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RESEARCH ARTICLE

Cardiac morbidity and mortality associated with the use of lamotrigine

Jakob Christensen[1,2] | **Betina B. Trabjerg**[1,3] | **Julie Werenberg Dreier**[1,3]

[1]National Center for Register-Based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

[2]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

[3]Center for Integrated Register-Based Research, Aarhus University, Aarhus, Denmark

Correspondence
Jakob Christensen, Department of Neurology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 165, DK-8200 Aarhus N, Denmark.
Email: jakob@farm.au.dk

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Abstract

Objective: The US Food and Drug Administration recently issued a warning against the use of the antiseizure medication lamotrigine in people at risk of cardiac rhythm and conduction abnormalities. This study assessed the risk of cardiac morbidity and mortality in new users of lamotrigine.

Methods: In a Danish population-based cohort study, we followed cohort members aged ≥15 years for the first 2 years after they initiated lamotrigine therapy. The main outcomes were cardiac conduction disorders in people without pre-existing cardiac morbidity and all-cause mortality in people with pre-existing cardiac morbidity. Cox proportional hazards models provided hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for comparison of the risk in current versus past users of lamotrigine.

Results: There were 91 949 (36 618 males [39.8%]) new users of lamotrigine (median age = 45.7 years, interquartile range = 32.0–60.2 years). Among users without pre-existing cardiac disease (n = 86 769), 194 (.23%) developed a cardiac conduction disorder. Comparison of the risk in current and past lamotrigine treatment periods yielded an adjusted HR of new onset cardiac conduction disorder of 1.03 (95% CI = .76–1.40). Among users with pre-existing cardiac disease (n = 5180), 1150 (22.2%) died. Comparison of the risk in current and past lamotrigine treatment periods yielded an adjusted HR for all cause-mortality of 1.05 (95% CI = .93–1.19).

Significance: In this large population-based study, lamotrigine use was associated neither with a risk of cardiac conduction disorders in people without pre-existing cardiac morbidity nor with all-cause mortality in people with pre-existing cardiac morbidity.

KEYWORDS

adverse effects, antiepileptic drugs, antiseizure drugs, bipolar disorder, epilepsy, antiseizure medication

1 | INTRODUCTION

Lamotrigine is an antiseizure medication widely used for epilepsy[1,2] and bipolar disorder.[3–5] Recently, the US Food and Drug Administration (FDA) issued a warning against its use in people at risk of cardiac rhythm and conduction abnormalities.[3,6] The warning was issued after an in vitro study[7] had shown that lamotrigine may slightly inhibit cardiac sodium channels, giving rise to class IB antiarrhythmic activity.[7,8] In a study of healthy individuals, lamotrigine did not cause prolongation of the depolarization of ventricles of the heart (the QRS complex).[9] However, concern exists that it may slow ventricular conduction (widen the QRS complex) and thus increase the risk of proarrhythmia and sudden death in people with structural or functional heart disease.[7] In addition, lamotrigine prolonged the period from the onset of atrial depolarization until the beginning of the QRS complex (the PR interval) at dosages between 50 and 200 mg twice daily in healthy subjects,[10] indicating delayed conduction of the sinoatrial nodal impulse to the ventricles. Therefore, the lamotrigine label warns about its use in patients with cardiac conduction disorders (e.g., second- or third-degree heart block), ventricular arrhythmias, and cardiac disease or abnormality (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome, or other sodium channelopathies).[3]

Concerns about the safety of treatment are central to the management of disease in people with epilepsy and bipolar disorder treated with lamotrigine. To address these concerns, we used Danish registers to study the risk of cardiac morbidity and mortality in people who use lamotrigine.

Key Points

- Lamotrigine is one of the most widely used antiseizure medications indicated for epilepsy and bipolar disorders
- Recently, the FDA issued a warning against the use of lamotrigine in people at risk of cardiac rhythm and conduction abnormalities
- This large population-based study assessed the risk of cardiac morbidity and mortality in >90 000 new users of lamotrigine aged ≥15 years
- Lamotrigine use was associated neither with a risk of cardiac conduction disorders in people without pre-existing cardiac morbidity nor with all-cause mortality in people with pre-existing cardiac morbidity
- The results do not support the FDA warning against the use of lamotrigine in people at risk of cardiac rhythm and conduction abnormalities

2 | MATERIALS AND METHODS

2.1 | Study design and population

We conducted a Danish population-based cohort study of new lamotrigine users aged ≥15 years initiating lamotrigine treatment between January 1, 1997 and December 31, 2016. Lamotrigine users were identified using the Danish National Prescription Register,[11] which holds information on filled prescriptions from 1995. We defined lamotrigine users as individuals who had redeemed a minimum of one prescription with Anatomical Therapeutic Classification (ATC) code N03AX09 (lamotrigine). We included persons who had a minimum of 2 years of residence in Denmark before treatment initiation to ensure that only new users were included. The 2-year time period was chosen because the adverse effects of lamotrigine would be expected to occur within a 2-year time period.[9,10] New lamotrigine users were followed from the date of their first filled prescription and for a period of up to 2 years, or until emigration, death, occurrence of a cardiac event, or end of follow-up (December 31, 2016).

