Title:

Sudden death and cardiac arrythmia with lamotrigine: a rapid systematic review.

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Abstract

Objective

A recent FDA warning concerning an arrhythmogenic potential of lamotrigine created concern in the neurological community. This warning was based on in vitro studies, but no clinically relevant risk was considered. This rapid systematic review aims to elucidate the risk of lamotrigine on sudden death or electrocardiogram abnormalities.

Methods

We conducted a systematic search of Ovid Medline and Ovid Embase, including randomized controlled trials and observational studies, studies of people with or without epilepsy, with one of the following outcome measures: SUDEP and sudden cardiac death, as well as the development or worsening of electrocardiogram abnormalities. All titles and abstracts were independently screened, and the full texts of relevant studies were obtained. We re-evaluated the sudden death definitions used in all included studies, as some could have used unclear or overlapping definitions. We used the American Academy of Neurology risk of bias tool to evaluate the class of evidence and the GRADE approach to evaluate our confidence in the evidence.

Results

We included 26 studies with 24,962 participants, of whom 2,326 used lamotrigine. Twelve studies showed no significant risk of SUDEP for lamotrigine users. One study reporting on sudden cardiac death and three studies with unclear sudden death definitions did not report an elevated risk of death in lamotrigine users compared to controls. In 10 studies reporting on electrocardiogram parameters, there was no statistically significant increased risk among lamotrigine users except for two studies. These two studies reported either “slight increases” in PR interval or an increased PQ interval that the primary study authors felt to be more related to structural cardiac differences rather than an effect of lamotrigine. One study was

rated class II while all others were class III or IV. We had “very low confidence” in the evidence following the GRADE assessment. None of the studies examined the risk of lamotrigine in people with pre-existing cardiac conditions.

Conclusion

There is insufficient evidence to support or refute that lamotrigine is associated with sudden death or electrocardiogram changes, in people with or without epilepsy as compared to ASM or placebo. This is due to the high risk of bias in most studies and low precision and inconsistency in the reported results.

Introduction

On 9 October 2020, the FDA issued an addition to the label for lamotrigine. In this addition, the FDA advised clinicians to: "avoid LAMICTAL (i.e. lamotrigine) in patients with certain underlying cardiac disorders or arrhythmias". This warning was based on in vitro testing of lamotrigine, where Class IB antiarrhythmic activity at therapeutically relevant concentrations was found. This effect could widen the QRS complex and induce new cardiac arrhythmias and sudden death. It stated that lamotrigine should be avoided in individuals with cardiac conduction abnormalities, ventricular arrhythmias, or structural heart disease. The FDA did not consider clinical data when adding this warning to the lamotrigine label.

In response to the FDA warning, the International League against Epilepsy (ILAE) and the American Epilepsy Society (AES) convened an ad hoc Joint Taskforce to advise healthcare professionals on minimizing any possible cardiac risk associated with lamotrigine use.[1] Following this strong response of the epilepsy community, the FDA issued another statement in March 2021, slightly moderating their earlier position.[2] They also stated that other sodium channel blockers might not be suitable alternatives as the pro-arrhythmogenic potential of lamotrigine may be a class effect.

Given lamotrigine's role in managing epilepsy and other conditions, in particular, its relative safety among women of child-bearing potential [3] and older adults with epilepsy,[4] the safety of lamotrigine regarding cardiac arrhythmias, sudden cardiac death, sudden unexpected death in epilepsy (SUDEP) is a pressing clinical question. We conducted a rapid systematic review to determine the evidence regarding the risk of sudden cardiac death, SUDEP, as well as cardiac arrhythmias and conduction disorders, among people treated with lamotrigine.

Methods

We followed the 2020 PRISMA guidelines and those of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and the Ottawa Non-Randomized Studies Workshop while preparing the study protocol and the study report.[5-7]

Search strategy and selection criteria

We conducted a systematic search of Ovid Medline (1946 to 2020) and Ovid Embase (1947 to 2020) on 17 November 2020, using a combination of MeSH/EMTREE terms and keywords. We updated this search on 21 June 2021. These search strategies, developed in consultation with epilepsy and epidemiology experts, are listed in the Table 1. We included: (1) randomized controlled trials and observational studies (with or without a comparator group); (2) studies of people with or without epilepsy; (3) articles where at least some of the active study group were taking lamotrigine with one of the following outcome measures: sudden cardiac death, SUDEP, or the development or worsening of cardiac arrhythmias, conduction disorders, or other electrocardiogram (ECG) abnormalities. We excluded studies with fewer than ten total participants (i.e. including those treated with lamotrigine and control subjects) and studies whose outcome was limited to the development of cardiovascular disease (e.g. ischemic heart disease or stroke) without discussing conduction disorders or arrhythmias. We also excluded systematic reviews from the final list of studies but carefully reviewed the bibliographies of any reviews in order to identify additional studies relevant to our research question. We did not exclude studies based on publication language but arranged for translation as necessary.

If multiple articles were based on the same study data, we included the most complete report not to overrepresent particular data. We manually searched the bibliographies of all included

studies for potentially relevant studies. We managed the records to be screened using the online instrument Rayyan (https://www.rayyan.ai/).

