The efficiency and tolerability of lacosamide therapy in adolescents and adults with new-onsetfocal epilepsy in terms of the epileptiform activity index

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Lacosamide (LCM) is one of the most promising antiepileptic drugs (AEDs) for focal epilepsy (FE); however, in Russia there are only a few works devoted to its practical application.

Objective: *to evaluate the efficiency of LCM therapy in adolescents and adults with new-onset FE.*

Patients and methods. *The investigation enrolled 36 patients aged 16-78 years. All the patients underwent video-ECG monitoring with quantification of the epileptiform activity index (EAI) at baseline and 1, 3, 6 and 12 months of treatment. The treatment efficiency was evaluated using the standard measures: drug-induced remission, a response rate of ≥50%, an insufficient efficiency of 450%, higher seizure rate, and therapy retention rates. Adverse events (AEs) were assessed using the SIDe-effects of AntiEpileptic Drugs (SIDAED) questionnaire.*

Results and discussion. *Just 3 months after starting treatment, the total EAI substantially decreased from 2.92 [0; 6.7] to 1.95 [0; 3.07] ($p<0.05$). LCM demonstrated a high efficacy and a good tolerance in the therapy of FE: by the end of 12-month follow-up, there was a considerable decrease in EAI by 1.57 times ($p<0.05$); the LCM monotherapy retention rate of 72.2% was achieved in 26 patients: 20 (55.6%) patients had drug-induced remission; six (16.7%) patients were responders. AEs were recorded in 5 (13.8%) cases.*

Conclusion. *LCM is an effective AED for the initial monotherapy of FE. The use of LCM in FE causes a considerable decrease in EAI by 1.57 times ($p<0.05$).*

Keywords: *focal epilepsy; lacosamide; epileptiform activity index; efficacy, tolerability.*

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For reference: *Karlov VA, Vlasov PN, Kozhokaru AB, et al. The efficiency and tolerability of lacosamide therapy in adolescents and adults with new-onset focal epilepsy in terms of the epileptiform activity index. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2020;12(3)56—62.* ***DOI****: 10.14412/2074-2711-2020-3-56-62*

Pharmacotherapy for epilepsy aims at achievement of clinical remission or significant decrease in epileptic seizures rate while taking antiepileptic drugs (AEDs) in the absence of adverse events (AEs) or with minimal AEs [1].

Rational therapy is ideally performed with one AED [2, 3]. In the absence of adequate control over epileptic seizures, an attempt is made to continue monotherapy with other drug products or to introduce additional AEDs into the treatment regimen [4]. Despite the presence of numerous available AEDs in a wide pharmacy network, only 37 % of patients with epilepsy receive modern AEDs, and more than half are treated with outdated AEDs [5]. In recent years, the rate of drug resistance has not significantly decreased averaging 30 %.

Problem of drug-resistant epilepsies makes the search for and development of new AEDs urgent, since uncontrolled epileptic seizures can lead to serious psychosocial consequences with the development of depression, suicide and significant risk of trauma and/or death [6, 7]. In patients with chronic epilepsy, sudden death syndrome occurs 2–3 times more often than in overall population [7, 8], and cardiac arrest can occur during normal daily activity with no temporary association with an epileptic seizure [8].

Timely modern pharmacotherapy aimed at controlling epileptic seizures significantly reduces such risks and therefore improves the quality of life of patients. At the same time, there remains a need to develop new effective AEDs with a good tolerance profile [5].

Lacosamide (LCM) is a modern third generation AED. LCM selectively enhances slow inactivation of voltage-dependent sodium channels without affecting rapid inactivation, which leads to decreased pathological hyperexcitability of neurons with no significant affect on the physiological neuronal

Пациенты и методы. Study enrolled 36 patients: 22 (61.1%) men and 14 (38.9%) women with FE aged 16–78 years (43.7 + 16.2 years).

Inclusion criteria: 1) new-onset FE; 2) informed consent to participate in the study.

Exclusion criteria*:* 1) unconfirmed epilepsy and non-epileptic seizures; 2) absence of epileptic seizures — drug/spontaneous remission; 3) idiopathic (genetic) age-dependent FE; 4) severe somatic pathology, decompensation of chronic diseases; 5) oncological diseases including neuro-oncological; 6) pregnancy and lactation; 7) refusal to participate in the study.

