Lacosamide-Related Arrhythmias: A Systematic Analysis and Review of the Literature

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Abstract

Lacosamide (LCM) is a new antiepileptic drug used as an adjunctive treatment for partial seizures with and without secondary generalization. One of the modes of action is the enhancement of slow inactivation of voltage-gated sodium channels. Experimental studies and clinical trials suggest that LCM acts upon both neurons and the heart and may increase the risk of cardiac arrhythmias. A systematic review was conducted to investigate characteristics of arrhythmias related to the use of LCM for the treatment of seizures. The search terms "lacosamide", "arrhythmias", "AV block", "atrial fibrillation/flutter", "cardiac conduction defects", "ventricular tachycardia", "ventricular fibrillation" were used. Case reports and retrospective studies were gathered by searching Medline/PubMed, Google Scholar, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane CENTRAL (Cochrane Central Register of Controlled Trials), and Web of Science databases. Seventeen articles were selected for review. Ventricular tachycardia was the most reported LCM related arrhythmia (29.4%), followed by new-onset atrial fibrillation (17.6%), complete heart block (17.6%), Mobitz type 1 Atrio-ventricular block (11.8%), sinus pauses (11.8%), pulseless electrical activity (5.9%) and widening QRS complex (5.9%). Further research and clinical trials are needed to explore the etiopathogenesis and causative relationship between the use of LCM and arrhythmias.

Categories: Cardiology, Internal Medicine, Neurology
Keywords: echocardiography, electrocardiography, sinus pauses, av block, heart block, atrial fibrillation, ventricular tachycardia, arrhythmias, : lacosamide

Introduction And Background

Lacosamide (LCM) is a new antiepileptic drug approved by the United States Food and Drug Administration (FDA) in October 2008 as an adjunctive treatment for partial seizures with and without secondary generalization [1]. It is composed of (R)-2-acetamido-N-benzyl-3-methoxyproionamide, causing slow inactivation of voltage-gated sodium channels in neurons [2]. Based on the above mechanism of action several reports of dose-dependent cardiac arrhythmias have been reported in the literature [3-6]. LCM inhibits cardiac sodium channel SCN5A that could be an underlying possible mechanism for cardiac arrhythmias, including ventricular tachycardia, sinus pauses, atrial fibrillation, and sudden death [7, 8]. Limited data is available on the relationship between the use of antiepileptic drugs/LCM and cardiac arrhythmias. Multiple isolated cases of arrhythmias have been associated with LCM use [5, 6, 9]. Here we present a systematic review of such cases of LCM-related arrhythmias to evaluate the need for assessment of risk factors and potentially warn physicians of the dose-related cardiac effects of LCM.