Study selection and data extraction

Two reviewers (N.H. and J.W.B.) independently screened all titles and abstracts identified by the initial search. Next, we obtained the full texts of any article deemed possibly relevant by either reviewer. These full-texts were then independently evaluated by two reviewers (N.H. or J.W.B. with M.R.K. or R.D.T.) to decide whether the study was to be included. Disagreements were settled by consensus.

Two reviewers (N.H. and J.W.B.) independently extracted the data from each study using a form specifically designed for this review, including study type, source population, sample characteristics, lamotrigine exposure, methods to adjust for (if any) confounding bias when applicable, and outcomes of interest. After the first five extractions, final adjustments were made to the data extraction form. Any disagreements on the extracted data were settled by consensus.

The data extracted from the primary studies for this rapid systematic review were not conducive to a meta-analysis (great heterogeneity in exposures and outcomes measured); we narratively summarized the data.

Definitions

SUDEP was defined as death in people with epilepsy occurring under benign circumstances and in the absence of known structural causes of death (i.e. not due to drowning, injury, intoxication, or other internal or external factors), where evidence of a preceding seizure may

or may not be present.[8] A death is generally labelled as "definite SUDEP" if a postmortem examination does not reveal an alternative cause of death. If such an examination was not performed, but potentially lethal alternative causes are clinically excluded, the death is labelled as "probable SUDEP". The term "possible SUDEP" is used in cases with competing causes of death or when data are insufficient to reasonably allow their classification.

Sudden cardiac death was defined as: sudden and unexpected death occurring within an hour of the onset of symptoms or occurring in an individual found dead within 24 hours of being asymptomatic and presumably due to cardiac arrhythmia or hemodynamic catastrophe.[9]

One reviewer (R.D.T.) evaluated all reports on sudden death to reassess the criteria applied to classify the death as SUDEP, sudden cardiac death, or unclassifiable if the operational definition of sudden cardiac death or SUDEP used by the investigators of the primary study did not meet our criteria. This reviewer did not reassess how definite, probable, or possible SUDEP labels were applied as we did not have access to the individual participant data from the primary studies.

Risk of bias

We assessed the risk of bias of each included study using the American Academy of Neurology risk of bias class of evidence scheme for therapeutic studies (Table 2).[10] This approach summarizes the risk of bias for each primary study from Class I (lowest risk) to Class IV (highest risk), based on a set of criteria. Two reviewers (N.H. and J.W.B.) independently assessed the risk of bias of each study. Disagreements were settled by consensus.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

We used the GRADE framework to assess our confidence level in the conclusions derived from the evidence identified by our rapid review. Based on the number of primary studies addressing a particular research question, and the risk of bias of those studies, the confidence in the conclusions was ranked very low, low, moderate, or high. We upgraded or downgraded this level of confidence based on prespecified cirteria. The exact methods we used are based on the original GRADE guidelines [11] but modified to accommodate the AAN Class system for the evaluation of the risk of bias.[12]

Modifications to our protocol to ensure a rapid systematic review

This study was performed as a rapid review, given the relative urgency of the research question, which are not strictly defined.[13] The modifications from a traditional systematic review are decided upon once considering the research question. The modifications we applied included limiting our search to two electronic databases (Ovid Medline and Ovid Embase), not searching the grey literature, and not contacting authors for additional data.[14] The Cochrane Rapid Reviews Methods Group recently published new recommendations for the conduct of rapid reviews.[15] These were not available when we were drafting our protocol and were therefore not considered. Our methods generally exceed the standards laid out by these recommendations, with two exceptions. We did not include the CENTRAL database in our search. It exclusively focuses on randomized controlled trials, which we judged less likely to provide data relevant to our research question than to observational studies. We did not register our protocol with PROSPERO given that PROSPERO is currently discouraging submissions that are not related to COVID-19 and not originating from the United Kingdom.

Results

We identified 1,423 articles with our initial search of electronic databases and a further 36 with the updated search. We obtained the full text for 234 items. Of these, we eventually included 23 articles. We included three further studies on reviewing the included studies' bibliographies (Figure 1).

Of the included articles, 16 discussed sudden death among lamotrigine users, including eight Class III and eight Class IV studies. Twelve studies reported on SUDEP (3,241 participants, at least 582 lamotrigine users), one on sudden cardiac death (6,808 participants, 1 lamotrigine user) , while three articles reported on sudden death that could not be classified as either SUDEP or sudden cardiac death (Table 3). This was because SUDEP was not defined, the provided definition for SUDEP did not meet our criteria, or the sudden cardiac death definition did not exclude SUDEP. Ten studies compared sudden death cases with non-sudden deaths as controls. In one of these studies, where SUDEP was not clearly defined, all adverse effects of antiseizure medications (ASMs) in Norway accumulated in the period 2004–2013 were reported.[e13] There were 34 SUDEP events reported, of which most were among valproate users (eight cases), lamotrigine users (six cases), and carbamazepine users (six cases). Another study without a clear SUDEP definition reported on 2,124 participants who used lamotrigine, gabapentin, or vigabatrin.[e14] They estimated a crude mortality rate of 1.7 per 100 patient-years for lamotrigine users, compared to crude mortality rates of 2.1 for gabapentin and 1.3 for vigabatrin. They reported standardized mortality ratios of 10.4 (95% CI: 7.1, 13.7) for lamotrigine, 7.8 (95% CI: 2.7, 12.9) for gabapentin, and 6.8 (95% CI: 4.3, 9.2) for vigabatrin, with greatly overlapping 95% CIs. The third unclassifiable study reported sudden cardiac death but used a definition that did not exclude SUDEP.[e15] Among their 10,758 participants were 63 people with epilepsy, of which three were lamotrigine users. Nine

hundred twenty-six people died suddenly, of whom 14 people with epilepsy and no lamotrigine users. There was no significant difference in the proportion of lamotrigine users between people who died suddenly and controls in included studies.

