RESEARCH ARTICLE

Risk of Ventricular Arrhythmia and Sudden Cardiac Arrest Among Older Patients Using Lamotrigine for Epilepsy

Gloria Y.F. Ho,[1,2] Daniel B. Horton,[1,3,4] Parin J. Patel,[5] Tobias Gerhard,[1,6] and Chintan V. Dave[1,6]

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Correspondence
Dr. Ho
gho@ifh.rutgers.edu

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Abstract

Background and Objectives

Lamotrigine, an antiseizure medication, blocks the activation of voltage-gated sodium channels and reduces the excitability of cardiomyocytes in vitro. Based on concerns for QT prolongation and case reports of arrhythmias among lamotrigine users, the US Food and Drug Administration placed a safety warning on lamotrigine's label in 2020. However, limited evidence exists on the cardiac risk of lamotrigine in patients with epilepsy. This study assessed whether lamotrigine users with epilepsy had an increased risk of ventricular arrhythmia and sudden cardiac arrest (VA/SCA) compared with users of levetiracetam.

Methods

This was a retrospective cohort study among Medicare-insured individuals aged 65 years or older with epilepsy (2007–2019). We identified new users of lamotrigine and levetiracetam without inpatient or emergency VA/SCA diagnosis in the 12-month continuous enrollment baseline period before initiation of treatment. Using inverse probability of treatment weighting derived from propensity scores based on baseline covariates, we compared adjusted incidence rates of inpatient or emergency VA/SCA events in lamotrigine vs levetiracetam users and estimated adjusted hazard ratios (HRs) with 95% CIs using Cox proportional hazard regression.

Results

The study cohort (mean age 77.6 years and 60.5% female) consisted of 11,786 new lamotrigine users and 147,130 new levetiracetam users. At baseline, lamotrigine users were younger and less likely to have cardiovascular and noncardiovascular comorbidities than the levetiracetam users. The incidence and HR of VA/SCA were not statistically higher among lamotrigine users (7.0 vs 8.2 per 1,000 person-years for the lamotrigine and levetiracetam users, respectively; HR 0.84, 95% CI 0.67–1.06). Secondary analyses stratified by baseline cardiac abnormalities showed significantly reduced risk among lamotrigine users in subgroups with baseline arrhythmia (HR 0.51, 95% CI 0.32–0.80) or use of antiarrhythmic drugs (HR 0.67, 95% CI 0.50–0.91).

Discussion

In older adults with epilepsy, lamotrigine was not associated with an increased risk of VA/SCA compared with levetiracetam, including among those with underlying heart disease. Our findings do not support the reported cardiac risks associated with lamotrigine or the recent changes to its safety label.

Introduction

Lamotrigine, a widely prescribed antiseizure medication, exerts its pharmacologic effects primarily through the inhibition of voltage-gated sodium channels,[1] a mechanism also implicated

[1]Center for Pharmacoepidemiology and Treatment Science, Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ; [2]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY; [3]Department of Pediatrics, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ; [4]Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Rutgers University, New Brunswick, NJ; [5]Ascension St. Vincent Heart Center, Indianapolis, IN; and [6]Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ.

Glossary

CMS = Centers for Medicare and Medicaid Services; **FDA** = Food and Drug Administration; **HR** = hazard ratio; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification; **ICD-10-CM** = International Classification of Diseases, Tenth Revision, Clinical Modification; **IPTW** = inverse probability of treatment weighting; **SMD** = standardized mean difference; **VA/SCA** = ventricular arrhythmia and sudden cardiac arrest.

in regulating cardiomyocyte excitability.[2] An in vitro electrophysiologic study had demonstrated that lamotrigine prolonged the cardiac action potential refractory period at therapeutically relevant concentrations.[3] This finding, along with case reports of arrhythmias in patients with heart disease using lamotrigine, prompted the US Food and Drug Administration (FDA) to update its label for lamotrigine in October 2020, highlighting its potential to slow ventricular conduction, prolong QT interval, induce new arrhythmias, and lead to sudden cardiac arrest in patients with underlying structural or functional heart disease.[4]

The relationship between lamotrigine and risk of ventricular arrhythmia and sudden cardiac arrest in humans is unclear. Experiments in rats have shown that high-dose lamotrigine, compared with low-dose lamotrigine or placebo, prolongs QT interval time,[5] particularly in epileptic animals.[6] However, it is uncertain whether these findings are applicable to human physiology. Furthermore, clinical trials are often inadequately powered to detect risks of rare outcomes, even after results from multiple trials are pooled.[7,8] In such instances, real-world data sources can help provide valuable insights to fill this gap. A recent, large study used Danish registry data and found no increased risk of ventricular arrhythmia or cardiac arrest among lamotrigine users; however, the lack of an active comparator group in this study complicates its interpretation because of the potential for residual confounding.[9] Finally, there are few data on the risk of severe cardiovascular events among high-risk populations of lamotrigine users highlighted by the FDA warnings, including those who also use medications that prolong the QT interval or have underlying structural or functional cardiac abnormalities.