2.2 | Lamotrigine treatment

Cardiac effects of lamotrigine were expected to present shortly after treatment initiation, continue during current treatment, and resolve shortly after treatment discontinuation. Therefore, in the primary analysis, we classified exposure status as either current or past treatment for each time point during follow-up (Figure S1). Periods of current treatment were estimated by assigning treatment duration to each prescription by adding the number of redeemed packs multiplied by the number of dose units per pack to the prescription date. The estimated number of dose units per pack was based on the defined daily dose (DDD) for lamotrigine, which is the assumed average daily maintenance dose for adults with epilepsy (300 mg). To account for individuals using daily dosages below the DDD (and who therefore do not need to refill prescriptions as soon as otherwise estimated), we added a 45-day grace period to each prescription period to ensure that all estimated treatment breaks of ≤45 days were defined as in-treatment periods. Periods following treatment (past treatment) were defined as starting on the day after the estimated end of a current treatment period, continuing until initiation of a new treatment period or end of follow-up. We used past users, rather than

nonusers, as comparator to better account for potential confounding by indication.

2.3 | Cardiac outcomes and mortality

Information on cardiac morbidity was obtained from the Danish National Patient Register.[12,13] The main outcome was (a) cardiac conduction disorders, defined as a composite of pacemaker implantation, advanced second- or third-degree atrioventricular block, or sinoatrial dysfunction. Secondary outcomes were (b) cardiac ventricular arrhythmia and cardiac arrest, which was a composite of implantable cardioverter–defibrillator implantation, ventricular arrhythmias, or cardiac arrest; (c) atrial fibrillation or flutter; and (d) heart failure. We furthermore studied (e) all-cause mortality and (f) cardiac mortality. The number of deaths due to conduction disorders and cardiac arrest was too low to analyze separately. Finally, because cardiac mortality may be misinterpreted as being seizure-related or an instance of sudden unexpected death in people with epilepsy (SUDEP),[14,15] we studied (g) mortality due to "epilepsy" and "unknown or unspecified causes." The date and the primary cause of death were retrieved from the Civil Registration System[16] and the Danish Register of Causes of Death,[17] respectively. All relevant International Classification of Diseases (ICD)-8, ICD-10, and surgical procedure codes for outcomes a–g are available in Table S1.

2.4 | Statistical analyses

Two main questions of interest were raised in the present study; first, whether lamotrigine treatment is associated with new onset cardiac conduction disorders in people without pre-existing cardiac morbidity; and, second, whether lamotrigine treatment is associated with increased all-cause mortality in people with pre-existing cardiac morbidity. Analyses addressing the first question were based on individuals with no cardiac morbidity (i.e., any of outcomes a–d) preceding lamotrigine initiation. Separate analyses were conducted for each of the outcomes a–g. Analyses addressing the second question were based on individuals with cardiac morbidity (i.e., any of outcomes a–d) preceding lamotrigine initiation. Separate analyses were conducted for each of the mortality outcomes (outcomes e–g). We estimated incidence rates and corresponding 95% confidence intervals (CIs), and used Cox proportional hazards models to obtain hazard ratios (HRs) comparing the risk of each outcome in periods of current to past treatment with lamotrigine included as a time-varying exposure. In these models, age was used as the underlying time scale. To account for possible confounding, we adjusted all HRs for a range of baseline characteristics at the time of lamotrigine initiation, including sex, calendar year, diagnosis of epilepsy (ICD-8: 345 [excluding 345.29]; ICD-10: G40),[12] diagnosis of a psychiatric disorder (ICD-8: 290–315; ICD-10: F00–F99),[18] Charlson Comorbidity Index score,[12] and family history of cardiac conduction disorder in first-degree relatives (i.e., parents, siblings, or children). Because the potential cardiac effects of lamotrigine are related to sodium channel-blocking properties, the risk of arrhythmias may increase further if lamotrigine is used in combination with other medicines that block sodium channels in the heart.[3] Thus, as time-varying covariates, we further adjusted HRs for concomitant use of other antiseizure medications affecting sodium channels and other drugs affecting atrioventricular block (see Table S2). To examine whether the association between lamotrigine treatment and cardiac morbidity and mortality varied with patient characteristics, we examined the interaction between such characteristics and lamotrigine exposure status, when possible.

