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Brief Communication

Long-term efficacy and safety of lacosamide and levetiracetam monotherapy in elderly patients with focal epilepsy: A retrospective study

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ABSTRACT

Objectives: Epilepsy management in elderly patients is often complex because of several concomitant comorbidities that may limit the use of some antiepileptic drugs (AEDs). Levetiracetam (LEV) is a second-generation AED widely used in elderly patients with epilepsy while lacosamide (LCM), which has been recently approved in European Union (EU) as monotherapy for the treatment of focal onset seizures, is affected by a scarcity of data in such frail population. This study is aimed at assessing the efficacy and the tolerability of LCM as monotherapy in elderly patients affected by focal onset epilepsy compared with those receiving LEV.
Methods: A retrospective chart review of patients aged ≥65 years suffering from focal onset seizures, with or without secondary generalization on LCM monotherapy or LEV monotherapy, was performed. Data regarding demographic characteristics, seizure type and etiology, LCM and LEV daily dose, number of lifetime AEDs, seizure frequency at baseline and at 12 months of follow-up, and seizure freedom rates were reported.
Results: In this observational retrospective study, 22 patients on LCM (10 males, 12 females, mean age: 76.23 ± 7.5) and 24 patients on LEV (10 males, 14 females, mean age: 73.58 ± 6.39) were enrolled. Mean LCM daily dose was 204.51 ± 88.51 mg and mean LEV daily dose was 1281.25 ± 378.15 mg. All patients had comorbidities on chronic treatment. At 12 months of follow-up, mean monthly seizure frequency reduced from 4.23 ± 8.53 to 0.33 ± 0.9 ($p < .001$) in LCM group and from 2.29 ± 6.11 to 0.2 ± 0.81 ($p < .001$) in LEV group. Furthermore, 16/22 (72.7%) LCM patients were seizure-free at 12 months of follow-up while seizure freedom was achieved by 17/24 (70.8%) patients in LEV group.
Discussion and conclusion: Epilepsy management in elderly patients is often challenging. In this retrospective real-life study, the efficacy and the tolerability of LCM as monotherapy was favorable even at low doses in older patients and comparable with LEV with a high rate of long-term seizure freedom. Considering the frequent comorbidities and the risk of drug–drug interactions, LCM monotherapy may be a valuable option in elderly patients with focal onset epilepsy because of its favorable pharmacokinetic profile.

1. Introduction

Although epilepsy represents the third most common neurological condition after cerebrovascular disorders and dementias in elderly patients, usually defined as aged ≥65 years, and the incidence of epilepsy is highest among older-aged subjects in comparison with other age groups, such patients are frequently excluded from clinical trials [1,2]. Epilepsy management in elderlies is often challenging since pharmacokinetics and pharmacodynamics of antiepileptic drugs (AEDs) are affected by aging and because of frequently concomitant chronic treatments due to comorbidities [3].

Levetiracetam (LEV) is a broad spectrum AED that is effective against focal and generalized seizures [4]. Aside from the possible psychiatric and behavioral side effects experienced by some patients, LEV has a high therapeutic index and wide margin of safety as compared with other AEDs; and it has been widely used in elderly patients with epilepsy in the last decade [5].

Different from other sodium-blocker AEDs, lacosamide (LCM) exerts anticonvulsant activity by selectively enhancing slow inactivation of voltage-gated sodium channels [6,7].

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Baulac and colleagues recently showed that LCM monotherapy met the study's noninferiority criteria when compared with controlled-release carbamazepine monotherapy [8]. Therefore, LCM has been recently approved in the European Union for use as monotherapy up to 600 mg/day for the treatment of focal onset seizures in adults [9]. So far, data about LCM use in elderlies are very limited either as adjunctive treatment or as monotherapy, even if safety and tolerability in epilepsy, as well in neuropathic pain, have been reported [7,10–12].

This study aimed at assessing efficacy and tolerability of LCM as monotherapy compared with LEV monotherapy over 12 months in elderly patients (ages ≥65 years) with focal epilepsy with or without secondary generalization.

2. Material and methods

A retrospective chart review of patients aged ≥65 years suffering from focal onset seizures, with or without secondary generalization on LCM monotherapy or LEV monotherapy, was performed. Observation points were the first day of LCM or LEV treatment and 6 and 12 months after the beginning of monotherapy. Epilepsy and seizure type were classified according to the International League Against Epilepsy classification, which has been recently revised [13–15].