Given the importance of lamotrigine in the management of epilepsy and the potential restrictions posed by the FDA warning on its real-world use, further research is needed to clarify its cardiac risk in patients with epilepsy. To address this, we conducted a real-world data analysis aimed at overcoming limitations of previous studies by incorporating active drug comparators and using validated definitions of epilepsy and cardiovascular outcomes. We specifically focused on older adults, a group at increased risk of cardiovascular events. Among older Medicare-insured individuals with epilepsy, we compared the risk of ventricular arrhythmia and sudden cardiac arrest among patients initiating lamotrigine vs levetiracetam, another antiseizure medication without known cardiac effects.

Methods

Data Source and Study Population

The study population was drawn from older individuals insured by Medicare, a US federal program that provides health care to US citizens older than 65 years. We used a 20% sample of Medicare fee-for-service patients with Part D prescription claims from January 1, 2007, to December 31, 2019. Pertinent data elements of interest included patient sociodemographics, medical and pharmacy enrollment status, outpatient pharmacy dispensing files, and inpatient and outpatient medical utilization claims, which contained information on International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology Fourth Edition codes, and Healthcare Common Procedure Coding System codes.

We identified cohorts of patients newly initiating either lamotrigine or levetiracetam, another frequently used antiseizure medication.[10,11] Levetiracetam was chosen as the comparator drug given that, in contrast to lamotrigine, its antiseizure mechanisms do not involve blockage of sodium channels and it is not known to prolong the QT interval.[12-14] The date of first dispensing was designated as the index date. We used all available previous data for each patient going back as far as January 2007 to exclude individuals who had used either lamotrigine or levetiracetam before their first prescription fill in the data.[15]

Patient characteristics and the eligibility criteria were ascertained using a fixed lookback window of 365 days before the index date (the baseline period). We excluded individuals not continuously enrolled in Medicare Parts A, B, and D or who were enrolled in managed care for any period during the baseline period. Cohort membership was further restricted to those with a baseline epilepsy diagnosis using a previously validated definition requiring ≥1 diagnosis code corresponding to epilepsy (ICD-9-CM: 345, 348.81; ICD-10-CM: G40, G41, G83.84, G93.81) or ≥2 codes for unspecified convulsions (ICD-9-CM: 780.39; ICD-10-CM: R56.9) at least 2 days apart.[10,11,16,17] The presence of a diagnosis code for epilepsy combined with a dispensed antiseizure medication (e.g., lamotrigine or levetiracetam) is associated with a positive predictive value of >80%.[16,18]

Baseline Covariates and Inverse Probability of Treatment Weighting

To mitigate the potential for confounding, we accounted for imbalances in patient characteristics across the 2 new-user populations using propensity score–based inverse probability

of treatment weighting (IPTW). Propensity scores were estimated using a logistic regression model of the probability of initiating lamotrigine vs levetiracetam using 116 baseline covariates (eTable 1). These covariates included sociodemographic variables (e.g., age, sex, race, and ethnicity), cardiovascular comorbidities (e.g., cardiac conduction disorders), noncardiovascular comorbidities (e.g., cancer), and prescription medications, such as antiseizure medications that could affect sodium channels (e.g., carbamazepine)[9,10,19] and drugs that may cause QT prolongation (e.g., azithromycin).[20]

Follow-Up and Study Endpoint

Patients contributed follow-up time from the index date up until the first occurrence of the following: end of medical or pharmacy enrollment, treatment switching to the comparator drug, discontinuation of the index exposure (defined as a 30-day treatment gap after the end of the last dispensed prescription), end of study data (December 31, 2019), or occurrence of the study outcome.

The primary study endpoint was a composite of ventricular arrhythmia and sudden cardiac arrest (VA/SCA), defined as an inpatient hospitalization or an emergency department visit with a primary discharge diagnosis pertaining to ventricular fibrillation or flutter (ICD-9-CM: 427.4, 427.41, 427.42; ICD-10-CM: I49.0, I49.01, I49.02), ventricular tachycardia (ICD-9-CM: 427.1; ICD-10-CM: I47.2, I47.20, I47.21, I47.29), cardiac arrest (ICD-9-CM: 427.5; ICD-10-CM: I46.2, I46.8, I46.9), or sudden cardiac death (ICD-9-CM: 798, 798.1, 798.2; not coded in ICD-10-CM after October 2015). The positive predictive value of this outcome algorithm is 85%.[21,22] Individuals who had VA/SCA outcome in the baseline period were excluded from analyses.

Statistical Analysis

Analyses were conducted using SAS Enterprise version 8.3 (SAS Institute Inc., Cary, NC). Differences in baseline characteristics between the treatment groups were examined before and after IPTW; treatment groups were considered balanced when the absolute values of the standardized mean differences (SMDs) of all covariates were <10% after IPTW. IPTW was incorporated in all statistical analyses to adjust for differences in baseline covariates. The per-protocol effect was the primary causal contrast of interest. We calculated the adjusted incidence

Figure 1 Selection of New Users of Lamotrigine or Levetiracetam With Epilepsy in Medicare Data, 2007–2019

