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Original Article

Topiramate Effectiveness as Add-on Therapy in Bulgarian Patients with Drug-resistant Epilepsy

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Abstract

Introduction: There are no reliable prospective studies on the effectiveness of topiramate in Bulgarian adult patients with drug-resistant epilepsy.

Aim: The aim of the study was to conduct an open, prospective study on various aspects of topiramate (TPM) effectiveness in Bulgarian patients with drug-resistant epilepsy.

Patients and methods: The study included patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria. Patients completed diaries for seizure frequency, seizure severity, and adverse events. There were regular documented visits at 3 or 6 months during the first year of TPM treatment and at 6 months afterwards, with a dynamic assessment of seizure frequency, severity, adverse events, and EEG recordings.

Results: TPM was used as an add-on treatment in 120 patients (69 males, mean age 37 years). There was a relatively mild and stable dynamic improvement of seizure severity, a satisfactory seizure frequency reduction in 37% of participants, a stable mean seizure frequency reduction (47%) from month 6 to month 24 of treatment and a stable responder rate (48-51%) during the same period. New seizure types (focal with impaired awareness with/without evolution to bilateral tonic-clonic seizures) occurred in 5 patients. There were adverse events (dizziness/vertigo, irritability, speech disturbances, memory impairment, concentration problems, tremor, loss of appetite and weight, weakness, numbness, bradypsychia, confusion, visual hallucinations, sleepiness, insomnia, headache, itching, unstable gait, nausea, and vomiting) in 20% of patients.

Conclusions: TPM treatment is associated with low and stable improvement of seizure severity, good and stable improvement of seizure frequency, possible worsening of seizure control and appearance of new seizure types, good safety and tolerability.

Keywords

adverse events, efficacy, seizure, tolerability

INTRODUCTION

Topiramate (TPM) is a newer-generation antiepileptic drug (AED) with several mechanisms of action: interaction with GABA, reduction of the effect of excitatory neurotransmitters through blockage of glutamatergic kainate and AMPA receptors, inhibition of calcium and sodium channels, carboanhydrase inhibition. TPM has been confirmed as

a monotherapy and add-on therapy drug in patients with focal seizures with and without evolution to bilateral tonic-clonic seizures and generalized tonic-clonic seizures in patients above 2 years of age, as well as add-on therapy in children and adults with Lennox-Gastaut syndrome. The favourable pharmacokinetics, lack of enzyme induction activity, and limited drug interactions have been proven as other advantages explaining the frequent usage of TPM in the medical practice. Some disadvantages requiring special attention are: the necessity of slow up-titration and the poorer tolerability with typical and frequent adverse events – cognitive disturbances, loss of weight, nephrolithiasis.

Seizure frequency dynamics is the main efficacy outcome reported by investigators from randomized, double-blind, placebo-controlled, and open prospective studies about the add-on treatment with TPM. Dose-dependent variations have been reported in 27% to 52% of responders in randomized, double-blind, placebo-controlled studies[1-8] and up to 82% in patients with focal seizures, up to 75% in patients with generalized tonic-clonic seizures, and up to 67% in patients with absences in open prospective studies.[9-14] Attention has not been focused on seizure severity, as well as on the correlation of seizure frequency and severity dynamics with demographics and clinical findings. There are no reliable prospective studies on the effectiveness of TPM 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 TPM in Bulgarian patients with drug-resistant epilepsy will provide additional useful data for the medical practice.

AIM

To perform an open, prospective study on various aspects of TPM effectiveness in Bulgarian patients with drug-resistant epilepsy.

PATIENTS AND METHODS

This is an open prospective study with a possibility of using available detailed retrospective information about some participants. It included 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 obtaining approval from the Local Ethics Committee of 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. A consent of the patient and relatives about giving the required information and medical records; 3. Age ≥ 18 years; 4. A 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. A completed diary about seizure frequency and 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 indications approved by the National Drug Agency.

Data were collected by a trained neurologist specialized in epilepsy through examination of the patients' medical documentation and a detailed interview about the disease onset, heredity, concomitant diseases, type and etiology of epilepsy, seizure type, frequency and severity, treatment with AEDs, efficacy of TPM, and adverse events from treatment. The seizure frequency dynamics was based on information from 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 Bulgarian version of the Liverpool Adverse Events profile validated by Kuzmanova et al.[15], a physical, and neurological status examination at every visit.

