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EEG EFFICACY OF SOME NEWER-GENERATION ANTIEPILEPTIC DRUGS IN BULGARIAN PATIENTS WITH REFRACTORY EPILEPSY

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ABSTRACT

Objectives: To perform an open, prospective study on EEG efficacy of some newer-generation antiepileptic drugs (AEDs) as add-on therapy in Bulgarian patients with drug-resistant epilepsy. **Methods:** The study was performed with the participation of 1259 patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria, for regular visits and completed diaries about seizure frequency, severity, and adverse events. EEG was performed at all visits. **Results:** Oxcarbazepine was used in 82 patients, topiramate - in 120 patients, lamotrigine – in 73 patients, levetiracetam – in 135 patients, pregabalin - in 47 patients, tiagabine – in 43 patients, gabapentin – in 18 patients, lacosamide – in 12 patients, retigabine – in 6 patients. We found EEG improvement in a small percentage of patients on treatment with most newer-generation AEDs. It correlated with male gender (oxcarbazepine), seizure severity reduction (oxcarbazepine, levetiracetam, tiagabine), seizure frequency reduction (levetiracetam, tiagabine) and initial epileptiform findings (topiramate, lamotrigine, levetiracetam, tiagabine). **Conclusion:** Most newer-generation AEDs have similar electrophysiological efficacy in a limited percentage of patients which may correlate with initial EEG findings, seizure frequency and severity dynamics, gender, and dose. Further larger comparative studies are needed to determine the impact of newer-generation AEDs on EEG.

KEYWORDS: newer-generation; antiepileptic drugs; epilepsy; EEG; efficacy

INTRODUCTION

EEG is a substantial method for diagnosis of epilepsy and monitoring of treatment efficacy in patients. Normal EEG however, does not exclude epilepsy or poor seizure control, and abnormal EEG without seizures does not necessarily mean epilepsy or high risk of seizures. That is why the main efficacy indicator reported in literature is seizure frequency improvement. Clinical efficacy of all newer-generation antiepileptic drugs (AEDs) as add-on treatment in patients with partial seizures and of some of them in patients with generalized seizures (lamotrigine, oxcarbazepine, levetiracetam, topiramate) has been confirmed by the results from a series of double-blind, randomized, placebo controlled and open prospective or retrospective studies. In a limited number of studies attention has been focused on dynamic EEG changes during treatment with newer-generation AEDs, but results about correlations of electrophysiological improvement with clinical findings are lacking. The small number of predominantly retrospective Bulgarian studies on add-on treatment with newer-generation AEDs do not provide sufficient data about long-term clinical and electrophysiological effectiveness of newer-generation AEDs.

OBJECTIVE: To perform an open, prospective study on EEG efficacy of some newer-generation antiepileptic drugs (levetiracetam, lamotrigine, topiramate, oxcarbazepine, tiagabine, gabapentin, lacosamide) as add-on therapy in Bulgarian patients with drug-resistant epilepsy.

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, and adverse events. The criteria for AEDs choice are in conformity with the approved by the National Drug Agency indications.

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 newer-generation drugs, 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,[1] a physical, and neurological status examination at every visit. EEG was performed at all visits.

Data were processed using STATA version 10 (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 outcome was EEG efficacy. Spearman coefficient (r) was used to analyze the correlation of EEG dynamics with demographic and clinical characteristics of patients, χ^2 – criterion was used for comparison of different aspects of AED efficacy. The complex influence of the significant demographic and clinical findings on EEG efficacy was determined by multivariate regression analysis. The level of significance was set at $P < 0.05$.

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). Oxcarbazepine was applied in 82 patients (44 males), topiramate - in 120 patients (69 males), lamotrigine – in 73 patients (47 males), levetiracetam – in 135 patients (86 males), pregabalin - in 47 patients (24 males), tiagabine – in 43 patients (24 males), gabapentin (GBP) – in 18 patients (11 males), lacosamide – in 12 patients (4 males), retigabine – in 6 patients (2 males). The demographic, clinical and EEG findings of participants at the study onset are presented in Table 1.

Dynamic EEG changes in patients on treatment with OCBZ, TPM, LTG, LEV and TGB on the 6th, 12th and 24th month of the study are presented in Tables 2, 3 and 4.

