

Evidence for frontal lobe associated cognitive impairment in patients with epilepsy on Topiramate. Effects beyond titration periods and dosage



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PURPOSE:

Topiramate (TPM) is a highly effective antiepileptic drug (AED) used in the treatment of partial onset epilepsy with or without secondary generalization. TPM can produce considerable cognitive side effects such as psychomotor slowing, impaired memory function, speech-related problems, and further cognitive complaints. It has been argued, that most of these effects develop during titration periods (generally within the first 2 months of treatment) as a result of high initial doses or rapid dose escalation¹⁾, and that problems usually resolve when patients become habituated to the agent or dosage is adjusted²⁾. In this study we investigated the effects of TPM on cognitive performance in patients with epilepsy, who had been receiving TPM for more than two months in relation to current blood serum levels of the agent.

METHODS:

This was a retrospective study. The neuropsychological test scores of a sample of 64 patients on TPM in long-term therapy were compared to those of a group of 86 patients on Lamotrigine (LTG) as corresponding agent (control). Groups were matched for study-relevant variables (**Tab.**). In contrast to TPM, no negative cognitive side effects were expected on LTG. Blood serum levels of TPM and LTG had been determined from blood samples taken either on the day of neuropsychological testing (44% of cases), or within an interval of 8 days (56% of cases, mean \pm 3.3 days). All patients had undergone neuropsychological assessment of language function, working memory, verbal and non-verbal memory and visuo-constructive abilities.

Tab. Patient and AED characteristics

	TPM (n = 64)	LTG (n = 86)
Age (median / min-max)	34 / 10-63	35.5 / 19-64
Gender (m / f)	38 / 26	55 / 31
Serum level (median / min-max in $\mu\text{g} / \text{ml}$)	4.0 / 0.9-14.9	4.7 / 0.2-15.6
Adjunctive AEDs (mean number)	1.69	1.44
Epilepsy onset (median age)	12	11
Duration of epilepsy (median years)	18.5	21
Generalized seizures ? (yes / no)	49 / 15	64 / 22
Temporal lobe epilepsy ? (yes / no)	32 / 32	53 / 33

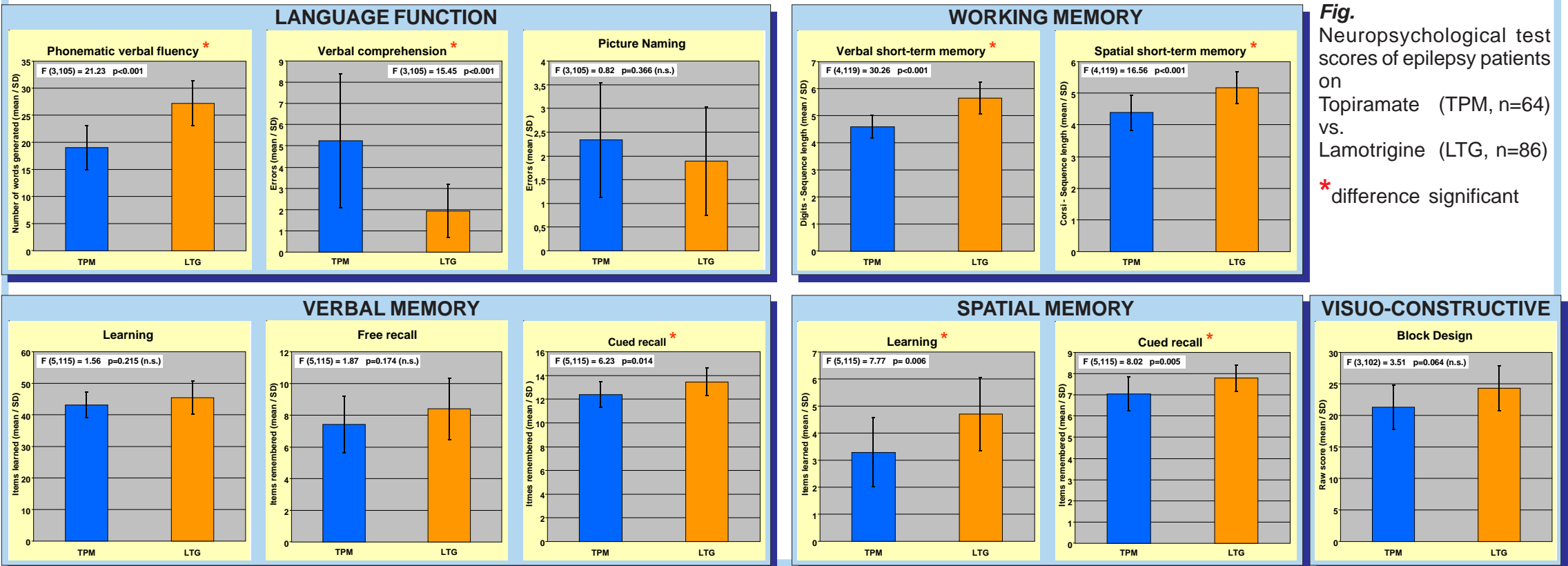
RESULTS:

- According to MANOVA, the TPM-group performed poorer on all tests administered as compared to the LTG-group.
- Differences became significant for verbal fluency (COWA, $p < 0.001$), verbal comprehension (TOKEN-

test, $p < 0.001$), measures of verbal and spatial working memory (DIGITS/ CORSI, $p < 0.001$), non-verbal learning (DCS, $p = 0.006$), and verbal (VLMT, $p = 0.014$) and non-verbal recognition memory (DCS, $p = 0.005$) (**Fig.**)

- None of the cognitive measures turned out to be corre-

lated to current blood serum levels of TPM [$\rho_{\text{max}} = 0.14$, $p = 0.053$ (n.s.) for serum level and verbal recognition memory].



DISCUSSION:

- There is evidence of TPM-induced cognitive impairment in patients on AED polytherapy.
- Patients had been on TPM in long-term therapy. Hence, the data do not support the suggestion that patients habituate to the agent after continued use or dosage adjustment.
- No correlations between blood serum levels and per-

formance were observed. Thus, many patients may develop adverse effects already at low dosages of TPM.

- In line with previous studies in epilepsy patients and healthy subjects^{3,4)}, neuropsychological tests assessing executive and thus frontal lobe associated function (verbal fluency, working memory) appear to be particularly sensitive for TPM-induced cognitive impairment.

- It cannot be excluded, that the negative impact of TPM results from negative interactions with other AEDs in polytherapy.
- TPM should be completely withdrawn before neuropsychological assessment in epilepsy patients, for test scores on TPM may not necessarily reflect organic but drug-induced brain dysfunction⁵⁾.

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