DOI: https://doi.org/10.2298/SARH171225066M
UDC: 615.213.015-053.2(497.11); 616.853-085.213-053.2(497.11)


ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

Nenad Milošević[1,2], Biljana Salak-Đokić[3], Mirjana Dejanović[1], Mirjana Stojanović-Tasić[1,2], Tatjana Novaković[1,2], Jovana Milošević[1], Zorica Stanojević-Ristić[1], Goran Trajković[4]

[1]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[2]Priština Clinical-hospital Center, Gračanica, Serbia;
[3]Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia;
[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

**SUMMARY**

**Introduction/Objective** The aim of this follow-up study was to determine the effects of topiramate therapy on cognitive functions in patients with pharmacoresistant 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** The most common side effects following the introduction of topiramate were cognitive impairments, reported by 45% of the participants. 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 alongside 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 magnetic resonance imaging 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

## INTRODUCTION

Topiramate (TPM) is effective as an adjunct treatment for pharmacoresistant 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, 3, 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 times 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, 11, 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 wider range formal neuropsychological tests is necessary.

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

**Received • Примљено:** December 25, 2017
**Revised • Ревизија:** June 11, 2018
**Accepted • Прихваћено:** October 5, 2018
**Online first:** October 16, 2018

**Correspondence to:**
Nenad MILOŠEVIĆ
University of Priština
– Kosovska Mitrovica
Faculty of Medicine
Vlade Ćetkovića 17/11
38220 Kosovska Mitrovica, Serbia
**mmnenad@yahoo.com**

## METHODS

This follow-up study included 40 TPM naive patients (all of whom spoke Serbian as native language) diagnosed with pharmacoresistant 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 done in accord with standards of the Institutional Committee on Ethics. 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, and 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 slower 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) as a CF screening test [16]. Wisconsin Card Sorting Test (WCST) was used for assessment of executive function [17]. Rey Auditory Verbal Learning test (RAVLT) focused on verbal learning and episodic verbal memory [17]. Rey–Osterrieth Complex Figure test (ROCF) assessed visuospatial ability and visual memory [18, 19]. Trail Making Test Part A (TMT-A) end Part B (TMT-B) examined psychomotor speed and attention, and cognitive flexibility [17]. Wechsler Memory Scale–Revised (WMS–R) focused on attention [20]. Verbal and Category Fluency measured capacity for verbal divergent thinking [15]. Boston Diagnostic Aphasia Examination (BDAE) focused on speech [21]. 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, $\chi^2$ 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

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

| Parameters | Value |
|---|---|
| Sex (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 lesioned brain MRI (%) | 19 (47.5) |

TPM – topiramate; MRI – magnetic resonance imaging

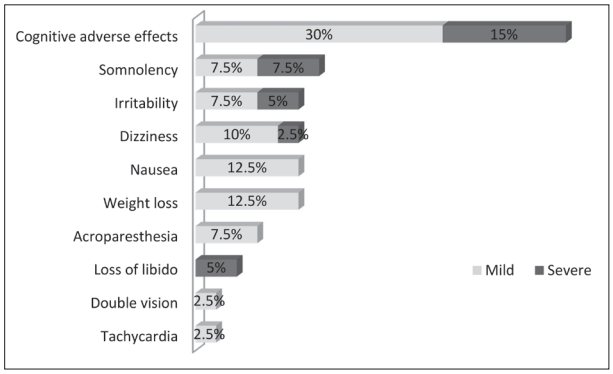


**Figure 1.** The frequency of adverse effects after reaching target dose of topiramate

self-assessment of general health status after achieving a stable dose of TPM, five (12%) patients felt significantly better, 17 (43%) felt better, two (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 slower 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.