2.5 | Sensitivity analyses

Defining treatment periods based on prescription patterns is based on assumptions about the amount of medication used per day. To assess the impact of such assumptions, we performed sensitivity analyses with varying grace period durations (from 0 to 90 days) and changed the assumed daily dosage of all prescriptions (from 50 to 500 mg) to capture the most relevant dosing range for lamotrigine users.

We also performed a sensitivity analysis using nonusers as a reference group identified by matching up to 10 randomly chosen reference persons with no history of lamotrigine use from the source population to each lamotrigine user, using exposure density sampling. Nonusers were matched on sex, birth year, pre-existing cardiac disease, epilepsy, and Charlson Comorbidity Index score at the time when the lamotrigine user filled the first lamotrigine prescription. Using Cox proportional hazards models with strata for each lamotrigine user and their corresponding set of matched reference persons, we compared current and past users of lamotrigine with the matched nonusers. Furthermore, we performed an analysis using new users of levetiracetam (ATC code N03AX14) as a reference group. Levetiracetam is an antiseizure medication with no effect on sodium channels.[19] New levetiracetam users were identified in the same period as the lamotrigine users, and we compared the risk of cardiac morbidity and mortality in current users of lamotrigine with that of current users of levetiracetam.

Finally, we conducted two positive control analyses to evaluate the sensitivity of the exposure classification and study design in detecting side effects of lamotrigine treatment and cardiac conduction disorders associated with drug exposure. First, as a positive control outcome analysis, we estimated the association of current lamotrigine treatment with erythema multiforme and medication-related skin rash (ICD-10: L51, L27.0, L27.1), a well-established side effect of lamotrigine use.[3,20] Second, as a positive control exposure analysis, we identified new users of lithium (ATC code N05AN01), a drug with an established risk of cardiac conduction disorder.[21] In this analysis, we compared the risk of cardiac morbidity and mortality in current versus past users of lithium.

Statistical analyses were performed using SAS version 9.4 (SAS Institute).

2.6 | Patient and public involvement statement

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination of the research. The study was supported by the Danish Epilepsy Association.

2.7 | Role of the funding source

The study was supported by the Danish Epilepsy Association, the Central Denmark Region, and the Novo Nordisk Foundation, which did not have any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

3 | RESULTS

We identified 91 949 persons (36 618 males [39.8%], median age = 45.7 years, interquartile range = 32.0–60.2 years) who filled their first prescription for lamotrigine between 1997 and 2016. This yielded 86 769 (33 871 males [39.0%]) users of lamotrigine without pre-existing cardiac disease and 5180 (2747 males [53.0%]) users of lamotrigine with pre-existing cardiac disease. Patient characteristics are shown in Table 1.

3.1 | Lamotrigine users without pre-existing cardiac disease

Among the users without pre-existing cardiac disease, 194 (.23%) developed a cardiac conduction disorder (outcome

TABLE 1 Characteristics of 91 949 lamotrigine users aged ≥15 years, with and without pre-existing cardiac disease, in Denmark between 1997 and 2016

Characteristics at treatment initiation	Lamotrigine users without pre-existing cardiac disease, *n* = 86 769[a]		Lamotrigine users with pre-existing cardiac disease, *n* = 5180[a]	
Sex				
Male	33 871	(39.04)	2747	(53.03)
Female	52 898	(60.96)	2433	(46.97)
Calendar year				
1997–2000	7136	(8.22)	362	(6.99)
2001–2004	12 449	(14.35)	745	(14.38)
2005–2008	18 443	(21.26)	1095	(21.14)
2009–2012	23 721	(27.34)	1444	(27.88)
2013–2016	25 020	(28.84)	1534	(29.61)
Age, years[b]				
15–39	35 823	(41.29)	222	(4.29)
40–59	31 753	(36.59)	881	(17.01)
60–74	13 316	(15.35)	1942	(37.49)
≥75	5877	(6.77)	2135	(41.22)
Epilepsy				
No	65 871	(75.92)	3074	(59.34)
Yes	20 898	(24.08)	2106	(40.66)
Psychiatric disorder				
No	46 006	(53.02)	3442	(66.45)
Yes	40 763	(46.98)	1738	(33.55)
Charlson Comorbidity Index score				
0	59 226	(68.26)	794	(15.33)
1	14 642	(16.87)	1208	(23.32)
2	7186	(8.28)	991	(19.13)
≥3	5715	(6.59)	2187	(42.22)
Family history of cardiac conduction disorder				
No	85 393	(98.41)	5108	(98.61)
Yes	1376	(1.59)	72	(1.39)
Use of other antiseizure medications affecting sodium channels[c]				
No	75 457	(86.96)	4572	(88.26)
Yes	11 312	(13.04)	608	(11.74)
Use of other drugs inducing atrioventricular block[c]				
No	71 515	(82.42)	1515	(29.25)
Yes	15 254	(17.58)	3665	(70.75)

Note: Values are given as *n* (%).