Ten articles assessing ECG changes in lamotrigine users were included (Table 4). Among these, there were 2,031 participants, including 684 lamotrigine users. These were one Class II, five Class III, and four Class IV studies. The ECG parameters studied by each primary study varied, including QTc interval, QRS interval, ST segment, J-waves, and PQ interval. Overall, lamotrigine was not associated with the development of ECG abnormalities, as none of the studies comparing lamotrigine users with controls reported differences between groups. Longitudinal studies yielded some contradictory findings on the QTc length, with one study reporting QTc shortening among lamotrigine users,[e17] while another study reported QTc lengthening.[e26] This was a study of lamotrigine toxicity, however, and thus does not necessarily reflect the effects of lamotrigine used in normal doses.[e13] In a report on the effects of ASMs on Brugada-type ST-elevation, there were no lamotrigine users among those with Brugada-type ST-elevation.[e23] The presence of Brugada-type ST-elevation, was associated with polytherapy with sodium channel-blocking ASMs, though there were no lamotrigine users among those with polytherapy and Brugada-type ST-elevation.[e23] Two other studies primarily investigated lamotrigine tolerability, but ECGs were also performed.[e19, e20] Both studies reported no indications that lamotrigine use adversely affected cardiac function.

Following our GRADE assessment of our level of confidence in the identified evidence, we found that there is low confidence (multiple class III and IV studies) regarding an association with sudden death, downgraded to very low confidence due to poor precision (i.e. wide 95% CI). We conclude that there is insufficient evidence to judge that lamotrigine is associated with sudden death in people with or without epilepsy compared to other ASMs or placebo. We also found that there is low confidence (one Class II study, multiple class III and IV

studies) with regards to an association with ECG abnormalities, downgraded to very low confidence due to poor precision and great inconsistency in the results. We conclude that there is insufficient evidence to judge that lamotrigine is associated or not with any ECG changes in people with or without epilepsy, as compared to other ASM or placebo.

Discussion

This rapid review of clinical evidence on the possible arrhythmogenic potential of lamotrigine yielded a sizeable number of studies that discussed the association with SUDEP and ECG abnormalities, three on unclassifiable sudden death, and one study reported on sudden cardiac death. Among 24,962 participants in 26 studies, we did not identify clear evidence for an increased risk of arrhythmia or sudden death among lamotrigine users. Of these 26 studies, only one was Class II, with the remainder Class III or IV (i.e. higher risk of bias).

An early report pointed to a possible increased risk of SUDEP caused by lamotrigine use in young women.[e2] This study had a small sample size, and the results were not adjusted for known SUDEP risk factors. The association between lamotrigine and SUDEP observed in this study was mainly explained by tonic-clonic seizure frequency and not lamotrigine use.[16, 17] In a pooled analysis of case-control studies, SUDEP risk (adjusted for age, sex, data source, and duration of epilepsy) was increased for lamotrigine users as compared to non-lamotrigine users.[18] This risk was also no longer evident with adjustment for the frequency of tonic-clonic seizures.[e10] A large meta-analysis of randomized controlled trials of lamotrigine showed no increased risk of SUDEP as compared to control groups (placebo, active-comparator, or crossover).[19]

The classification of premature death as sudden cardiac death or SUDEP in a person with epilepsy is often challenging. This occurs because the definitions of both conditions may overlap and that sudden deaths are generally unwitnessed, and postmortem examinations are

lacking.[20, 21] We cannot be certain whether the cases of sudden death were, in fact, sudden cardiac death or SUDEP or could, on some occasions, be counted as both. We minimized this uncertainty by reassessing the definitions used in each of the primary studies and reclassifying them. Many of these used clear SUDEP definitions. We reclassified two SUDEP studies as sudden unclassifiable death because the SUDEP definitions used were unclear. [e13, e14] Only one study assessed the risk of sudden cardiac death in people with epilepsy using clear criteria without overlap with SUDEP.[e16] Another study ascertained sudden cardiac death but used a definition that did not exclude SUDEP and was thus reclassified as sudden unclassifiable death.[e15]

There are many reports of ECG changes in people with epilepsy, but the association with ASM use is often disputed.[22, 23] The possible pro-arrhythmogenic effect that is seen in "in vitro" studies may not be limited to lamotrigine. There are indications that it may be a class effect among sodium channel blockers, as sodium channels play an essential role in cerebral and cardiac conduction.[24] Carbamazepine, lacosamide, and phenytoin have been linked to atrioventricular conduction delays.[25-28] Lacosamide has occasionally been implicated in atrial fibrillation and atrial flutter, predominantly among older adults.[29] Lamotrigine and carbamazepine are among the preferentially avoided medications in Brugada syndrome as they could potentially cause arrhythmias in people with this syndrome.[30] This is further illustrated by a case report where a 60-year-old woman using lamotrigine and levetiracetam who was undergoing an ajmaline sodium channel blockade test as part of the diagnostic procedure for Brugada syndrome.[31] During ST-elevation testing, QRS-broadening and the development of bigeminy were observed. The ECG normalized after the ajmaline testing was stopped, and a repeat test off lamotrigine showed a type 1 Brugada pattern with no QRS-broadening or electrical alternans.