Data were analysed using STATA (Stata Corp., College Station, TX, USA) and SPSS v. 19.0 (SPSS Inc., Chicago, IL, USA). The results for quantitative variables were expressed as means ± SE (standard error) and the results for qualitative variables were given in 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 χ^2 test and Friedman test. The level of significance was set at $p<0.05$.

RESULTS

The total number of patients diagnosed with epilepsy who attended the Clinic of Neurology between 2003 and 2016 was 1259 (in- and outpatients). TPM was used in 120 patients aged 18 to 65 years (mean age 37±13.36 years). The onset of epilepsy varied from 1 day to 54 years of age, mean age onset 16±13.69 years. The mean epilepsy duration varied from 2 to 60 years, mean duration was 22±12.7 years. The observation continued from 5 days to 144 months, (mean duration 37±29.67 months). The commonest dosage of TPM was 200 or 300 mg/d, mean dosage 224±7.99 mg/d. The demographic and clinical characteristics of study participants are presented in **Table 1**.

The percentage of participants with seizure severity

Table 1. Demographic and clinical characteristics of patients on treatment with TPM

Demographic / clinical characteristic	N	P (%)	SE
Gender			
- males	69	57.5	4.53
- females	51	42.5	4.53
Age at baseline (years)			
- ≤ 25	35	29.2	4.17
- 26-35	24	20.0	3.67
- 36-45	18	15.0	3.27
- > 45	43	35.8	4.39
Age at epilepsy onset			
- ≤ 18 years	83	69.2	4.23
- > 18 years	37	30.8	4.23
Epilepsy duration			
- ≤ 10 years	25	20.8	3.72
- > 10 years	95	79.2	3.72
Study duration (months)			
< 6	6	5.0	2.0
- 6	21	17.5	3.48
- 12	16	13.3	3.11
- 24	17	14.2	3.20
- 36	13	10.8	2.85
- 48	16	13.3	3.11
- 60	13	10.8	2.85
- 72	8	6.7	2.29
- 84	6	5.0	2.0
- 96	1	0.8	-
- 120	1	0.8	-
-144	2	1.7	-
Seizure type			
- focal seizures with impaired awareness	4	3.3	-
- focal with evolution to bilateral tonic-clonic seizures	49	40.8	4.51
- generalized tonic-clonic seizures	28	23.3	3.88
- generalized atonic seizures	1	0.8	-
- focal and generalized seizures	38	31.7	4.27
Type of epilepsy			
- focal	76	63.3	4.42
- generalized	44	36.7	4.42
Etiology of epilepsy			
- genetic	9	7.5	2.41
- structural/metabolic (traumatic, vascular, inflammatory, tumor, encephalopathy, hippocampal sclerosis, brain malformations	50	41.7	4.52
- unknown	61	50.8	4.58
Concomitant diseases			
- no	76	63.3	4.42
- somatic	34	28.3	4.13
- psychiatric	5	4.2	1.83
- neurological	5	4.2	1.83
Seizure clusters and/or status epilepticus in the disease course			
- yes	58	48.3	4.58
- no	62	51.7	4.58
Cognitive functions			
- normal	96	80.0	3.67
- mental retardation/ cognitive deficit	24	20.0	3.67
Neurological status			
- normal	93	77.5	3.83
- with focal neurological signs	27	22.5	3.83