[a]Cardiac disease includes cardiac conduction disorders, cardiac ventricular arrhythmia and cardiac arrest, atrial fibrillation or flutter, and heart failure.Abbreviation: IQR, interquartile range.

[b]Among all 91 949 lamotrigine users, the median age was 45.7 years (IQR = 32.0–60.2); among 86 769 users of lamotrigine without pre-existing cardiac disease, the median age was 44.4 years (IQR = 31–58 years); and among 5180 users of lamotrigine with pre-existing cardiac disease, the median age was 72.1 years (IQR = 62–80 years).

[c]At any point between the date of the first filled prescription for lamotrigine and 2 years after initiation (or December 31, 2016).

(a); Table 2) and 4004 (4.6%) died (outcome (e); Table 2) within 2 years of initiating lamotrigine. Comparison of current with past lamotrigine users yielded an adjusted HR of new onset cardiac conduction disorder (outcome (a)) of 1.03 (95% CI = .76–1.40; Table 2). We observed no association between lamotrigine use and cardiac conduction disorder (outcome (a)) in any of the examined patient subgroups; all *p*-values for interaction were >.05 (Figure 1). Furthermore, current treatment with lamotrigine was not associated with the risk of any of the other cardiac outcomes (Table 2; outcome (b) cardiac ventricular arrhythmia and cardiac arrest (HR = .91, 95% CI = .67–1.23), outcome (c) atrial fibrillation or flutter (HR = .88, 95% CI = .74–1.04), or outcome (d) heart failure (HR = .93, 95% CI = .77–1.12). Current users of lamotrigine experienced a slightly higher risk of all-cause mortality (outcome (e)) than past users (HR = 1.10, 95% CI = 1.03–1.18). This was also found for mortality from epilepsy and unknown and unspecified causes (outcome (g)) (HR = 1.55, 95% CI = 1.11–2.15). Cardiac mortality in general (outcome (f)) did not differ between current and past lamotrigine users (HR = .88, 95% CI = .68–1.14).

3.2 | Lamotrigine users with pre-existing cardiac disease

Among users with pre-existing cardiac disease, 1150 (22.2%) died within 2 years of initiating lamotrigine, including 236 (4.6%) from cardiac mortality. Comparison of current with past lamotrigine users yielded an adjusted HR of all-cause mortality of 1.05 (95% CI = .93–1.19; Table 3). We found no association between lamotrigine use and all-cause mortality in any of the examined patient subgroups; all *p*-values for interaction were >.05 (Figure 2). When considering cardiac mortality in general, we recorded a lower risk among current lamotrigine users than among past users (HR = .75, 95% CI = .57–.97); although the

TABLE 2 Risk of cardiac morbidity and mortality associated with lamotrigine treatment, within 2 years of lamotrigine initiation in 86 769 users without pre-existing cardiac disease

Outcome	Cases, *n*	IR_{1000} (95% CI)	Basic adjusted HR 95% (CI)[a]	Fully adjusted HR 95% (CI)[b]
(a) Cardiac conduction disorder				
Current lamotrigine treatment	122	1.34 (1.12–1.60)	1.09 (.81–1.46)	1.03 (.76–1.40)
Past lamotrigine treatment	72	1.10 (.87–1.39)	1.00 (ref)	1.00 (ref)
(b) Cardiac ventricular arrhythmia and cardiac arrest				
Current lamotrigine treatment	114	1.25 (1.04–1.51)	1.05 (.79–1.41)	.91 (.67–1.23)
Past lamotrigine treatment	74	1.13 (.90–1.42)	1.00 (ref)	1.00 (ref)
(c) Atrial fibrillation or flutter				
Current lamotrigine treatment	343	3.78 (3.40–4.20)	.92 (.78–1.08)	.88 (.74–1.04)
Past lamotrigine treatment	244	3.74 (3.29–4.23)	1.00 (ref)	1.00 (ref)
(d) Heart failure				
Current lamotrigine treatment	281	3.09 (2.75–3.48)	.95 (.79–1.15)	.93 (.77–1.12)
Past lamotrigine treatment	195	2.98 (2.59–3.43)	1.00 (ref)	1.00 (ref)
(e) All-cause mortality				
Current lamotrigine treatment	2585	28.41 (27.34–29.53)	1.21 (1.14–1.29)	1.10 (1.03–1.18)
Past lamotrigine treatment	1419	21.63 (20.54–22.79)	1.00 (ref)	1.00 (ref)
(f) Cardiac mortality in general				
Current lamotrigine treatment	151	1.66 (1.42–1.95)	.92 (.72–1.19)	.88 (.68–1.14)
Past lamotrigine treatment	104	1.59 (1.31–1.92)	1.00 (ref)	1.00 (ref)
(g) Mortality from epilepsy or of unknown and unspecified causes				
Current lamotrigine treatment	144	1.58 (1.34–1.86)	1.95 (1.41–2.69)	1.55 (1.11–2.15)
Past lamotrigine treatment	50	.76 (.58–1.01)	1.00 (ref)	1.00 (ref)