We did not include some studies because they did not specifically look at lamotrigine, but still bear mentioning. Three studies reported ECG changes in people with epilepsy and had lamotrigine users among their study population. In the first of these, the ECG's of people with epilepsy and controls without epilepsy were compared.[32] After adjustment for covariates, epilepsy was found to be associated with ERP and severe QTc prolongation. Medications were categorized, with lamotrigine considered among the depolarization-blocking drugs. QTc prolongation was found to be associated with the use of these depolarization-blocking drugs. In the second study, there was no significant difference in HRV parameters between people with epilepsy on ASM therapy (which included lamotrigine) and those without.[33] Still, there was a trend for the HRV values to be more suppressed among people who were not using ASMs. The third report revealed no significant changes in early repolarization before and after ASM use or seizure control.[34] In this study, SUDEP occurred in two individuals during a median follow-up of seven years.

The FDA lamotrigine update was met with surprise as lamotrigine is generally seen as a safe and effective broad-spectrum ASM.[35-37] Lamotrigine is often the ASM of choice for those with psychiatric comorbidities as it is helpful as a mood stabilizer.[38] Older people with epilepsy tolerate lamotrigine better than most other ASMs.[4] It is a preferred treatment option for women of child-bearing potential, given its low risk of teratogenicity.[3] A recent large, pragmatic, open-label, randomized controlled trial compared the effectiveness of levetiracetam, zonisamide, and lamotrigine in people with focal seizures.[39] After two years of follow-up, lamotrigine was the ASM with the fewest reported adverse effects, with two lamotrigine users reporting cardiac disorders (compared with two among levetiracetam and one among zonisamide users). There were 37 deaths during the trial, of which 15 among lamotrigine users (four possibly seizure-related), 12 among levetiracetam users (two possibly seizure-related), and ten among zonisamide users (two possibly seizure-related). This study

concluded that lamotrigine should remain a first-line and standard treatment for people with focal epilepsy.[39]

Our study has strengths. We included 26 articles on 24,962 people, making this a comprehensive review on this subject. We chose to include studies published in any language, making our results complete and inclusive. We included studies on all lamotrigine users, not just people with epilepsy. This allows our results to be more generalizable, although by far most of the included studies focused on people with epilepsy.

Our study has limitations. As the safety of lamotrigine with regards to cardiac conduction abnormalities, cardiac arrhythmias, sudden cardiac death and arrest, as well as SUDEP, is a pressing clinical question, we chose to do a rapid review instead of a more formal systematic review. This carries the risk of a loss of accuracy in identifying the relevant material and data extraction. We took care to minimize any impact this streamlined process would have on our results. We did not register our study protocol with PROSPERO for the reasons listed under our methods section. An additional limitation was accounting for polypharmacy in the primary studies. Many of the people in the included studies used multiple ASMs, making it difficult to attribute the observed outcome to a single medication. Another potential limitation is that most of the included studies did not consider statistical methods to accommodate time-varying exposure to lamotrigine or other ASMs. The composition of the control groups in the included studies varied. Most compared with other ASMs, but some with placebo or no medication. None of the studies we identified assessed whether the presence of pre-existing cardiac disease may modify any risk associated with lamotrigine. The recent FDA warning explicitly targets this population.

In this rapid systematic review, we have found insufficient evidence to support or refute that lamotrigine is associated with sudden death or ECG changes, in people with or without epilepsy, compared to ASM or placebo. Further research is warranted, given recent in vitro

data. Ideally, ongoing surveillance of sudden death using existing large registries of SUDEP and sudden cardiac death should be initiated. Attention should be paid to whether these potential risks differ between populations (based on age, sex, presence of pre-existing cardiac conditions). The clinical impact of screening ECGs in different populations treated with lamotrigine should be assessed to check if these ECG changes ever lead to important changes in clinical care. Most importantly, any clinically relevant arrhythmogenic effect of ASMs may be a class effect applicable to all sodium-channel antagonists.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram

Table 1. Electronic database search strategies

Database: Ovid MEDLINE(R) ALL
Search Strategy:
---
1 exp Lamotrigine/
2 (lamotrigine or lamictal).ti,ab,kf.
3 (antiepileptic* or anticonvulsant*).ab,ti,kf.
4 exp Sudden unexpected death in epilepsy/
5 Sudden unexplained death in epilepsy.ti,ab,kf.
6 Sudden unexpected death in epilepsy.ti,ab,kf.
7 SUDEP.ti,ab,kf.
8 exp Death, sudden/
9 (sudden adj2 death).ti,ab,kf.
10 cardiac arrest.ti,ab,kf.
11 exp Arrhythmias, Cardiac/
12 Arrhythm*.ti,ab,kf.
13 or/1-3
14 or/4-11
15 and/13-14