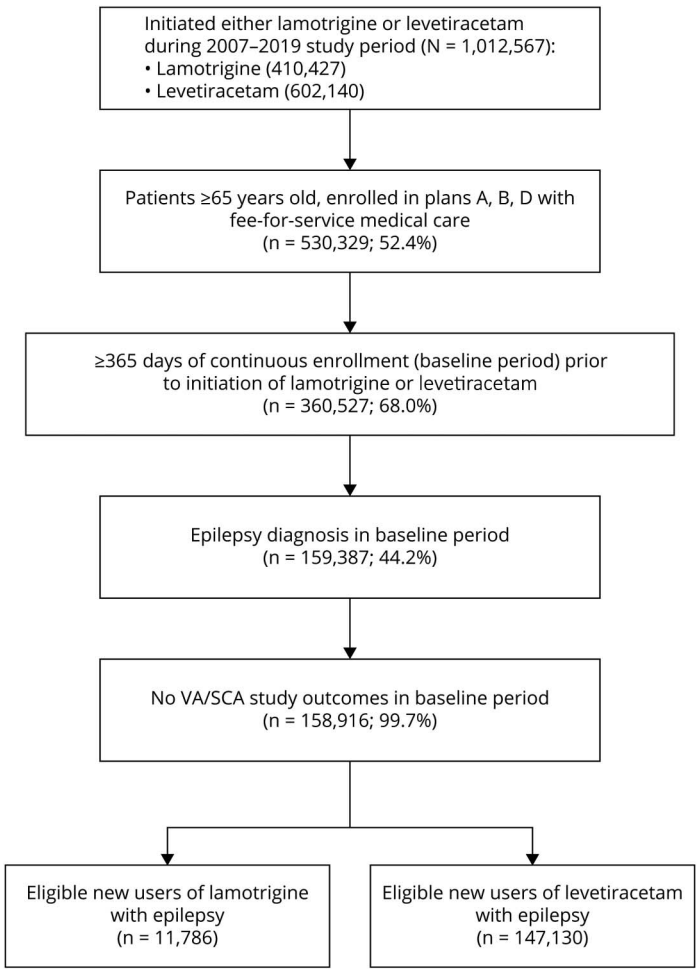


Table 1 Baseline Characteristics of New Users of Lamotrigine or Levetiracetam With Epilepsy

Baseline characteristics	N (%) before weighting		SMD before weighting, %[a]	SMD after weighting, %[a]
	Lamotrigine (N = 11,786)	Levetiracetam (N = 147,130)		
Demographics				
Age, y, median (interquartile range)	74 (69–81)	77 (71–84)	**26.3**	6.1
Male	4,242 (36.0)	58,468 (39.7)	7.7	0.3
Ethnicity				
Non-Hispanic White	9,690 (82.2)	107,350 (73.0)	**22.3**	1.7
Black	992 (8.4)	24,085 (16.4)	**24.3**	3.0
Hispanic	689 (5.9)	10,107 (6.9)	4.2	0.4
Asian/Pacific Islander	207 (1.8)	3,284 (2.2)	3.4	0.2
Others/unknown	208 (1.8)	2,304 (1.6)	1.6	1.4
Cardiac comorbidities				
Ischemic heart disease				
Angina	1,061 (9.0)	16,679 (11.3)	7.7	1.7
Myocardial infarction	1,332 (11.3)	25,485 (17.3)	**17.3**	1.7
Other ischemic heart diseases	4,349 (36.9)	65,734 (44.7)	**15.9**	2.0
Structural heart disease				
Cardiomyopathy	681 (5.8)	13,130 (8.9)	**12.1**	0.7
Valvular heart disease	2,887 (24.5)	48,884 (33.2)	**19.4**	2.7
Congenital heart disease	264 (2.2)	4,048 (2.8)	3.3	1.5
Heart failure	2,828 (24.0)	52,002 (35.3)	**25.0**	4.1
Heart block/conduction disorder	1,395 (11.8)	24,631 (16.7)	**14.1**	0.6
Arrhythmia	3,783 (32.1)	65,758 (44.7)	**26.1**	0.9
Other comorbidities				
Hypercholesterolemia	8,357 (70.9)	109,434 (74.4)	7.8	1.2
Hypertension	9,845 (83.5)	133,819 (91.0)	**22.4**	0.3
Stroke	5,133 (43.6)	89,360 (60.7)	**34.9**	1.8
Cancer	3,101 (26.3)	47,442 (32.2)	**13.1**	0.4
Type 1 diabetes	774 (6.6)	12,524 (8.5)	7.4	1.3
Type 2 diabetes	4,381 (37.2)	66,502 (45.2)	**16.4**	0.2
Asthma	1,355 (11.5)	16,909 (11.5)	0.01	1.1
Chronic obstructive pulmonary disease	3,086 (26.2)	46,427 (31.6)	**11.9**	2.9
Chronic kidney disease	2,218 (18.8)	41,951 (28.5)	**23.0**	2.4
Chronic glomerulonephritis/kidney failure	1,662 (14.1)	27,925 (19.0)	**13.2**	2.5
Liver disease	1,205 (10.2)	20,806 (14.1)	**12.0**	0.8
Bipolar disorder	1,469 (12.5)	4,794 (3.3)	**34.7**	0.4
Depression	5,122 (43.5)	53,686 (36.5)	**14.3**	0.6
Anxiety disorder	3,870 (32.8)	38,750 (26.3)	**14.3**	1.0
Dementia	6,037 (51.2)	85,789 (58.3)	**14.3**	5.0