Note: Cardiac disease includes cardiac conduction disorders, cardiac ventricular arrhythmia and cardiac arrest, atrial fibrillation or flutter, and heart failure.

Abbreviations: CI, confidence interval; HR, hazard ratio; IR_{1000}, incidence rate per 1000 person years; ref, reference.

[a]Basic adjusted estimates are adjusted for sex and year of initiation of lamotrigine use (1997–2000, 2001–2004, 2005–2008, 2009–2012, and 2013–2016).

[b]Fully adjusted models are further adjusted for epilepsy, psychiatric disorder, Charlson Comorbidity Index score, family history of cardiac conduction disorder at the time of initiation of lamotrigine use, use of other antiseizure medications affecting sodium channels, and use of other drugs inducing atrioventricular block as time-varying covariates.

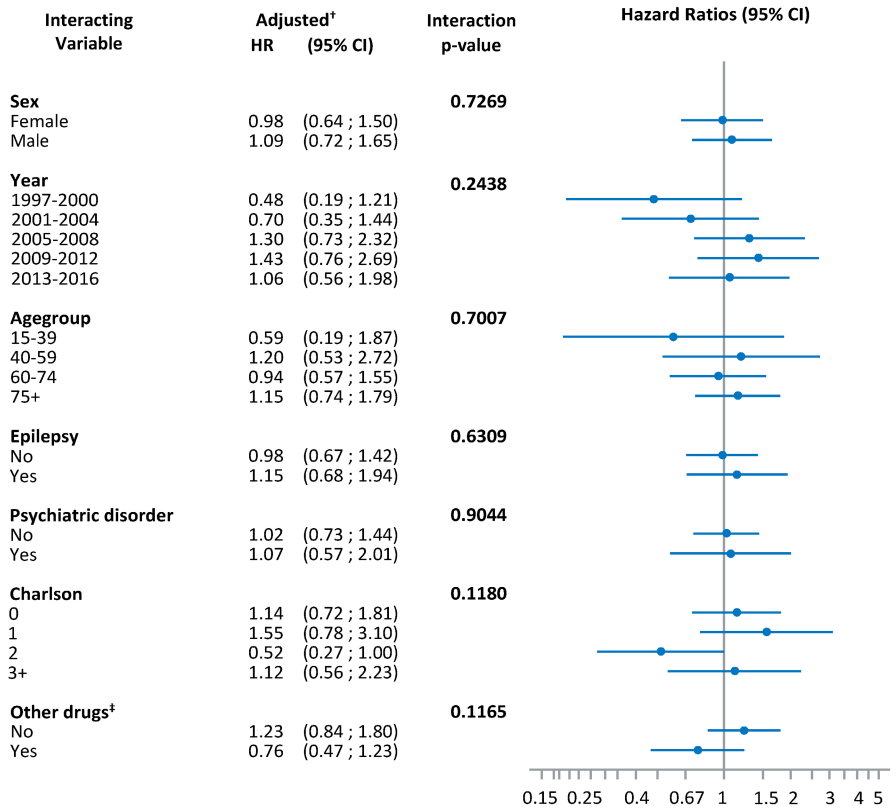

FIGURE 1 Risk of cardiac conduction disorder associated with lamotrigine treatment by patient characteristics, within 2 years of lamotrigine initiation in 86 769 users without pre-existing cardiac disease; cardiac disease includes cardiac conduction disorders, cardiac ventricular arrhythmia and cardiac arrest, atrial fibrillation or flutter, and heart failure. †Adjusted for sex, calendar year (1997–2000, 2001–2004, 2005–2008, 2009–2012, and 2013–2016), epilepsy, psychiatric disorder, Charlson Comorbidity Index score, family history of cardiac conduction disorder at the time of initiation of lamotrigine use, use of other antiseizure medications affecting sodium channels, and use of other drugs inducing atrioventricular block as time-varying covariates. ‡Use of other drugs inducing atrioventricular block. CI, confidence interval; HR, hazard ratio