Review

Method

A comprehensive literature search was conducted by two authors, using Medline/Pubmed, Google Scholar, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane CENTRAL (Cochrane Central Register of Controlled Trials), and Web of Science databases, for relevant studies since 2008. The terms "lacosamide, arrhythmias, AV block, atrial fibrillation/flutter, cardiac conduction defects, ventricular tachycardia, ventricular fibrillation, cardiac conduction defects" were used to identify cases of myocardial arrhythmias associated with LCM use. A total of 108 articles were found related to LCM and arrhythmias. Only articles that reported LCM use and the presence of cardiac arrhythmias were included. Seventeen studies that included the case reports were then deemed eligible for inclusion in this review as shown in Table 1. Studies were excluded if: 1) Articles were not case reports, case series or observational studies, or 2) Articles were reviews or editorials. The reference list of each report was reviewed for potential additional cases. All cases were reviewed in detail. The present analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A PRISMA flow diagram detailing the process of identification, selection, and inclusion of studies is shown in Figure 1.
| Year of publication, author references | Age/sex | CV risk factors | Indication for LCM | EKG | TIE | Arrhythmia | Final diagnosis of arrhythmia | Me of arrhythmia | Cardiac arrest | Death |
|--------------------------------------|--------|----------------|-------------------|-----|-----|------------|-------------------------------|----------------|--------------|------|
| 2010, Digeorgia [9]                  | 32/M   | None           | Seizures          | Afib, HR~100-130 bpm, turning into asb | NA  | New-onset atrial fibrillation | LCM dced          | No             | No      |      |
| 2011, Nizam[3]                      | 45/M   | None           | Seizures          | Mobitz 1 & RBBB | WNL | Mobitz type 1 & bradycardia | Mobitz type I    | LOM dced       | No             |      |
| 2011, Majmundar                     | 6/M    | HTN, Hypokalemia | Seizures          | Complete AV node block; 15 mins after LCM bolus, 20 mins later | NA  | Complete heart block and pauses o3-up to 10 secs | AVB type III     | LOM dued and AF reversion | Yes             | Yes     |
| 2011, Wittstock                     | 45/F   | HTN, CAD, 5/M AVB, left unroofed TVA, hypokalemia | Seizures          | Initially 5/M, after LCM complete AV block, block on, atrial flutter | NA  | Complete heart block with asystole for 30 secs | AVB type III     | Lomotin, LOM dued & metoprolol | No             | No      |
| 2011, Krause                        | 3/M    | Hypokalemia    | Seizures          | Initial NSR~ 90 bpm with PVCs, after LOM As with RVR~ 132 bpm | NA  | No WMA, EF~95%, bid atr, tr, bid | VT                  | LOM dued        | No             | No      |
| 2012, Ghosh                          | 32/M   | None           | Seizures          | P^2 AVB with LRF & severe QRS widening; NSR after LOM was dued | NA  | Sustained VT on outpatient stress test | VT                  | LOM dued        | No             | No      |
| 2012, Chinnasara [12]              | 45/M   | None           | Seizures          | Baseline before LCM- SB~54 bpm | NA  | JER & pauses (33 times, longest~ 24 sec), also ST~118 bpm & SB~36 bpm | Sinus pause         | Holter monitor and LCM dued | No             | No      |
| 2015, Lourda                        | 3/M    | Congenital hypoplastic left heart syndrome, well-controlled MAT | Seizures          | Baseline EKG-NSR After LCM | NA  | WCT~240-260 bpm, in addition to NCT with 1:1 and 2:1 | VT                  | Amiodarone infusion, fusciculate treatment | No             | No      |
| 2015, Chun-Taew                    | 16/F   | None           | Seizures          | Admission-ST@134 bpm, then ST~108 BPM terminal RAD | WNL | Cardiac arrest, secondary to pulseless VT with bradycardia & asystole | VT                  | AOLS protocol with shocks, epinephrine, amitrine, bicarbonate, on MB drip | No             | No      |
| 2017, Basu                          | 7/M    | HTN, RHd-vlp, AVR and AVN, Type 2 ischemic pain | Seizures          | Baseline EKG-NSR After LCM | AV  | Wide complex monomorphic VT 2 hours after second dose of LOM | VT                  | Amiodarone infusion, cardiovascular LOM dued | No             | No      |
| 2018, Lochtuer                      | 8/M    | HTN, angina    | Seizures          | NSR and LBBB at baseline, After LCM - SB which progressed to extreme bradycardia 36 bpm and complete AVB | NA  | Complete heart block with extreme bradycardia to 30 bpm preceded by SB | AVB Type III | ICU admission, atropine 13. IV isoprenaline, LOM and bicaprolid dued | No             | No      |
| 2019, Hagi                          | 46/F   | None           | Seizures          | Overdose toxicity | NA  | Widening of QRS complex | Wide QRS complexes | Sodium bicarb without relief, with supportive care | No             | No      |
| 2020, Hou                          | 73/M   | CAD, CHF, HTN, Asb, HLD, ICH | Seizures          | No formal EKG | NA  | Bradiycardia with unstable hemodynamic that progressed to PEA | PEA                  | Amiproben 1-round CPR with dopamine 10, TCP and isoprorenal | Yes             | No      |
| 2020, Wigmundur                    | 95/M   | TA, HTN        | Seizures          | Baseline- AV~ (PR 270 ms). After LCM- AV~ (PR 375 ms) | AV~| Lengthening PR interval, new-fosl LBBB, widened QRS and episodes of SB to 36 bpm and sinus pause~ 3 sec noted | Sinus pause         | Switching LOM to biphasic, external pacing, and 24 hours observation in CCDU | No             | No      |
| 2020, Stern                        | 12/M   | Baseline SB with early repolarization, occasional | Seizures          | F^2 AVB, J point elevation, and early repolarization, EKG | NA  | AVB with progression to Mobitz type | LOM dued          | No             | No      |
intermittent palpitations at baseline returning to baseline, sinus bradycardia with PR WNL. Mobitz I after IV LCM.

