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Nenad Milošević^{1,2†}, Biljana Salak-Đokić³, Mirjana Dejanović¹, Mirjana Stojanović-Tasić^{1,2}, Tatjana Novaković^{1,2}, Jovana Milošević¹, Zorica Stanojević-Ristić¹, Goran Trajković⁴

The effects of topiramate on cognitive functions of patients with focal epilepsy – a follow-up study in a Serbian sample

Утицај топирамата на когнитивне функције болесника са фокалном епилепсијом – студија праћења у српском узорку

¹University of Priština, Faculty of Medical Sciences, Kosovska Mitrovica, Serbia;

²Priština Clinical-Hospital Center, Gračanica, Serbia;

³Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia;

⁴University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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† **Correspondence to:**

Nenad MILOŠEVIĆ

University of Priština, Faculty of Medical Sciences, Vlade Četkovića 17/11, 38220 Kosovska Mitrovica, Serbia

Email: mmnenad@yahoo.com

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SUMMARY

Introduction/Objective The aim of this follow-up study was to determine the effects of topiramate therapy on cognitive functions in patients with pharmaco-resistant focal epilepsy.

Methods The study sample comprised of 40 topiramate naive patients. The topiramate starting dose was 25 mg, with a fortnightly titration schedule of 25 mg. A wide range of cognitive functions was evaluated through extensive neuropsychological testing at baseline and six months after reaching the target dose (200 mg/day).

Results Cognitive impairments, reported by 45% of the participating patients, were the most common side-effects following the introduction of topiramate. The neuropsychological scores on attention, executive function, verbal content recall, improved cognitive flexibility, as well as visuospatial ability and speech, obtained at six-month follow-up were significantly lower than at baseline. However, statistically significant correlation between neuropsychological scores and the number of antiepileptic drugs taken along side topiramate could not be established. Similarly, no statistically significant differences were noted between the percentage of reduced neuropsychological scores at follow-up pertaining to patients with lower and higher baseline cognitive performance. Moreover, regression analysis indicates that the percentage change in the majority of cognitive scores is unrelated to the age at the epilepsy onset, epilepsy duration, presence of brain pathology on MRI and percentage change in the depression scale score.

Conclusion Despite slow introduction and administration of a relatively small dose, topiramate exhibits adverse effects on a wide range of cognitive functions, which appear unrelated to the number of additional antiepileptic drugs, baseline cognitive functioning, age at the onset of epilepsy and its duration, presence of brain pathology and the extent of depressive symptoms.

Keywords: Topiramate, cognitive functions, epilepsy

САЖЕТАК

Увод/Циљ Циљ ове студије био је да се утврди ефекат топирамата на когнитивне функције пацијената са фармакорезистентном фокалном епилепсијом.

Метод Студија је обухватила 40 пацијената који нису лечени топираматом. Почетна доза топирамата била је 25 mg, са брзином повећања дозе од 25 mg на сваких 14 дана. Широки спектар когнитивних функција процењен је обимним неуропсихолошким тестирањем у два одвојена интервала, пре него што је уведен топирамат и шест месеци након достизања циљне дозе (200 mg/дан).

Резултати Најчешћи нежељени ефекти након увођења топирамата биле су когнитивне сметње, које је пријавило 45% пацијената. Неуропсихолошки скорови добијени након увођења топирамата су знатно нижи него пре топирамата на мерењима пажње, егзекутивних функција, присећања вербалног садржаја, брзине когнитивне флексибилности, као и визуоспацијалне способности и говора. Међутим, није нађена значајна корелација између неуропсихолошких скорова и броја антиепилептичких лекова додатих топирамату. Поред тога, није нађена значајна разлика у учесталости погоршања неуропсихолошких скорова између пацијената са нижим и вишим базичним когнитивним перформансама. Такође, вредност проценатне промене на већини когнитивних мерења није значајно повезана са годинама на почетку епилепсије, трајањем епилепсије, присуством можданих лезија на НМР и процентуалном променом на скали депресије.