TABLE 3 Risk of mortality associated with lamotrigine treatment, within 2 years of lamotrigine initiation in 5180 users with pre-existing cardiac disease

Outcome	Cases, *n*	IR_{1000} (95% CI)	Basic adjusted HR 95% (CI)[a]	Fully adjusted HR 95% (CI)[b]
(e) All-cause mortality				
Current lamotrigine treatment	757	144.1 (134.2–154.8)	1.11 (.98–1.26)	1.05 (.93–1.19)
Past lamotrigine treatment	393	129.8 (117.6–143.3)	1.00 (ref)	1.00 (ref)
(f) Cardiac mortality in general				
Current lamotrigine treatment	135	25.70 (21.71–30.42)	.78 (.60–1.01)	.75 (.57–.97)
Past lamotrigine treatment	101	33.36 (27.45–40.54)	1.00 (ref)	1.00 (ref)
(g) Mortality from epilepsy or of unknown and unspecified causes				
Current lamotrigine treatment	29	5.52 (3.84–7.94)	1.25 (.65–2.40)	1.06 (.54–2.07)
Past lamotrigine treatment	13	4.29 (2.49–7.39)	1.00 (ref)	1.00 (ref)

Note: Cardiac disease includes cardiac conduction disorders, cardiac ventricular arrhythmia and cardiac arrest, atrial fibrillation or flutter, and heart failure.
Abbreviations: CI, confidence interval; HR, hazard ratio; IR_{1000}, incidence rate per 1000 person-years; ref, reference.

[a]Basic adjusted estimates are adjusted for sex and year of initiation of lamotrigine use (1997–2000, 2001–2004, 2005–2008, 2009–2012, and 2013–2016).

[b]Fully adjusted models are further adjusted for epilepsy, psychiatric disorder, Charlson Comorbidity Index score, family history of cardiac conduction disorder at the time of initiation of lamotrigine use, use of other antiseizure medications affecting sodium channels, and use of other drugs inducing atrioventricular block as time-varying covariates.

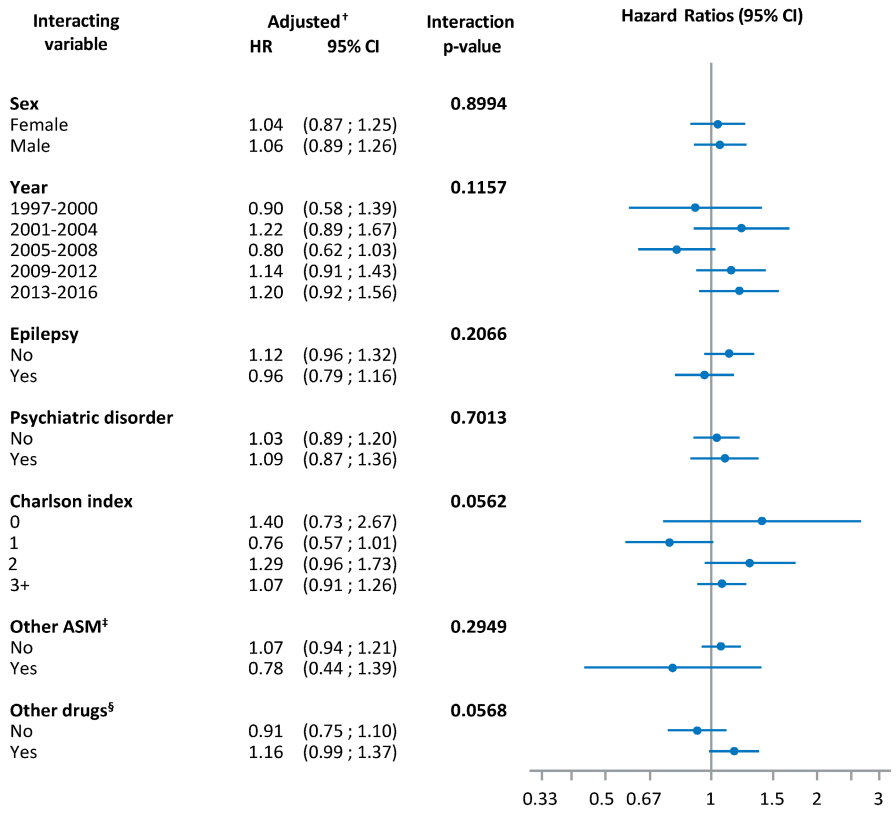

FIGURE 2 Risk of all-cause mortality associated with lamotrigine treatment by patient characteristics, within 2 years of lamotrigine initiation in 5180 users with pre-existing cardiac disease; cardiac disease includes cardiac conduction disorders, cardiac ventricular arrhythmia and cardiac arrest, atrial fibrillation or flutter, and heart failure. †Adjusted for sex, calendar year (1997–2000, 2001–2004, 2005–2008, 2009–2012, and 2013–2016), epilepsy, psychiatric disorder, Charlson Comorbidity Index score, family history of cardiac conduction disorder at the time of initiation,use of other antiseizure medications (ASMs) affecting sodium channels, and use of other drugs inducing atrioventricular block as time-varying covariates. ‡Use of other ASMs affecting sodium channels. §Use of other drugs inducing atrioventricular block. CI, confidence interval; HR, hazard ratio