Main epileptic syndromes were: temporal (n = 18; 50.0%), frontal (n = 14; 38.0%), occipital (n = 2; 6%) and parietal (n = 2; 6%) epilepsy. Structural FE was revealed in 75% (n = 27) of patients, FE of unknown etiology — in 25% (n = 9) of patients. The main structural findings were: gliotic changes in the cerebral cortex detected in 16 (44.4%) patients, including 11 (30.5%) due to closed craniocerebral injury and 5 (13.9%) due to stroke; sclerosis of the hippocampus in 6 (16.7%) patients; focal cortical dysplasia of the frontal hemispheres in 2 (5.6%) patients and cavernomas in 3 (8.3%) patients.

In almost half of the patients — in 17 (47.2%) — initial attacks were common (≤3 per month), in 13 (36.1%) — rare (once every 2–3 months), in 5 (13, 9%) — very common (≥4 per month) and in 1 (2.8%) — single (once every six months).

Majority of patients had single seizures (n = 23; 63.9%), repeated (double; n = 9; 25.0%) and serial (n = 4; 11.1%) seizures were not common.

Patients were divided into two equal subgroups depending

function [9, 10]. At the same time, binding to collapsin response mediator protein-2 (CRMP-2) which is involved in the transmission of neurotrophic signals, LCM provides a neuroprotective effect, preventing the formation of abnormal neuronal connections in the brain [11]. This drug product is considered as one of the most promising in patients with focal epileptic seizures with or without secondary generalization [9, 12, 13]. LCM has been used in domestic clinical practice since 2010, but only a few publications are devoted to its practical use in Russia [5, 12, 14—17]. There are experimental data confirming the effect of LCM on electroencephalography (EEG) parameters [18].

Objective: to evaluate the efficiency of LCM therapy in adolescents and adults with new-onset FE.

on LCM daily dose: < 400 mg/day (n = 18; 50.0%); ≥ 400 mg/day (n = 18; 50.0%).

Diagnosis was established based on the current definition of the disease, criteria for epileptic syndrome and type of seizures in accordance with the recommendations of the International League Against Epilepsy (International League Against Epilepsy, ILAE, 2014) [19].

All patients underwent clinical and neurological examination. Clinical and biochemical blood tests, common urine analysis were performed at baseline and were repeated if necessary. During each visit, video-EEG monitoring results were assessed. Clinical and subclinical EEG patterns of focal epileptic seizures, focal and diffuse epileptiform activity during wakefulness before sleep and after sleep, during sleep and fragmentary awakenings were analyzed with an assessment of epileptiform activity index (EAI) which was calculated by the formula:

$$\text{EAI} = \frac{\text{Charges amount}}{\text{Time unit}} \cdot 100$$
$$\text{(study duration)}$$

Total EAI was also evaluated, which is the sum of EAI obtained during the periods of wakefulness before and after sleep, during sleep and fragmentary awakenings.

Study lasted 12 months, during which 5 follow-up visits to the doctor were planned: 1st visit — establishing diagnosis and obtaining consent of the patient to start antiepileptic therapy; 2nd visit — 1 month after taking initial dose and before reaching AED saturating dose; 3rd visit — 2 months after AED therapy start; 4th visit — 6 months after therapy start; 5th visit — 12 months after therapy start. If it was necessary to change therapy due to insufficient efficacy or AEs, extraordinary visit to the doctor took place.

Efficacy of LCM therapy was assessed by such parameters as: drug remission; responders > 50% decreased seizures; insufficient effect — < 50% decreased attacks; therapy retention — complex index of efficacy/tolerance; emergence of new types of seizures and/or increased seizures — pharmacodynamic aggravation.

If it was necessary to correct LCM regimen associated with lack of control over seizures and signs of intolerance, the dose was increased. In the absence of control over the seizures, when the patient received the maximum tolerated dose, it was reduced and a second AED was added, with a further assessment of the efficacy of this combination and subsequent possible LCM withdrawal. In the event of unacceptable dose-dependent AEs at the baseline of dose selection, LCM was immediately replaced [3].