Seizure frequency, at baseline (1-month total seizure count) and at 6 and 12 months of follow-up, and seizure freedom rates were reported. Data regarding demographic characteristics (age, gender, age at epilepsy onset), seizure type (focal aware seizure, focal impaired awareness seizure, and focal to bilateral tonic–clonic seizure), etiology (structural or unknown epilepsy), LCM and LEV daily dose, number of lifetime AEDs, and comorbidities were collected. Titration was performed according to common clinical practice for LCM and LEV. All the patients continued the treatment for at least 1 year.

2.1. Statistical analysis

Descriptive statistics are reported as absolute numbers with percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). Groups were compared using the Student's t-test or the Pearson χ^2 test, and with the Mann–Whitney U test for nonnormally distributed variables. Two-sided statistical significance was set at a p level <0.05. Statistical analyses were performed with SPSS Statistics version 20.0 and R statistical software (package 'BSDA'). This retrospective observational study protocol was approved by the Independent Ethical Committee of the Policlinico Tor Vergata.

3. Results

3.1. Patients

In this retrospective study, 22 patients on LCM (10 males, 12 females, mean age: 76.23 ± 7.5, range: 66–88 years old; age at epilepsy onset: 71.5 ± 8.13 years old) and 24 patients on LEV (10 males, 14 females, mean age: 73.58 ± 6.39, range: 65–88 years old; age at epilepsy onset: 65.75 ± 13 years old) were enrolled. Mean LCM daily dose was 204.51 ± 88.51 mg and mean LEV daily dose was 1281.25 ± 378.15 mg. Patients on LCM were comparable with LEV patients in terms of demographic data; moreover, the two groups did not significantly differ for seizure frequency at baseline, age at epilepsy onset, epilepsy and seizure type, and number of lifetime AEDs. Demographic data, seizure type, and etiology are shown in Table 1. Eight out of 22 LCM patients and five out of 24 LEV patients had structural epilepsy. All patients had at least one comorbidity on chronic treatment. The most concomitant diseases were hypertension, hyperlipidemia, and diabetes mellitus, which were comparable in the two groups, whereas concomitant psychiatric diseases (including depression and obsessive–compulsive disorders) were exclusively evident in the LCM group. As expected, cardiac comorbidities (atrial fibrillation, coronary artery disease, and presence of pacemaker) were more frequent in LEV group (see Fig. 1).

Table 1
Demographic and clinical data of LCM and LEV patients.

	LCM n = 22	LEV n = 24	p-Value
Age, mean ± SD	76.23 ± 7.5	73.58 ± 6.39	NS
Gender	10 M, 12 F	10 M, 14 F	NS
Age at epilepsy onset, mean ± SD	71.5 ± 8.13	65.75 ± 13	NS
Etiology	8 structural 14 unknown	5 structural 19 unknown	NS
Seizure type	10 FIAS 2 FAS 6 FIAS and FBTCS 2 FAS 2 FAS and FIAS and FBTCS	15 FBTCS 5 FIAS 4 FAS	NS
Daily dosage, mg, mean ± SD	204.51 ± 88.51	1281.25 ± 378.15	NA
Baseline (seizure/month)	4.23 ± 8.53	2.29 ± 6.11	NS

FAS, focal aware seizure; FIAS, impaired awareness seizure; FBTCS, focal to bilateral seizure tonic–clonic seizure. NS, not significant. NA, not applicable.

No patient was affected by learning or intellectual disabilities. Data regarding etiology, seizure type, magnetic resonance imaging (MRI) findings, and comorbidities of each patient are reported in Tables 2 and 3.

3.2. Efficacy and tolerability

At 6 months and 12 months of follow-up, mean monthly seizure frequency decreased from 4.23 ± 8.53 to 0.33 ± 0.90 ($p < .001$) in LCM group; a reduction of mean monthly seizure frequency was observed in LEV group from 2.29 ± 6.11 to 0.20 ± 0.81 ($p < .001$) at 6 months of follow-up and to 0.21 ± 0.81 ($p < .001$) at 12 months of follow-up. Furthermore, 16/22 (72.7%) LCM patients were seizure-free at 6 months of follow-up while seizure freedom was achieved by 17/24 (70.8%) patients in LEV group (see Table 4 and Fig. 2). The percentage of seizure freedom was stable at 12 months of follow-up. Seizure frequency at baseline, 6, and 12 months of follow-up did not significantly differ in LCM *vs* LEV patients (−3.12 ± 7.23 *vs* −2.15 ± 5.16).