Continued

Table 1 Baseline Characteristics of New Users of Lamotrigine or Levetiracetam With Epilepsy *(continued)*

Baseline characteristics	N (%) before weighting		SMD before weighting, %[a]	SMD after weighting, %[a]
	Lamotrigine (N = 11,786)	Levetiracetam (N = 147,130)		
Obesity/bariatric complication	1,633 (13.9)	23,478 (16.0)	5.9	2.0
Tobacco use disorder	2,782 (23.6)	44,486 (30.2)	**15.0**	0.3
Alcohol abuse	633 (5.4)	8,987 (6.1)	3.2	1.2
Drug abuse	685 (5.8)	7,022 (4.8)	4.6	0.01
Electrolyte and fluid disorders	5,264 (44.7)	88,855 (60.4)	**31.9**	2.2
Prescription drug classes				
Antiepileptic drugs affecting sodium channel	4,256 (36.1)	31,149 (21.2)	**33.5**	5.2
Antiepileptic drugs not affecting sodium channel	3,901 (33.1)	34,096 (23.2)	**22.2**	1.8
Drugs associated with QT prolongation	7,277 (61.7)	85,075 (57.8)	8.0	0.4
Beta-blockers (class II antiarrhythmics)	4,858 (41.2)	70,973 (48.2)	**14.2**	0.2
Calcium channel blockers (class IV antiarrhythmics)	756 (6.4)	11,381 (7.7)	**12.1**	0.9
Digoxin (class V antiarrhythmics)	469 (4.0)	7,607 (5.2)	5.7	0.3
Other antiarrhythmics[b]	304 (2.6)	5,544 (3.8)	6.8	0.4
Insulin	1,131 (9.6)	19,586 (13.3)	**11.7**	0.1
Metformin	1,368 (11.6)	19,640 (13.4)	5.3	2.6
Antidepressants	5,873 (49.8)	59,911 (40.7)	**18.4**	0.3

Abbreviations: IPTW = inverse probability of treatment weighting; SMD = standardized mean difference.
[a] SMDs between treatment groups before and after weighting with IPTW. Values in bold are absolute SMDs ≥10%.
[b] Other antiarrhythmic medications included class I sodium channel blockers and class III potassium channel blockers.

rates (per 1,000 person-years) for the primary endpoint and estimated the adjusted hazard ratios (HRs) along with their 95% CIs using Cox proportional hazard models.

We conducted additional secondary analyses. First, we reported the incidence for VA and SCA separately. Second, we performed subgroup analyses with stratification by age group, sex, race, presence of baseline ischemic or structural heart disease, and baseline use of QT prolongation or antiarrhythmic drugs. Within each subgroup, the propensity score was re-estimated, and patients were reweighted on the newly estimated propensity score.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Rutgers University Institutional Review Board, and the appropriate data use agreements were in place.

Data Availability

The authors declare that the raw data used in the manuscript are not publicly available to share because of data use agreements in place with the Centers for Medicare and Medicaid Services (CMS). Raw data may be acquired individually through the CMS.

Results

We identified 1,012,567 patients who had used either lamotrigine or levetiracetam between 2007 and 2019 (Figure 1). After the application of new use and continuous eligibility criteria, a total of 360,527 initiators of either agent were identified, which reduced to 159,387 after restricting the study cohort to individuals with epilepsy. Finally, after excluding patients who had the outcome in the baseline period, we identified 11,786 new users of lamotrigine and 147,130 new users of levetiracetam.

Before IPTW adjustment, lamotrigine users differed from levetiracetam users regarding pertinent baseline characteristics as indicated by an absolute value of SMD ≥10% (eTable 1). For instance, lamotrigine users were more likely to be younger and White, be diagnosed with bipolar disorder and depression, and have used other antiseizure agents in the past but were less likely to have a diagnosis of cardiovascular and noncardiovascular conditions than the levetiracetam users (Table 1). After IPTW adjustment, all 116 covariates were well balanced between the treatment groups (Table 1; eTable 1).

Risk of VA/SCA

Median follow-up durations were 158 days and 162 days for the lamotrigine and levetiracetam groups, respectively. The

Table 2 Risk of VA/SCA Among New Users of Lamotrigine or Levetiracetam With Epilepsy

Incident outcome	No. of patients	No. of events	Adjusted incidence/1,000 person-years (95% CI)[a]	*p* Value	Adjusted hazard ratio (95% CI)[a]	*p* Value
Total treatment period						
VA/SCA						
Levetiracetam (reference)	147,130	1,240	8.2 (7.8–8.7)			
Lamotrigine	11,786	63	7.0 (5.6–8.7)	0.15	0.84 (0.67–1.06)	0.13
VA						
Levetiracetam (reference)	147,130	211	1.4 (1.2–1.6)			
Lamotrigine	11,786	11	1.2 (0.7–2.1)	0.61	0.86 (0.50–1.48)	0.58
SCA						
Levetiracetam (reference)	147,130	1,032	6.9 (6.5–7.3)			
Lamotrigine	11,786	52	5.8 (4.5–7.3)	0.17	0.83 (0.65–1.07)	0.16
First 180 d of treatment						
VA/SCA						
Levetiracetam (reference)	147,130	729	13.8 (12.8–14.8)			
Lamotrigine	11,786	27	11.3 (8.4–15.1)	0.20	0.81 (0.60–1.10)	0.17
After first 180 d of treatment						
VA/SCA						
Levetiracetam (reference)	69,522[b]	511	3.9 (3.6–4.2)			
Lamotrigine	5,514[b]	36	3.5 (2.5–4.8)	0.51	0.88 (0.63–1.25)	0.49