Electrophysiological efficacy of treatment with OCBZ

We did not find statistically significant dynamics in EEG findings of patient on treatment with OCBZ $P > 0.05$ ($\chi^2 = 7.39$; $\chi^2 = 7.39$; $\chi^2 = 11.16$ respectively) during the study. There was no correlation of EEG dynamics on the 6th, 12th and 24th month and changes in seizure frequency - $P > 0.05$ ($\chi^2 = 18.45$), $P > 0.05$ ($\chi^2 = 14.8$), $P > 0.05$ ($\chi^2 = 3.94$) respectively, and seizure severity on the 6th and 12th month of treatment $P > 0.05$ ($\chi^2 = 22.89$), $P > 0.05$ ($\chi^2 = 19.3$) respectively. EEG dynamic changes on the 24th month of the study were associated with seizure severity changes $P > 0.05$ ($\chi^2 = 24.22$). Most patients without seizure severity changes (90.9%) had the same EEG finding, the only participant with recorded EEG improvement had less severe seizures, 2 (66.7%) patients with normalized EEG also had less severe seizures, in the only patient with more severe seizures EEG was worsened. On the 6th month of study EEG dynamics correlated moderately with gender – all women (37) had no EEG changes, 34 (77.3%) men also had no EEG changes, in 5 (11.4%) men EEG was improved, in the rest 5 (11.4%) – EEG was worsened $P < 0.05$ ($r = 0.34$). There was a similar correlation on the 12th month of the study – 29 (93.5%) women had no EEG changes, 23 (69.7%) men also had no changes, in 6 (18.1%) men EEG was improved, in the rest 4 (12.1%) – EEG was worsened $P < 0.05$ ($r = 0.31$). On the 12th month of treatment there was a mild correlation of EEG dynamics with OCBZ dose – in patients on treatment with low doses of 600-900 mg/d, with doses 1500 mg/d and 2100 mg/d, and most on 1800 mg/d, there were no EEG changes $P < 0.05$ ($r = 0.25$). In patients on treatment with the most frequent dose of 1200 mg/d 23 (74.2%) EEG was not changed, in 2 (6.4%) EEG was improved, in 5 (16.2%) EEG was worsened. EEG dynamics did not correlate with other demographic and clinical characteristics $P > 0.05$.

Electrophysiological efficacy of treatment with TPM

There was a mild to moderate correlation of EEG dynamics on the 6th, 12th and 24th month of study with initial EEG $P < 0.05$ ($\chi^2 = 18.84$), $P < 0.01$ ($r = 0.27$); $P < 0.01$ ($\chi2 = 21.39$), $P < 0.001$ ($r = 0.44$); $P < 0.001$ ($\chi^2 = 27.89$), $P < 0.001$ ($r = 0.51$) respectively. EEG was improved predominantly in patients with epileptiform findings at the study onset, while in those with initial normal EEG or with nonspecific findings no dynamics was recorded. EEG dynamics did not correlate with demographic and other clinical characteristics $P > 0.05$.

Electrophysiological efficacy of treatment with LTG

There was a mild to significant correlation of EEG dynamics on the 6th, 12th and 24th month of study with initial EEG P < 0.001 (χ2 = 38.34), P < 0.001 (r = 0.45); P < 0.001 (χ2 = 25.08), P < 0.001 (r = 0.54); P < 0.01 (χ^2 = 17.91), P < 0.001 (r = 0.49) respectively. EEG was improved only in patients with epileptiform findings at the study onset, while in those with initial normal EEG or with nonspecific findings no dynamics was recorded. EEG dynamics did not correlate with demographic and other clinical characteristics P > 0.05.

Electrophysiological efficacy of treatment with LEV

There was a moderate correlation of EEG dynamics on the 6th, 12th and 24th month of study with initial EEG P < 0.001 (r = 0.45), P < 0.01 (r = 0.34), P < 0.01 (r = 0.40) respectively. EEG was improved predominantly in patients with epileptiform findings at the study onset, while in those with initial normal EEG or with nonspecific findings no dynamics was recorded. On the 6th month of treatment there was a mild correlation of EEG dynamics and changes in seizure frequency (P < 0.05, r = 0.18) and in seizure severity (P < 0.05, r = 0.21). In 62 (58.5%) patients without EEG dynamics seizure severity was the same. In 46 (43.4%) participants without EEG dynamics seizure frequency was the same, in 14 (10.69%) seizure free patients or with seizure frequency reduction EEG was improved. The multivariate regression analysis confirmed an association of EEG dynamics with initial EEG findings P = 0.003 (B = 0.575; 95%CI 0.206-0.944) and with seizure frequency changes P = 0.002 (B = -0.872; 95%CI = -1.427-(-0.316)). These variables explained 13% of EEG dynamics on the 6th month of treatment P < 0.001 (F = 9.75). On the 12th month of treatment there was no correlation of EEG dynamics with changes in seizure frequency and severity P > 0.05. On the 24th month of study there was a mild correlation of EEG dynamics with changes in seizure frequency (P < 0.05, r = 0.26) and a moderate correlation of EEG dynamics with changes in seizure severity (P < 0.01, r = 0.36). In 28 (54.9%) participants without EEG dynamics there were no changes in seizure severity. In 19 (37.3%) patients without EEG dynamics there were no changes in seizure frequency, in 12 (16%) patients without seizures or with seizure reduction EEG was improved.