In the LCM group, no patient reported cardiac side effects or significant changes in the PR interval period, measured in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS complex, in normal follow-up protocol. Transient and mild adverse effects (dizziness and asthenia) were reported by 2 LCM and 3 LEV patients during the titration period.

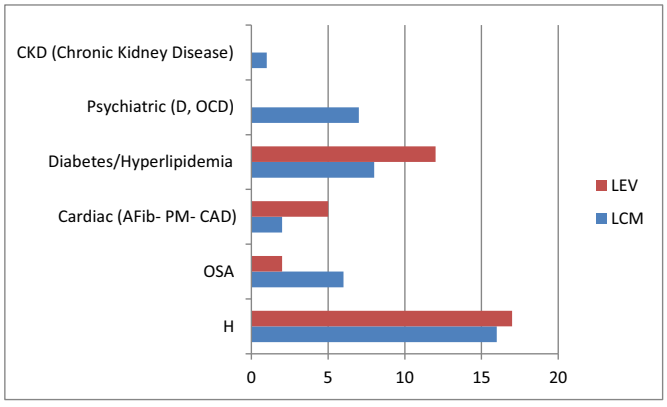

Fig. 1. Comorbidities. CKD, chronic kidney disease; D, depressive disorder; OCD, obsessive–compulsive disorder; AFib, atrial fibrillation; PM, pacemaker; CAD, coronary artery disease; OSA, obstructive sleep apnea; H, hypertension.

Table 2
Etiology, seizure type and comorbidities of patients on LCM monotherapy.

Pts	Etiology	MRI	Seizure type	Comorbidities
1	Unknown	Nonspecific white-matter changes	FIAS	H, O, OSA
2	Unknown	Nonspecific white-matter changes	FIAS, FBTCS	H
3	Unknown	Nonspecific white-matter changes	FIAS, FBTCS	H, PM, AFib, COPD
4	Structural	Posterior right temporal venous malformation	FAS, FIAS	G
5	Unknown	Nonspecific white-matter changes	FAS, FIAS, FBTCS	H
6	Structural	Right temporal–parietal vascular injury	FIAS	H, OSA, D, CKD
7	Unknown	Nonspecific white-matter changes	FAS, FIAS	D
8	Unknown	Normal	FIAS, FBTCS	H, DM, D, HLD, BPH
9	Unknown	Nonspecific white-matter changes	FAS, FIAS	H, G, HLD, OSA
10	Unknown	Nonspecific white-matter changes	FIAS	BPH, H, DM, HLD, OSA
11	Structural	Right frontal meningioma	FIAS	HLD, COPD
12	Unknown	Nonspecific white-matter changes	FIAS	H, HLD, CAD, OCD, OSA
13	Structural	Left vascular injury	FBTCS	H, HLD
14	Structural	Fahr disease	FIAS	H, CKD, D
15	Unknown	Nonspecific white-matter changes	FIAS	H, HLD
16	Unknown	Normal	FAS, FIAS, FBTCS	H, D
17	Unknown	Nonspecific white-matter changes	FIAS, FBTCS	H, COPD
18	Structural	Left frontotemporal vascular injury	FAS, FIAS	OSA, H, DM, UT, D
19	Unknown	Normal	FAS, FIAS	MCI, CAD, G
20	Structural	Right frontal meningioma	FIAS	CAD, BPH, COPD
21	Structural	Left parietooccipital meningioma	FBTCS	H
22	Unknown	Normal	FIAS	H

FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic–clonic seizure; OSA, obstructive sleep apnea; H, hypertension; CKD, chronic kidney disease; DM, diabetes mellitus; O, obesity; PM, pacemaker; AFib, atrial fibrillation; ACs, oral anticoagulants; G, gastritis; UT, underactive thyroid; D, depressive disorder; COPD, chronic obstructive pulmonary disease; HLD, hyperlipidemia; CAD, coronary artery disease; OCD, obsessive–compulsive disorder; BPH, benign prostatic hyperplasia; MCI, mild cognitive impairment; CC, colorectal cancer; UC, uterine cancer; LC, lung cancer.

4. Discussion

The purpose of this study was to evaluate long-term use of LCM as monotherapy compared with LEV monotherapy in elderly patients.

The efficacy of LCM in focal epilepsy, as conversion to monotherapy and as monotherapy, has been established in multicenter randomized studies that included patients aged 16 to 70 years old [16,17]. Giraldez et al. [18] described a LCM good outcome, efficacy and tolerability both in patients whose seizures were naive to AED therapy and those whose seizures had previously been treated with other AEDs.

