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(RESEARCH ARTICLE)

Lamotrigine: how effective is it as add-on therapy in Bulgarian patients with drug-resistant epilepsy

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Abstract

The study purpose was to perform an open, prospective study on various aspects of Lamotrigine (LTG) effectiveness in Bulgarian patients with drug-resistant epilepsy. The study was performed with the participation of patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria. The patients completed diaries about seizure frequency, severity, and adverse events. There were regular documented visits at 3 or 6 months during the first year of treatment with LTG and at 6 months afterwards, with dynamic assessment of seizure frequency, severity, adverse events, and EEG recordings. LTG was applied as add-on treatment in 73 patients (47 males, mean age 36 years). There was a relatively mild and stable dynamic improvement of seizure severity, a satisfactory seizure frequency reduction in 39.7% of participants, a stable mean seizure frequency reduction (43-59%) from the 6th to the 36th month of treatment and a stable responder rate (55.7-59.4%) during the same period. There were adverse events (dizziness/vertigo, generalized edema, irritability, aggressiveness, speech disturbances, visual hallucinations, sleepiness, insomnia, headache, diplopia, nystagmus, impaired balance, muscle cramps, gastrointestinal discomfort, generalized rash, fatigue, nausea) in 12.3% of patients. In conclusion, LTG treatment is associated with: a low and stable improvement of seizure severity, a good and stable improvement of seizure frequency, a possible worsening of seizure control, a good safety and tolerability.

Keywords: Lamotrigine; Epilepsy; Efficacy; Tolerability; Adverse events

1. Introduction

Lamotrigine (LTG) is a newer-generation antiepileptic drug (AED) with several mechanisms of action: improvement of GABA-ergic inhibition, reduction of the effect of excitatory neurotransmitters, inhibition of calcium and sodium channels, carboanhydrase inhibition. LTG has been confirmed as an appropriate drug for monotherapy and add-on therapy in children and adult patients with all types of epilepsy, here included West syndrome, Angelman syndrome [1], Lennox-Gastaut syndrome [2]. The neuroprotective effect, favorable, although dependent on the combination with other AEDs, pharmacokinetics, lack of enzyme induction activity, and rare adverse events on cognition have been proven as advantages explaining the frequent usage of LTG in the medical practice. Some disadvantages requiring special attention are: the complex interactions with valproate, the necessity of a slow up-titration and the poorer tolerability with typical and frequent adverse events, some of them idiosyncratic – generalized rash, Stephens-Johnson syndrome or toxic epidermal necrolysis, nausea, fatigue [3-5].

Seizure frequency and severity dynamics are the main efficacy outcomes reported by investigators from randomized, double-blind, placebo-controlled, and open prospective studies on add-on treatment with LTG in patients with focal and generalized epilepsy, here included older people, patients with cognitive disturbances, or cases with conversion to monotherapy and dose reduction of the concomitant AEDs. Dose-dependent variations from 22% to 33% of

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responders' percentage and seizure severity improvement have been reported in patients with focal epilepsy, as well as 50% and 33% of responders' percentage in patients with generalized tonic-clonic seizures and absences respectively [6-12]. The percentage of responders in open prospective studies varies from 35-91%, with seizure free patients from 7-20% [2, 13-21]. Attention has not been focused on the retention rate of LTG and the correlation of seizure frequency and severity dynamics with demographics and clinical findings. There are no reliable prospective studies on effectiveness of LTG in Bulgarian adult patients with drug-resistant epilepsy. Therefore, the conduction of an open, prospective study on various aspects of effectiveness of add-on therapy with LTG in Bulgarian patients with drug-resistant epilepsy will provide additional useful data for the medical practice.

Our purpose is to perform an open, prospective study on various aspects of LTG effectiveness in Bulgarian patients with drug-resistant epilepsy.

2. Patients and methods

The study is open, prospective, with a possibility of using available detailed retrospective information about some participants. It was performed with the participation of patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria for a regular examination in cases of unsatisfactory seizure control or for adverse events from treatment.