Database: Embase
Search Strategy:
---
1 exp Lamotrigine/
2 (lamotrigine or lamictal).ti,ab.
3 (antiepileptic* or anticonvulsant*).ti,ab.
4 SUDEP.ti,ab.
5 Sudden unexplained death in epilepsy.ti,ab.
6 Sudden unexpected death in epilepsy.ti,ab.
7 exp Death, sudden/
8 (sudden adj2 death).ti,ab.
9 cardiac arrest.ti,ab.
10 Arrhythm*.ti,ab.
11 or/1-3
12 or/4-10
13 and/11-12

Table 2. American Academy of Neurology risk of bias tool for therapeutic studies[a]

	Criteria
Class I	RCT in a representative population. Triple-masked studies (i.e. the patient, treating provider, and outcome assessors are unaware of treatment assignment). Relevant baseline characteristics of treatment groups (or treatment order groups for crossover trials) are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences. Additional Class I criteria: a. Concealed allocation. b. No more than two primary outcomes specified. c. Exclusion and inclusion criteria clearly defined. d. Adequate accounting of dropouts (with at least 80 percent of participants completing the study) and crossovers. e. Additional criteria for noninferiority or equivalence trials.
Class II	RCT that lacks one or two Class I criteria a-e. Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics (e.g., propensity score matching) meeting Class I criteria b–e (see above). Randomized crossover trial missing one of the following two criteria: a. Period and carryover effects described. b. Baseline characteristics of treatment order groups presented. All relevant baseline characteristics are presented and substantially equivalent across treatment groups (or treatment order groups for crossover trials), or there is appropriate statistical adjustment for differences. Masked or objective outcome assessment.
Class III	Controlled studies (including studies with external controls such as well-defined natural history controls). Crossover trial missing both of the following two criteria: a. Period and carryover effects. b. Presentation of baseline characteristics. A description of major confounding differences between treatment groups that could affect outcome. Outcome assessment performed by someone who is not a member of the treatment team.
Class IV	Studies not meeting Class I, II, or III criteria.

[a] Adapted from the American Academy of Neurology Clinical Practice Guidelines Process Manual.[10]

Table 3. Sudden death risk in lamotrigine users

Article	Study type	Population	Sudden death classification	Cases	Controls	% of LTG users among sudden deaths (95% CI)	% of LTG users among controls (95% CI)	Summary measure of risk/odds of sudden death in LTG users	Risk of bias[a]
Sveinsson 2020 [e1]	Retrospective case-control study	All individuals who were registered at any time during 1998–2005 in the Swedish National Patient Register with an ICD-10 code for epilepsy and who were alive on 30 June 2006, with follow-up from 1 July 2006 and 31 December 2011 for cases of SUDEP	SUDEP	255 SUDEP cases, of which 167 definite and 88 probable; 27 on LTG monotherapy and 38 on LTG polytherapy, 40% women	1148 matched living controls (5 per case); 104 on LTG monotherapy and 177 on LTG polytherapy, 41% women	25.5 (20.1, 30.8) (total), 10.6 (6.8, 14.4) (only those with LTG monotherapy)	24.5 (22.0, 27.0) (total), 9.1 (7.4, 10.7) (only those with LTG monotherapy)	OR (95% CI): 1.39 (0.81, 2.40)[b], 1.42 (0.79, 2.57)[c], 0.93 (0.41, 2.12)[d]	Class III
Aurlien 2012 [e2]	Retrospective case-control study	All SUDEP cases in Rogaland County, Norway between 1995–2005. For each case, at least three living controls, who had been registered in the database of Stavanger University Hospital	SUDEP	26 SUDEP cases, of which 16 definite, 3 probable and 7 possible; 10 LTG users (some polytherapy) among cases of which 8 with probable/definite SUDEP, 63% women	63 living controls with a diagnosis of epilepsy in the same year as the SUDEP case; 15 LTG users, 65% women	38.5 (19.8, 57.2) (total SUDEP), 42.1 (19.9, 64.3) (probable/definite SUDEP only)	23.8 (13.3, 34.3)	NA	Class III
Einarsdottir 2019 [e3]	Case series	General population of Iceland, including all individuals with epilepsy who died unexpectedly from 1 January, 1991 through 31 December, 2010	SUDEP	37 SUDEP cases, of which 29 definite SUDEP, 4 definite SUDEP plus, and 4 probable SUDEP, 6 LTG users (some with ASM polytherapy), 30% women	NA	16.2 (4.3, 28.1)	NA	NA	Class IV
Leestma 1997 [e4]	Case series	People with epilepsy included in LTG trials in the US, Europe, Australia and South Africa, including 2,988 LTG users from clinical studies, and 1,712 compassionate-use users, with 5,747 patient-years of LTG exposure	SUDEP	24 SUDEP cases, of which 18 probable or definite SUDEP and 6 possible SUDEP (of which 2 discontinued LTG), all LTG users, 33% women	NA	All SUDEP cases treated with LTG by study design; 3.5 cases of SUDEP per 1,000 patient-years of exposure to LTG	NA	NA	Class IV