2020, Eleftheriou

38/F HOCM, HTN, prolonged QTc

Seizures

An episode of VT f.b. 27 episodes of life-threatening VF after a 3rd IV dose of 400 mg LCM

Cardioversion @200J, NSR after LCM discontinuation

Yes

2020, Corbellini

88/M Obesity, HTN, HLD, mild MR and AR, G1DD

Seizures

NSR, 66 bpm with 1st AVB at baseline, after IV LCM - Arrhythmia with RVR to 140 bpm

New-onset Afib with RVR @140 bpm

Amiodarone infusion, LCM dced

No

TABLE 1: Summary of study characteristics of all the searched articles.

ACLS-advanced cardiac life support; Afib-atrial fibrillation; Aflutter-atrial flutter; AR-aortic regurgitation; AV-atrioventricular; AVB-atrioventricular block; AVR-aortic valve repair; bpm-beats per minute; CAD-coronary artery disease; CCU-coronary care unit; CHF-congestive heart failure; CVA-cerebrovascular accident; CV-cardiovascular; dced-discontinued; EF-ejection fraction; EKG-electrocardiography; f.b.-followed by; F-female; G1DD-grade1 diastolic dysfunction; HLD-hyperlipidemia; HOCM-hypertrophic obstructive cardiomyopathy; HR-heart rate; HTN-hypertension; ICH-intracranial hemorrhage; IVF-intravenous fluids; JER-junctional escape rhythm; LCM-lacosamide; LFB-left fascicular block; LVH-left ventricular hypertrophy; MAT-multifocal atrial tachycardia; M-male; MR-mitral regurgitation; MVR-mitral valve replacement; NA-not available; NCT-narrow complex tachycardia; NDE-norepinephrine; NSR-normal sinus rhythm; PEA-pulseless electrical activity; PHT-pulmonary hypertension; PVC-premature ventricular complexes; RAD-right axis deviation; RBBB-right bundle branch block; RHD-rheumatic heart disease; RVR-rapid ventricular rate; SB-sinus bradycardia; ST-sinus tachycardia; TCP-transcutaneous pacing; TIA-transient ischemic attack; TR-Tricuspid regurgitation; TTE-transthoracic echocardiography; VF-ventricular fibrillation; VT-ventricular tachycardia; WCT-wide complex tachycardia; WMA-wall motion abnormalities; WNL-within normal limits

FIGURE 1: Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

LCM-lacosamide
Data was collected by four authors that included demographic data, cardiovascular (CV) risk factors, indication for LCM use, electrocardiography (EKG) findings, transthoracic echocardiography (TTE) findings, type of arrhythmias, cardiac arrest, and management when available as shown in Table 1.

**Result**

Table 2 summarizes the result of our systematic review of LCM-related arrhythmias. A total of 17 cases were identified with a median age of 48± -27.2, of whom 59% were females and 41% were males. Seizure/epilepsy was the indication for LCM use in all cases (100%) however 5.88% of the cases that were reported had LCM toxicity due to suicidal overdose. The prevalence of cardiovascular/arrhythmogenic risk factors was hypertension (HTN) in 52.9%, hyperlipidemia (HLD) in 17.6%, hypokalemia in 17.6%, and coronary artery disease (CAD) in 11.8%. Obesity, atrial fibrillation, transient ischemic attack (TIA), hypertrophic cardiomyopathy, prolonged QTc, history of mitral and aortic valve replacement, and multifocal atrial tachycardia were reported in 5.9% in each. Beta-blocker usage was reported in 23.5% and use of flecainide in 5.9%. Ventricular tachycardia was the most reported LCM related arrhythmia (29.4%), followed by new-onset atrial fibrillation (17.6%), complete heart block (17.6%), Mobitz type 1 atrioventricular block (11.8%), sinus pauses (11.8%), pulseless electrical activity (5.9%) and widening QRS complex (5.9%). Transthoracic echocardiography (TTE) was done in six patients, all of whom had normal ejection fractions. Temporary pacemaker placement was reported in 17.6% and permanent pacemaker placement in 5.9%. Cardiac arrest was reported in 35.29% and death was reported in 5.9% of the cases.

