

CASE REPORT

Recovery of cognitive and emotional functioning following withdrawal of topiramate maintenance therapy

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The present investigation reports cognitive improvement following withdrawal of topiramate (TPM) maintenance therapy in two patients with intractable seizures. The first patient received a neuropsychological evaluation after 10 months of adjunctive TPM treatment and was reassessed after complete withdrawal. The second patient received a first evaluation without TPM therapy. A reassessment was conducted after 13 weeks of stable TPM add-on therapy, and a third evaluation was performed after TPM withdrawal. During TPM treatment, the first patient demonstrated dysfunction on both verbal and non-verbal measures, suggesting bilateral impairment. Reassessment yielded cognitive improvement, and was consistent with a lateralized lesion as supported by seizure semiology, magnetic resonance imaging (MRI), and electroencephalogram (EEG) data. The second patient showed cognitive and emotional declines during TPM therapy. Reassessment, without TPM, demonstrated recovery on a majority of variables. These results illustrate the risk for considerable cognitive side effects after TPM habituation and support good recovery after withdrawal. Attempting to withdraw TPM and conducting a re-evaluation may be especially justified in the presence of a deflated neuropsychological profile that is inconsistent with a patient's estimated level of cognitive functioning. Reducing the influence of medical effects that could mimic bilateral dysfunction is particularly important in presurgical evaluations.

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Key words: topiramate; antiepileptic drugs; adverse effects; cognitive side-effect; neuropsychology; cognitive function.

INTRODUCTION

Topiramate (TPM) is an anticonvulsant for adjunctive treatment of partial seizures with or without secondary generalization¹. Recent findings suggest mild cognitive decline during TPM therapy². Exceptions to these findings need further analysis to avoid inaccurate conclusions regarding organicity.

In the present report, we investigated the cognitive recovery in two patients following withdrawal of TPM maintenance therapy.

CASE 1

The patient was a 25 year-old, right-handed, female college student with intractable simple partial seizures. Magnetic resonance imaging (MRI) showed a right-

sided mesial temporal sclerosis. Scalp electrode recording demonstrated seizure activity restricted to the right fronto-temporal region.

Carbamazepine monotherapy had been complemented with add-on TPM therapy 10 months before the patient received a presurgical neuropsychological assessment, containing 14 cognitive measures^{3–13}. When first assessed, she was receiving carbamazepine 800 mg per day in combination with TPM 200 mg per day. TPM was then tapered with 50 mg decrements at 4 week intervals. The neuropsychological testing was repeated 5 weeks after discontinuing TPM therapy and 27 weeks after the first assessment. Retesting was conducted exclusively for functions that fell ≥ 1 SD under the norm-referenced mean during the first assessment.

Table 1: Case 1: Raw scores with normative means and standard deviations.

Function	Test 1 with TPM	Test 2 without TPM	M	SD	Improvement
Naming	42	52	55.7	3.3	*
Auditory comprehension ^a	13	15			
Verbal learning ^b	104	23	50.0	49.0	*
Verbal retention ^c	67	100	87.4	12.8	**
Auditory working memory	2	7	7.1	1.3	**
Visuo-spatial memory	7	15	24.8	4.2	*
Verbal fluency	25	39	45.7	12.7	*
Problem solving:					
Errors	65	37	18.5	14.1	*
Perseverations	39	30	9.7	7.8	*
Fine motor speed:					
Dominant hand	47	54	54.1	6.2	*
Non-dominant hand	41	49	47.2	5.7	*
Psychological functioning ^d	33	18	15.9	16.4	

* 1–1.9 SD improvement; ** ≥ 2 SD improvement

^a This measure does not yield a normal distribution. Impaired performance is based on a less-than-perfect performance with ≥ 2 errors as a cut-off (4); ^b weighted score with a higher weight for words not recalled following each repetition of a word list, i.e. lower score indicates better performance; ^c per cent recalled from word list after 30 minutes; ^d score indicates sum of endorsed symptoms.

Consistent with clinical practice, cognitive dysfunction was indicated when a test performance fell ≥ 2 SD below age-related normative means, whereas performances within 1 SD were regarded as within normal limits. Intra-individual changes of ≥ 1 SD were considered to be of significant magnitude.

RESULTS

Raw scores from the two evaluations along with normative means and standard deviations are demonstrated in Table 1.

At the first testing (with TPM), the following measures fell within normal limits: visuo-spatial skill⁶, facial recollection⁸, and selective attention¹⁰. The following areas were impaired: naming skills⁵; auditory comprehension⁴; auditory working memory⁹; visuo-spatial memory⁶; and problem solving skills¹². All remaining measures fell 1–2 SD below normative means, suggesting possible cognitive and emotional decline. Self-report contained complaints about cognitive disability.

At the second testing (after withdrawal of TPM), all tested cognitive domains showed significant improvement and the patient reported increased cognitive ability. Visuo-spatial memory⁶ and problem solving¹² stayed impaired whereas all remaining cognitive functions fell within normal limits.