statistical power of the analyses by patient characteristics was low, this was generally the pattern across the examined patient characteristics (Figure S2). Among lamotrigine users with pre-existing cardiac morbidity, we found no increased risk of mortality from epilepsy or from unknown and unspecified causes (HR = 1.06, 95% CI = .54–2.07).

3.3 | Sensitivity analyses

Changing the duration of the grace period and the assumed daily dosage had little impact on the cardiac morbidity measures (Tables S3 and S4). For instance, the risk of cardiac conduction disorder in current versus past lamotrigine users was HR = 1.10 (95% CI = .81–1.49) when the grace period was set to 0 days, and HR = .91 (95% CI = .67–1.24) when the grace period was set to 90 days. Reducing the assumed daily dose to 50 mg also did not change the estimate much (HR = 1.02, 95% CI = .75–1.40), nor did increasing the daily dose to 500 mg (HR = .95, 95% CI = .66–1.37). In contrast, the mortality measures generally seemed to be more sensitive to changes in the grace period and assumed daily dosage, producing both increased and decreased HRs for various scenarios (see Tables S3 and S4).

In the sensitivity analysis using nonusers of lamotrigine as a reference group identified by matching up to 10 randomly chosen reference persons with no history of lamotrigine use from the source population (nonusers) to each lamotrigine user, current lamotrigine users did experience a greater risk of cardiac conduction disorders than matched nonusers of lamotrigine (HR = 2.20, 95% CI = 1.78–2.70; Table S5). However, we found increases of a similar magnitude when we compared past lamotrigine users with matched nonusers of lamotrigine (HR = 1.89, 95% CI = 1.45–2.47), suggesting that the increases associated with both current and past lamotrigine treatment are likely related to the indication for treatment rather than to treatment per se.

In analyses comparing current lamotrigine users with current levetiracetam users without pre-existing cardiac disease, no difference was recorded in the risk of cardiac

conduction disorders (HR = 1.14, 95% CI = .73–1.76). However, all-cause mortality was lower in current lamotrigine users than in current levetiracetam users, both in persons without (HR = .65, 95% CI = .60–.71) and with (HR = .85, 95% CI = .73–.99) pre-existing cardiac disease (Table S6).

The positive control analyses detected an increased risk of erythema multiforme (HR = 4.16, 95% CI = 2.61–6.62) in current versus past lamotrigine treatment periods (Table S7), as well as an increased risk of cardiac conduction disorders in current versus past lithium treatment periods (HR = 3.07, 95% CI = 1.24–7.62; Table S8).

4 | DISCUSSION

In this nationwide population-based study including >90 000 new lamotrigine users aged ≥15 years, we recorded no increased risk of cardiac conduction disorders in persons without pre-existing cardiac morbidity, and no increased all-cause mortality in persons with pre-existing cardiac morbidity associated with lamotrigine use. Thus, these findings do not support the recent FDA warning against the use of lamotrigine in people at risk of cardiac rhythm and conduction abnormalities.[3]

People with epilepsy experience higher rates of cardiac morbidity and mortality than the general population.[22,23] In this study, we found that the risk of cardiac conduction disorders was similar among current and past users of lamotrigine, but higher in both groups than among nonusers. These findings suggest that persons initiating treatment with lamotrigine have a higher baseline risk of developing new onset cardiac conduction disorder than the general population, but that lamotrigine use per se is unrelated to this risk. These findings were further substantiated in analyses showing that current lamotrigine users did not face a higher risk of cardiac conduction disorders than current users of levetiracetam, an antiseizure medication also indicated for epilepsy, but with no effect on the sodium channels.[19]