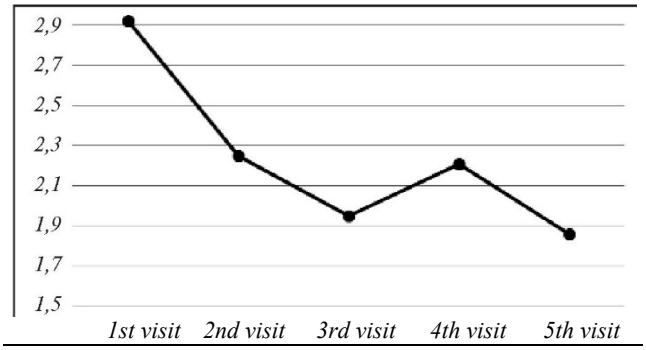
AEs were subdivided into tolerable, which were corrected by LCM dose variation or by prescribing additional drug products, and serious, i.e., intolerable, requiring LCM replacement. AEs were analyzed using Side-effects of anti-epileptic drugs (SIDAED) scale, which includes 10 categories/46 items. According to this scale, < 20 score — tolerable AEs, > 20 score — intolerable AEs requiring a change of AED [20].

Statistica 6.0 software was used for statistical processing of results. Normality of data distribution was determined using Kolmogorov—Smirnov test. Data were presented as M + SD (M — mean, SD — standard deviation) with normal distribution and as median (Me [25th and 75th percentiles]) with abnormal distribution. Mann-Whitney test was used to compare two groups, and the differences were considered statistically significant at $p < 0.05$. Correlation analysis was performed using Pearson and Spearman method (< 0.2 — very weak, 0.2–0.5 — weak, 0.5–0.7 — medium, 0.7–0.9 — strong and > 0.9 — very strong correlation) to determine the relationship between total EAI and disease clinical characteristics.

Results

EAI

Total EAI before the start of treatment amounted to 2.92 [0; 6.7]. One month after the start of AED intake and titration to saturating dose (2nd visit), it decreased to 2.25 [0; 4.73] ($p > 0.05$), after 3 months (3rd visit) — up to 1.95 [0; 3.07], which turned out to be significantly lower compared to the initial index ($p < 0.05$), after 6 and 12 months (4th and 5th visits) — up to 2.21 [0; 4.41] and 1.86 [0; 3.37] (see Figure). In general, during follow-up EAI decreased by 1.57 ($p < 0.05$).



Follow-up dynamics of total EAI

Correlation analysis revealed an average strength relationship between total EAI and attack rate ($r = 0.559$; $p < 0.001$), which allows to consider total EAI as an additional objective index of therapy efficacy.

Regimen correction

During the *2nd visit*, regimen was corrected in 9 (25.1%) patients as follows:

— LCM dose increase due to insufficient efficacy was required for 2 (5.6%) patients: one receiving < 400 mg/day, and the second receiving > 400 mg/day;

— LCM replacement due to intolerable AEs was performed in 4 (11.1%) patients, 3 of whom received < 400 mg/day and 1 received > 400 mg/day. Levetiracetam (n = 2), topiramate (n = 1), and valproic acid (n = 1) were prescribed as the new monotherapy;

— addition of a second AED (levetiracetam) due to therapy inefficacy (persistence of seizures and subclinical patterns of focal epileptic seizures observed in EEG) was required for 3 (8.4%) patients, 1 (2.8%) of whom received LCM < 400 mg/day and 2 (5.6%) — ≥ 400 mg/day.

During the *3rd visit*, only 1 (2.8%) patient who received LCM 400 mg/day underwent LCM replacement with levetiracetam due to intolerable AEs. Another 1 (2.8%) patient received the second drug product (levetiracetam) in addition due to inefficacy of LCM > 400 mg/day dose.

During the *4th visit*, levetiracetam was added for 1 (2.8%) patient due to insufficient efficacy of LCM > 400 mg/day.

During the *5th visit*, no change was required for the patients. See Table 1 for regimen changes during each visit.