Закључак Упркос постепеном увођењу и примени релативно ниских доза, топирамат изазива нежељене ефекте на широки спектар когнитивних функција, чија појава није повезана са бројем додатих антиепилептичких лекова, базичним когнитивним функционисањем, узрастом на почетку епилепсије и њеним трајањем, присуством можданих лезија и степеном депресије.

Кључне речи: Топирамат, когнитивне функције, епилепсија

INTRODUCTION

Topiramate (TPM) is effective as an adjunct treatment for pharmaco-resistant focal epilepsy [1]. However, empirical evidence indicated that it can induce various cognitive adverse events (CAEs), including memory and attention problems, as well as poor performance in verbal fluency tasks [2-4]. Data suggest that up to 10% of patients treated with TPM may complain of cognitive issues [5]. The risk of cognitive complaints is 2–5 higher in TPM-treated patients compared to those taking placebo [6]. When compared to patients on other antiepileptic drugs (AEDs), cognitive impairments were more frequently reported by patients receiving TPM therapy [7]. Consequently, cognitive impairments during TPM treatment are the most frequently cited reason for therapy discontinuation [8]. It seems that the CAEs that occurred following TPM introduction are at least partly caused by high initial doses and/or rapid drug introduction [9]. Thus, slow titration, administration of the lowest possible doses and monotherapy may decrease the risk of cognitive impairments [10-12]. However, in extant studies, prolonged therapy, even at low doses of a single drug, was associated with a significant incidence of CAEs [13]. Some authors explain these findings by noting that hippocampal sclerosis, rather than epilepsy duration or polytherapy, is the major risk factor for the development of CAEs [14].

Although the cognitive profile of TPM has been extensively studied, further assessment of cognitive complaints during dose titration using a wider range formal neuropsychological tests is necessary.

The aim of this first follow-up study of this kind in a Serbian sample was to determine the effects of topiramate on CF in patients with pharmaco-resistant cryptogenic or symptomatic focal epilepsy.

METHODS

This follow-up study included 40 TPM naive patients (all of whom spoke Serbian as native language) diagnosed with pharmaco-resistant cryptogenic or symptomatic focal epilepsy (according to the ILAE criteria), none of whom had any progressive neurological diseases, psychiatric comorbidity or mental retardation. Study participants were prospectively recruited from the outpatient clinic of the Epilepsy Department of the Neurology Clinic, Clinical Center of Serbia in Belgrade.

The study protocol was approved by the local ethics committee. All participants were informed of the purpose, procedures, and the scope of the neuropsychological evaluations and provided written informed consent for their inclusion in the study. The TPM starting dose was 25 mg, with fortnightly

titration of 25 mg to reaching a stable dose of 200 mg/day. At the study onset, the therapy prescribed to the participants comprised of one or more of the following AEDs: carbamazepine, valproic acid, lamotrigine, phenobarbital, clobazam and phenytoin.

Demographic and clinical data (gender, age, level of education, age at seizure onset, epilepsy duration, and current antiepileptic therapy) were obtained from each patient at the beginning of the study. Patients' written records regarding epileptic seizures and accompanying side-effects, starting two months prior to the TPM introduction and covering the entire study period, were also collected. Seizure frequency before commencing TPM therapy, as well as that when patient was on a stable dose, was classified as 1–10/11–20/>20 seizures/2 months. Cognitive and other side-effects after the introduction of TPM were arbitrarily classified as mild or severe according to their interference with daily activities. CAEs that were not present before the introduction of TPM included impaired memory, impaired attention, and slowed thinking, among others. At the end of the study, the patients self-rated their general condition in relation to the period before the introduction of TPM as much better, better, unchanged, or worse.

In addition to the above procedures, study participants underwent neuroimaging using a 1.5 T MRI scanner (Siemens Avanto, Siemens AG, Erlangen, Germany). A standardized scanning protocol was adopted, with the option of detecting hippocampal sclerosis and other pathologies of the temporal and non-temporal lobes, as well as other parts of the brain. However, a scan was not performed on patients that underwent brain MRI on the same machine utilizing the same scanning protocol within six months prior to the start of this study, as this information was used in the analyses.