| Cases identified (n) | 17 |
|----------------------|----|
| Age; n ± SD          | Median 48 ± 27.2 |
| Sex; n (%)           |    |
| Males                | 7/17 (41%) |
| Females              | 10/17 (59%) |
| Indication of LCM; n |    |
| Overdose toxicity    | 2   |
| Seizures/epilepsy    | 15  |
| Cardiovascular risk factors; n (%) | |
| HTN                  | 9/17, (2.9%) |
| HLD                  | 3/17, (17.6%) |
| Hypokalemia          | 3/17, (17.6%) |
| CAD                  | 2/17, (11.8%) |
| DM                   | 1/17, (5.9%) |
| Obesity              | 1/17, (5.9%) |
| Afib                 | 1/17, (5.9%) |
| TIA                  | 1/17, (5.9%) |
| History of aortic and mitral valve replacement | 1/17, (5.9%) |
| Hypertrophic cardiomyopathy | 1/17, (5.9%) |
| Prolonged QTc        | 1/17, (5.9%) |
| Multifocal atrial tachycardia | 1/17, (5.9%) |
| Patients on relevant medications; n, (%) | |
| Beta-Blockers        | 4/17, (23.5%) |
| Flecainide           | 1/17, (5.9%) |
| Reported arrhythmia; n, (%) | |
| Ventricular tachycardia | 5/17, (29.4%) |
| New onset AFib       | 3/17, (17.6%) |
TABLE 2: Summary of the result of the systematic review of LCM related arrhythmias.

| Arrhythmia                        | n, (%)          |
|----------------------------------|-----------------|
| Complete heart block             | 3/17, (17.6%)   |
| Mobitz type I                    | 2/17, (11.8%)   |
| Sinus pause                      | 2/17, (11.8%)   |
| Precordial pause                  | 2/17, (11.8%)   |
| Pulseless electrical activity     | 1/17, (5.9%)    |
| Widening of QRS complex          | 1/17, (5.9%)    |
| TTE reported; n, (%)             |                 |
| TTE mentioned in 6 articles- all had normal EF | 6/6, (100%) |
| No TTE data available           | 12/17, (70.5%)  |
| Pacemaker; n, (%)                |                 |
| Temporary pacing                 | 3/17, (17.6%)   |
| Permanent pacemaker              | 1/17, (5.9%)    |
| Cardiac arrest; n, (%)           |                 |
| 6/17, (35.29%)                   |
| Death; n, (%)                    |                 |
| 1/17, (5.9%)                     |

Abbreviations: HTN-hypertension; HLD-hyperlipidemia; CAD-coronary artery disease; DM-diabetes mellitus; Afib-atrial fibrillation; TIA-transient ischemic attack; TTE-transthoracic echocardiography; EF-ejection fraction

Discussion

LCM is a novel antiepileptic agent used for add-on therapy in patients with partial and secondarily generalized seizures [2]. Intravenous LCM has been used for the treatment of status epilepticus [2]. Its main mechanism of action is the enhancement of the slow inactivation of voltage-gated sodium channels thus reducing the ability of neurons to sustain prolonged firing bursts [3]. Experimental studies and clinical trials suggest that LCM acts upon both neurons and the heart and may increase the risk of cardiac arrhythmias [4]. The action potentials of most of the cardiac tissues, including the His-Purkinje system, are generated through voltage-gated sodium channels however that of AV node is through voltage-gated calcium channels [4, 7]. As seen with other anticonvulsant agents, dose-dependent inhibition of sodium channels produces infra-Hisian delays and conduction defects that could be one of the postulated mechanisms of cardiac arrhythmias with the use of LCM [2, 4]. It follows linear pharmacokinetics with a maximum concentration reached within 1-4 hours and a half-life of 13 hours [2]. Clinical trials [4, 23] have shown the association of LCM, dose-ranging from 200-600 mg/day, with cardiac conduction defects including atrial fibrillation and flutter. Few case reports suggesting first-degree AV block and third-degree AV blocks with LCM use have been retrieved from the literature [10] [24]. Traditional sodium channel blocking agents such as carbamazepine and phenytoin cause the fast inactivation of voltage-dependent sodium channels and may have potential synergistic action with LCM [12].