Verducci 2019 [e5]	Case series	All SUDEP cases from the US and Canada as reported to a SUDEP registry from October 2011 to June 2018	SUDEP	237 SUDEP cases, of which 135 definite, 25 definite plus and 77 probable SUDEP. Data on ASM use was available for 180 cases; 47 LTG users (some with ASM polytherapy)[e], 38% women	NA	26.1 (19.7, 32.5)	NA	NA	Class IV
Alsfouk 2019 [e6]	Prospective cohort study (although SUDEP results analyzed as a case-control study)	Consecutive people with epilepsy aged 13–19 years at treatment initiation, followed at the Western Infirmary in Glasgow, Scotland, including 124 LTG users and 208 LTG non-users, with median follow-up of 4 years	SUDEP	3 SUDEP cases (probable or definite, no further subdivision given); all using LTG (all with ASM polytherapy), 53% women (in total group)	329 people newly diagnosed with epilepsy who did not die of SUDEP during follow-up; 121 LTG users of which 79 on monotherapy, 53% women (in total group)	100 (43.9, 100.0)[f]	36.8 (31.6, 42.0)	NR	Class IV
Lathers 2011 [e7]	Case series	All deaths investigated by the Allegheny County Coroner's Office (US) from 1 January, 2001 to 31 December, 2001	SUDEP	11 SUDEP cases, of which 7 definite and 4 possible SUDEP; 1 LTG user (with ASM polytherapy), 36% women	NA	9.1 (0, 26.1)	NA	NA	Class IV
Opeskin 1999 [e8]	Retrospective case control study	All deaths reported to coroner and with autopsy performed between 1991 and 1998 in Victoria, Australia	SUDEP	44 consecutive SUDEP cases (no subdivision in categories); 4 LTG users (some with ASM polytherapy), 43% women	44 deceased controls consisting of consecutive cases with epilepsy for which the cause of death was not related to epilepsy; 2 LTG users	9.1 (0.6, 17.6)	4.5 (0, 10.7)	NR	Class III
Opeskin 2003 [e9]	Retrospective case control study	All deaths that occurred in Victoria, Australia, that were reported to the coroner and autopsied between December 1997 and August 1999	SUDEP	50 SUDEP cases (no subdivision in categories); 9 LTG users (some with ASM polytherapy), 46% women	50 controls with epilepsy who died of something other than SUDEP; 8 LTG users, 22% women	18.0 (7.4, 28.7)	16.0 (5.8, 26.2)	NR	Class III
Hesdorffer 2012 [e10]	Retrospective case control study	Combined analysis of three case, control studies on SUDEP in Sweden, the US, and	SUDEP	160 SUDEP cases (no subdivision in categories), 37% women	674 living controls, 49% women	NR	NR	Crude OR (95% CI): 1.5 (0.4, 6.2); OR	Class IV

		the UK. Duration of follow-up not specified.						(95% CI) adjusted for GTCS: 0.7 (0.1, 3.6)	
Kloster 1999 [e11]	Retrospective case control study	People with epilepsy treated at outpatient clinics in Norway who died between 1965 and 1996	SUDEP	42 SUDEP cases (no subdivision in categories); 1 LTG user (possible ASM polytherapy), 38% women	37 deceased controls, no LTG users, 51% women	2.4 (0, 7.0)	0	NR	Class III
Edey 2014 [e12]	Case series	Pregnant or post-partum women in the years 2006–2008 in the UK, with death during or shortly after pregnancy	SUDEP	11 SUDEP cases (no subdivision in categories); 9 LTG users (possible ASM polytherapy)	NA	81.8 (59.0, 100)	NA	NA	Class IV
Baftiu 2019 [e13]	Case series	Anonymous data of all reported adverse effects of ASMs in Norway accumulated during the period 2004–2013 from the EudraVigilance database	Unclassifiable (no definition of SUDEP)	34 sudden deaths reported; 6 LTG users (possible ASM polytherapy), 55% women (total group)	NA	17.6 (4.8, 30.5)	NA	NA	Class IV
Wong 2011 [e14]	Prospective cohort study	People treated for epilepsy at tertiary centers in the UK from December 1993 to September 1996, with 1050 LTG users (2355 patient-years of follow-up), 361 GBP users (432 patient years of follow-up), and 713 VGB users (2391 patient years of follow-up)	Unclassifiable (no definition of SUDEP)	31 sudden deaths; 18 LTG users (possible ASM polytherapy), 50% women on LTG, 57% women on GBP, and 49% women on VGB	2093 living controls; 1032 LTG users (possible ASM polytherapy), 50% women on LTG, 57% women on GBP, and 49% women on VGB	58.1 (40.7, 75.4)	49.3 (47.2, 51.5)	SMR (95% CI) with LTG: 10.4 (7.1, 13.7); with GBP: 7.8 (2.7, 12.9); with VGB (4.3, 9.2)	Class III
Bardai 2015 [e15]	Retrospective case control study	All people aged ≥18 years in a Dutch GP database with at least 1 year follow-up, resulting in 478,661 individuals with 1,905,382 person-years of follow-up	Unclassifiable (SCD definition did not exclude SUDEP)	926 sudden deaths of which 14 people with epilepsy; no LTG users, 38% women	9832 living controls of which 49 with epilepsy; 3 LTG users, 36% women	0[e]	6.1 (0, 12.8)[e]	NR	Class III
Hookana 2016 [e16]	Retrospective case control study	Post mortem confirmed SCD victims in the Province of Oulu, Northern Finland between 1998 and 2013	SCD	3,727 SCD cases of which 68 ASM users; 1 LTG user (possible ASM polytherapy), 20% women	3081 controls of which 20 ASM users; no LTG users	1.5 (0, 4.3)[e]	0[e]	NR	Class III