Recent seizure frequency			
- 1-11 seizures/ year	6	5.0	2.0
- 1-3 seizures/ month	33	27.5	4.09
- 1-6 seizures/ week	66	55.0	4.56
- daily	15	12.5	3.03
Recent seizure severity			
- mild	13	10.8	2.85
- severe	107	89.2	2.85
AED treatment at study onset			
- monotherapy	56	46.7	4.57
- polytherapy	64	53.3	4.57
Initial TPM dosage			
- 75 mg/d	1	0.83	-
- 100 mg/d	6	5.00	2.0
- 150 mg/d	8	6.67	2.29
- 200 mg/d	67	55.83	4.55
- 250 mg/d	3	2.50	-
- 300 mg/d	30	25.00	3.97
- 400 mg/d	5	4.17	1.83
Concomitant AEDs or monotherapy TPM			
- monotherapy TPM 200 mg/d	1	0.83	-
- VPA 1000-2000 mg/d	38	31.67	4.26
- CBZ 400-1000 mg/d	6	5.00	2.0
- CZP 0.5 mg/d	2	1.67	-
- PHT 100 mg/d	1	0.83	-
- OCBZ 1200-1800 mg/d	6	5.00	2.0
- VPA 1500-2000 mg/d + CBZ 400-1200 mg/d	14	11.67	2.94
- VPA 900-2500 mg/d + OCBZ 900-2100 mg/d	14	11.67	2.94
- VPA 1250-2000 mg/d + CZP 1.5-4 mg/d	5	4.17	1.83
- VPA 2000 mg/d + PB 150 mg/d	1	0.83	-
- VPA 1500-1750 mg/d + LEV 2000-3000 mg/d	5	4.17	1.83
- VPA 2000 mg/d + LTG 200 mg/d	1	0.83	-
- VPA 1500 mg/d + PHT 150-300 mg/d	2	1.67	-
- VPA 2000 mg/d + PB 150 mg/d	1	0.83	-
- CBZ 600-1050 mg/d + CZP 1-6 mg/d	3	2.50	-
- CBZ 800 mg/d + Diazepam 10 mg/d	1	0.83	-
- PHT 200 mg/d + OCBZ 1800 mg/d	2	1.67	-
- LEV 3000 mg/d + LTG 400 mg/d	1	0.83	-
- OCBZ 1800 mg/d + LEV 2000 mg/d	3	2.50	-
- TGB 30 mg/d + LEV 2000 mg/d	2	1.67	-
- OCBZ 1200 mg/d + LTG 300 mg/d	1	0.83	-
- CZP 2 mg/d + OCBZ 1800 mg/d	1	0.83	-
- PHT 200 mg/d + LTG 400 mg/d	1	0.83	-
- VPA 1500-1800 mg/d + OCBZ 600-1200 mg/d + CZP 1.5-6 mg/d	3	2.50	-
- CBZ 600 mg/d + CZP 6 mg/d + VPA 1000 mg/d	1	0.83	-
- VPA 1000 mg/d + CZP 4 mg/d + PB 200 mg/d	1	0.83	-
- VPA 1200 mg/d + CBZ 800 mg/d + PHT 100 mg/d	1	0.83	-
- VPA 1500 mg/d + OCBZ 1200-1800 mg/d + GBP 1200-1600 mg/d	2	1.67	-
- VPA 1500 mg/d + LEV 2000 mg/d + TPM 300 mg/d	1	0.83	-
EEG at the study onset			
- normal	62	51.7	4.58
- focal activity	36	30.0	4.20
- generalized paroxysmal activity	5	4.2	1.83
- diffuse epileptiform activity	3	2.5	-
- scattered abnormalities, no focus formation	5	4.2	1.83
- diffuse slow-wave activity	3	2.5	-
- focal + diffuse findings	6	5.0	2.0

Abbreviations - VPA: valproate; CBZ: carbamazepine; PHT: phenytoin; PB: phenobarbital; OCBZ: oxcarbazepine; TPM: topiramate; GBP: gabapentin; CZP: clonazepam; LTG: lamotrigine; LEV: levetiracetam; TGB: tiagabine

reduction persisted between months 6 and 24 (18.8% at 6 months, 17.6% at 12 months, 16% at 24 months). The number of patients continuing the TPM treatment after 24 months was very small so they were not included in the statistical analyses. We came to the conclusion about a mild and stable improvement of the seizure severity by treatment with TPM.

There was no correlation of the seizure severity dynamics with the initial seizure severity at 6, 12, and 24 months of treatment (χ^2=3.45, χ^2=2.98, χ^2=9.65, respectively, p>0.05). The seizure severity improvement did not correlate with the TPM dosage (χ^2=19.77, p>0.05).

The assessment of seizure frequency up to 24 months of TPM treatment is presented in **Table 2**.

The most significant improvement of the seizure frequency was observed at 6 months of treatment followed by retention of a high responder rate of about 50% (48.33% at 6 months, 56.5% at 12 months, 51.3% at 24 months) and gradual increase of the percentage of patients without seizures up to 14.5% **(Table 2)**. The statistical analysis of the results confirmed that there was no significant decrease in the seizure frequency between month 6 and month 12, and between month 6 and month 24 (Friedman Test = 3.32, p>0.05). We found the following dynamics in the mean seizure frequency reduction – 46.93% at 6 months, 49.14% at 12 months, and 47.31% at 24 months. Therefore, regarding seizure frequency, the efficacy of TPM was good and stable for the study period.