Each patient was subjected to neuropsychological assessment at baseline (i.e., before the introduction of TPM), and six months after reaching a stable dose. None of the patients experienced seizures in the 24-hour period prior to testing. An objective CF assessment was conducted using a battery of flexible neuropsychological tests [15]. All tests were conducted in a standardized manner and were adapted for Serbian population [15]. The battery of tests included *Mini-Mental State Exam (MMSE)* [16] as a CF screening test; *Wisconsin Card Sorting Test (WCST)* [17] for assessment of executive function; *Rey Auditory Verbal Learning test (RAVLT)* [17] focusing on verbal learning and episodic verbal memory; *Rey–Osterrieth Complex Figure test (ROCF)* [18,19] assessing visuospatial ability and visual memory; *Trail Making Test Part A (TMT-A) end Part B (TMT-B)* [17] examining psychomotor speed and attention, and cognitive flexibility; *Wechsler Memory Scale–Revised (WMS–R)* [20] focusing on attention; *Verbal and Category Fluency* [15] measuring capacity for verbal divergent thinking; and *Boston Diagnostic Aphasia Examination (BDAE)* [21] focusing on speech. In addition, the depression level was assessed via *Hamilton Depression Rating Scale (HDRS)* [22].

Statistical analyses were performed using SPSS Statistics (Statistical Package for Social Sciences) for Windows, version 20. The results were reported as the arithmetic mean±standard deviation, as well as maximum and minimum values. The obtained data were further subjected to the student's t test, chi square test, the Spearman's correlation, the sign test, linear regression models, and the McNemar's test, where appropriate. Differences and correlations were considered statistically significant at $p < 0.05$.

RESULTS

Study participants' demographic data and general clinical characteristics at the start of the study are shown in Table 1. As can be seen from the tabulated results, most patients experienced a significant reduction ($p = 0.001$; sign test) in the total number of seizures in the two-month period of TPM treatment at target doses (15.8 ± 54.3) compared to the two-month period before TPM was introduced (21 ± 61.4). Once the target TPM dose of 200 mg/day was reached, 40% of the patients were seizure-free. Among the remaining patients, a significant reduction of seizure incidence ($>50\%$) was observed in 11 (27.5%) cases, while 13 (32.5%) patients experienced a $<50\%$ reduction. On the other hand, depression incidence at the end of the study (14 patients) was not statistically significantly different ($p = 0.243$; McNemar's test) from that at baseline (18 patients). The difference in depression scores before and after the administration of TPM was not statistically significant either (t-test -0.46 , $p = 0.648$). Based on their self-assessment of general health status after achieving a stable dose of TPM, 5 (12%) patients felt significantly better, 17 (43%) felt better, 2 (5%) felt worse than before the introduction of TPM, and 16 (40%) patients reported no changes in their condition.

Figure 1 shows the adverse effects the patients reported after reaching the TPM target dose. It can be seen that cognitive impairments were by far the most common adverse effects experienced, and were reported by 18 (45%) patients. At the end of the study, six months after reaching the target TPM dose, most patients (38.9%) reported multiple CAEs. Specifically, 16.7% participants complained of impaired memory, impaired attention and word-finding difficulties, while slowed thinking was experienced by 11.1% of the sample. None of the participants reported remission of any of the cognitive impairments after their onset until the end of the study. Table 2 shows the number of patients that reported cognitive impairments during the TPM dose titration period.

The results of the applied neuropsychological tests and corresponding statistical findings are presented in Table 3. The 6-month follow-up scores related to measurements of attention, executive function, verbal content recall, enhanced cognitive flexibility, as well as visuospatial abilities and speech, obtained when the patients had been receiving the TPM target dose of 200 mg/day for six

months, were statistically significantly lower than at baseline. On the other hand, differences in scores on visual memory tests at baseline and at 6-month follow-up were not statistically significant (Table 3). Table 4 shows the percentage changes in the cognitive scores after the introduction of TPM with respect to the baseline, in relation to the independent variables, such as the age at the epilepsy onset, duration of epilepsy, presence of pathology on the brain MRI, and the percentage change in the depression scale score. Regression analysis findings indicated that the percentage change in the majority of cognitive scores was unrelated to the aforementioned independent variables. In addition, percentages of patients whose cognitive performance declined at the 6-month follow-up relative to the baseline were examined separately for each test. The mean MMSE score served as the baseline CF level, as it provided a measure of the patients' overall cognitive status. When the participants were grouped by their MMSE baseline score (≤ 27 vs. > 27), no statistically significant differences were found in the percentage of patients whose individual test scores declined on 6-month assessment relative to the corresponding baseline values.