Abbreviations: IPTW = inverse probability of treatment weighting; VA/SCA = ventricular arrhythmia and sudden cardiac arrest.
[a] IPTW-adjusted for baseline covariates.
[b] Numbers remained at risk after the first 180 days of treatment.

IPTW-adjusted incidence rate of VA/SCA was numerically, but not statistically, lower in the lamotrigine group (7.0 per 1,000 person-years, 95% CI 5.6–8.7) than in the levetiracetam group (8.2 per 1,000 person-years, 95% CI 7.8–8.7), corresponding to an adjusted HR of 0.84 (95% CI 0.67–1.06) (Table 2). Results were consistent for the individual components of the primary outcome, and lamotrigine was not associated with an increased risk of VA (HR 0.86, 95% CI 0.50–1.48) or SCA (HR 0.83, 95% CI 0.65–1.07). There was no significant difference between treatment groups in risk of VA/SCA before or after 180 days of follow-up. The IPTW-adjusted Kaplan-Meier curves were not suggestive of an increased risk of VA/SCA among lamotrigine users ($p = 0.25$; Figure 2).

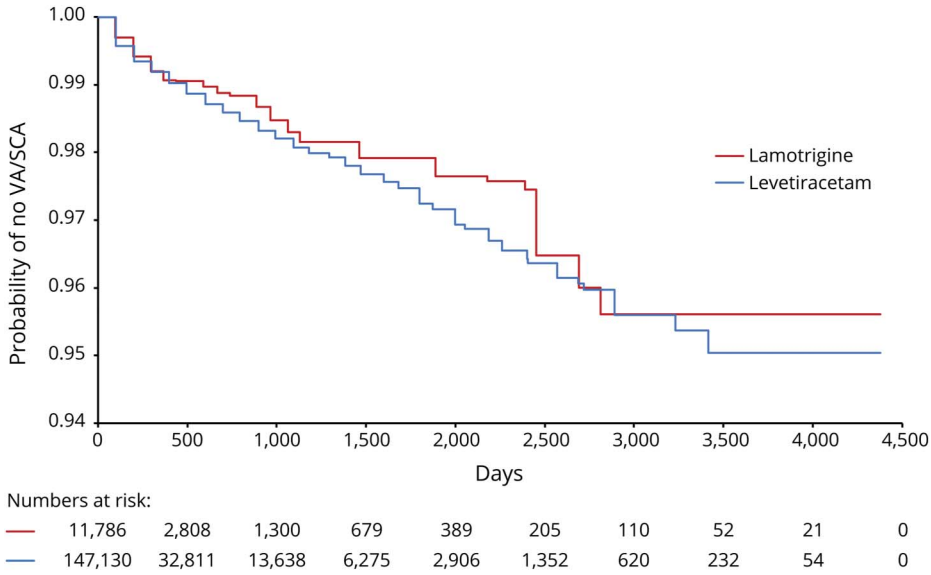
The risk of the outcome did not vary meaningfully across subgroups of age, biological sex, or race (Figure 3). Lamotrigine users who had a baseline history of ischemic or structural heart disease, heart failure, cardiac conduction disorders, or arrhythmias, or had used other QT-prolonging or antiarrhythmic medications, did not have an increased risk of VA/SCA compared with levetiracetam users. Lamotrigine users had significantly reduced risk of VA/SCA if they had a history of arrhythmias (adjusted HR 0.51, 95% CI 0.32–0.80) or had used antiarrhythmic medications (HR 0.67, 95% CI 0.50–0.91).

Discussion

It has been postulated that lamotrigine increases the risk of VA/SCA because of its pharmacodynamic properties. However, this association has not been previously studied in older adults who have an increased risk of experiencing such events, or among those with a history of underlying structural or functional heart disease. Our study examined the national Medicare data and found that when compared with patients initiating levetiracetam, lamotrigine users did not have an increased risk of VA/SCA. Notably, study findings were consistent across a range of subgroups, including age, sex, race, and history of cardiovascular conditions. These findings do not support the recent FDA safety warning that lamotrigine might induce arrhythmias or sudden death in high-risk patients.[4]

Our results corroborate and extend those of previous studies. There were several lamotrigine randomized clinical trials,[7] and the largest one with over 300 lamotrigine users with

Figure 2 Kaplan-Meier Curves for the Proportion of New Users of Lamotrigine or Levetiracetam With Epilepsy Remaining Free of VA/SCA[a]



Numbers at risk:

Lamotrigine	11,786	2,808	1,300	679	389	205	110	52	21	0
Levetiracetam	147,130	32,811	13,638	6,275	2,906	1,352	620	232	54	0

[a]IPTW-adjusted proportions free of VA/SCA were plotted in 100-day intervals. *p* Value for the log-rank test = 0.25. IPTW = inverse probability of treatment weighting; VA/SCA = ventricular arrhythmia and sudden cardiac arrest.