Electrophysiological efficacy of treatment with TGB

There was a moderate correlation of EEG dynamics on the 6th and 24th month of study with initial EEG findings P < 0.05 (r = 0.32), P < 0.05 (r = 0.56) respectively. EEG was improved only in patients with epileptiform findings at the study onset. On the 12th month of there was no correlation of EEG dynamics with initial EEG findings P > 0.05 (χ^2 = 7.92). On the 6th month of treatment there was a moderate correlation of EEG dynamics and changes in seizure frequency P < 0.05 (r = 0.34) and in seizure severity P < 0.05 (χ^2 = 7.92), P < 0.05 (r = 0.37). The multivariate regression analysis confirmed an association of EEG dynamics with initial EEG findings and changes in seizure frequency P < 0.01 (R = 0.51; F = 6.67). These variables explained 26% of EEG dynamics – seizure frequency P = 0.003 (β = 0.441; 95%CI = 0.623-2.850), initial EEG findings P = 0.027 (β = 0.323; 95%CI = 0.099-1.510). On the 12th month of treatment there was a significant correlation of EEG dynamics with seizure frequency changes only P < 0.05 (χ^2 = 12.41), P < 0.01 (r = 0.62). On the 24th month of treatment there was a significant correlation of EEG dynamics with seizure frequency changes P < 0.05 (r = 0.54) and seizure severity changes P < 0.05 (χ^2 = 12.41). The multivariate regression analysis confirmed the predictive role of only seizure frequency changes, the latter explaining 31% of EEG dynamics on this stage of the study P < 0.05 (F = 6.37).

Electrophysiological efficacy of treatment with GBP and LCM

Dynamic EEG changes in patients on treatment with GBP and LCM on the 6th, 12th and 24th month of the study are presented in Table 5.

The comparative analysis of electrophysiological efficacy of the treatment with OCBZ, LTG, LEV, TPM and TGB did not prove any statistically significant difference on the 6th month P > 0.05 (χ^2 = 3.82), 12th month P > 0.05 (χ^2 = 3.51) and 24th month P > 0.05 (χ^2 = 5.78) of the study. The patients on treatment with GBP and LCM did not participate in the comparative statistical analysis because of the small number of participants.