All study procedures were performed after the approval of the Local Ethics Commission at the Medical University, Plovdiv. Every patient was introduced to the study design and signed an informed consent form before participating in the study procedures. The following inclusion criteria were used: 1. A signed informed consent form; 2. Consent of the patient and relatives about giving the required information and medical records; 3. Age ≥ 18 years; 4. Diagnosis of epilepsy; 5. Good compliance of patients to recommended treatment; 6. A stable dose of concomitant AEDs in the recent 3 months; 7. A period of prospective observation of at least 3 months; 8. Completed diary about seizure frequency, severity, and adverse events; 10. Regular documented visits at 3 or 6 months during the first year of treatment and at 6 months or 1 year afterwards, with dynamic assessment of seizure frequency, severity, adverse events, and EEG recordings. The criteria for AEDs choice are in conformity with the approved by the National Drug Agency indications.

The data were collected by a trained neurologist specialized in epilepsy through an examination of the patients' medical documentation and a detailed interview on the disease onset, heredity, concomitant diseases, type and etiology of epilepsy, seizure type, frequency and severity, treatment with AEDs, efficacy of LTG, adverse events from treatment. Seizure frequency dynamics was based on patients' seizure diaries. Seizure severity was estimated on the basis of information about seizure duration, traumatism during seizures, duration of consciousness loss, severity of postictal manifestations. Adverse events from treatment were assessed as type, severity (mild, moderate, severe), and duration based on reports from patients and relatives, a standardized interview based on the validated by Kuzmanova et al. Bulgarian version of the Liverpool Adverse Events profile [22], a physical, and neurological status examination at every visit.

The data were processed using STATA (Stata Corp., College Station, TX, USA) and SPSS (Statistical Package for the Social Sciences) version 13.0 (SPSS Inc., Chicago, IL, USA). The results for quantitative variables were expressed as means ± SE (standard error) and the results for qualitative variables as percentages. The principal outcomes were: clinical efficacy (effect on seizure frequency and severity, treatment duration and reasons for withdrawal, new seizure types, treatment changes), and tolerability (adverse events). The association of dynamics in seizure frequency and severity with demographics, and clinical findings was tested by means of $\chi 2$-test and F-test. The Wilcoxon signed-rank test was used to compare LTG efficacy in different study periods. Spearman coefficient was used to analyze the correlation of LTG efficacy with clinical and demographic findings. The complex influence of the significant demographics and clinical findings on LTG efficacy was determined by multivariate regression analysis. The level of significance was set at $P < 0.05$.

3. Results

The total number of patients diagnosed with epilepsy who have attended the Clinic of Neurology for the period 2003-2016, was 1259 (in- and outpatients). LTG was applied in 73 patients of 18-60 years of age (mean age 36.48 ± 1.38). The onset of epilepsy varied from 6 months to 53 years of age, mean age onset 16.63 ± 1.49 years. The mean epilepsy duration varied from 1 to 46 years, mean duration - 20.21 ± 1.41 years. The observation continued from 5 days to 120

months, (37 ± 3.43 months). The commonest dosage of LTG was 200 mg/d and 300 mg/d, mean dosage 230 ± 8.89 mg/d. The demographic and clinical characteristics of the study participants are presented in Table 1.

Table 1 Demographic and clinical characteristics of patients on treatment with LTG

Demographic/ clinical characteristic		**N**	**P (%)**	**SE**
Gender	Males	47	64.4	5.64
	Females	26	35.6	5.64
Age at the study onset (years)	≤ 25	12	16.4	4.36
	26-35	25	34.2	5.59
	36-45	17	23.3	4.98
	> 45	19	26.0	5.17
Age at epilepsy onset	≤ 18 years	52	71.23	5.34
	> 18 years	21	28.77	5.34
Epilepsy duration	≤ 10 years	22	30.1	5.41
	> 10 years	51	69.9	5.41
Study duration (months)	< 6	6	8.2	3.23
	6	7	9.6	3.47
	12	11	15.2	4.23
	24	11	15.2	4.23
	30-36	11	15.2	4.23
	48	9	12.3	3.87
	60	6	8.2	3.23
	72	4	5.5	-
	84	2	2.7	-
	96	5	6.8	3.0
	120	1	1.4	-
Seizure type	Focal seizures with impaired awareness	1	1.4	-
	Focal with evolution to bilateral tonic-clonic seizures	28	38.4	5.73
	Generalized tonic-clonic seizures	22	30.1	5.41
	Focal and generalized seizures	22	30.1	5.41
Type of epilepsy	Focal	43	58.9	5.8
	Generalized	30	41.1	5.8
Etiology of epilepsy	Genetic	9	12.3	3.87
	Structural/ metabolic (traumatic, vascular, inflammatory, tumor, perinatal pathology, hippocampal sclerosis, brain malformations, tuberous sclerosis, hydrocephalus)	31	42.5	5.83
	Unknown	33	45.2	5.87
Concomitant	No	46	63.0	5.69