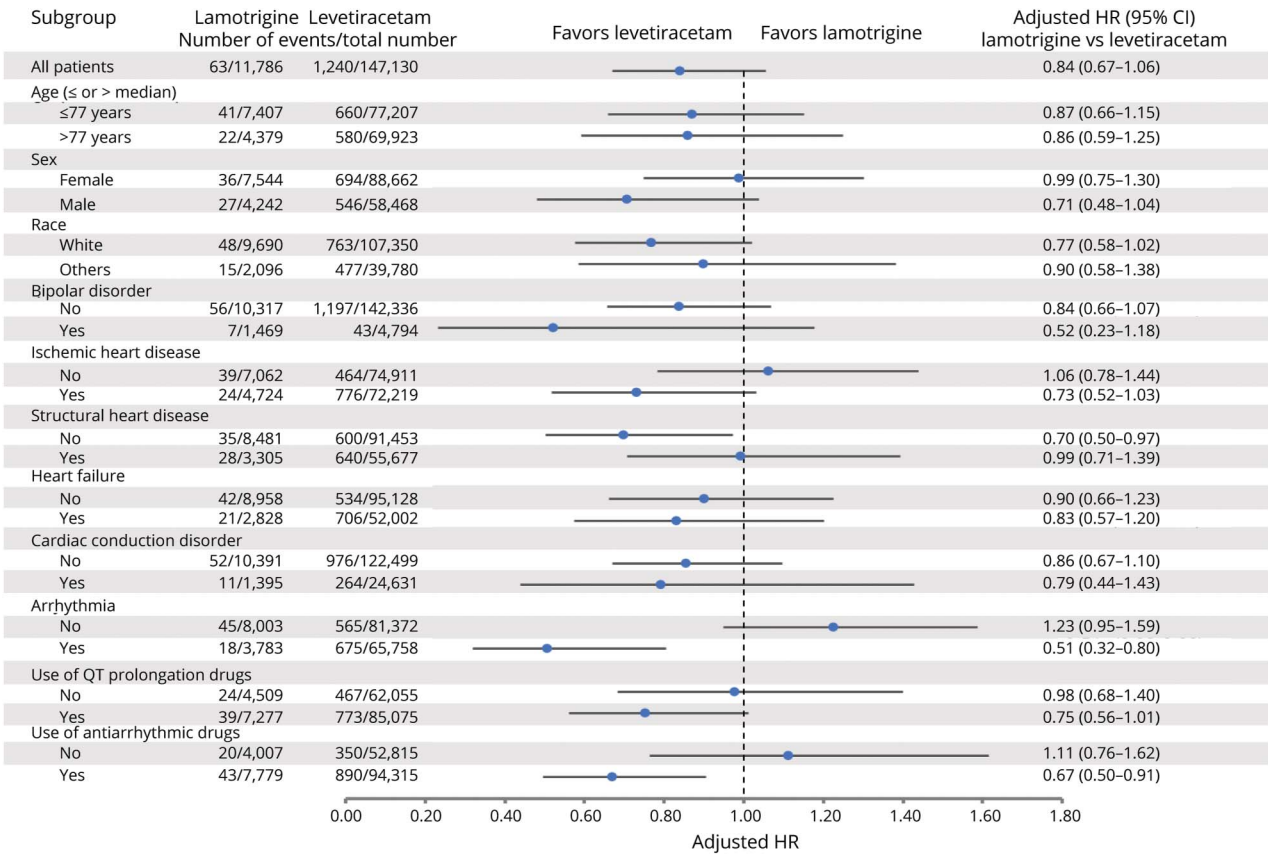
refractory focal seizures did not find differences in ECG between the lamotrigine and placebo groups.[23] Furthermore, observational studies that assessed the cardiac safety of lamotrigine through serial ECG measurements did not report any significant ECG changes among lamotrigine users.[7] A study in a Danish population[9] did not find a difference in risk of VA/SCA in a secondary analysis comparing lamotrigine and levetiracetam users (HR 1.05). However, this analysis had fewer than 100 events in total and did not report findings for older adults aged older than 65 years. Another Danish study combined lamotrigine and levetiracetam users into one treatment group and focused on overall and heart failure–related mortality, resulting in findings not comparable with our own.[24]

Lamotrigine is a commonly prescribed antiseizure medication, which represents approximately 10% of all antiseizure medication use and 4% of monotherapy prescriptions in the Medicare epilepsy population.[11,25] However, given the recent FDA safety warning, patients with epilepsy who may be good candidates to receive lamotrigine to control their seizures but have a history of cardiovascular abnormalities may be precluded from being prescribed this agent, hence limiting the use of an effective treatment modality from the clinical management of patients with epilepsy. Our study findings that lamotrigine did not increase risk of VA/SCA, including among individuals with cardiovascular comorbidities, have important clinical implications in guiding the care of patients with epilepsy.