Table 1. Demographic, clinical and EEG findings of study participants

Demographic/ clinical finding	**OCBZ**	**TPM**	**LTG**	**LEV**	**TGB**	**GBP**	**LCM**
Age (yrs) mean ± SE	40.46 ± 0.39	37.13±1.22	36.48±1.38	35.65±1.08	39.1±1.88	36 ± 0.81	35.83 ± 0.97
Age at epilepsy onset (yrs) mean ± SE	19.66±0.42	16.21±1.25	16.63±1.49	16.8±1.04	18.76±2.25	13.06 ± 0.79	15.5 ± 1.09
Epilepsy duration (yrs) mean ± SE	21.76 ± 0.39	21.67±1.67	20.21±1.41	29.44±2.11	20.74±3.53	22.94 ± 0.76	20.33 ± 0.92
Initial dosage (mg/d) mean ± SE	1242±2.12	224.38±0.73	230.0±8.89	1892.0±1.78	35.0 ± 1.08	1366.67 ± 4.41	320.83 ± 2.34
Etiology of epilepsy N (p%)							
- idiopathic	8 (9.8%)	9 (7.5%)	9 (12.3%)	9 (6.7%)	3 (7.0%)	2 (11.1%)	1 (8.3%)
- symptomatic	37 (45.1%)	50 (41.7%)	31 (42.5%)	62 (45.9%)	18 (41.9%)	7 (38.9%)	4 (33.4%)
- unknown	37 (45.1%)	61 (50.8%)	33 (45.2%)	64 (47.4%)	22 (51.2%)	9 (50.0%)	7 (58.3%)
EEG N (p%)							
- normal	37 (45.1%)	62 (51.7%)	33 (45.2%)	66 (48.9%)	23 (53.5%)	9 (50.0%)	4 (33.4%)
- focal activity	26 (31.7%)	36 (30.0%)	25 (34.2%)	44 (32.6%)	14 (32.6%)	5 (27.8%)	4 (33.4%)
- generalized paroxysmal activity	3 (3.7%)	5 (4.2%)	3 (4.1%)	2 (1.5%)	1 (2.3%)	0 (0%)	0 (0%)
- diffuse epilep-tiform activity	3 (3.7%)	3 (2.5%)	3 (4.1%)	4 (3.0%)	0 (0%)	1 (5.6%)	1 (8.3%)
- diffuse slow wave activity	6 (6.1%)	3 (2.5%)	3 (4.1%)	9 (6.7%)	2 (4.7%)	1 (5.6%)	1 (8.3%)
- focal + diffuse activity	5 (5.1%)	6 (5.0%)	3 (4.1%)	8 (5.9%)	3 (7.0%)	1 (5.6%)	1 (8.3%)
- scattered pathological activity, without focus formation	3 (3.7%)	5 (4.2%)	3 (4.1%)	2 (1.5%)	0 (0%)	1 (5.6%)	1 (8.3%)

* N – number of participants, p% - percentage of patients

** OCBZ – oxcarbazepine, LTG – lamotrigine, LEV – levetiracetam, TPM – topiramate, TGB – tiagabine, GBP – gabapentin, LCM - lacosamide

Table 2: Dynamic EEG changes in patients on treatment with OCBZ, TPM, LTG, LEV and TGB on the 6th month of the study.

Initial EEG finding	**EEG finding on the 6th month of study**			**Total N (p%)**
	No change N (p%)	**Worsening N (p%)**	**Improvement N (p%)**	
Normal				
- OCBZ	23 (92.0%)	2 (8.0%)	0 (0.0%)	25 (100.0%)
- TPM	56 (90.3%)	5 (8.0%)	1 (1.6%)	62 (100.0%)
- LTG	30 (93.8%)	2 (6.2%)	0 (0.0%)	32 (100.0%)
- LEV	48 (92.3%)	4 (7.7%)	0 (0.0%)	52 (100.0%)
- TGB	21 (91.3%)	2 (8.7%)	0 (0.0%)	23 (100.0%)
Nonspecific activity				
- OCBZ	7 (100.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
- TPM	7 (87.5%)	1 (12.5%)	0 (0.0%)	8 (100.0%)
- LTG	5 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)
- LEV	7 (77.8%)	1 (11.1%)	1 (11.1%)	9 (100.0%)
- TGB	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)

Epileptiform activity				
- OCBZ	22 (68.8%)	4 (12.5%)	6 (18.7%)	32 (100.0%)
- TPM	33 (67.3%)	4 (8.2%)	12 (24.5%)	49 (100.0%)
- LTG	23 (66.7%)	2 (5.7%)	10 (28.6%)	35 (100.0%)
- LEV	24 (50.0%)	4 (8.3%)	20 (41.7%)	48 (100.0%)
- TGB	12 (66.7%)	2 (11.1%)	4 (22.2%)	18 (100.0%)
Total				
- OCBZ	52 (81.2%)	6 (9.4%)	6 (9.4%)	64 (100.0%)
- TPM	96 (80.7%)	10 (8.4%)	13 (10.9%)	119 (100.0%)
- LTG	58 (80.6%)	4 (5.5%)	10 (13.9%)	72 (100.0%)
- LEV	79 (72.5%)	9 (8.3%)	21 (19.2%)	109 (100.0%)
- TGB	34 (81.0%)	4 (9.5%)	4 (9.5%)	42 (100.0%)

Table 3. Dynamic EEG changes in patients on treatment with OCBZ, TPM, LTG, LEV and TGB on the 12th month of the study