Table 2. Seizure frequency assessment during treatment with TPM

	Seizure frequency dynamics				Total N (p%)
	No change N (p%)	Reduction 50-99% N (p%)	Reduction 100% N (p%)	Increase N (p%)	
At 6 months	51 (43.2%)	45 (38.1%)	12 (10.2%)	10 (8.5%)	118 (100.0%)
At 12 months	34 (37.0%)	38 (41.3%)	14 (15.2%)	6 (6.5%)	92 (100.0%)
At 24 months	30 (39.5%)	28 (36.8%)	11 (14.5%)	7 (9.2%)	76 (100.0%)

The seizure frequency dynamics did not correlate with the initial seizure frequency at 6, 12, and 24 months of treatment (χ^2=10.78, χ^2=13.39, χ^2=8.69, respectively, p>0.05). The seizure frequency improvement did not correlate with the TPM dosage (χ^2 =17.74, p>0.05).

The seizure frequency improvement by TPM monotherapy or various combinations of TPM with other AEDs at the end of the study is presented in **Table 3**. In one case, the investigational drug was added to another AEM and then the other one was withdrawn in a short period of time due to inefficacy.

The small number of patients treated with various combinations is a limitation for statistical analyses. Three combinations with other AEDs proved to be more frequent: 1. VPA + TPM in 37 (31.09%) patients – effective in 27.03%, 5.4% were seizure free; 2. VPA + OCBZ + TPM in 14 (11.76%) patients – there were no responders; 3. VPA + CBZ + TPM - in 14 (11.76%) patients, only 2 (14.29%) were responders. Seizure frequency did not change in the participant on monotherapy with TPM.

At the end of the study the seizure frequency was increased in 23 (19.3%) participants, there was no or unsatisfactory improvement (seizure frequency reduction <50%) in 52 (43.7%) patients. Responders were 44 (37%) patients – 17 (14.3%) were with seizure reduction >75%, 8 (6.7%) – without seizures. The final seizure frequency reduction correlated with a low initial seizure frequency (χ^2=11.21, p<0.05). Responders were the participants with a low initial seizure frequency (1 to 11 seizures/year – 66.7%) and those with very frequent (daily) seizures at the study baseline (53.3%). The final seizure frequency reduction did not correlate with any other clinical or demographic findings (p>0.05).

There was a modification of the seizure type in a small number of patients: a manifestation of focal seizures with impaired awareness in 2 patients with generalized epilepsy and of GTCS in 1 patient with focal epilepsy at 6 months of study, focal seizures with/without impaired awareness in one patient with generalized epilepsy at 36 months of study, focal seizures with impaired awareness in one patient with focal seizures without impaired awareness and generalized tonic-clonic seizures at 60 months of study.

In 33 (27.5%) patients TPM treatment was discontinued for various reasons: 1. Adverse events from treatment – in 13 (10.8%) patients; 2. Lack of efficacy, transient efficacy or increased seizure frequency – in 11 (9.2%) patients; 3. A combination of adverse events and lack of efficacy – 7 (5.8%); 4. Other – difficulties with prescribing or finding the drug – 2 (1.7%).

In 6 patients, TPM was stopped very early (before 6 months of treatment), at 6 months of treatment TPM was stopped in 5 other patients, at 12 months – in 4 patients, at 24 months – in none, at 36 months – in 3 patients, and at 48 months in 2 patients. Therefore, we found a gradual decrease of the percentage of patients continuing TPM treatment, i.e. the retention rate was 90.83% at 6 months, 87.5% at 12 and 24 months, 85% at 36 months, 83.33% at 48 months, the decrease being significant during the first 6 months.

The total duration of TPM treatment was 4377 months. The total duration of effectiveness was 2456 months, therefore TPM was effective in 56.11% of the treatment time of