Subclinical patterns of focal epileptic seizures

Long-term video-EEG monitoring was performed to study the dynamics of epileptiform activity. For 12 months of follow-up, only during the 2nd and 3rd visits when analyzing the repeated video-EEG monitoring in 16.7% (n = 6) patients, subclinical EEG patterns of focal epileptic seizures were revealed, which required regimen correction.

In 13.9% (n = 5) of patients with structural temporal lobe epilepsy, in most cases, subclinical EEG patterns of epileptic seizures were defined as local rhythmic grouped oscillations of alpha-theta range, usually in the temporal regions of the right or left hemisphere, independently of a sinusoidal or pointed nature, with a subsequent increase in amplitude and transformation into sharp-wave or peak-wave activity and propagation to adjacent parts of the ipsilateral hemisphere. As the sublinear EEG patterns of seizures were completed, initial picture of the 1st or 2nd stage of slow-wave sleep was observed. Less often (in 2 cases), after completion of the pattern, lateralized delta waves were also recorded with the subsequent rhythm restoration of the 2nd stage of sleep.

In 1 (2.8%) patient suffering from structural frontal epilepsy, in the 2nd stage of sleep, rhythmic regional activity of the theta range in the right frontal region was recorded, followed by increased amplitude and transformation into diffuse theta-delta activity with amplitude predominance in frontal parts of the hemispheres. After the end of epileptiform activity recording, a picture of the 2nd stage of slow-wave sleep was observed.

In terms of morphology, all the indicated graphical elements underwent electrographic evolution of the pattern of focal epileptic seizure without any clinical

Table 1. *Follow-up regimen correction, p (%)*

Therapeutic tactics	Visit			
	2nd	3rd	4th	5th
LCM (monotherapy)	29 (80.5)	27 (75.0)	26 (72.2)	26 (72.2)
Primary drug product dose increase	2 (5.6)	-	-	-
Drug product replacement (monotherapy)	4 (11.1)	1 (2.8)	-	-
Primary drug product dose decrease and/or second drug product addition	3 (8.4)	1 (2.8)	1 (2.8)	

Table 2. *Attack rate change in follow-up groups, p (%)*

Parameter	Dose, mg/day	2nd visit (n = 36)	3rd visit (n = 28)	4th visit (n = 26)	5th visit (n = 26)	Total (n = 36)	Total (n = 36)
No attacks (drug remission)	< 400 ≥ 400	12 (33.3) 9 (25.0)	12 (42.8) 8 (28.6)	12 (46.2) 8 (30.8)	12 (46.2) 8 (30.8)	20 (55.5)	26 (72.2)
Attack rate decrease by ≥50% (responders)	< 400 ≥ 400	2 (5.6) 5 (13.9)	1 (3.6) 5 (17.8)	1 (3.8) 5 (19.2)	1 (3.8) 5 (19.2)	6 (16.7)	
Attack rate decrease by ≤50% (insufficient effect)	< 400 ≥ 400	1 (2.8) 3 (8.3)	1 (3.6)	-	-	5 (13.9)	5 (13.9)
AE + aggravation (increased seizures rate and/or their severity, or new type of seizure)	< 400 ≥ 400	1 (2.8) 3 (8.3)	1 (3.6)	-	-	5 (13.9)	5 (13.9)

Table 3. *12 months attack rate dynamics, p (%)*

Therapy	Remission of seizures	Attack rate decrease by ≥50% (responders)	Attack rate decrease by ≤50% (insufficient effect)	Total (n = 36)
		Monotherapy		
LCM	20 (55.5)	6 (16.7)	-	26 (72.2)
Levetiracetam	2 (5.5)	-	-	2 (5.5)
Valproic acid	2 (5.5)	-	-	2 (5.5)
Topiramate	1 (2.9)	-	-	1 (2.9)
		Duotherapy		
LCM + Levetiracetam	1 (2.9)	2 (5.5)	2 (5.5)	5 (13.9)
Total	26 (72.2)	8 (22.3)	2 (5.5)	36 (100)

manifestations and as a rule with slow-wave sleep pattern restoration.

