependent variable, logistic analysis was performed with age, gender, combination therapy, and the top ten AEs of deaths as independent variables. Logistic regression models were used to calculate the odds ratios (OR) (Figure 4, A). Among the AED-related death cases, there were 1439 cases of arrhythmia, with an OR of 2.67 (95% CI, 2.52-2.83), indicating it as a risk factor for death. After stratifying into three subtypes, the OR for bradyarrhythmia was 2.76 (95% CI, 2.55-2.99), for tachyarrhythmia was 2.32 (95%CI, 2.11 ~ 2.54), and for nonspecific cardiac arrhythmia was 3.98 (95%CI, 3.39 ~ 4.69), consistent with the overall risk. In the population receiving AED treatment, with the reference age group being 18-64 years, the OR for those aged 65 and above was 1.42 (95% CI, 1.37-1.47). Using females as the reference, the OR for males was 1.61 (95% CI, 1.56-1.65). The OR for combination therapy with two or more AEDs, compared to AED alone, was 1.12 (95%CI, 1.09 ~ 1.15). The logistic regression analysis indicated that advanced age, male gender, and the concurrent use of AEDs are risk factors for mortality in patients with arrhythmia. Details of the risk of single-agent induction of arrhythmia are provided in Table S7.

A statistical analysis of the clinical outcomes of arrhythmia with AED alone and AED combination therapy (Figure 4, B/C) showed that death accounted for 0.00%-25.00% in the suspected primary drug group and 0.00%-58.48% in the combination therapy group. The top three combination therapy regimens with the highest death rates were VPA+GBP, TPM+CBZ,

and LEC+CZP, with death rates of 58.46%, 50.00%, and 21.28% respectively. The rest were all below 20.00%, indicating a significant increase in mortality compared to AED monotherapy and other combination therapies, suggesting a severe outcome with AED combination therapy.

Discussion

To the best of our knowledge, this study constitutes the inaugural drug vigilance analysis aimed at evaluating the risk of arrhythmias associated with AEDs and their concomitant use with two additional medications, utilizing data from the FAERS database. Our investigation serves to augment real-world data, thereby enhancing the comprehension of the clinical characteristics and drug-induced factors that contribute to the occurrence of arrhythmias. The research indicated that AEDs notably heightened the risk of arrhythmias, particularly bradyarrhythmias, and were closely linked to negative outcomes. Among the 11 AEDs that indicated potential arrhythmia risks, LEV and VPA were newly recognized as risk factors, despite their prescribing guidelines not mentioning arrhythmic side effects. The likelihood of arrhythmia was considerably greater when AEDs were used in combination rather than as a single treatment, especially with regimens based on LEV or CBZ, which not only showed more signs of DDIs but also led to worse outcomes. Furthermore, older adults and male patients were identified as independent risk factors for adverse arrhythmic events, indicating that these groups should be monitored more carefully when prescribed AEDs.

This research offers the inaugural examination of the relationship between AEDs and the long-term risk of arrhythmias, including their various subtypes, revealing that AEDs are particularly associated with an elevated risk of bradyarrhythmias. Specifically, LCM and other AEDs have been reported to induce bradycardia and first-degree atrioventricular block in approximately 0.8% to 2.6% of cases^[10-13]. Furthermore, another study documented adverse reactions, including tachycardia (0.5%),

palpitations (0.3%), bradycardia (0.2%), first-degree atrioventricular block (0.2%), and angina pectoris (<0.1%) in patients administered brevacidin, although additional cardiac monitoring was deemed unnecessary^[14]. Additionally, a retrospective cohort study identified atrioventricular block in 2 out of 28 patients treated with intravenous fosphenytoin^[15]. The findings of this study, derived from the FEARS database, further substantiate the cardiotoxicity associated with this class of medications and underscore the necessity for vigilant cardiac health monitoring in patients prescribed AEDs. It is noteworthy that among the 11 drugs identified in the single-drug sensitivity analysis (including LEV and VPA), no arrhythmia-related warnings are currently marked in the data tables, suggesting that the safety information of these drugs needs to be updated. Moreover, a meta-analysis reported arrhythmia rates of 0.71% and 2.37% for LEV and LCM, respectively^[16]. A retrospective cohort study also noted atrioventricular block in 2 of 28 patients receiving intravenous fosphenytoin. Additionally, certain AEDs, particularly CBZ and VPA, have been linked to an increased risk of arrhythmias in patients with epilepsy. CBZ, which exerts its anticonvulsant effects on voltage-gated sodium channels, is commonly utilized as a first-line treatment for newly diagnosed focal epilepsy; however, previous reports have indicated its propensity to induce cardiac dysfunction and metabolic abnormalities in this patient population^[17, 18]. VPA, a broad-spectrum AED employed in the management of various epilepsy types, modulates gamma-aminobutyric acid (GABA), voltage-gated sodium channels, and T-type calcium channels^[19]. Several smaller studies have explored the relationship between VPA and cardiac function, yielding mixed outcomes. Two studies comparing QT intervals in users and non-users of VPA align with our findings, suggesting that users may be more susceptible to ventricular arrhythmias^[20, 21]. Furthermore, GABA is intricately linked to cardiovascular regulation and can influence the cardiovascular system; for instance, research on GABA receptor modulation in rat cardiac sympathetic