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

TPM monotherapy/ AEDs in combination with TPM	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%)	
Monotherapy TPM 200 mg/d	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
VPA 1000-2000 mg/d	16 (43.2%)	5 (13.5%)	8 (21.6%)	2 (5.4%)	6 (16.2%)	37 (100%)
CBZ 400-1000 mg/d	3 (50%)	1 (16.7%)	1 (16.7%)	0 (0%)	1 (16.7%)	6 (100%)
CZP 0.5 mg/d	0 (0%)	1 (50%)	0 (0%)	1 (50%)	0 (0%)	2 (100%)
PHT 100 mg/d	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1(100%)
OCBZ 1200-1800 mg/d	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3%)	6 (100%)
VPA 1500-2000 mg/d + CBZ 400-1200 mg/d	4 (28.6%)	2 (14.3%)	2 (14.3%)	0 (0%)	6 (42.9%)	14 (100%)
VPA 900-2500 mg/d + OCBZ 900-2100 mg/d	5 (35.7%)	4 (28.6)	0 (0%)	0 (0%)	5 (35.7%)	14 (100%)
VPA 1250-2000 mg/d + CZP 1.5-4 mg/d	4 (80%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	5 (100%)
VPA 2000 mg/d + PB 150 mg/d	0 (0%)	1(100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
VPA 1500-1750 mg/d + LEV 2000-3000 mg/d	1 (20%)	2 (40%)	1 (20%)	0 (0%)	1 (20%)	5 (100%)
VPA 2000 mg/d + LTG 200 mg/d	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
VPA 1500 mg/d + PHT 150-300 mg/d	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
CBZ 600-1050 mg/d + CZP 1-6 mg/d	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
CBZ 800 mg/d + Diazepam 10 mg/d	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
PHT 200 mg/d + OCBZ 1800 mg/d	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
LEV 3000 mg/d + LTG 400 mg/d	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
OCBZ 1800 mg/d + LEV 2000 mg/d	1 (33.3%)	0 (0%)	2 (66.7%)	0 (0%)	0 (0%)	3 (100%)
TGB 30 mg/d + LEV 2000 mg/d	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
OCBZ 1200 mg/d + LTG 300 mg/d	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
CZP 2 mg/d + OCBZ 1800 mg/d	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
PHT 200 mg/d + LTG 400 mg/d	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
VPA 1500-1800 mg/d + OCBZ 600-1200 mg/d + CZP 1.5-6 mg/d	2 (66.7%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	3 (100%)
CBZ 600 mg/d + CZP 6 mg/d + VPA 1000 mg/d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1(100%)	1 (100%)
VPA 1000 mg/d + CZP 4 mg/d + PB 200 mg/d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)
VPA 1200 mg/d + CBZ 800 mg/d + PHT 100 mg/d	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
VPA 1500 mg/d + OCBZ 1200-1800 mg/d + GBP 1200-1600 mg/d	2(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
VPA 1500 mg/d + LEV 2000 mg/d + TPM 300 mg/d	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)

Abbreviations. VPA: valproate; CBZ: carbamazepine; PHT: phenytoin; PB: phenobarbital; OCBZ: oxcarbazepine; TPM: topiramate; GBP: gabapentin; CZP: clonazepam; LTG: lamotrigine; LEV: levetiracetam; TGB: tiagabine

all patients. The mean effectiveness duration was 20±5.34 months. The effectiveness duration is presented in **Table 4**.

Safety and tolerability of TPM treatment

There were adverse events from treatment in 24 (20%) of the study participants, without any correlation with the TPM dosage (χ^2=16.71, p>0.05). The distribution of patients with somatic and CNS-associated adverse events according to the TPM dosage is presented in **Table 5**. More detailed information about adverse events is included in **Table 6**.

The commonest adverse events were: loss of appetite and weight – in 10 (8.33%), asthenia – in 6 (5%), sleepiness – in 4 (3.33%) patients. The severity of adverse events was most frequently moderate and severe and they were associated with treatment termination in some patients.

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Table 4. Duration of TPM effectiveness

Effectiveness	Number of patients (N)	P%	SE
Worsening	9	7.6	1.56
No effect	45	37.8	4.46
6 months	7	5.9	2.17
9 months	1	0.8	-
12 months	12	10.1	2.77
18 months	1	0.8	-
20 months	1	0.8	-
23 months	1	0.8	-
24 months	10	8.4	6.52
30 months	2	1.7	-
36 months	7	5.9	2.17
45 months	1	0.8	-
48 months	6	5.0	2.01
59 months	1	0.8	-
60 months	4	3.4	-
72 months	5	4.2	2.17
80 months	1	0.8	-
84 months	2	1.7	-
96 months	1	0.8	-
120 months	1	0.8	-
144 months	1	0.8	-
Total	119	100.0	