CASE 2

The second patient was a 38 year-old male entrepreneur with 9 years of education who presented

with intractable secondary generalized seizures and complex partial seizures without preceding aura. MRI suggested cavernous angioma in the left frontal medio-basal region. Electroencephalogram (EEG) with subdural strips revealed early seizure activity both in the left temporal lobe and in mesio-basal structures of the left frontal lobe. The patient was left-handed and Wada testing confirmed speech dominance in the right hemisphere. MRI after resection showed complete removal of the lesion and histopathology verified cavernoma diagnosis. Seizure control was not obtained through surgery and lamotrigine monotherapy was therefore complemented with TPM.

This patient underwent three neuropsychological evaluations. The first assessment was performed prior to surgery and contained 14 cognitive measures^{3–13}. The post-surgical evaluations were conducted 26 and 31 months after the first testing. Measures showing significant deterioration from the first to the second assessment were repeated in the third testing.

The patient was on lamotrigine monotherapy 600 mg per day during the first evaluation. TPM was instituted at a starting dose of 50 mg per day and with 50 mg increments at 2-week intervals. The second testing was performed after 13 weeks of lamotrigine 600 mg per day and TPM 200 mg per day in stable dosing. TPM was then tapered with 50 mg decrements at 4 week intervals without any change in seizure frequency. The third neuropsychological assessment was completed when the patient had been off TPM for 6 weeks.

Table 2: Case 2: Raw scores with normative means and standard deviations.

Function	Test 1 without T	Test 2 with T	Test 3 without T	M	SD	Change
Verbal learning ^a	22	165	114	99.7	66.0	*
Verbal retention ^b	80	50	70	79.6	18.7	*
Visuo-spatial memory	26	18	21.5	20.5	5.5	*
Verbal fluency	47	30	52	46.1	12.6	*
Psychological functioning ^c	30	62	32	15.9	16.4	*

*Significant change (1–1.9 SD) in one or two pairwise comparisons. — and — indicate significant pairwise comparisons.

^a Weighted score with a higher weight for words not recalled following each repetition of a word list, i.e. lower score indicates better performance; ^b per cent recalled from word list after 30 minutes; ^c score indicates sum of endorsed symptoms.

RESULTS

Raw scores from the three evaluations along with normative means and standard deviations are demonstrated in Table 2.

At the first testing (without TPM), the patient performed within normal limits or above on all measures.

At the second testing (with TPM), significant reductions were observed for verbal learning⁷, verbal retention⁷, visuo-spatial memory⁶, verbal fluency¹¹, and psychological functioning¹³. Self-rated emotional symptoms fell 2.8 SD above the normed mean, and the patient complained about cognitive disability.

The third testing (without TPM): All measures were within normal limits. Significant improvement was demonstrated in verbal retention⁷, verbal fluency¹¹, and psychological functioning¹³. Verbal learning⁷ remained significantly inferior to the performance obtained in the first testing. Visuo-spatial memory⁶ fell between the scores obtained during the two previous assessments without significantly deviating from these.

DISCUSSION

These patients showed considerable cognitive deficits after months of TPM treatment within standard dosage ranges. TPM-related cognitive reduction was indicated by improvements within a large range of independent cognitive functions following discontinuation of TPM therapy.

During TPM–carbamazepine treatment, the first patient demonstrated significant dysfunction of cognitive functioning with both verbal and non-verbal

domains. Since the evaluation suggested unexpected bilateral dysfunction, a Wada test was scheduled. Retesting after TPM discontinuation revealed no signs of bilateral impairment and the Wada test was cancelled. Visuo-spatial memory and problem solving remained significantly impaired, consistent with a right mesial sclerosis and seizure activity in the right fronto-temporal region. The patient recently received surgery and has demonstrated good recovery.

Patients may differ in sensitivity to cognitive adverse effects. A study of factors affecting long-term retention¹⁴ suggests that patients with learning disabilities are less prone to discontinue TPM treatment. Patients with normal, or above normal, intelligence may be less tolerant of cognitive decline. As in a previous case report on cognitive adverse effects from TPM¹⁵, our patients had, at least, normal levels of intelligence and were dependent on higher cognitive skills in their daily lives. They complained about cognitive disability and showed elevated emotional distress during TPM treatment. Taken together, our findings and those of McCabe & Eslinger¹⁵ suggest that type of employment and estimates of intelligence should be taken into consideration in evaluations of TPM effects.

Attempting to withdraw TPM and conducting a re-evaluation may be especially justified in the presence of a deflated neuropsychological profile that is inconsistent with a patient's estimated level of cognitive functioning. Minimizing medical adverse effects is of particular importance in pre-surgical evaluations where indication of bilateral dysfunction may determine decisions regarding invasive pre-surgical procedures.

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