nerves demonstrated that VGB elevated endogenous GABA levels in the paraventricular nucleus, resulting in decreased mean arterial pressure and heart rate^[22]. Another study indicated that PGB mitigated increases in blood pressure and heart rate induced by colonic dilatation in rats while reducing visceral autonomic responses^[23]. However, pregabalin may elicit adverse effects that exacerbate the condition of patients with unstable cardiac function, as evidenced by a case report of an elderly patient with paroxysmal atrial fibrillation who developed tachycardia, atrial fibrillation, and congestive heart failure 15 hours post-administration of pregabalin^[24].

Given the specific characteristics of epilepsy, approximately 20% to 30% of patients with active intractable epilepsy are typically treated with a combination of multiple AEDs, which may lead to complex drug interactions^[25]. As the disease progresses and drug resistance develops, the combination of AEDs is garnering increased attention. Many current studies have concentrated on sudden cardiac events, primarily focusing on single-drug-induced adverse effects, thereby neglecting the risks associated with combination therapies. Consequently, analyses of the signal strength of AED combination regimens in relation to arrhythmic adverse events indicate that combination therapy poses a higher risk of arrhythmias compared to monotherapy. Additionally, this study identified that the two-drug combination regimen involving LEV or CBZ as a foundational drug exhibited more signals of arrhythmia due to DDIs, with a pronounced signal for tachyarrhythmia when AEDs were combined. This phenomenon may be attributed to the metabolic kinetic interactions of AEDs, which are often associated with the induction or inhibition of hepatic enzymes. The impact of conventional AEDs on hepatic cytochrome P450, along with the myriad potential interactions between them and other concurrently administered medications, can alter the metabolism of other AEDs and/or additional drugs^[26]. For instance, AEDs that strongly induce hepatic enzymes (such as CBZ, PHB and

PHT) activate a broad spectrum of P450 enzymes, thereby enhancing the clearance of drugs metabolized via these enzymes^[26]. Conversely, hepatic enzyme inhibitors diminish the clearance of enzymatically metabolized drugs, prolonging their half-lives. For example, VPA inhibits the metabolism of drugs such as PHB, CBZ, and LTG^[27]. Newer AEDs exhibit a reduced propensity for pharmacokinetic/pharmacodynamic interactions, rendering them preferable for combination therapy. Animal studies conducted by Danielsson et al.^[28] on embryonic rats have demonstrated that AEDs that block ion channels, when used in multidrug combinations, are more likely to obstruct fast delayed rectifier potassium ion currents than monotherapies, significantly prolonging the time to cardiomyocyte repolarization and potentially leading to uncontrollable arrhythmias. Furthermore, pharmacokinetic interactions may result in decreased drug clearance when drugs are combined, thereby substantially increasing the risk of arrhythmias with certain medications, an effect that is concentration-dependent. Consequently, individual drug metabolism, along with hepatic or renal dysfunction, may influence the metabolism or clearance of a drug, significantly elevating the blood concentration of a medication that may otherwise be less arrhythmogenic, thereby precipitating adverse reactions^[29, 30].

In addition to drug-related factors, the characteristics of a patient's underlying diseases are crucial variables that influence the risk of arrhythmia induced by AEDs. Prior investigations have established that individuals with epilepsy are at an increased risk for developing a range of arrhythmias, encompassing bradyarrhythmias, tachyarrhythmias, and nonspecific arrhythmias^[5, 10]. When AEDs are used to treat psychiatric disorders or psychiatric comorbidities in epilepsy patients, this risk of arrhythmias increases further. The underlying mechanism involves autonomic nervous system dysfunction caused by central nervous system disturbances, characterized by increased sympathetic tone and

decreased heart rate variability, which together form the electrophysiological basis for arrhythmogenesis^[31, 32]. Moreover, psychiatric disorders are often associated with persistent low-grade inflammation and oxidative stress, which further promote atrial structural remodeling and the development of arrhythmogenic substrates^[32-35]. Managing psychiatric disorders often involves combination drug therapies, and both antipsychotics and antidepressants are known to have cardiac side effects, including prolongation of the QT interval^[32, 36].