Levetiracetam is not known to be associated with QT prolongation or affect cardiac conductivity.[12,26] The findings that levetiracetam use was associated with a higher risk of VA/SCA than lamotrigine use, particularly in subgroups of individuals who had arrhythmias or used antiarrhythmic medications in the baseline period, could be due to channeling bias toward levetiracetam treatment. Levetiracetam is one of the most common antiseizure medications with minimal drug interactions, fewer side effects, and broad-spectrum efficacy.[10,11,14] Because of its favorable safety profile, levetiracetam could be more likely to be prescribed than other antiseizure medications in the frail elderly, particularly in those with a cardiac comorbidity. Age-related frailty in addition to a history of arrhythmias could increase susceptibility to VA/SCA among levetiracetam users. Another possible explanation of our observation is that lamotrigine is a potent class 1 antiarrhythmic medication that could potentially prevent VA/SCA among those who had a history of arrhythmias. The FDA safety recommendations of lamotrigine in 2020, however, could not cause a bias toward prescribing levetiracetam instead of lamotrigine in our study, because Medicare data were excluded from 2020 onward.

This epidemiologic study examined the risk of VA/SCA in older adults with and without underlying risk factors that increase the risk of such events. Although randomized trials are the gold standard to assess pharmaceutical efficacy, they are often inadequately powered to detect differences in rare events such as VA or SCA. This study, which included over 150,000 patients, represents the largest real-world study on the effects of lamotrigine on VA/SCA risk in individuals with epilepsy performed to date. We also took several steps to decrease bias by characteristics associated with both treatment selection and risk of outcomes, that is, confounding by indication. We adjusted for 116 covariates and used an active comparator, new-user design, potentially mitigating the

Figure 3 Adjusted Hazard Ratios Comparing the Risk of VA/SCA in Lamotrigine vs Levetiracetam Users With Epilepsy, Stratified by Baseline Characteristics



HR = hazard ratio; VA/SCA = ventricular arrhythmia and sudden cardiac arrest.

likelihood of confounding by indication, selection bias, and immortal time bias that can limit the validity of studies. Unlike previous studies, we used previously validated definitions of epilepsy and VA/SCA, mitigating concerns for misclassification of the study population and outcomes. Study findings were consistent across a range of pertinent subgroups, including underlying cardiac abnormalities and concomitant QT-prolonging therapies, bolstering the robustness of the study findings.

Our study also has certain limitations. Fatal VA/SCA events that occurred outside hospitals and emergency departments would have been missed in our study, leading to outcome misclassification. Moreover, sudden unexpected death in epilepsy, a leading cause of death in people with epilepsy, may sometimes occur because of VA/SCA. Nevertheless, differential outcome misclassification by lamotrigine or levetiracetam exposure is unlikely. ECG assessments are not available in Medicare data, and we could not evaluate the direct effects of lamotrigine on cardiac myocyte excitability, although a focus on clinical outcomes is ultimately most clinically relevant. While we accounted for numerous pharmacodynamic interactions, particularly those related to cardiovascular outcomes, we acknowledge that not all potential drug interactions were assessed, given the extensive number of known interactions with lamotrigine. In addition, while we adjusted for a wide range of confounders, residual confounding is possible.

In summary, in a large real-world cohort of older adults using lamotrigine for epilepsy, we did not find an increased risk of VA/SCA in new lamotrigine users. These findings do not support the FDA safety warning about lamotrigine use in people with a history of structural or functional heart disease.

Author Contributions

G.Y.F. Ho: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D.B. Horton: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. P.J. Patel: study concept or design; analysis or interpretation of data. T. Gerhard: study concept or design; analysis or interpretation of data. C.V. Dave: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