Initial EEG finding	**EEG finding on the 12th month of the study**			**Total** N (p%)
	No change N (p%)	Worsening N (p%)	Improvement N (p%)	
Normal				
- OCBZ	23 (92.0%)	2 (8.0%)	0 (0.0%)	25 (100.0%)
- TPM	44 (93.6%)	3 (6.4%)	0 (0.0%)	47 (100.0%)
- LTG	27 (96.4%)	1 (3.6%)	0 (0.0%)	28 (100.0%)
- LEV	27 (84.4%)	5 (15.6%)	0 (0.0%)	32 (100.0%)
- TGB	13 (86.7%)	3 (13.3%)	0 (0.0%)	16 (100.0%)
Nonspecific activity				
- OCBZ	6 (100.0%)	0 (0.0%)	0 (0.0%)	6 (100.0%)
- TPM	3 (60.0%)	1 (20.0%)	1 (20.0%)	5 (100.0%)
- LTG	3 (75.0%)	0 (0.0%)	1 (25.0%)	4 (100.0%)
- LEV	4 (57.1%)	3 (42.9%)	0 (0.0%)	7 (100.0%)
- TGB	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Epileptiform activity				
- OCBZ	23 (69.7%)	2 (6.1%)	8 (24.2%)	33 (100.0%)
- TPM	23 (57.5%)	4 (10.0%)	13 (32.5%)	40 (100.0%)
- LTG	14 (66.7%)	1 (6.7%)	13 (26.7%)	28 (100.0%)
- LEV	20 (55.6%)	2 (5.6%)	14 (38.9%)	36 (100.0%)
- TGB	10 (66.7%)	1 (6.7%)	4 (26.6%)	15 (100.0%)
Total				
- OCBZ	52 (81.2%)	6 (9.4%)	6 (9.4%)	64 (100.0%)
- TPM	70 (76.1%)	8 (8.7%)	14 (15.3%)	92 (100.0%)
- LTG	44 (73.3%)	2 (3.3%)	14 (23.4%)	60 (100.0%)
- LEV	51 (68.0%)	10 (13.4%)	14 (18.6%)	75 (100.0%)
- TGB	24 (77.5%)	3 (9.6%)	4 (12.9%)	31 (100.0%)

Table 4. Dynamic EEG changes in patients on treatment with OCBZ, TPM, LTG, LEV and TGB on the 24th month of the study

Initial EEG finding	**EEG finding on the 24th month of the study**			**Total** N (p%)
	No change N (p%)	**Worsening N (p%)**	**Improvement N (p%)**	
Normal				
- OCBZ	15 (83.3%)	3 (16.7%)	0 (0.0%)	18 (100.0%)
- TPM	36 (97.3%)	1 (2.7%)	0 (0.0%)	37 (100.0%)
- LTG	19 (90.5%)	2 (9.5%)	0 (0.0%)	21 (100.0%)
- LEV	19 (86.4)	3 (13.6%)	0 (0.0%)	22 (100.0%)
- TGB	8 (100.0%)	0 (0.0%)	0 (0.0%)	8 (100.0%)
Nonspecific findings				
- OCBZ	2 (50.0%)	1 (25.0%)	1 (25.0%)	4 (100.0%)
- TPM	3 (75.0%)	1 (25.0%)	0 (0.0%)	4 (100.0%)
- LTG	3 (75.0%)	0 (0.0%)	1 (25.0%)	4 (100.0%)
- LEV	3 (75.0%)	0 (0.0%)	1 (25.0%)	4 (100.0%)

- TGB	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Epileptiform activity				
- OCBZ	16 (76.2%)	2 (9.5%)	3 (14.3%)	21 (100.0%)
- TPM	23 (79.3%)	2 (6.9%)	4 (13.8%)	29 (100.0%)
- LTG	11 (45.8%)	0 (0.0%)	13 (54.2%)	24 (100.0%)
- LEV	12 (48.0%)	1 (4.0%)	12 (48.0%)	25 (100.0%)
- TGB	4 (50.0%)	2 (25.0%)	2 (25.0%)	2 (25.0%)
Total				
- OCBZ	33 (76.7%)	6 (13.9%)	4 (9.3%)	43 (100.0%)
- TPM	62 (88.6%)	4 (5.7%)	4 (5.7%)	70 (100.0%)
- LTG	33 (67.3%)	2 (4.1%)	14 (28.6%)	49 (100.0%)
- LEV	34 (66.7%)	4 (7.8%)	13 (25.5%)	51 (100.0%)
- TGB	12 (75.0%)	2 (12.5%)	2 (12.5%)	16 (100.0%)

Table 5: Dynamic EEG changes in patients on treatment with GBP and LCM on the 6th, 12th and 24th month of the study.