During the 2nd visit (1 month after LCM therapy start) 5 (13.9%) patients had subclinical EEG patterns of epileptic seizures, while in 4 (11.1%) of them, with structural temporal lobe epilepsy, they were detected during sleep and in 1 (2.8%) patient, with structural frontal epilepsy, they were revealed during wakefulness and sleep of 36.2 + 27.4 s (from 3 to 75 s) long.

3 patients had 1 subclinical pattern, 1 patient had

2 subclinical patterns and 1 patient had 3 subclinical patterns.

After 3 months of therapy (visit 3), only 1 (2.8%) patient with structural temporal lobe epilepsy had 1 subclinical EEG pattern of a focal epileptic seizure identified during sleep, with a total duration of 41 s.

Therapy efficacy

Seizure rate dynamics in accordance with dose and AED taken over 12 months was as follows. Already by the time of the 2nd visit, 58.3% (n = 21) patients had no seizures (drug remission), 19.5% (n = 7) had decreased seizure rate by > 50% (responders), 11.1% (n = 4) had decreased seizures rate by < 50% (insufficient effect) and 11.1% (n = 4) developed intolerable AEs (n = 3) and new type of seizure (n = 1), generalized myoclonic seizures, which happened after LCM therapy start (patient revealed structural frontal epilepsy and focal versatile seizures with impaired consciousness). Patients with insufficient effect and AE/aggravation were excluded from further analysis.

By the time of the *3rd visit*, seizures were absent in more than half of the patients — in 71.4% (n = 20); in 21.4% (n = 6) patients the rate decreased by > 50%, in 3.6% (n = 1) patients the rate decreased by < 50%, another 3.6% (n = 1) patients developed intolerable AEs.

Both by the *4th* and *5th visits*, 55.5% (20 out of 36) patients achieved drug remission, 16.7% (6 out of 36) were responders, 13.9% (5 out of 36) showed insufficient effect and 13.9% (5 out of 36) developed AE and aggravation of seizures (Table 2).

Table 3 demonstrates that 12 months LCM monotherapy was continued in 26 (72.2%) patients, other drug products monotherapy was prescribed to 5 (13.9%) patients, LCM duotherapy was also prescribed to 5 (13.9%) patients.

Thus, after 12 months of LCM use, monotherapy retention rate was achieved in 72.2% patients (n = 26), while half of the patients (13 out of 36) was prescribed

< 400 mg/day and the second half (13 of 36) was prescribed ≥400 mg/day.

LCM-associated AEs

Follow-up AEs SIDAED scale analysis showed intolerable AEs in 5 (13.8%) patients: during the 2nd visit — in 4 (11.1%) patients with 1 patient receiving

≥ 400 mg/day and 3 patients receiving < 400 mg/day; during the 3rd visit — in 1 (2.7%) patient receiving LCM < 400 mg/day. LCM was replaced with another drug product due to AEs onset.

AE included general CNS symptoms, behavioral disorders (increased irritability), bad mood episode, impaired cognitive functions, movement disorders/coordination disorders, visual changes (transient loss of visual fields), headache, dermatological complaints (allergic reaction in the form of urticaria), gastrointestinal tract disorders (dyspeptic symptoms), impaired libido and menstruation. These AEs were observed in all 5 patients with epilepsy, only impaired libido and/or menstruation were observed during the 2nd visit in 2 patients.

Discussion. LCM is the first AED in its subgroup with a qualitatively new mechanism of action: it selectively enhances slow inactivation of voltage-dependent sodium channels. LCM is used in mono- and combined therapy of FE [3, 13, 21]. Additional positive aspect of LCM clinical use is intravenous dosage form which makes it possible to significantly expand indications for use and to perform rapid titration [22, 23].

LCM use results for FE in the Russian Federation were published in a number of studies which are still extremely limited [16, 17].

Results of recent studies (double-blind studies in patients with epilepsy of cerebrovascular etiology) indicate a high antiepileptic efficacy of LCM and its good tolerability when compared to carbamazepine [24]. Initially, 27 patients received LCM, and 34 patients received long-release carbamazepine, who were later transferred to LCM monotherapy. In LCM group, a large number of patients completed 6-months (81.5%) and 12-months (66.7%) study periods without seizures. Among AEs, the most common (≥10%) were headache, dizziness and fatigue, rare were drowsiness and cognitive impairment. Authors concluded that LCM is highly effective and well tolerated, in particular in patients with epilepsy of cerebrovascular etiology [24].