diseases	Somatic	18	24.7	5.08
	Psychiatric	7	9.6	3.47
	Neurological	2	2.7	-
Seizure clusters and/or status epilepticus in the disease course	Yes	28	38.4	5.73
	No	45	61.6	5.73
Cognitive functions	Normal	63	86.3	4.05
	Mental retardation/ cognitive deficit	10	13.7	4.05
Neurological status	Normal	60	82.2	4.51
	With focal neurological signs	13	17.8	4.51
Recent seizure frequency	1-11 seizures/ year	7	9.6	3.47
	1-3 seizures/ month	19	26.0	5.17
	1-6 seizures/ week	34	46.6	5.88
	Daily	13	17.8	4.51
Recent seizure severity	Mild	12	16.4	4.36
	Severe	61	83.6	4.36
AED treatment at study onset	Monotherapy	38	52.1	5.89
	Polytherapy	35	47.9	5.89
Initial LTG dosage	50 mg/d	1	1.4	
	75 mg/d	1	1.4	-
	100 mg/d	5	6.8	3.0
	150 mg/d	5	6.8	3.0
	200 mg/d	31	42.5	5.83
	250 mg/d	1	1.4	-
	300 mg/d	26	35.6	5.64
	400 mg/d	3	4.1	-
Concomitant AED	VPA 600-2000 mg/d	18	24.7	5.08
	CBZ 600-800 mg/d	5	6.8	3.0
	CZP 1 mg/d	1	1.4	-
	PHT 200-300 mg/d	2	2.7	-
	OCBZ 1200-2400 mg/d	10	13.7	4.05
	LEV 2000 mg/d	1	1.4	-
	TPM 300 mg/d	1	1.4	-
	VPA 1000-1500 mg/d + CBZ 450-1200 mg/d	5	6.8	3.0
	VPA 1000-2000 mg/d + OCBZ 900-1800 mg/d	7	9.6	3.47
	VPA 900-1500 mg/d + CZP 0.5-3 mg/d	5	6.8	3.0
	VPA 2000 mg/d + PB 150 mg/d	1	1.4	-
	VPA 900 mg/d + Diazepam 10 mg/d	1	1.4	-

	VPA 1250-1750 mg/d + LEV 2000-3000 mg/d	4	5.5	-
	VPA 1500 mg/d + TPM 300 mg/d	1	1.4	-
	VPA 1500 mg/d + GBP 1600 mg/d	1	1.4	-
	CBZ 800 mg/d + CZP 1-6 mg/d	2	4.7	-
	CBZ 900 mg/d + PHT 200 mg/d	1	1.4	-
	PHT 200 mg/d + TPM 300 mg/d	1	1.4	-
	TPM 300 mg/d + PGB 300 mg/d	1	1.4	-
	VPA 1500 mg/d + CBZ 600 mg/d + CZP 3 mg/d	1	1.4	-
	VPA 1500 mg/d + TPM 200 mg/d + CZP 3 mg/d	1	1.4	-
	VPA 1500 mg/d + OCBZ 1800 mg/d + LEV 2000 mg/d	1	1.4	-
	PHT 200 mg/d + LEV 3000 mg/d + LCM 300 mg/d	1	1.4	-
	OCBZ 1800 mg/d + LEV 2000 mg/d + VGB 1000 mg/d	1	1.4	-
EEG at the study onset	Normal	33	45.2	5.87
	Focal activity	25	34.2	5.59
	Generalized paroxysmal activity	3	4.1	-
	Diffuse epileptiform activity	3	4.1	-
	Scattered abnormalities, no focus formation	3	4.1	-
	Diffuse slow-wave activity	3	4.1	-
	Focal + diffuse findings	3	4.1	-

* VPA – valproate, CBZ – carbamazepine, PHT – phenytoin, PB – Phenobarbital, OCBZ – oxcarbazepine, TPM – topiramate, GBP – gabapentin, CZP – clonazepam, LTG – lamotrigine, LEV – levetiracetam, PGB – pregabalin, TGB – tiagabine, LCM – lacosamide, VGB – vigabatrin