	EEG dynamics					
	No change N (p%)	**Norma-lization** N (p%)	**Improvement of diffuse epileptiform activity** N (p%)	**Improvement of focal/ paroxysmal activity** N (p%)	**Worsening** N (p%)	**Total** N (p%)
6th month						
- GBP	15 (83.3%)	1 (5.6%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	18 (100.0%)
- LCM	8 (66.6%)	2 (16.7%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	12 (100.0%)
12th month						
- GBP	13 (86.6%)	1 (6.7%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	15 (100.0%)
- LCM	3 (37.5%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	8 (100.0%)
24th month						
- GBP	12 (92.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (100.0%)
- LCM	1 (33.3%)	1 (33.3%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	3 (100.0%)

DISCUSSION

We found EEG improvement in a small percentage (less than 10%) of patients on treatment with OCBZ which correlated mildly in some periods of the study with male gender, seizure severity reduction and dose of 1200 mg/d. There were few studies results reported in literature about a favorable effect of OCBZ on abnormal EEG findings - focal pathological activity and generalized paroxysmal activity.[2-5]

EEG was also improved in a small percentage (up to 15.3%) of patients on treatment with TPM, predominantly in those with initial epileptiform findings. Results from single studies in literature supported the favorable effect of TPM on abnormal EEG findings (background slow wave activity and generalized epileptic discharges) in some patients, in conformity with the clinical effect.[6] It was explained with a probable inhibition of processes of interictal epileptic activity generation by TPM.[7]

EEG was improved in some (13.9-28.6%) patients on treatment with LTG, predominantly in those with initial epileptiform findings. Similar results about LTG electrophysiological efficacy on the background, interictal and ictal EEG activity were reported in literature.[8-14]

We discovered gradual increase of the percentage of patients on treatment with LEV and EEG improvement (up to 38.7%), predominantly in those with initial epileptiform findings. On the 6th month of treatment predictors of this efficacy were initial EEG findings and seizure frequency changes $P < 0.001$ ($F = 9.75$). Later EEG dynamics correlated with initial EEG findings and seizure frequency and severity changes. Similar data about good efficacy of LEV on abnormal EEG findings (background, diffuse abnormal activity and generalized epileptic discharges, here included photoparoxysmal response in patients with juvenile myoclonic epilepsy) in a significant percentage of patients and in conformity with clinical efficacy were reported by some other investigators.[15-25]

EEG was improved in some patients on treatment with TGB (up to 25%). On the 6th month of treatment EEG dynamics correlated moderately with the changes in seizure frequency and severity and initial EEG findings and seizure frequency changes proved to be its predictors $P < 0.01$ ($R = 0.51$; $F = 6.67$). On the 12th month of study EEG dynamics correlated significantly only with seizure frequency changes $P < 0.05$ ($\chi^2 = 12.41$), $P < 0.01$ ($r = 0.62$). On the 24th month EEG dynamics correlated significantly with changes in seizure severity $P < 0.05$ ($\chi^2 = 12.41$) and frequency $P < 0.05$ ($r = 0.54$), the latter explaining 31% of EEG dynamics $P < 0.05$ ($F = 6.37$). We found the results of only one study in literature performed by Kälviäinen et al. with 37 participants with partial epilepsy in which the EEG effect of TGB was studied for a period of 18-24 months. The percentage of

patients with EEG dynamics and with improvement was slightly higher (respectively 40% and 16%) compared to our study (respectively 25% and 12.5%), but no correlation with clinical characteristics was invstigated.[26]

EEG was improved in a small percentage of patients on treatment with GBP (less than 10%) and in single patients on treatment with LCM. During the only study on EEG efficacy of GBP in children Naidenov et al. (2002) confirmed reduction of focal and generalized paroxysmal activity in most participants.[27] We did not find literature data about electrophysiological efficacy of LCM.

Our results did not prove a statistically significant difference between most newer-generation AEDs regarding their electrophysiological efficacy and we did not find any comparative studies on this aspect of effectiveness in literature.

CONCLUSION

Most newer-generation AEDs have similar electrophysiological efficacy in a limited percentage of patients which may correlate with initial EEG findings, seizure frequency and severity dynamics, gender, and dose. Further larger comparative studies are needed to determine the impact of newer-generation AEDs on EEG.

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