In 31 of the 40 participating patients (77%), TPM was added to a preexisting medication, with valproic acid (VPA) (13 patients), carbamazepine (CBZ) (14 patients), lamotrigine (LTG) (14 patients) and phenobarbital (PHB) (5 patients) identified as the most frequently used comedications. However, no correlation between neuropsychological scores and the number of AEDs used alongside TPM was established.

DISCUSSION

The findings yielded by the present study indicate that TPM therapy can compromise a wide range of CFs in patients with pharmacoresistant focal epilepsy. Patients' subjective complaints were the first indication of the adverse neuropsychological profile of TPM, which was subsequently confirmed through comprehensive neuropsychological assessments. Fortunately, the results reported in this paper also reveal that TPM was effective in reducing the frequency of epileptic seizures. This could be the reason why patients on a stable TPM dose predominantly rated their health condition as better or significantly better compared to the period before the introduction of the drug.

In the clinical evaluation of newer AEDs, the highest incidence of adverse effects was noted among patients taking TPM [23]. In the present study, cognitive impairments were by far the most common reason for patients' complaints, and involved multiple CAEs in most cases. In addition, the first reports of CF impairments (primarily slow thinking and attention difficulties) were noted at the low dose of only 50 mg/day, while speech disorders became more prevalent at the target dose of 200mg/day (Table 2). This dose-related incidence of cognitive impairments was previously confirmed

in a pooled analysis of clinical trials in which TPM was used as an adjuvant therapy in the treatment of pharmaco-resistant focal epilepsy [3].

In addition to evaluating patients' subjective cognitive complaints, the formal neuropsychological assessment conducted as a part of this investigation also revealed adverse effects of TPM on CF. The assessment of verbal memory and learning by RAVLT showed that patients on TPM obtained lower delayed-recall scores at 6-month follow-up relative to baseline. This aspect of memory was also proven to be affected by TPM in the study conducted by Thompson et al. [4]. Attention deficit after TPM introduction was confirmed by lower scores on the Digit Span and Visual Memory Span measures, as well as by WMSR (attention index). In an earlier study, Burton and Harden confirmed the adverse effect of TPM on Digit Span scores in adults with epilepsy who had been treated with TPM for ≥ 3 months. These authors also established an inverse link between TPM dose and the Digit Span scores [24].

Although speech disorders were the least frequently reported cognitive complaints, findings yielded by the formal neuropsychological assessment revealed significantly lower test scores while patients were undergoing TPM therapy. In addition to deteriorating speech recognition results, TPM also had an adverse effect on the verbal fluency scores, which is consistent with the findings of other studies on patients with epilepsy [25].

When executive functions were evaluated through the WCST, a significantly higher number of perseverative responses in the second measurement confirmed their susceptibility to TPM. This result indicated a reduced ability to suppress previous choices, including the non-adaptive ones, and to switch to the correct choice, which is one of the important characteristics of impaired executive functions [26]. The deterioration of multiple CF observed in the present study can likely be attributed to the impaired working memory, which is at the core of executive functions and represents a critical step in almost all cognitive processes [27]. The working memory impairment suggested by the test findings could arise due to the reduced information processing speed, stemming from the potentiation of inhibitory processes in the brain by gamma-aminobutyric acid (GABA). Indeed, ample body of evidence indicates that TPM increases GABA levels in the brain [28]. This simplified mechanism is further supported by the fact that AEDs that do not primarily impact GABA neurotransmission, such as lamotrigine, are rarely associated with serious cognitive impairments [29].