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

| Type of cognitive impairment | [a]25 mg n (%) | [a]50 mg n (%) | [a]100 mg n (%) | [a]150 mg n (%) | [a]200 mg 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) |

n – number of patients;
[a]two weeks after reaching a given dose of topiramate

The results of the applied neuropsychological tests and corresponding statistical findings are presented in Table 3. The six-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 six-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 six-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 ($\leq 27$ *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) (five 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 thought 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 200 mg/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 pharmacoresistant 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

**Table 3.** Neuropsychological test results before and 6 months after achievement of the 200 mg of TPM;
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)

| Measure | Before TPM | After six 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 categorical 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-Ostterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS–R – Wechsler Memory Scale–Revised

**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 patology | 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-Ostterith Complex Figure; BDAE – Boston Diagnostic Aphasia Examination; WMS–R – Wechsler Memory Scale–Revised; MRI – magnetic resonance imaging; HDRS – Hamilton Depression Rating Scale;
*$p < 0.05$

memory and learning by RAVLT showed that patients on TPM obtained lower delayed-recall scores at six-month follow-up relative to baseline. It was also proved that this aspect of memory was 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 [24] 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.

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 CFs 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 may result in an increased number of cognitive complaints [30, 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 the 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 were noted with respect to a small number of measurements, this did 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 was 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.

**Conflict of interest:** None declared.

## REFERENCES

1. Pulman J, Jette N, Dykeman J, Hemming K, Hutton JL, Marson AG. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database Syst Rev. 2014; (2):1–52.
2. Lee S, Syiklas V, Andermann F, Farnham S, Risse G, Gustafson M, et al. The effects of adjunctive topiramate on cognitive function in patients with epilepsy. Epilepsia. 2003; 44(3):339–47.
3. Reife RA, Pledger GW. Topiramate as adjunctive therapy in refractory partial epilepsy: pooled analysis of data from five double-blind, placebo-controlled trials. Epilepsia. 1997; 38:31–3.
4. Thompson PJ, Baxandale SA, Dunkan JS, Sander JW. Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry. 2000; 69(5):636–41.
5. Mula M. Topiramate and cognitive impairment: evidence and clinical implications. Ther Adv Drug Saf. 2012; 3(6):279–89.
6. Jette N, Hemming K, Hutton JL, Marson AG. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database Syst Rev. 2008; 16(3):CD001417.
7. Javed A, Cohen B, Detyniecki K, Hirsch LJ, Legge A, Chen B, et al. Rates and predictors of patient-reported cognitive side effects