In addition to underlying medical conditions, demographic characteristics also influence the distribution of risk. Studies show that women account for a higher proportion of single-drug-related arrhythmia cases than men, with the 18–64 age group exhibiting the highest incidence (33.33%–60.91%). Furthermore, in reports related to lacosamide, elderly patients comprised 34.10% of cases. Krause et al.^[37] reported a case involving an 89-year-old male with impaired renal function who was concurrently taking two other medications known to negatively affect conduction. The patient received two intravenous injections of 400 mg lacosamide each within a six-hour period. The PQ interval remained normal before and after the first injection; however, approximately 30 minutes after the second injection, a reversible complete atrioventricular block developed. It is recommended that heightened caution be exercised when administering high doses of lacosamide, especially in elderly patients with renal impairment and cardiac risk factors.

This study presents several limitations. Firstly, as the FAERS database is a spontaneous reporting system, the data are susceptible to reporting bias, underreporting, and incomplete information. Notably, the association signals detected in this analysis represent statistical imbalances and do not suffice to establish causality between the drugs and arrhythmias. Although adjustments were made for variables including age and sex, with particular consideration given to psychiatric and epilepsy

indications, and patients with pre-existing arrhythmias prior to medication were excluded, the possibility of residual confounding cannot be entirely dismissed. For instance, factors such as epileptic seizures themselves, unrecorded cardiac comorbidities, or other clinical parameters (e.g., specific electrocardiogram measurements) may still influence risk assessment. Furthermore, the absence of an accurate denominator for the medication-exposed population precludes calculation of the true incidence of adverse events. Consequently, the findings of this study should be interpreted as indicative risk signals, with their clinical relevance and causal relationships requiring validation through more rigorous methodologies, such as prospective studies.

Conclusions

This investigation, utilizing data from the FAERS database, demonstrates a significant correlation between AEDs and the occurrence of arrhythmias, with a pronounced emphasis on bradyarrhythmias. Subsequent analyses reveal that combination therapy regimens present more robust signals of drug interactions and are associated with reports of more severe adverse clinical events. These results underscore the necessity for heightened vigilance and systematic assessment of arrhythmias during the clinical administration of antiepileptic drugs, particularly in the context of combination therapies and agents exhibiting identified safety concerns.

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TABLE1

DRUG	Cases	ROR	ROR 95%CI	χ^2	PRR	PRR 95%CI	p
LEV	3137	8.96	(8.64,9.29)	20700.3	8.52	(8.23,8.81)	0.000
TGB*	3	5.66	(1.82,17.62)	7.25	5.62	(1.82,17.34)	0.007
LCM*	723	3.04	(2.83,3.28)	965.21	3.00	(2.79,3.22)	0.000
PHB*	12	2.88	(1.63,5.08)	12.71	2.85	(1.63,5.01)	0.000
CBZ*	518	1.57	(1.44,1.71)	104.88	1.56	(1.43,1.7)	0.000
PHT*	1124	1.56	(1.47,1.65)	221.7	1.55	(1.47,1.65)	0.000
ZNS*	46	1.88	(1.41,2.51)	17.89	1.87	(1.4,2.5)	0.000
VPA	3117	1.53	(1.48,1.59)	564.57	1.53	(1.47,1.58)	0.000
LTG*	3093	1.26	(1.21,1.3)	157.59	1.25	(1.21,1.3)	0.000
TPM*	422	1.21	(1.1,1.33)	14.46	1.20	(1.09,1.32)	0.000
CZP*	550	1.18	(1.08,1.28)	14.09	1.17	(1.08,1.28)	0.000
PR*	192	1.13	(0.98,1.3)	2.56	1.13	(0.98,1.3)	0.109
OXA*	96	0.87	(0.72,1.07)	1.57	0.88	(0.72,1.07)	0.211
PER	16	0.76	(0.47,1.25)	0.94	0.76	(0.47,1.25)	0.332
GBP	841	0.74	(0.69,0.79)	77.35	0.74	(0.69,0.79)	0.000
FFA*	8	0.72	(0.36,1.45)	0.59	0.72	(0.36,1.45)	0.442
PGB*	1150	0.57	(0.54,0.6)	375.97	0.57	(0.54,0.6)	0.000
VGB	31	0.47	(0.33,0.67)	17.72	0.47	(0.33,0.67)	0.000
ETX	5	0.01	(0.01,0.03)	339.27	0.01	(0.01,0.03)	0.000