Furthermore, LCM has a favorable pharmacokinetic profile with minimal drug–drug interactions neither inducing nor inhibiting the CYP450 enzyme system, which are key features when treating elderlies.

To date, only few studies reported on the efficacy and tolerability of LCM in elderly patients [10–12].

Villanueva et al. [19] showed that the retention rate in patients on LCM as conversion to monotherapy was higher in patients aged ≥65 years compared with younger subjects. Although dizziness is the most common adverse drug reaction, it induced drug discontinuation in a small number of patients. Furthermore, a good psychiatric outcome

Table 3
Etiology, seizure type and comorbidity of patients on LEV monotherapy.

Pts	Etiology	MRI	Seizure type	Comorbidity
1	Unknown	Nonspecific white-matter changes	FAS	AFib, COPD, HLD, H, BPH
2	Unknown	Nonspecific white-matter changes	FIAS	AFib, DM, MCI, BPH
3	Unknown	Nonspecific white-matter changes	FBTCS	H, HLD
4	Unknown	Normal	FIAS	AFib, H, HLD
5	Structural	Acute cerebrovascular injury	FAS	H, HLD
6	Unknown	Nonspecific white-matter changes	FIAS	H, HLD
7	Unknown	Normal	FAS	AFib, H, COPD
8	Unknown	Normal	FBTCS	UT
9	Unknown	Nonspecific white-matter changes	FBTCS	CAD, DM
10	Unknown	Normal	FBTCS	H
11	Structural	Cerebral aneurysm	FAS	H
12	Unknown	Nonspecific white-matter changes	FBTCS	H, HLD, UT, UC
13	Structural	Subarachnoid hemorrhage	FBTCS	H
14	Structural	Right temporal dysplasia	FBTCS	LC
15	Unknown	Nonspecific white-matter changes	FBTCS	H
16	Unknown	Nonspecific white-matter changes	FBTCS	H, OSA
17	Unknown	Nonspecific white-matter changes	FBTCS	HLD
18	Unknown	Nonspecific white-matter changes	FBTCS	H, DM, HLD
19	Unknown	Nonspecific white-matter changes	FBTCS	H, HLD
20	Unknown	Nonspecific white-matter changes	FBTCS	H, HLD, UT
21	Unknown	Nonspecific white-matter changes	FBTCS	H
22	Structural	Acute cerebrovascular injury	FBTCS	H, DM, CC
23	Unknown	Nonspecific white-matter changes	FIAS	H
24	Unknown	Normal	FIAS	PM, OSA

FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic–clonic seizure; OSA, obstructive sleep apnea; H, hypertension; CKD, chronic kidney disease; DM, diabetes mellitus; O, obesity; PM, pacemaker; AFib, atrial fibrillation; ACs, oral anticoagulants; G, gastritis; UT, underactive thyroid; D, depressive disorder; COPD, chronic obstructive pulmonary disease; HLD, hyperlipidemia; CAD, coronary artery disease; OCD, obsessive–compulsive disorder; BPH, benign prostatic hyperplasia; MCI, mild cognitive impairment; CC, colorectal cancer; UC, uterine cancer; LC, lung cancer.

Table 4
Clinical efficacy. Comparison between LCM and LEV monotherapy.

LCM					LEV				
Seizures, number per month					Seizures, number per month				
Baseline	6 months	12 months	p-Value[a]	p-Value[b]	Baseline	6 months	12 months	p-Value[a]	p-Value[b]
4.23 ± 8.53	0.33 ± 0.90	0.33 ± 0.90	<.001	<.001	2.29 ± 6.11	0.20 ± 0.81	0.21 ± 0.81	<.001	<.001
LCM					LEV				
Seizure-free					Seizure-free				
Baseline	6 months	12 months	p-Value[a]	p-Value[b]	Baseline	6 months	12 months	p-Value[a]	p-Value[b]
0/22	16/22 (72.7%)	16/22 (72.7%)	<.001	<.001	0/24	17/24 (70.8%)	17/24 (70.8%)	<.001	<.001

Statistical analysis. Mann–Whitney U test for non normally distributed variables.
[a] p value: 6 months *versus* baseline.
[b] p value: 12 months *versus* baseline.

was described for LCM *versus* other AEDs [20], and a recent study has reported LCM efficacy in psychiatric disorders [21].

The sole contraindication in LCM use is represented by the Atrioventricular (AV) block grade II. In addition, a PR prolongation has been described in some papers [22,23].