3.1. Efficacy of LTG treatment

We did not find significant difference in the percentage of patients without improvement of seizure severity up to the 36th month of treatment. The percentage of participants with seizure severity reduction persisted between the 6th and 36th month (12.9% on the 6th month, 18% on the 12th month, 14.3% on the 24th month, 11.1% on the 36th month). Because of the small number of patients, who continued LTG treatment after the 36th month, they were not included in statistical analysis. We came to the conclusion about a mild and stable improvement of seizure severity by treatment with LTG. There was no correlation of seizure severity dynamics with the initial seizure severity on the 6th, 12th, 24th, and 36th month of treatment $P > 0.05$ ($\chi^2 = 3.11$; $\chi^2 = 0.34$; $\chi^2 = 1.16$; $\chi^2 = 0.45$ respectively). There was a moderate correlation of seizure severity dynamics with the initial seizure frequency $P < 0.05$ ($r = 0.36$) on the 6th month of treatment. Seizure severity improvement was most frequent in patients with high initial seizure frequency – in 12.5%) of those with high weekly frequency and 30.8% of those with daily seizures.

Table 2 Seizure frequency assessment during treatment with LTG

	Seizure frequency dynamics				**Total N (p %)**
	No change N (p %)	**Reduction 50-99% N (p %)**	**Reduction 100% N (p %)**	**Increase N (p %)**	
6th month	31 (44.3%)	27 (38.6%)	12 (17.1%)	0 (0.0%)	70 (100.0%)
12th month	22 (36.6%)	24 (40.0%)	10 (16.7%)	4 (6.7%)	60 (100.0%)
24th month	15 (30.6%)	20 (40.8%)	9 (18.4%)	5 (10.2%)	49 (100.0%)
36th month	9 (24.3%)	13 (35.2%)	9 (24.3%)	6 (16.2%)	37 (100.0%)

The multiple regression analysis confirmed that seizure severity dynamics correlated with the initial seizure frequency P = 0.16 (β = -0.390; 95%CI = -0.796-(-0.217)) and the initial seizure severity P = 0.038 (β = 0.236; 95%CI = 0.039-1.382) on the 6th month of treatment. These variables explained 19% of seizure severity changes during this stage of treatment P < 0.001 (F = 7.58). Seizure severity improvement did not correlate with the LTG dosage P > 0.05 (F = 0.26). Seizure severity dynamics correlated with: 1. Age – seizure severity was most frequently reduced in patients between 26 and 35 years of age (44.4%) P < 0.05 (r = 0.28); 2. Epilepsy duration the greater duration correlated with lacking seizure severity improvement P < 0.05 (χ^2 = 13.65) – 79.6% of the participants with no change in seizure severity were with significant epilepsy duration P < 0.001 (r = 0.43); 3. A history of seizure clusters/ status epilepticus in the disease course – seizure severity improvement was more frequent in patients without such a history P < 0.05 (r = 0.27). The assessment of seizure frequency up to the 36th month of LTG treatment is presented in Table 2.

The most significant improvement of seizure frequency was on the 6th month of treatment followed by retention of a high responder rate of about 55-60% (55.7% on the 6th month, 56.7% on the 12th month, 59.2% on the 24th month and 59.4% on the 36th month) and gradual increase of the percentage of patients without seizures up to 24.3% – Table 2. There was also gradual increase of participants with seizure frequency increase – Table 2. The tendency of seizure frequency dynamic changes during the 36 months of treatment is shown in Fig. 1.