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References

1. Matsuo F. Lamotrigine. *Epilepsia*. 1999;40(suppl 5):S30-S36. doi:10.1111/j.1528-1157.1999.tb00917.x
2. Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurol*. 2010;9(4):413-424. doi:10.1016/S1474-4422(10)70059-4
3. Harmer AR, Valentin JP, Pollard CE. On the relationship between block of the cardiac Na^+ channel and drug-induced prolongation of the QRS complex. *Br J Pharmacol*. 2011;164(2):260-273. doi:10.1111/j.1476-5381.2011.01415.x
4. French JA, Perucca E, Sander JW, et al. FDA safety warning on the cardiac effects of lamotrigine: an advisory from the Ad Hoc ILAE/AES Task Force. *Epilepsia Open*. 2021;6(1):45-48. doi:10.1002/epi4.12475
5. Yıldız A, Vardı N, Parlakpınar H, Ateş B, Çolakoğlu N. Effects of low- and high-dose valproic acid and lamotrigine on the heart in female rats. *Cardiovasc Toxicol*. 2022;22(4):326-340. doi:10.1007/s12012-021-09714-6
6. Contreras Vite JA, Vega Valle C, Biekeu Mbem H, Boivin SM, Dumaine R. Epilepsy-induced high affinity blockade of the cardiac sodium current I(Na) by lamotrigine; a potential for acquired arrythmias. *Pharmaceuticals (Basel)*. 2022;15(10):1208. doi:10.3390/ph15101208
7. Restrepo JA, MacLean R, Celano CM, Huffman JC, Januzzi JL, Beach SR. The assessment of cardiac risk in patients taking lamotrigine; a systematic review. *Gen Hosp Psychiatry*. 2022;78:14-27. doi:10.1016/j.genhosppsych.2022.06.004
8. Bunschoten JW, Husein N, Devinsky O, et al. Sudden death and cardiac arrythmia with lamotrigine: a rapid systematic review. *Neurology*. 2022;98(17):e1748-e1760. doi:10.1212/WNL.0000000000200164
9. Christensen J, Trabjerg BB, Dreier JW. Cardiac morbidity and mortality associated with the use of lamotrigine. *Epilepsia*. 2022;63(9):2371-2380. doi:10.1111/epi.17339
10. Kalilani L, Friesen D, Murray P. Treatment patterns in patients with a new diagnosis of epilepsy and psychiatric comorbidities. *Epilepsy Behav*. 2019;99:106405. doi:10.1016/j.yebeh.2019.07.006
11. Thurman DJ, Faught E, Helmers S, Kim H, Kalilani L. New-onset lesional and nonlesional epilepsy in the US population: patient characteristics and patterns of antiepileptic drug use. *Epilepsy Res*. 2019;157:106210. doi:10.1016/j.eplepsyres.2019.106210
12. Jia L, Verkerk AO, Tan HL. The anti-epileptic drugs lamotrigine and valproic acid reduce the cardiac sodium current. *Biomedicines*. 2023;11(2):477. doi:10.3390/biomedicines11020477
13. Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database Syst Rev*. 2017;12(12):CD011412. doi:10.1002/14651858.CD011412.pub3
14. Deshpande LS, Delorenzo RJ. Mechanisms of levetiracetam in the control of status epilepticus and epilepsy. *Front Neurol*. 2014;5:11. doi:10.3389/fneur.2014.00011
15. Conover MM, Stürmer T, Poole C, et al. Classifying medical histories in US Medicare beneficiaries using fixed vs all-available look-back approaches. *Pharmacoepidemiol Drug Saf*. 2018;27(7):771-780. doi:10.1002/pds.4435
16. Mbizvo GK, Schnier C, Simpson CR, Duncan SE, Chin RFM. Validating the accuracy of administrative healthcare data identifying epilepsy in deceased adults: a Scottish data linkage study. *Epilepsy Res*. 2020;167:106462. doi:10.1016/j.eplepsyres.2020.106462
17. Kee VR, Gilchrist B, Granner MA, Sarrazin NR, Carnahan RM. A systematic review of validated methods for identifying seizures, convulsions, or epilepsy using administrative and claims data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):183-193. doi:10.1002/pds.2329
18. Holden EW, Grossman E, Nguyen HT, et al. Developing a computer algorithm to identify epilepsy cases in managed care organizations. *Dis Manag*. 2005;8(1):1-14. doi:10.1089/dis.2005.8.1
19. Terman SW, Youngerman BE, Choi H, Burke JF. Antiseizure medication treatment pathways for US Medicare beneficiaries with newly treated epilepsy. *Epilepsia*. 2022;63(6):1571-1579. doi:10.1111/epi.17226
20. South & West Devon Formulary and Referral. An Initiative of NHS NEW Devon CCG. Drugs that prolong the QT interval. Accessed June 22, 2023. southwest.devonformularyguidance.nhs.uk/formulary/chapters/2.-cardiovascular/drugs-that-prolong-the-qt-interval.
21. Hennessy S, Leonard CE, Freeman CP, et al. Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in Medicaid and Medicare claims data. *Pharmacoepidemiol Drug Saf*. 2010;19(6):555-562. doi:10.1002/pds.1869
22. Hennessy S, Leonard CE, Newcomb C, Kimmel SE, Bilker WB. Cisapride and ventricular arrhythmia. *Br J Clin Pharmacol*. 2008;66(3):375-385. doi:10.1111/j.1365-2125.2008.03249.x
23. Schachter SC, Leppik IE, Matsuo F, et al. Lamotrigine: a six-month, placebo-controlled, safety and tolerance study. *J Eliplepsy*. 1995;8(3):201-209. doi:10.1016/0896-6974(95)00034-b
24. Liang D, Gardella E, Kragholm K, Polcwiartek C, Sessa M. The relationship between valproate and lamotrigine/levetiracetam use and prognosis in patients with epilepsy and heart failure: a Danish register-based study. *J Card Fail*. 2022;28(4):630-638. doi:10.1016/j.cardfail.2021.07.020
25. Terman SW, Lin CC, Kerr WT, DeLott LB, Callaghan BC, Burke JF. Changes in the use of brand name and generic medications and total prescription cost among Medicare beneficiaries with epilepsy. *Neurology*. 2022;99(8):e751-e761. doi:10.1212/WNL.0000000000200779
26. Hulhoven R, Rosillon D, Bridson WE, Meeus MA, Salas E, Stockis A. Effect of levetiracetam on cardiac repolarization in healthy subjects: a single-dose, randomized, placebo- and active-controlled, four-way crossover study. *Clin Ther*. 2008;30(2):260-270. doi:10.1016/j.clinthera.2008.02.002