LTG = lamotrigine, SUDEP = sudden unexpected death in epilepsy, OR = odds ratio, CI = confidence interval, NR = not reported, ASM = anti-seizure medication, NA = not applicable, US = United States, UK = United Kingdom, GTCS = generalized tonic-clonic seizures, GBP = gabapentin, VGB = vigabatrin, GP = general practitioner, SCD = sudden cardiac death, SMR = standardized mortality ratio

[a] as calculated using the AAN risk of bias tool[7]

[b] adjusted for matching variables (sex and calendar time) and age

[c] adjusted for the same variables as (2) together with duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, and education level

[d] adjusted for the same variables as (3) together with history of GTCS, GTCS frequency last year of observation, and nocturnal GTCS last year of observation

[e] calculated over ASM users only

[f] The 95% CI was not presented by the primary study authors but calculated using the Wilson method.

Table 4. ECG abnormalities in lamotrigine users

Article	Study type	Population	ECG parameters reported	Number of LTG users	Number of non LTG users	Outcomes	Risk of bias[a]
Dixon 2008 [e17]	Randomized controlled trial	Healthy UK participants, non-smokers, non-smokers, aged 18-55 years with a BMI 18.5-29.9 kg/m^2 and a normal ECG at baseline, randomized to a single dose of LTG or placebo.	12 serial 12-lead ECGs over 24 hours post LTG dose - QTc	62 LTG users	70 non-LTG users (placebo)	No QTc prolongation in LTG users. There was in fact a "small reduction" in QTc relative to placebo.	Class II
Saetre 2009 [e18]	Norwegian sub-cohort (fewer than 80% of the total sample) of a multinational randomized controlled trial	People aged above 65 years old and with a history of at least two focal seizures or tonic-clonic seizures. Those with pre-existing AV-conduction defects were excluded. Participants were randomized to a 40-week treatment with LTG or sustained-release carbamazepine. Of 107 participants, 33 discontinued their ASM before 40 weeks and 15 did not have complete ECG data.	1 baseline 12-lead ECG and another at 40 weeks - HR - QRS - QTc - PQ	31 LTG users	29 CBZ users	There were no statistically significant differences between LTG and CBZ in the average change over 40 weeks in HR, QRS, QTc, or PQ. LTG was associated with a statistically significant decrease in HR between baseline and 40 weeks (from 80 to 67 beats/min, p = 0.001). CBZ was associated with a statistically significant decrease in HR (from 70 to 66 beats/min, p = 0.009), as well as a statistically significant increase in PQ (from 170 to 180 ms, p = 0.001). There were no significant changes in QRS or QTc.	Class III
Matsuo 1993 [e19]	Randomized controlled trial	People aged 18 to 65 with refractory focal epilepsy from 15 clinical centers in the US. People with newly diagnosed epilepsy or recent VPA intake were excluded. Participants were randomized to lamotrigine versus placebo for a 24-week treatment period.	Baseline 12-lead ECG and then repeated at an unclear frequency during follow-up - PR - HR - QT	143 LTG users (71 = 300 mg and 72 = 500 mg; all in polytherapy)	73 non-LTG users (placebo)	"Slight (0.005 seconds) but statistically significant" increases in mean PR interval among participants treated with LTG, at certain times during their follow-up. No statistically significant changes in HR and QT (results not shown).	Class III
Schachter 1995 [e20]	Randomized controlled trial	People aged 18-65 years with refractory focal epilepsy from 34 centers in the US, with at least one seizure in the 12 weeks preceding randomization. People with newly diagnosed epilepsy, a diagnosis of primary generalized seizures, seizures secondary to another disease, or recent status epilepticus were excluded. Participants were randomized to 24 weeks treatment followed by 3 weeks taper of LTG versus placebo.	12-lead ECG done at baseline then at the end of the maintenance treatment (week 24) - HR - PR - QT - QRS	334 LTG users (all in polytherapy)	112 non-LTG users (placebo)	"ECGs were generally unremarkable and similar in the LTG and placebo groups." Otherwise, no data presented.	Class III