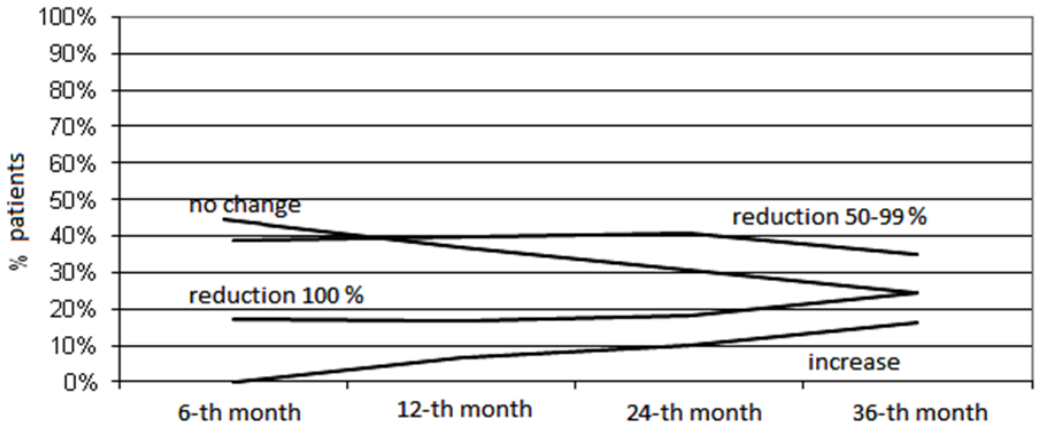

Figure 1 Dynamic assessment of seizure frequency in patients treated with LTG

The statistical analysis of results confirmed that there was no significant decrease in seizure frequency between the 6th and 12th month P > 0.05 (Wilcoxon signed-rank test = 1.05), between the 6th and 24th month P > 0.05 (Wilcoxon signed-rank test = 0.67), and between the 6th and the 36th month of treatment P > 0.05 (Wilcoxon signed-rank test = 0.98). We found the following dynamics in the mean seizure frequency reduction – 43% on the 6th month, 53% on the 12th month, 54% on the 24th month, 59% on the 36th month. Therefore, regarding seizure frequency, the efficacy of LTG was very good and stable for the study period. Seizure frequency dynamics correlated with the initial seizure frequency on the 6th month P < 0.05 (χ^2 = 9.99; r = -0.31) – improvement was more frequent in patients with lower initial seizure frequency. Seizure frequency improvement did not correlate with LEV dosage P > 0.05 (r = 0.32). Seizure frequency dynamics correlated with: 1. Age – seizure frequency was most frequently reduced in patients between 26 and 35 years of age (90.7%) P < 0.05 (r = 0.28); 2. Epilepsy duration - the greater duration correlated with lacking seizure frequency improvement P < 0.05 (χ^2 = 11.74) – 74.2% of the participants with no change in seizure frequency were with significant epilepsy duration P < 0.05 (r = 0.30); 3. A history of seizure clusters/ status epilepticus in the disease course – seizure frequency improvement was more frequent in patients without such a history (63% of responders and 91.7% of seizure free patients) P < 0.05 (χ^2 = 6.88), P < 0.05 (r = 0.31).

Seizure frequency improvement by various combinations of LTG with other AEDs at the end of the study is presented in Table 3.

The small number of patients treated with various combinations is a limitation for statistical analyses. Two combinations with other AEDs proved to be more frequent: 1. VPA + LTG in 15 (20.55%) patients – effective in 73.33%, 40% were seizure free; 2. OCBZ + LTG in 10 (13.7%) – 20% were responders, no seizure free participants. There was no change in the seizure frequency of the only one patient on monotherapy with LTG.

Table 3 Seizure frequency improvement by various combinations of LTG with other AEDs at the end of the study