Levetiracetam (LEV); Tiagabine (TGB); Lacosamide (LCM); Phenobarbitone (PHB); Carbamazepine (CBZ); Phenytoin (PHT); Zonisamide (ZNS); Sodium valproate (VPA); Lamotrigine (LTG); Topiramate (TPM); Clonazepam (CZP); Primidone (PR); Oxcarbazepine (OXA); Perampanel (PER); Gabapentin (GBP); Fenfluramine (FFA); Pregabalin (PGB); Vigabatrin (VGB); Ethosuximide (ETX); Reporting Odds Ratio (ROR); Proportional Reporting Ratio (PRR); 95% Confidence Interval (95% CI).

FIG LEGEND

Figure1 The flow chart of the study.

Note: DRUGPS*: AEDs as Primary Suspect Drug; DRUGALL*: AEDs as Primary Suspect drug, Secondary Suspected drug or Concomitant

drug; INDI*: The indications were arrhythmia related diseases

Figure2 Risk Assessment of Arrhythmia Events Associated with AEDs as the Primary Suspected Agents

(A) Bubble Map of Arrhythmia and Subtype Risks Associated with AEDs as Primary Suspected Agents. (B) Time-to-Onset Distribution of AED-Associated Arrhythmia Events: Boxplot Analysis with Interquartile Ranges. (C) Adjusted Risk Estimates of Arrhythmia Associated with AEDs: Forest Plot of Multivariable Regression Analysis. Antiepileptic drugs (AEDs); Levetiracetam (LEV); Tiagabine (TGB); Lacosamide (LCM); Phenobarbitone (PHB); Carbamazepine (CBZ); Phenytoin (PHT); Zonisamide (ZNS); Sodium valproate (VPA); Lamotrigine (LTG); Topiramate (TPM); Clonazepam (CZP); Primidone (PR); Oxcarbazepine (OXA); Perampanel (PER); Gabapentin (GBP); Fenfluramine (FFA); Pregabalin (PGB); Vigabatrin (VGB); Ethosuximide (ETX); 95% Confidence Interval (95% CI); Odds Ratio (OR).

Figure3 Risk assessment of arrhythmic events associated with AEDs combinations

(A) Heatmap of Case Counts and Risk Levels for Arrhythmia Associated with Antiepileptic Drug (AED) Polytherapy. (B) Bubble Plot of Arrhythmia Subtype Risks Stratified by AED Combination Regimens. (C) Temporal Distribution of Arrhythmia Onset Following AED Polytherapy: Boxplot Analysis with Interquartile Ranges (IQR). Antiepileptic drugs (AEDs); Levetiracetam (LEV); Tiagabine (TGB); Lacosamide (LCM); Phenobarbitone (PHB); Carbamazepine (CBZ); Phenytoin (PHT); Zonisamide (ZNS); Sodium valproate (VPA); Lamotrigine (LTG); Topiramate (TPM); Clonazepam (CZP); Primidone (PR); Oxcarbazepine (OXA); Perampanel (PER); Gabapentin (GBP); Fenfluramine (FFA); Pregabalin (PGB); Vigabatrin (VGB); Ethosuximide (ETX); 95% Confidence Interval (95% CI); Odds Ratio (OR).

Figure4 Hazard Ratios of Arrhythmia-Related Mortality for AEDs as Mono- and Adjunctive Therapy

Levetiracetam (LEV); Tiagabine (TGB); Lacosamide (LCM); Phenobarbitone (PHB); Carbamazepine (CBZ); Phenytoin (PHT); Zonisamide (ZNS); Sodium valproate (VPA); Lamotrigine (LTG); Topiramate (TPM); Clonazepam (CZP); Primidone (PR); Oxcarbazepine (OXA); Perampanel (PER); Gabapentin (GBP); Fenfluramine (FFA); Pregabalin (PGB); Vigabatrin (VGB); Ethosuximide (ETX); Reporting Odds Ratio (ROR); Adverse Events.