However, clinical trials [25] did not show any additional adverse effects with concomitant use of other sodium channel blockers. Several studies, including our systematic review, have documented cardiac arrhythmias with the use of LCM hence recommendations before the initiation may include baseline EKG, evaluation of cardiac risk factors, electrolytes levels, and adjusting the dose of LCM based on renal and hepatic functions.

Conclusions

Arrhythmias associated with the use of LCM in seizures have been documented in several case reports and studies. LCM inhibits the cardiac sodium channel by enhancing slow inactivation in a concentration-dependent manner. The timing of several cardiac arrhythmias after initiation of LCM and their resolution after discontinuation suggests a possible pro-arrhythmic role of LCM as described in Table 1. Identification of any pre-existing cardiac/arrhythmogenic risk factors may prove to be beneficial before commencing treatment with LCM. One must also consider reviewing the home medications and their dosage to prevent any drug-drug interactions with the use of LCM. In our systematic review study, ventricular tachycardia was the most reported of LCM-related arrhythmia, and wide QRS complex was the least common one. Discontinuation of LCM was one of the common factors that helped to restore the sinus rhythm in most of the studied case reports. Comparative studies may be warranted for defining the role of a higher dosage of LCM-600 mg/day as compared to ~400mg/day in causing arrhythmias. Further research and clinical trials are needed to explore the etiopathogenesis and causative relationship between the use of LCM and arrhythmias.
In addition, further investigations are needed to study the cardiac effects of LCM and its interactions with other antiepileptic drugs involving the inhibition of cardiac sodium channels. Electrocardiographic (ECG) testing before and during LCM therapy along with close monitoring may help to avoid cardiac arrhythmias.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following:  
**Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.  
**Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.  
**Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**References**