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

Adverse events		TPM dosage (mg/d)							Total
		75	100	150	200	250	300	400	
None	N	1	4	6	55	2	25	4	97
	p%	100%	66.7%	75%	82.1%	66.7%	83.3%	80%	80.8%
Somatic	N	0	0	1	3	1	2	0	7
	p%	0%	0%	12.5%	4.5%	33.3%	6.7%	0%	5.8%
Associated with CNS	N	0	2	0	6	0	1	1	10
	p%	0%	33.3%	0%	8.9%	0%	3.3%	20%	8.4%
Somatic + associated with CNS	N	0	0	1	3	0	2	0	6
	p%	0%	0%	12.5%	4.5%	0%	6.7%	0%	5.0%
Total	N	1	6	8	67	3	30	5	120
	p%	100%	100%	100%	100%	100%	100%	100%	100.0%

The most severe adverse events associated with treatment termination were: asthenia, sleepiness, and speech disturbances. Some adverse events (visual hallucinations, memory impairment, loss of appetite and weight) were manifested later than treatment beginning. We did not confirm a correlation of adverse events with demographic and clinical factors.

DISCUSSION

In our study, TPM was used as an add-on treatment in 120 patients (mean age 37 years) with long duration epilepsy with predominant severe and 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 a relatively mild and stable dynamic improvement of the seizure severity. These results could not be compared with other studies for the lack of literature data.

The described satisfactory seizure frequency reduction in 37% of the participants (6.7% seizure free), the stable mean seizure frequency reduction (46.93-47.31%) from 6 months to 24 months of the study, as well as the high and stable responder rate (48.3-51.3%) during the same period,

Table 6. Adverse events from TPM treatment

Adverse event	Number of patients	Dosage (mg/d)	Severity	TPM termination	Duration of adverse event
Dizziness / vertigo	1	200	Moderate	Yes	60 days
Irritability	1	300	Mild	No	150 days
	1	200	Moderate	Yes	360 days after 12 months
Speech disturbances	1	200	Moderate	No	11 days
	1	100	Severe	Yes	5 days
Memory impairment	1	100-250	Moderate	No	420 days
	1	100	Severe	Yes	90 days
	1	200	Moderate	Yes	360 days after 12 months
Concentration problems	1	300	Severe	Yes	180 days
Tremor of hands	1	200	Moderate	No	90 days
Loss of appetite and weight	1	200	Moderate	Yes	330 days
	1	300	Severe	Yes	180 days
	1	200	Severe	Yes	180 days
	1	300	Moderate	Yes	360 days
	1	200	Severe	Yes	90 days
	1	300	Mild	No	150 days
	1	150	Moderate	Yes	170 days
	1	300	Moderate	No	150 days
	1	250	Moderate	No	1260 days
	1	200	Moderate	Yes	1260 days after 12 months
Asthenia	1	300	Severe	Yes	180 days
	1	200	Moderate	No	11 days
	1	200	Severe	Yes	90 days
	1	200	Severe	Yes	55 days
	1	200	Severe	Yes	30 days
	1	150	Mild	No	1750 days
Numbness of extremities	1	200	Severe	Yes	30 days
Bradypsychia	1	200	Severe	Yes	270 days
Confusion	1	100	Severe	Yes	90 days
Visual hallucinations	1	200	Severe	Yes	180 days after 6 months
Sleepiness	1	200	Moderate	No	11 days
	1	200	Severe	Yes	90 days
	1	100	Severe	Yes	5 days
	1	400	Moderate	No	90 days
Insomnia	1	100	Severe	Yes	90 days
Headache	1	300	Mild	No	50 days
Itching	1	300	Mild	No	150 days
Unstable gait	1	200	Severe	Yes	55 days
Nausea	1	150	Mild	No	150
Vomiting	1	200	Severe	Yes	60 days
	1	200	Severe	Yes	55 days

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are similar to the results obtained in some double-blind, randomized studies[6,16,17], and to those from some open prospective studies with the exception of a lacking dose-dependent effect reported by some investigators.[2,16] Seizures became significantly rarer in patients with low or very high initial seizure frequency. Investigators have not focused attention on the percentage of patients with worsened seizure control during TPM treatment, probably because of the uncertain association with the 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 (19.3% and 43.7% respectively), and suggests focusing attention in future studies, moreover the lack of efficacy is the reason for TPM treatment termination in 15% of study participants.

The appearance of new seizure types in 5 patients (focal seizures with impaired awareness with/without evolution to bilateral tonic-clonic seizures), raises the question whether this phenomenon is associated with some of its mechanisms of action or is a result of the disease course. There are no similar data and a discussion of this problem in literature.