AEDs in combination with LTG (mg/d)	Seizure frequency change at the end of the study					Total N (p %)
	0-50% N (p %)	50-75% N (p %)	75-99% N (p %)	100% N (p %)	Increase N (p %)	
CBZ 600-800 mg/d	2 (50%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (25.0%)	4 (100.0%)
VPA 600-2000 mg/d	2 (13.33%)	3 (20.0%)	2(13.33%)	6 (40.0%)	2 (13.33%)	15 (100.0%)
OCBZ 1200-2400 mg/d	5 (50.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	3 (30.0%)	10 (100.0%)
PHT 200-300 mg/d	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2 (100.0%)
CZP 1 mg/d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)	1 (100.0%)
LEV 2000 mg/d	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	1 (100.0%)
TPM 300 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
LTG 300 mg/d monotherapy	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
VPA 1000-1500 mg/d + CBZ 450-1200 mg/d	3 (60.0%)	1 (20.0%)	1 (20.0%)	0 (0%)	0 (0%)	5 (100.0%)
VPA 1000-2000 mg/d + OCBZ 900-1800 mg/d	5 (71.42%)	1 (14.29%)	0 (0%)	0 (0%)	1 (14.29%)	7 (100.0%)
CBZ 800 mg/d + CZP 1-6 mg/d	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2 (100.0%)
VPA 900 mg/d + Diazepam 10 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
VPA 1500 mg/d + GBP 1600 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
VPA 900-1500 mg/d + CZP 0.5-3 mg/d	1 (20.0%)	2 (40.0%)	1 (20.0%)	1 (20.0%)	0 (0%)	5 (100.0%)
VPA 1250-1750 mg/d + LEV 2000-3000 mg/d	1 (25.00%)	1 (25.00%)	1 (25.00%)	0 (0%)	1 (25.00%)	4 (100.0%)
VPA 2000 mg/d + PB 150 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
CBZ 900 mg/d + PHT 200 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
PHT 200 mg/d + TPM 300 mg/d	0 (0%)	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
TPM 300 mg/d + PGB 300 mg/d	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	0 (0%)	1 (100.0%)
VPA 1500 mg/d + TPM 300 mg/d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)	1 (100.0%)
VPA 1500 mg/d + TPM 200 mg/d + CZP 3 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
PHT 200 mg/d + LEV 3000 mg/d + LCM 300 mg/d	0 (0%)	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
VPA 1500 mg/d + OCBZ 1800 mg/d + LEV 2000 mg/d	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	1 (100.0%)
VPA 1500 mg/d + CBZ 600 mg/d + CZP 3 mg/d	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
OCBZ 1800 mg/d + LEV 2000 mg/d + VGB 1000 mg/d	0 (0%)	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
CBZ 600-800 mg/d	2 (50%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (25.0%)	4 (100.0%)
VPA 600-2000 mg/d	2 (13.33%)	3 (20.0%)	2 (13.33%)	6 (40.0%)	2 (13.33%)	15 (100.0%)
OCBZ 1200-2400 mg/d	5 (50.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	3 (30.0%)	10 (100.0%)
PHT 200-300 mg/d	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)	2 (100.0%)
CZP 1 mg/d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)	1 (100.0%)

At the end of the study seizure frequency was increased in 12 (16.4%) participants, there was no or unsatisfactory improvement (seizure frequency reduction <50%) in 29 (39.7%) patients. Responders were 29 (39.7%) patients - 11 (15.1%) were with seizure reduction 50-75%, 9 (12.3%) – with seizure reduction >75%, 9 (12.3%) – without seizures. The observation period was too short in 3 patients and the assessment of seizure control was not possible. The final seizure frequency reduction correlated with the initial mono- or polytherapy $P < 0.05$ ($r = -0.22$). Most seizure free participants (88.9%) and 51.7% of responders were with initial monotherapy. The results from a multivariate regression analysis confirmed a correlation of the seizure frequency reduction at the 6th month of the study with the initial seizure frequency $P = 0.08$ ($\beta = -0.30$; 95%CI = -0.445-(-0.070)), the initial seizure severity $P = 0.034$ ($\beta = 0.226$; 95%CI = 0.035-0.847), age of patients $P = 0.05$ ($\beta = -0.31$; 95%CI = -0.032-(-0.006)), and the presence of clusters and/or status epilepticus in the disease course $P = 0.042$ ($\beta = -0.225$; 95%CI = -0.670-(-0.013)). These variables explained 26% of the changes in seizure frequency at the 6th month of the study $P < 0.001$ ($F = 7.53$). There was no similar correlation at other study periods. The final seizure frequency reduction did not correlate with any other clinical or demographic findings $P > 0.05$. There was no modification of seizure type in any of the study participants.

In 20 (27.4%) study participants LTG treatment was terminated for various reasons: 1. Adverse events from treatment – in 7 (9.6%) patients; 2. Lack of efficacy, transient efficacy or increased seizure frequency – in 7 (9.6%) patients; 3. A combination of adverse events and lack of efficacy – 2 (2.7%); 4. Other – difficulties with prescribing or finding the drug – 4 (1.5%).

In 3 patients LTG was stopped very early (before the 6th month of treatment), on the 6th month of treatment LTG was stopped in 6 other patients, on the 12th month – in 4 patients, on the 24th month – in 3 patients, on the 36th month – in 3 patients, and on the 48th month – in 2 patients. Therefore, we found gradual decrease of the percentage of patients continuing LTG treatment, i.e. the retention rate was 87.67% on the 6th month, 82.19% on the 12th month, 78.08% on the 24th month, 73.97% on the 36th month, and 69.86% on the 48th month, the most significant decrease being during the first 6 months of the treatment.