In analyzing the risk factors that contribute to the emergence of cognitive impairments following TPM introduction, some authors speculated that the adverse effect of TPM on mood [30] may result in an increased number of cognitive complaints [31]. Others are of view that the effect of TPM on cognition can be attributed to the synergistic effect of polytherapy [8]. Extant studies also suggest that cognitive abnormalities prior to adding TPM to the epilepsy therapy could predispose

patients to CF impairments [32]. Even though a statistically significant relationship between percentage changes in cognitive scores and independent variables (age at the onset of epilepsy, epilepsy duration, presence of brain pathology and depression severity) examined in this study was noted with respect to a small number of measurements, this does not provide sufficient evidence to propose a causal link between these factors and the observed changes in CF. In addition, a significant correlation between neuropsychological scores and the number of AEDs taken alongside TPM is not supported by our findings. Similarly, it has not been established that lower cognitive performance at baseline is associated with a more pronounced CF deterioration when patients are treated with a stable TPM dose. Therefore, the impact of TPM on CF is independent of the observed variables.

Generally, given that TPM is an effective AED, the greatest clinical importance should be placed on determining the mechanisms and the factors that can contribute to the onset of CAEs. We thus believe that further studies are needed to determine the profile of patients in whom topiramate administration would have a therapeutically beneficial effect without significant cognitive impairment.

CONCLUSION

The findings reported in this work indicate that TPM, despite slow introduction as adjuvant therapy and low-dosage titration, has an adverse effect on the CF in patients with pharmacoresistant focal epilepsy. In our sample, attention, verbal memory, executive function, visuospatial ability, and speech were affected by TPM treatment. We also established that the adverse effects of topiramate are independent of the number of antiepileptic drugs taken alongside topiramate, baseline cognitive functioning, age at the epilepsy onset, epilepsy duration, presence of brain pathology, and depression severity. Despite occurrence of the aforementioned adverse TPM effects, most patients had a positive assessment of their condition following TPM treatment, most probably due to its effectiveness in controlling seizures, which was confirmed in our study.

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Table 1. Demographic and clinical data of the patients on start of the study

Parameters	Value
Gender (female/male)	24/16
Age, years (range)	41 ± 14.1 (18-68)
Patients with education ≤ 11 years (%)	10 (25)
Age at seizure onset, years (range)	25.9 ± 17.9 (2-68)
Duration of epilepsy, years (range)	14.8 ± 12.2 (1-50)
Seizure frequency before TPM (2 months), 1-10/11-20/ > 20	27/5/8
Patients with depression, mild/severe	8/10
Patients with laesional brain MRI (%)	19 (47.5)

TPM – topiramate, MRI – magnetic resonance imaging

Table 2. The number of patients with complaints on cognitive difficulties during titration dose of TPM

Type of cognitive impairment	^a 25mg n (%)	^a 50mg n (%)	^a 100mg n (%)	^a 150mg n (%)	^a 200mg n (%)
Impaired memory	-	-	7 (17.5)	9 (22.5)	10 (25)
Impaired attention	-	2 (5)	7 (17.5)	10 (25)	10 (25)
Slowed thinking	-	2 (5)	2 (5)	4 (10)	7(17.5)
Word-finding difficulties	-	-	-	3 (7.5)	5 (12.5)

TPM – topiramate;

^atwo weeks after reaching a given dose of TPM

Table 3. Neuropsychological test results before and 6 months after achievement of the 200 mg of topiramate