of antiepileptic drugs: An extended follow-up. Seizure. 2015; 29:34–40.
8. Tatum WO, French JA, Faught E, Morris GL, Liporace J, Kanner A. Postmarketing experience with topiramate and cognition. Epilepsia. 2001; 42(9):1134–40.
9. Privitera M, Fincham R, Penry J, Reife R, Kramer L, Pledger G, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1000-mg daily dosages. Topiramate YE Study Group. Neurology. 1996; 46(6):1678–83.
10. Guberman A, Neto W, Gassmann-Mayer C, EPAJ-119 Study group. Low-dose topiramate in adults with treatment-resistant partial-onset seizures. Acta Neurol Scand. 2002; 106(4):183–9.
11. Sommer BR, Mitchell EL, Wroolie TE. Topiramate: Effects on cognition in patients with epilepsy, migraine headache and obesity. Ther Adv Neurol Disord. 2013; 6(4):211–27.
12. Ramsay E, Faught E, Krumholz A, Naritoku D, Privitera M, Schwarzman L, et al. Efficacy, tolerability, and safety of rapid initiation of topiramate versus phenytoin in patients with new-onset epilepsy: a randomized double-blind clinical trial. Epilepsia. 2010; 51(10):1970–7.
13. Lee HW, Jung DK, Suh CK, Kwon SH, Park SP. Cognitive effects of low-dose topiramate monotherapy in epilepsy patients: A 1-year follow-up. Epilepsy Behav. 2006; 8(4):736–41.
14. Mula M, Trimble MR, Sander JW. The role of hippocampal screrosis in topiramate-related depression and cognitive deficits in people with epilepsy. Epilepsy. 2003; 44(12):1573–7.
15. Pavlović DM. [Diagnostic tests in neuropsychology]. Belgrade, Grafos; 2003. Serbian.
16. Folstein MF, Folstein SE, Mchugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–98.
17. Lezak MD. Neuropsychological assessment. New York, NY: Oxford University Press; 1995.
18. Rey A. L'examen psychologique dans les cas d'ecephalopathie traumatique. Archives de Psychologie. 1941; 28:286–340.
19. Osterrieth PA. Filetest de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire. Archives de Psychologie. 1944; 30:286–356.
20. Wechsler D. Wechsler's Memory Scale–Revised (WMS–R), manual. San Antonio, TX: The Psychological Corporation, Harcourt Brace Jovanovich; 1987.
21. Goodglas H, Kaplan E. The assessment of aphasia and related disorders. Philadelphia, Lea&Febiger; 1983.
22. Hamilton M. Development of a rating scale for primary depressive illnes. Brit J Soc Clin Psychol. 1967; 6(4):278–96.
23. Arif H, Buchsbaum R, Weintraub D, Pierro J, Resor SR, Hirsch LJ. Patient-reported cognitive side effects of antiepileptic drugs: predictors and comparison of all commonly used antiepileptic drugs. Epilepsy Behav. 2009; 14(1):202–9.
24. Burton La, Harden C. Effect of topiramate on attention. Epilepsy Res. 1997; 27(1):29–32.
25. Baker G, Taylor J, Aldekamp A. Newly diagnosed epilepsy: cognitive outcome after 12 months. Epilepsia. 2011; 52(6):1084–91.
26. Godefroy O, Azouvi P, Robert P, Roussel M, Legall D, Meulemans T. Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group. Dysexecutive syndrome: diagnostic criteria and validation study. Ann Neurol. 2010; 68(6):855–64.
27. Roerts Ac, Robbins Tw, Weiskrantz L. The Prefrontal Cortex: Executive and Cognitive Functions. Oxford: Oxford University Press; 2002.
28. Petroff OA, Hyder F, Rothman DL, Mattson RH. Topiramate rapidly raises brain GABA in epilepsy patients. Epilepsia. 2001; 42(4):543–48.
29. Aldekamp AP, Baker G. A systematic review of the effects of lamotrigine on cognitive function and quality of life. Epilepsy Behav. 2001; 2(2):85–91.
30. Mula M, Trimble M, Lhatoo S, Sander J. Topiramate and psychiatric adverse events in patients with epilepsy. Epilepsia. 2003; 44(5):659–63.
31. Kanner A, Wuu J, Faught E, Tatum WO, Fix A, French JA, et al. A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. Epilepsy Behav. 2003; 4(5):548–52.
32. Gerber PE, Hamiwka L, Connolly MB, Farrell K. Factors associated with behavioral and cognitive abnormalities in children receiving topiramate. Pediatr Neurol. 2000; 22(3):200–3.

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

Ненад Милошевић[1,2], Биљана Салак-Ђокић[3], Мирјана Дејановић[1], Мирјана Стојановић-Тасић[1,2], Татјана Новаковић[1,2], Јована Милошевић[1], Зорица Станојевић-Ристић[1], Горан Трајковић[4]

[1]Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;
[2]Клиничко-болнички центар Приштина, Грачаница, Србија;
[3]Клинички центар Србије, Клиника за неурологију, Београд, Србија;
[4]Универзитет у Београду, Медицински факултет, Београд, Србија

**САЖЕТАК**

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

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

**Резултати** Најчешћи нежељени ефекти после увођења топирамата биле су когнитивне сметње, које је пријавило 45% болесника. Неуропсихолошки скорови добијени после 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 болесника 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 видљивих на нуклеарној магнетној резонанци и процентуалном променом на скали депресије.

**Закључак** Упркос постепеном увођењу и примени релативно ниских доза, топирамат изазива нежељене ефекте на широк 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