The total duration of LTG treatment was 2699 months. The total duration of effectiveness was 1684 months, therefore LTG was effective in 62.65% of the treatment time of all patients. The mean effectiveness duration was 28.56 ± 0.64 months. The effectiveness duration is presented in Table 4.

Table 4 Duration of LTG effectiveness

Effectiveness	Number of patients (N)	P%	SE
Worsening	12	17.2	4.54
No effect	14	20.0	4.82
6 months	6	8.6	3.38
9 months	1	1.4	-
12 months	7	10.0	3.61
24 months	5	7.1	3.09
30 months	2	2.9	-
36 months	5	7.1	3.09
45 months	1	1.4	-
48 months	4	5.7	-
60 months	6	8.6	3.38
72 months	3	4.3	-
84 months	1	1.4	-
96 months	2	2.9	-
106 months	1	1.4	-
Total	70	100.0	

3.2. Safety and tolerability of LTG treatment

There were adverse events from treatment in 9 (12.33%) of study participants, without any correlation with the LTG dosage $P > 0.05$ ($\chi 2 = 3.22$). The distribution of patients with somatic and associated with the central nervous system (CNS) adverse events according to LTG dosage is presented in Table 5.

Table 5 Distribution of patients with somatic and associated with the CNS adverse events according to LTG dosage

Adverse events		LTG dosage (mg/d)								Total
		50	75	100	150	200	250	300	400	
No	N	0	1	5	3	27	1	24	3	64
	P %	0%	100%	100%	60%	87.0%	100%	92.3%	100%	87.7%
Somatic	N	0	0	0	1	2	0	1	0	4
	P%	0%	0%	0%	20%	6.5%	0%	3.8%	0%	5.5%
Associated with CNS	N	1	0	0	0	2	0	1	0	4
	P%	100%	0%	0%	0%	6.5%	0%	3.8%	0%	5.5%
Somatic + associated with CNS	N	0	0	0	1	0	0	0	0	1
	P%	0%	0%	0%	20%	0%	0%	0%	0%	1.4%
Total	N	1	1	5	5	31	1	26	3	73
	P%	100%	100%	100%	100%	100%	100%	100%	100%	100.0%

More detailed information about adverse events is included in Table 6.

The severity of adverse events was most frequently moderate and they were associated with treatment termination in some patients. The most severe adverse events, associated with treatment termination were: sleepiness, generalized rash, speech disturbances, and generalized edema. Some adverse events were manifested later than the treatment onset: dizziness/vertigo, impaired balance, irritability, aggressiveness, muscle cramps and fatigue.

LTG was administered in 2 patients during pregnancy. There were no adverse events in one of them, the delivery was normal, there were no adverse events in the baby as well. A spontaneous abortion was registered in the other woman, the dosage of LTG was 300 mg/d, but the association with the drug intake was not confirmed and LTG was not terminated afterwards.

We did not confirm a correlation of adverse events with demographic and clinical factors.

Table 6 Adverse events from LTG treatment

Adverse event	Number of patients	Dosage (mg/d)	Severity	LTG termination	Duration
Dizziness/ vertigo	1	300	Moderate	No	360 days
	1	300	Severe	Decreased dose and terminated	180-360th day
	1	300	Severe	Decreased dose and terminated	180-360th day
	1	200	Moderate	Yes	360 days
Generalized edema	1	200	Severe	Yes	20 days
	1	300	Severe	Yes	50 days
Irritability	1	400	Moderate	No	180-360th day
Aggressiveness	1	400	Moderate	No	180-360th day
Speech disturbances	1	50	Severe	Yes	5 days
Visual hallucinations	1	250	Severe	Yes	120 days

Sleepiness	1	50	Severe	Yes	5 days
Insomnia	1	200	Moderate	Yes	360 days
Headache	1	200	Moderate	Yes	360 days
Diplopia	1	300	Moderate	Decreased dose and terminated	360 days
Nystagmus	1	300	Moderate	No	180 days
Impaired balance	1	300	Moderate	Decreased dose and terminated	360 days
	1	200	Moderate	No	30 days following the 48th month
Muscle cramps	1	200	Moderate	No	30 days following the 48th month
Gastrointestinal discomfort	1	300	Severe	Yes	85 days
Generalized rash	1	150	Severe	Yes	30 days
	1	200	Severe	Yes	20 days
Fatigue	1	150	Moderate	No	60 days following the 48th month
Nausea	1	300	Moderate	Decreased dose and terminated	360 days

4. Discussion

In our study LTG was applied as add-on treatment in 73 patients of mean age 36 years with long duration epilepsy with predominant severe and very frequent focal, a combination of focal and generalized, and generalized tonic-clonic seizures, refractory to the prescribed, usually combined treatment with a variety of AEDs.