Levetiracetam is being increasingly administered as a first-line drug in focal seizures in adults [24], and in the last decade, it has been widely used in elderlies with epilepsy [5], probably because of its high therapeutic index and proven margin of safety compared with other AEDs. It is well known that age may affect clearance of AEDs. In particular, LEV clearance had been found to be reduced by 40–60% among elderly patients. Therefore, such population may benefit from therapeutic drug monitoring when using LEV [4,5].

Our study reports a population with many different comorbidities, which were similar to those reported in previous studies concerning elderlies affected by focal epilepsy [10,25]. Most of our patients had an epilepsy onset over 65 years old, and all of them had comorbidities, which were chronically treated with several drugs.

Levetiracetam and LCM share a favorable pharmacokinetic profile, as the ideal AED in elderly patient should exhibit a low potential for drug interaction.

The number of elderly subjects enrolled in the pivotal focal epilepsy trials with LCM as add on treatment was very low, and data about LCM as monotherapy for focal epilepsy are scarce [8]. Promising data have been reported by a subgroup analysis from a LCM clinical trial in patients affected with diabetic neuropathic pain that showed a safety profile with low incidence of adverse events and low discontinuation rate in elderlies [10]. In our real-life observational study, most elderly subjects with newly diagnosed epilepsy required low doses of LEV or LCM to maintain seizure control.

We believe that a fixed-dose of AEDs commonly used in randomized clinical trials may lead to higher overall discontinuation rates, mostly in elderlies. The AEDs efficacy observed in such population, often at low dosages, may be caused by slow metabolism and by the "benign" etiology of epilepsy with late onset. Moreover, data obtained in younger adults can be misleading in elderlies, since age-related changes affect the gastrointestinal tract, the hepatic enzyme capacity, the protein binding, and the kidney function.

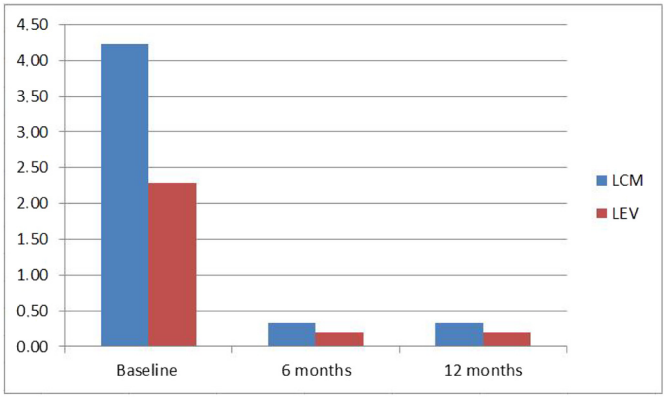

Fig. 2. Comparison of seizures frequency per months between LCM and LEV monotherapy.

Our results indicate that in the elderly population, the efficacy of LCM monotherapy was comparable with LEV. Daily doses of both drugs administered to our patients were low, often lower than those recommended in the individual product labels.

The above findings support the recommendation that initial dosing of epilepsy medication for elderly patients should be low, with a titration schedule slower than that used in younger adults, in order to reduce the risk of tolerability issues [26].

A further benefit of LEV or LCM use in elderlies is the lack of significant interaction with vitamin K antagonist oral anticoagulants, different from several older AEDs. In such respect, five patients in our sample were on stable treatment with warfarin because of atrial fibrillation.

Regarding nonvitamin K antagonist oral anticoagulants (also known as direct oral anticoagulants (DOACs)), most AEDs are contraindicated. Data on newer AEDs are still largely unknown. Levetiracetam received a recent warning from the European Heart Rhythm Association Practical Guide [27], even if it exerts only a potential effect on P-glycoprotein activity [28]. Conversely, LCM, which does not affect significantly CYP activity *in vitro*, might be safer for patients on DOACs, even though its effects on P-gp are not well known yet [28].

We are aware of the limitations of our study stemming from its retrospective design and the small size of the enrolled population, although such characteristics do reflect real life data and the very recent release of the authorization of the LCM as monotherapy in EU.

5. Conclusion

Considering the high rate of comorbidities and the risk of drug–drug interactions in elderly patients having focal onset seizures, the efficacy and tolerability of the LCM and LEV monotherapy was remarkably favorable, even at low doses, as seizure freedom persisted in more than half of patients at long-term follow-up.

Our retrospective real-life study suggests that LCM and LEV are valuable options in the studied frail population, confirming the need of tailoring dose to be based on subjects' response and tolerability in order to obtain the highest drug retention and efficacy at the lowest dosages.

Conflicts of interest

The authors declare no conflicts of interest.

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