A new update to the label for lamotrigine by the U.S. Food and Drug Administration has caused concerns in the epilepsy community

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On 9 October 2020, the FDA issued a warning to the lamotrigine (LMT) datasheet. The warning included the following statement: “avoid LAMICTAL (i.e., lamotrigine) in patients with certain underlying cardiac disorders or arrhythmias”. According to the update, in vitro LMT testing suggests Class I.B. antiarrhythmic activity at therapeutically relevant concentrations. This effect could result in a widening of the QRS complex, induce new cardiac arrhythmias and sudden death. It stated that LMT should be avoided in individuals with cardiac conduction abnormalities, ventricular arrhythmias, or structural heart disease.

The updated FDA warning, however, is based upon in vitro data. Studies have shown that LMT does not cause Q.T. prolongation and only mild P.R. interval increases in healthy individuals with unclear clinical relevance.[1] Epilepsy and antiseizure medication (ASM) use appear to be associated with sudden death.[2] One sizeable case-control study suggested that sodium channel blockers were associated with an increased risk of sudden cardiac death (SCD).[3] This association was mainly driven by carbamazepine and gabapentin. Of note, according to the case definition, SCD cases likely included instances of SUDEP. None in this SCD cohort were, however, taking LMT. An analysis of over 40 randomised controlled trials of LMT, including twelve potential SUDEP cases, did not identify a significant association between LMT exposure and SUDEP.[4]

Many reports of electrocardiogram changes in epilepsy are available, but the associations with ASM use are often disputed. In the case of LMT, some recent concerns that it may have pro-arrhythmogenic potential has generated considerable discussion within the epilepsy community. This pro-arrhythmogenic effect may not be limited to LMT, as there are indications that it may be a class effect of sodium channel blockers. Particularly carbamazepine, lacosamide and phenytoin have been associated with bradyarrhythmias and atrioventricular conduction delays, mostly in older individuals and those with pre-existing cardiac conduction disorders.[2] LMT and carbamazepine are among the medications preferentially avoided in Brugada syndrome. Lacosamide has occasionally been implicated in atrial fibrillation and atrial flutter, again predominantly in the elderly.[2] Among individuals with sodium channel mutations, sodium channel blockers should be avoided. For example, in people with Dravet syndrome (associated with SCN1A mutations), sodium channel blockers are often ineffective. The use of sodium channel blockers may also lead to worse cognitive outcomes, particularly in those with still-developing brains.[5]

Following the FDA’s update, an ad hoc Joint Taskforce of the International League against Epilepsy and the American Epilepsy Society extensively reviewed the available evidence to advise healthcare professionals on minimising cardiac safety risks associated with LMT use (Infobox 1). Given the importance of LMT in the management of epilepsy, its use in those with a low-to-no risk of structural heart disease should not be discouraged. Clinical data and experience with LMT accumulated over more than three decades have left clinicians confident in this medication’s efficacy and safety. We are heartened by a new FDA communication released on 31 March 2021 after the Joint Task

Force's review.[1] This new advisory removes the recommendation to "avoid" LMT, emphasises the risk of stopping it abruptly and the need to weigh potential LMT risks against its well-established benefits (e.g., women of child-bearing age and older adults). Further studies are needed to determine whether the preclinical findings that resulted in this label update translate to an increased risk of cardiological side-effects in those with structural heart disease.

Infobox

Advisory by the Ad Hoc International League against Epilepsy and the American Epilepsy Society Task Force in response to the FDA Safety Warning on the Cardiac Effects of Lamotrigine Co-chairs: Jacqueline French, Emilio Perucca; ILAE members: Josemir Sander, Lennart Bergfeldt, Michel Baulac; Advisory: David Auerbach, Mark Keezer, Roland Thijs, Orrin Devinsky; AES contributors: David Vossler, Timothy Welty
The ILAE/AES Taskforce has published its recommendations regarding which measures to take when prescribing lamotrigine (LMT) (https://www.ilae.org/files/ilaeGuideline/ILAE_AES_Lamotrigine-advisory-FINAL-2021-0126.pdf). The Taskforce emphasised that the likelihood of asymptomatic cardiac disease is low among individuals under age 60 years without cardiovascular risk factors or symptoms. Therefore, no additional precautions were recommended with the initiation of LMT. The Taskforce recommended that a cardiologist opinion be considered before starting LMT in people with comorbid cardiac conditions. In people over the age of 60, an ECG should be performed upon LMT initiation. Members of the Taskforce argued that it is unnecessary to delay LMT initiation but that the ECG is requested as LMT is initiated. A driver for this assertion is that any LMT effect on cardiac conduction is dose-dependent, and the generally slow initiation strategy used with LMT is a mitigating factor

REFERENCES

1. French JA, Perucca E, Sander JW, Bergfeldt L, Baulac M, Auerbach DS, Keezer M, Thijs RD, Devinsky O, Vossler DG, Welty TE. FDA safety warning on the cardiac effects of lamotrigine: An advisory from the Ad Hoc ILAE/AES Task Force. *Epilepsia Open* 2021; 6:45-48.

2. Surges R, Shmuely S, Dietze C, Ryvlin P, Thijs RD. Identify patients with epilepsy at high risk of cardiac death: recognise signs, risk factors and initial management of high risk of cardiac death. *Epileptic Disord* 2021; 23:17-39.

3. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MC, Tan HL. (2015) Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications. *Heart* 2015; 101:17-22.

4. Tomson T, Hirsch LJ, Friedman D, et al. Sudden unexpected death in epilepsy in lamotrigine randomised-controlled trials. *Epilepsia* 2013; 54:135-40.

5. de Lange IM, Gunning B, Sonsma AC, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN 1A-related seizure phenotypes. *Epilepsia* 2018; 59: 1154-65.

AUTHORS CONTRIBUTIONS

NH: drafting, and revision of the manuscript.

RDT: Original concept and critical revision of manuscript.

JWB: drafting and revision of manuscript.

MRK: Original concept and critical revision of manuscript.

JWS: Original concept and critical revision of manuscript.

DECLARATION OF INTERESTS

NH and JWB have no conflicts of interest to disclose.

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