The following combinations of TPM with other AEDs were more frequent: 1. VPA + TPM (31.09%) – 27.03% responders; 2. OCBZ + TPM – (11.76%) - no responders; 3. CBZ + TPM (11.75%) – with low efficacy (14.29% responders). There was a significant decrease of the percentage of patients continuing TPM treatment to 90.83% at 6 months followed by a retention rate of 87.5% at 12 and 24 months, and a mild decrease to 83.33% at 48 months of study. We found only one retrospective study with 470 patients in literature focusing attention on the retention rate of TPM. Bootsma et al. reported a significantly higher and quicker decrease of TPM retention rate – from 53% at the end of the first year to 30% after 4 years, mainly because of adverse events and/or inefficacy.[18]

TPM showed good safety and tolerability in our study participants. The frequency of reported adverse events (20%) is similar to the literature data, they are usually with moderate severity and become a cause of treatment termination in a similar percentage of patients – 16.6%.[2,16-21] The most severe adverse events associated with treatment termination were: asthenia, sleepiness, and speech disturbances. The most severe adverse events, which were manifested early in some participants and were associated with a rapid termination of TPM treatment were: asthenia, sleepiness, and speech disturbances. Most adverse events are similar to the ones reported in literature and are not associated with a higher TPM dose.[2,5,6,9,10,16-31] Loss of appetite (10 patients), asthenia (6 patients) and sleepiness (4 patients) were the more frequent adverse events. Unusual adverse events were found in 3 patients – hands tremor (in 1 patient, with moderate severity), insomnia (in 1 patient, severe), and mild, transient itching (in 1 patient). They could result in TPM termination in some patients and necessitate attention for the possibility of manifestation in the medical practice.

CONCLUSIONS

TPM 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, possible appearance of new seizure types, good safety and tolerability. Future studies are needed with an emphasis on seizure control worsening by TPM treatment, new seizure type manifestations in the course of treatment, and correlations of efficacy and adverse events from treatment with patients' demographic and clinical characteristics.

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Conflict of Interests

The authors have declared that no competing interests exist.

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Эффективность топирамата в качестве дополнительной терапии у болгарских пациентов с лекарственно-устойчивой эпилепсией

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Резюме

Введение: Не существует надёжных проспективных исследований эффективности топирамата у болгарских пожилых пациентов с лекарственно-устойчивой эпилепсией.

Цель: Целью исследования было провести открытое проспективное исследование различных аспектов эффективности топирамата (ТПМ) среди болгарских пациентов с лекарственно-устойчивой эпилепсией.

Пациенты и методы: В исследование включены пациенты с эпилепсией, обратившиеся в неврологическую клинику Университетской больницы „Св. Георгий“ в Пловдиве, Болгария. Пациенты заполняли дневники с указанием частоты приступов, тяжести приступов и побочных эффектов. Регулярные документированные визиты проводились через 3–6 месяцев в течение первого года лечения ТПМ и через 6 месяцев после этого с динамической оценкой частоты и тяжести приступов, нежелательных явлений и данных ЭКГ.

Результаты: ТПМ использовался в качестве дополнительной терапии у 120 пациентов (69 мужчин, средний возраст 37 лет). Отмечалось относительно небольшое и динамическое улучшение тяжести приступов, удовлетворительное снижение частоты приступов у 37% участников, стабильное среднее снижение частоты приступов (47%) с 6 по 24 месяц лечения и стабильная частота ответа (48 – 51%) за тот же период. Новые типы приступов (очаговые с нарушением сознания с / без развития двусторонних тонико-клонических приступов) возникли у 5 пациентов. Были побочные эффекты (головокружение / вертиго, раздражительность, нарушения речи, нарушение памяти, проблемы с концентрацией внимания, тремор, потеря аппетита и веса, слабость, скованность, брадипсихия, спутанность сознания, зрительные галлюцинации, сонливость, бессонница, головная боль, зуд, нестабильность походки, тошнота и рвота) у 20% пациентов.

Заключение: Лечение ТПМ связано с низким и стабильным улучшением тяжести приступов, хорошим и стабильным улучшением частоты приступов, возможным ухудшением контроля над приступами и появлением новых типов приступов, хорошей безопасностью и переносимостью.

Ключевые слова

побочные эффекты, эффективность, судороги, переносимость