In this study, LCM 12 months monotherapy retention rate was 72.2% (n = 26); drug remission was achieved in 55.5% (n = 20) patients; decreased attack rate by≥ 50% was observed in 16.7% (n = 6) patients; drug product was changed in 13.9% (n = 5) patients, LCM duotherapy was prescribed to 13.9% (n = 5) patients. Thus, the results obtained confirm high efficacy of LCM in FE despite the small representative sample size.

This study data are consistent with the results obtained earlier by V. Villanueva et al. [13], where LCM monotherapy retention rate was 62.5%. This retrospective non-interventional study analyzed LCM therapy in patients aged 16 years and older. Authors concluded that LCM is effective and well tolerated when used as a first-line drug or when switched to monotherapy in adults and elderly patients with FE [13].

In this study, pharmacodynamic aggravation in the form of generalized myoclonic seizures was observed in 1 (2.8%) patient

with structural frontal epilepsy during the 2nd visit. Similar negative dynamics of epilepsy with properly prescribed therapy can be observed with any AED prescribed, however the causes of its occurrence have not yet been sufficiently studied [3, 25].

Follow-up AEs SIDAED rate was 13.8% (n = 5). AEs included behavioral disorders (increased irritability), symptoms of depression, dizziness, headache which were comparable with 11.8% obtained by V. Villanueva et al. [13] and 10% obtained by F. Rosenow et al. [24]. All AEs were observed at baseline of LCM therapeutic dose selection. SIDAED scale used in the study is in our opinion more comprehensive and reflects changes in various body systems in comparison with Liverpool University Neuroleptic Side-Effect Rating Scale which has been widely used since 1995, and other AEs rating scales.

EAI analysis in dynamics revealed its decrease by the 12th month by 1.57 ($p < 0.05$) and direct correlation between total EAI and seizures rate ($r = 0.559$; $p < 0.001$). Thus, EAI turned out to be an additional objective efficacy index of LCM therapy in FE.

In a standard short-term EEG study (20 min artifact-free recording), epileptic seizures and their subclinical EEG patterns are rarely recorded. Long-term video-EEG monitoring is a reliable tool for differential diagnosis of epileptic/non-epileptic seizures and determination of their clear semiological pattern. In this study, during the 2nd and 3rd visits during video- EEG monitoring, subclinical EEG patterns of focal epileptic seizures were identified in 6 (16.7%) patients, which required a change of the regimen. This indicates that video-EEG monitoring is a more reliable method of dynamic antiepileptic therapy assessment, LCM in particular.

Conclusion. Thus, LCM showed to be effective and promising drug product for FE initial treatment when used in monotherapy. LCM 12 months retention rate was 72.2% (n = 26): including 55.6% (n = 20) patients achieving drug remission, and 16.7% (n = 6) patients showed decreased attack rate by > 50% (responders). As for tolerability, total AEs over 12 months of follow-up amounted to 13.8%. LCM use in FE leads to a significant decrease in EAI by 1.57 ($p < 0.05$) and reflects therapy efficacy.

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Поступила/отрецензирована/принята к печати

Received/Reviewed/Accepted

22.04.2020/18.05.2020/28.05.2020

Заявление о конфликте интересов/Conflict of Interest Statement

Статья спонсируется компанией ООО «ЮСБ Фарма». Спонсор участвовал в разработке проекта исследования и поддержке исследовательской программы, а также принятии решения о представлении статьи для публикации. Конфликт интересов не повлиял на результаты исследования. Авторы несут полную ответственность за предоставление окончательной версии рукописи в печать. Все авторы принимали участие в разработке концепции статьи и написании рукописи. Окончательная версия рукописи была одобрена всеми авторами.

This article has been supported by UCB Pharma S.A. The sponsor has participated in the development of the investigation project and supported the investigation program, as well as in the decision to submit the article for publication. The conflict of interest has not affected the results of the investigation. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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