Measure	Before TPM	After 6 months	t-test	p
MMSE	27.4 ± 2.4	24.7 ± 4.6	4.42	0.001
RAVLT (immediate recall)	42.7 ± 9.8	40.8 ± 11.0	1.94	0.060
RAVLT (recall after 20 minutes)	7.3 ± 3.3	6.5 ± 3.6	2.32	0.026
RAVLT (recognition)	11.2 ± 2.9	11.2 ± 3.5	-0.18	0.857
TMT-A	60.1 ± 31.4	63.2 ± 34.7	-0.83	0.413
TMT-B	143.3 ± 59.8	172.6 ± 81.4	-3.34	0.002
WCST (categories completed)	3.7 ± 2.0	4.1 ± 2.1	-1.59	0.121
WCST (perseverative responses)	34.0 ± 18.8	25.6 ± 20.7	2.76	0.009
WCST (inability to maintain set)	1.2 ± 1.3	1.1 ± 1.7	0.36	0.722
Test of phonemic fluency (S)	8.2 ± 2.6	7.0 ± 2.8	2.98	0.005
Test of phonemic fluency (K)	9.9 ± 4.0	7.6 ± 3.5	3.53	0.001
Test of phonemic fluency (L)	7.7 ± 2.7	5.4 ± 2.8	5.14	0.001
Test of categorial fluency	14.3 ± 4.3	12.2 ± 4.1	3.73	0.001
ROCF (copying)	26.9 ± 5.2	23.8 ± 6.0	3.56	0.001
ROCF (drawing by recall)	12.2 ± 6.5	11.0 ± 6.7	1.71	0.095
BDAE (complex ideational material)	9.8 ± 1.8	9.3 ± 1.7	2.10	0.042
BDAE (repetitive speech)	6.8 ± 1.2	6.7 ± 1.5	0.26	0.793
BDAE (orders)	14.9 ± 0.4	14.4 ± 0.9	3.73	0.001
WMS-R (attention index)	71.2 ± 15.3	59.1 ± 17.5	6.76	0.001
WMS-R (digit span)	5.7 ± 0.9	4.7 ± 1.0	6.02	0.001
WMS-R (visual span)	4.6 ± 0.8	3.8 ± 1.0	4.49	0.001

TPM – topiramate; MMSE – Mini Mental State Examination; RAVLT – Rey Auditory Verbal Learning Test; TMT-A – Trail Making Test Part A; TMT-B – Trail Making Test Part B; WCST – Wisconsin Card Sorting Test; S, K and L – words beginning with letter S, K, and L; ROCF – Rey-Osterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS-R – Wechsler Memory Scale – Revised; Data are presented as arithmetic mean with simple standard deviation; results were compared by Student's t-test; a higher score means a better result, except on TMT-A and TMT-B (opposite)

Table 4. Linear regression models with percent change in cognitive tests performance as dependent variables

Dependent variable (Neuropsychological tests)	Independent variables			
	Age on onset of disease	Duration of epilepsy	Presence of MRI brain pathology	Percentage change on HDRS
MMSE	-0.31	0.07	-1.42	-0.02
RAVLT (immediate recall)	-0.02	0.02	-3.28	0.06
RAVLT (recall after 20 minutes)	-0.32	0.53	4.15	0.02
RAVLT (recognition)	-0.32	-0.13	-5.15	-0.05
TMT-A	0.52	-0.68	-2.44	-0.01
TMT-B	0.33	0.35	-4.19	-0.15
WCST (categories completed)	-1.73	0.07	6.52	0.61
WCST (perseverative responses)	0.62	0.46	-11.57	-0.20
WCST (inability to maintain set)	-0.26	-0.77	8.78	0.97*
Test of phonemic fluency (S)	-0.21	0.72	7.26	0.11
Test of phonemic fluency (K)	0.43	1.34*	2.85	-0.23
Test of phonemic fluency (L)	0.47	1.58*	-2.65	-0.35*
Test of categorial fluency	0.15	-0.07	-9.15	-0.03
ROCF (copying)	0.19	0.28	-3.30	0.00
ROCF (drawing by recall)	-0.08	0.10	-15.11	0.17
BDAE (complex ideational material)	0.25	0.19	-1.56	-0.10
BDAE (repetitive speech)	0.19	-0.10	-8.91	-0.12
BDAE (orders)	0.05	0.03	2.36	0.02
WMS-R (attention index)	-0.04	0.29	2.24	-0.05
WMS-R (digit span)	0.10	0.17	-13.05	-0.09
WMS-R (visual span)	-0.34	0.27	3.76	-0.10

MMSE – Mini Mental State Examination; RAVLT – Rey Auditory Verbal Learning Test; TMT-A – Trail Making Test Part A; TMT-B – Trail Making Test Part B; WCST – Wisconsin Card Sorting Test; S, K and L – words beginning with letter S, K, and L; ROCF – Rey-Osterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS-R – Wechsler Memory Scale – Revised; MRI – magnetic resonance imaging; HDRS – Hamilton Depression Rating Scale;

* $p < 0.05$