1. Degiorgio CM: Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. Epilepsy Behav. 2010, 18:322-4. 10.1016/j.yebeh.2010.04.043
2. Kellinghaus C: Lacosamide as treatment for partial epilepsy: mechanisms of action, pharmacology, effects, and safety. Ther Clin Risk Manag. 2009, 5:757-66. 10.2147/tcrm.s5189
3. Ben-Menachem E, Biton V, Jatuitsis D, Abou-Khail B, Doty P, Rudd GD: Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007, 48:1308-17. 10.1111/j.1528-1167.2007.01188.x
4. Shahbani A, Fares S, Selam JL, Arslanian A, Simpson J, Sen D, Borgardt S: Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. J Pain. 2009, 10:818-28. 10.1016/j.jpain.2009.01.322
5. Nizam A, Mulyavaru K, Thomas D, Briskin K, Wu B, Saluja D, Wong S: Lacosamide-induced second-degree atrioventricular block in a patient with partial epilepsy. Epilepsia. 2011, 52:e153-5. 10.1111/j.1528-1167.2011.03212.x
6. Krause LU, Broduowski KO, Kellinghaus C: Atrioventricular block following lacosamide intoxication. Epilepsy Behav. 2011, 20:725-7. 10.1016/j.yebeh.2011.02.006
7. DeGiorgio AC, Desso TE, Lee L, DeGiorgio CM: Ventricular tachycardia associated with lacosamide co-medication in drug-resistant epilepsy. Epilepsy Behav Case Rep. 2015, 1:22-5. 10.1016/j.ebr.2012.10.006
8. 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, 164:260-75. 10.1111/j.1476-5381.2011.01415.x
9. Tomson T, Kennebäck G: Arrhythmia, heart rate variability, and antiepileptic drugs. Epilepsia. 1997, 38:548-51. 10.1111/j.1528-1157.1997.00128.x
10. Wittstock M, Bernecke R, Roenicke J: Transient third-degree atrioventricular block following rapid lacosamide titration in a patient with nonconvulsive status epilepticus. Epileptologia. 2011, 19:165-9.
11. Kaufman KR, Velez AE, Wong S, Mani R: Low-dose lacosamide-induced atrial fibrillation: ase analysis with literature review. Epilepsy Behav Case Rep. 2013, 1:22-5. 10.1016/j.ebcr.2012.10.006
12. Chinnasami S, Rathore C, Duncan JS: Sinus node dysfunction: an adverse effect of lacosamide. Epilepsia. 2015, 54:e90-3. 10.1111/epi.12108
13. Loomba RS, Singh AK, Kovach J, Gulausky TM: Lacosamide-induced atrial tachycardia in a child with hypoplastic left-heart syndrome: the importance of assessing additional proarrhythmic risks. Cardiol Young. 2015, 25:806-9. 10.1017/S1047711814001188
14. Chu-Tuan JL, Cao D, Iwanciuk IL, Hoyte CO: Cardiac sodium channel blockade after an intentional ingestion of lacosamide, cyclobenzaprine, and levetiracetam: case report. Clin Toxicol (Phila). 2015, 53:565-6. 10.3109/15563650.2015.1040157
15. Bereti TJ, Lillyblad MP, Almingst AK: Lacosamide-induced recurrent ventricular tachycardia in the acute care setting. J Pharm Pract. 2018, 31:222-6. 10.1177/0897190017700557
16. Lachuer C, Corni J, Bézie Y, Ferchichi S, Durand-Gasselin B: Complete atrioventricular block in an elderly patient treated with low-dose lacosamide. Cardiovasc Toxicol. 2018, 18:579-82. 10.1007/s12108-018-9467-x
17. Ng PC, Schimmel J, Wang GS: Lacosamide overdose: a case of QRS prolongation and seizure. J Emerg Med. 2019, 56:552-6. 10.1016/j.jemermed.2019.01.018
18. Hsu L, Dekitani K, Betancourt J: Lacosamide and metoprolol: an uncommon yet potentially deadly combination. A43 Crit Care Case Rep Toxicol Poison. 2020, May:A1695. 10.1114/j.crcm-conference.2020.201.1_MeetingAbstracts.A1695
19. Majmundar MM, Kanara T, Shah P, Zala H, Chaudhari S: Right bundle branch block: a reversible pernicious effect of lacosamide. Cureus. 2020, 12:e10234. 10.7759/cureus.10234
20. Stamm B, Sheikh A, Schaeue S, Tempelr JW: Lacosamide-associated second-degree atrioventricular block in a healthy, young athlete. Epilepsy Behav Rep. 2020, 14:100572. 10.1016/j.ebr.2020.100572
21. Ellerbroken G, Bureta R, Gallo M, Giampreti A, Faraoni L, Contessa MG, Facio G: Lacosamide-induced recurrent ventricular fibrillation: a case report. Int J Clin Pharmacol Ther. 2020, 58:756-9. 10.14114/CP2005813
22. Corbellini ÂB, Torre PP, Hristova VN, et al.: Cardioembolic acute cerebral micro-infarcts in the context of atrial fibrillation after low-dose intravenous infusion of lacosamide. Epileptic Disord. 2020, 22:83-9. 10.1684/epd.2020.1156
23. Wymyr JP, Simpson J, Sen D, Borgardt S: Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. Clin J Pain. 2009, 25:576-85. 10.1097/AJP.0b013e318199d2b6

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24. Rudd GD, Haverkamp W, Mason JW, et al.: Lacosamide cardiac safety: clinical trials in patients with partial-onset seizures. Acta Neurol Scand. 2015, 132:355-63. 10.1111/ane.12414

25. Sake JK, Hebert D, Isojärvi I, et al.: A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs. 2010, 24:1055-68. 10.2165/11587550-000000000-00000