All-cause mortality associated with lamotrigine use was slightly increased in users without pre-existing cardiac disease. This higher all-cause mortality was not due to a higher risk of cardiac mortality, but mortality was increased from "epilepsy" and "unknown and unspecified causes." A possible association between lamotrigine use and SUDEP has been a source of intense discussions,[24–26] and although not a primary objective of this study, the results do not exclude that lamotrigine may be associated with an increased SUDEP risk. The mechanism behind a possible lamotrigine-associated increase in SUDEP risk remains unknown, but may be unrelated to the heart and instead due to altered brainstem respiratory rhythm generation.[27] Nevertheless, it may be difficult to differentiate individual causes of death when using information from death certificates, and it is likely very difficult to distinguish between cause of death due to new onset cardiac arrhythmia and cause of death from SUDEP in persons with epilepsy, who die suddenly and unexpectedly. Thus, it is possible that some of the increased risk of "mortality from epilepsy or of unknown and unspecified causes" (suggestive of SUDEP) associated with current use of lamotrigine in person without pre-existing cardiac disease, may actually be due to misclassified deaths from cardiac arrhythmia. A similar increase in all-cause mortality was not found in lamotrigine users with pre-existing cardiac disease; however, because the baseline mortality rate was very high in this group, it would be difficult to detect a subtle increase in mortality risk.

4.1 | Strengths and limitations

In observational studies, identifying potential adverse effects associated with drug exposures comes with a number of challenges, including determining when each person is currently in or off treatment based on prescription fill patterns. We assumed that each person used a daily dose of 300 mg and introduced a 45-day grace period to account for individuals using lower dosages. Using this approach, we detected a strong association with severe cutaneous adverse reactions with lamotrigine use. All other scenarios with alternative grace periods and assumed daily dosages (Tables S3 and S4) produced lower HRs for this outcome, supporting our main exposure classification (i.e., a 45-day grace period). Furthermore, we analyzed lithium users using a similar approach and detected an increased risk of cardiac conduction disorders.[21] Thus, collectively, these analyses suggest that the employed study design would have been able to detect an increased risk of cardiac conduction disorder associated with lamotrigine use, had there been one. However, epilepsy is a heterogeneous disorder that affects patients with rare sodium channel gene variants[28] that may contribute to seizures as well as cardiac disorders, including sensitivity to drugs (e.g., lamotrigine).[29] Adverse events in these very rare epilepsies are unlikely to have been picked up by the current design and thus warrant continuous efforts to ensure the safety of the affected patients.

In the current study, 23 004 (25%) persons out of the entire population of 91 949 new lamotrigine users were diagnosed with epilepsy prior to initiation of lamotrigine treatment, suggesting that lamotrigine is used for indications other than epilepsy (Table 1). This finding is in accordance with a recent Norwegian drug utilization study showing that nonepilepsy indications

accounted for 71% of the total ASM use among adults in 2018 (neuropathic pain 55%, psychiatric disorders 43%, and migraine 2%).[30] To account for these differences in underlying indication for lamotrigine treatment, we adjusted all risk estimates for a number of variables including epilepsy, psychiatric disorders, and Charlson Comorbidity Index score, and when possible carried out stratified analyses by these indications. The association between lamotrigine use and the various outcomes did not differ according to these indications, and we therefore do not expect that including users of lamotrigine given for nonepilepsy indications explains the findings of this study.

5 | CONCLUSIONS

The study was initiated in response to the FDA warning regarding the risk of cardiac rhythm and conduction abnormalities.[3,6] Although observational studies cannot provide conclusive evidence, the present study does not support the FDA warning against the use of lamotrigine. Thus, further studies evaluating heart risk across the drug class of sodium channel blockers are highly relevant, as also suggested by the FDA.[31]

AUTHOR CONTRIBUTIONS

Jakob Christensen and Julie Werenberg Dreier initiated the study and obtained funding. All authors participated in the design of the study. Betina B. Trabjerg constructed the dataset and analyzed the data. Jakob Christensen and Julie Werenberg Dreier prepared the first draft and the revised subsequent versions. All authors interpreted the results, revised the manuscript, and approved the final version.

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CONFLICT OF INTEREST

Jakob Christensen has received honoraria from serving on the Scientific Advisory Board of UCB Nordic and Eisai, has received honoraria for lectures imparted from UCB Nordic and Eisai, and has received funding for a trip from UCB Nordic. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data were based on Danish national registers, and individual level data cannot be shared. However, summary statistics, in addition to the results provided in the Results section and supplementary material, may be provided on request.

TRANSPARENCY STATEMENT

The lead author affirms that this article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

ACCESS TO DATA AND DATA ANALYSIS

Betina B. Trabjerg and Julie Werenberg Dreier take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all study data.

ORCID

Jakob Christensen https://orcid.org/0000-0002-9385-6435
Betina B. Trabjerg https://orcid.org/0000-0001-6282-2614
Julie Werenberg Dreier https://orcid.org/0000-0002-9339-4170

TWITTER

Jakob Christensen @JakobChristen12
Julie Werenberg Dreier @julie_dreier

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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