Svalheim 2012 [e22]	Prospective cohort study	People with epilepsy from Swiss specialist clinics aged 12 to 70. ECGs were "performed regularly" in ten people before and during LTG use, ten during LTG use only, and 11 people who did not use LTG. Participants were followed from April 1991 to November 1992, with a mean of 1.85 clinic follow-ups each.	1-3 ECGs (presumably 12-lead) were carried out per subject - HR - PQ - QRS - QTc	20 LTG users (all in polytherapy)	11 non-LTG users	The PQ duration was longer for those using LTG and who had an ECG only during LTG exposure (n = 10), compared to those not using LTG (130.230 ms vs 126.166 ms, $p < 0.05$). This difference in PQ was not statistically significant when comparing those exposed to LTG who had ECGs before and during LTG use (n = 10) to those without LTG (results not reported further), and the authors concluded that any PQ differences seen with the first group were likely not related to LTG exposure but rather differences in cardiac structures between individuals. One person developed SVES and first grade AV-block under LTG but these abnormalities resolved even after using higher doses of LTG. There were no statistically significant changes in HR, QRS, or QTc with LTG therapy.	Class III
Ishizue 2016 [e23]	Prospective cohort study	People with newly diagnosed epilepsy in an outpatient clinic in Norway, not previously treated with an ASMs and without a history of cardiac disease.	12-lead ECG and a signal-averaged ECG done at baseline and 3-9 months later - PR - QRS - QTc - VLP - HFLA	15 LTG users	10 CBZ users	Neither standard ECG nor signal-averaged ECG showed statistically significant changes in the studied parameters between baseline and 3–9-month follow-up after initiation of either LTG or CBZ. No one developed VLPs with ASM initiation.	Class III
Stock 2018 [e24]	Retrospective cross-sectional study	Consecutive people who were diagnosed with epilepsy and treated in the Kitasato University Hospital in Japan at any point between 2005 and 2013.	12-lead ECG carried out at an unspecified time-point for each participant - HR - PR - QRS - QTc - Brugada-type ST elevation - J-wave-like ECG abnormality	5 LTG users (some in polytherapy)	115 non-LTG users (CBZ, PHT, TPM, GBP, PB, VPA, ZNS, BZD)	HR, PR, QRS, and QTc were "within the normal range" for all study participants. None of the LTG users (0/5) had Brugada-type ST-elevation. 47% (7/15) of those with Brugada-type ST elevation used polytherapy sodium channel blocking ASM (excluding LTG), compared with 23% (24/105) among those without ST elevation ($p = 0.048$). The proportion of LTG users amongst those with J-wave-like ECG abnormality was not statistically different from those without such an abnormality (6% versus 4%, $p = 0.563$. of people with a were LTG users (2/35). The proportion of polytherapy sodium channel blocking ASMs amongst those with J-wave-like ECG abnormality was significantly smaller than those without such an abnormality (14% versus 32%, $p = 0.049$).	Class IV

Rejdak 2011 [e25]	Retrospective cross-sectional study	People receiving care in the US Veterans Administration health system from 2006 to 2009 with PTSD diagnosis and QT prolongation and matched controls (age, sex, visit date and setting, Selim physical comorbidity score) with PTSD without QT prolongation.	How people with QT prolongation were identified is not described - QT	6 LTG users (some in polytherapy)	874 non-LTG users	176 people with QT prolongation and 704 controls were included. There was no statistically significant difference in the number of LTG users among the cases with QT prolongation versus controls (0.6% vs 0.7%, p = 1.00).	Class IV
Moore 2013 [e26]	Prospective cross-sectional study	Consecutive adults aged younger than 46 years with confirmed epilepsy, without a history of cardiac disease, medications influencing the cardiovascular system, or recent seizure (< 3 days before ECG) in Poland. The control group consisted of healthy volunteers.	ECG (presumably 12-lead) and a signal-averaged ECG done at baseline and 3-9 months later - VLP	11 LTG users (some in polytherapy)	34 people with epilepsy but without LTG, and 19 healthy volunteers without epilepsy	Among those with VLP, there was no statistically significant difference in the proportion of LTG users versus those without VLP (27% versus 22%, $p \geq 0.05$).	Class IV
	Retrospective case series	Case records with LTG poisoning admitted to a toxicology center in the US from 2003-2012. The amount of LTG ingested varied from 0.5 to 13.5 grams.	ECG (presumably 12-lead), unspecified number done and timing. - QRS - QTc	57 people with possible LTG toxicity, but only 9 with LTG-only ingestions.	NA	Of the 9 with LTG-only ingestions, 2 people experienced QRS prolongation (114-116 ms), and 4 had QTc prolongation (463-586 ms).	Class IV

ECG = electrocardiogram, LTG = lamotrigine, BMI = body mass index, UK = United Kingdom, HR = heart rate, CBZ = carbamazepine, US = United States, VPA = valproic acid, PHT = phenytoin, TPM = topiramate, GBP = gabapentin, PB = phenobarbital, ZNS = zonisamide, BZD = benzodiazepine, ASM = anti-seizure medication, NA = not applicable, SBP = systolic blood pressure, DBP = diastolic blood pressure, HRV = heart rate variability, SA-QRS = signal-averaged QRS duration, RMS40 = root mean square of the terminal 40 ms, LAS40 = low amplitude signal duration, VLP = ventricular late potential, SAECG = signal-averaged ECG, HFLA = high-frequency low-amplitude, PTSD = post traumatic stress disorder, SVES = supraventricular extrasystole, QTc = corrected QT interval

[a] as calculated using the AAN risk of bias tool[7]

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