There was relatively mild and stable dynamic improvement of seizure severity, which correlated with younger age, higher initial seizure frequency, lower epilepsy duration and lacking history of seizure clusters / status epilepticus in the disease course. These results could not be compared with other studies, for the lack of literature data. Investigators have focused attention on this characteristic rarely – only Smith et al. (1993) confirmed the favorable impact of LTG treatment on seizure severity in patients with focal epilepsy, no correlations were found [7].

The described above satisfactory seizure frequency reduction in 39.7% of participants (12.3% seizure free), the stable mean seizure frequency reduction (43-59%) from the 6th to the 36th month of the study, as well as the high and stable responder rate (55.7-59.4%) during the same period, are similar to the presented in literature results from double-blind, randomized studies [6-12], and to those from some open prospective studies [2, 16-18, 20-21, 23, 24]. Investigators have not focused attention on the percentage of patients with worsened seizure control during LTG treatment, probably because of the uncertain association with drug intake in all patients. The percentage of our study participants with worse seizure control, without improvement or minimal efficacy, is not a small one (16.4% and 39.7% respectively), and suggests focusing attention in future studies, moreover the lack of efficacy is the reason for LTG treatment termination in 12.3% of study participants. The final seizure frequency reduction correlated with the initial monotherapy. The initial seizure frequency and severity, age, and the presence of seizure clusters and/or status epilepticus in the disease course proved to be predictors and explained 26% of changes in seizure frequency on the 6th month of treatment $P < 0.001$ ($F = 7.53$). We did not find similar correlations in literature. The combination of LTG with VPA was more frequent (20.55%) and effective – 73.33% were responders, 40% were seizure free. There was gradual decrease of the percentage of patients continuing LTG treatment from 87.67% on the 6th month to 78.08% on the 24th month. We did not find studies in literature focusing attention on the retention rate of LTG.

LTG showed good safety and tolerability in our study participants. The frequency of reported adverse events (12.33%) was lower than literature data, they were usually with moderate severity and became a cause of treatment termination in a similar percentage of patients – 9.6% [3, 4, 8, 21, 25, 26]. Unusual adverse events were found in 9 patients – generalized rash, aggressiveness, speech disturbances, visual hallucinations, diplopia, nystagmus, muscle cramps, gastro-intestinal discomfort. They may result in LTG termination and necessitate attention for the possibility of manifestation in the medical practice. The most severe adverse events associated with rapid termination of LTG treatment were: sleepiness, speech disturbances, generalized rash, and generalized edema. Most adverse events were similar to the ones reported in literature and were not associated with higher LTG dose [2-4, 25, 27-37]. The skin rash as a typical adverse event, associated with treatment termination in 11.6% according to literature data [4, 5], was observed in 2 patients during the first month and resulted in LTG termination. Some adverse events (dizziness/vertigo, impaired balance, irritability, aggressiveness, muscle cramps, fatigue) were manifested later and were not associated with treatment termination. We registered a spontaneous abortion in 1 of the two pregnant patients, but the correlation of this adverse event with LTG intake was not confirmed. The results of a meta-analysis of Veroniki et al. (2017) proved a lower risk of fetal malformations in women on treatment with LTG and LEV compared to those on treatment with the conventional or newer-generation AEDs [38].

5. Conclusion

LTG treatment is characterized with: low and stable improvement of seizure severity, good and stable reduction of seizure frequency, a possibility of worsening of seizure control, good safety and tolerability. Future studies are needed with emphasis on seizure control worsening by LTG treatment and correlations of efficacy and adverse events from treatment with patients' demographic and clinical characteristics.

Compliance with ethical standards

Disclosure of conflict of interest

We have no conflict of interest to disclose.

Statement of ethical approval

All study procedures were performed after the approval of the Local Ethics Commission at the Medical University, Plovdiv.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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