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Topiramate: a prospective study on the relationship between concentration, dosage and adverse events in epileptic patients on combination therapy

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ABSTRACT – *Rationale.* The relationship between topiramate (TPM) concentration, dosage and adverse events in patients with epilepsy is still controversial. We therefore performed a prospective study in patients with poorly controlled epilepsy treated with TPM, predominantly in combination with other antiepileptic drugs. The goal of the study was to investigate the relationship between the occurrence of adverse events due to TPM and its serum concentration or dosage, respectively. *Methods.* The relationship between the occurrence of adverse events and TPM serum concentration or dosage, respectively, was examined in a group of 42 young adult and adult patients with poorly controlled epilepsy. Within 22 months, all patients treated with TPM had been included in the study. The 8 adverse events occurring most frequently (difference ≥ 10%) in TPM-treated patients in 5, double-blind, placebo-controlled, parallel group studies, were checked regularly. This side effect profile has been presented by Reife *et al.* (1995a). Other possible or probable adverse events were also documented. *Results.* The difference in TPM serum concentrations and TPM dosages (mg/kg) for patients without an adverse event, and patients with a given adverse event was statistically significant for "abnormal thinking, impaired concentration, weight loss, dizziness, speech problems, somnolence, ataxia, increased seizure frequency and paresthesia". To avoid adverse events, we recommend an initial "maintenance serum concentration" of below 4 µg/mL. As regards the TPM dosage, our results suggest initial maintenance dosages of 100 TPM or lower, 1.5 mg/kg or lower, respectively. These conclusions are limited by the relatively small number of patients.

Key words: topiramate, serum concentration, dosage, cognition, adverse events

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Topiramate (TPM) was officially approved in Germany for combination therapy in July 1999 and for monotherapy in July 2002. The relationship between TPM serum concentration and efficacy and between serum concentration and toxicity is still under discussion. Reife *et al.* (1995a) reported as early as 1995 that in patients on TPM combination therapy, the mean TPM serum concentrations were generally higher for patients experiencing a given adverse event than for patients who did not experience that event. Significantly higher mean serum concentrations occurred in subjects experiencing anorexia or weight loss, symptoms related to cognition (*e.g.* impaired concentration, confusion), and symptoms related to emotional state (*e.g.* anxiety, depression). According to the data of Kockelmann *et al.* (2002) however, cognitive impairment appeared to be more an idiosyncratic feature of TPM than a dose-dependent event. In 2004, this result was modified by the authors in so far as they concluded that the severity of the cognitive side effects of TPM might, to a certain extent, be related to dosing (Kockelmann *et al.* 2004). Perucca (2000) stated: "Although at present there are not sufficient data to justify the measurement of serum TPM levels on a routine basis, this drug shows promise for further evaluation as a TDM (Therapeutic Drug Monitoring) candidate". According to the experience with "old" anticonvulsants such as phenobarbital, phenytoin or carbamazepine, "therapeutic drug level ranges" are useful for optimizing dosages and identifying possible adverse events (Fröscher *et al.* 1999). In the case of TPM, the results of the correlation of adverse events with TPM serum concentration, and adverse events with TPM dosage are conflicting: in some studies with TPM as add-on therapy (Sachdeo 1998, Contin *et al.* 2002, Kockelmann *et al.* 2002, Ferrari *et al.* 2003), the TPM serum concentration allowed no reliable prediction of the occurrence of adverse events. In other studies of TPM add-on therapy, there were significant correlations between the TPM serum concentration and some adverse events *e.g.* anorexia, weight loss, cognitive and emotional symptoms (Reife *et al.* 1995a, Nagel *et al.* 2001). We therefore investigated the relationship between serum concentration and adverse events in the case of the new drug TPM. A significant correlation would allow the specification of an approximate upper limit for a "therapeutic range" of TPM serum concentrations. Furthermore, we examined whether adverse events of TPM correlate more closely with the serum concentrations than with the dosage.

It should also be mentioned that the results of studies on the correlation of TPM serum concentration and seizure reduction are contradictory. Reife *et al.* (1995a) did not find a significant correlation between seizure reduction and TPM serum concentration. In other studies, seizure-free patients, as well as patients with a seizure reduction of at least 50%, had a TPM serum concentration of 2-25 µg/mL (Reife *et al.* 1995a, Patsalos 1999, Stephen *et al.* 2000, Burcet-Dardé 2002, Ferrari *et al.* 2003), thus the range of an effective serum concentration is very broad. According to Christensen *et al.* (2003) however, an optimal treatment response is most likely to be found at serum concentrations higher than 2 µg/mL, but no further increase in efficacy seems to occur at concentrations above 10.5 µg/mL. As a consequence of these conflicting results, the recommended target range of TPM given in the literature varies between 2-5 µg/mL (Fröscher *et al.* 1999) and 2-25 µg/mL (Glauser and Pippenger 2000).

Patients and methods

We included prospectively all 42 outpatients and inpatients with epilepsy, treated with TPM in our department of neurology and epileptology between December 1999 and September 2001. We included patients who had started with TPM before the beginning of our study as well as patients who received TPM for the first time during the study. Probable or certain adverse events of TPM were documented and blood samples were taken to determine the serum concentration of TPM at the same time. Medical history and clinical findings were documented on special forms. Examinations during this period and special investigations such as EEG were performed only if clinically necessary. In case of combination therapy, the serum concentrations of the following anticonvulsants were also measured: carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid. The serum concentrations of other anticonvulsants were not measured because an appropriate method was not available in our hospital.

The record of adverse events was based on questioning (medical interview) and examination of the patients. The patients were asked if they had noticed any adverse events, with special emphasis on dizziness, abnormal thinking (mental slowing, can't think as clearly, dull thinking), somnolence, ataxia, fatigue, confusion, impaired concentration and paresthesia. These 8 adverse events occurred in 5, double-blind, placebo-controlled, parallel group studies more often (≥ 10%) in patients on TPM treatment than in patients on placebo (Reife *et al.* 1995b, Sachdeo 1998). The 42 patients were examined up to 9 times (median 2) during the study period; 15 of the 42 patients were examined only once, the observation period of the other 27 patients was 6 to 554 days (median 74 days). The demographic and clinical characteristics of the patients are given in *table 1*. At the first examination, 41 patients were treated with TPM in combination with up to 4 additional anticonvulsants (median 2), one patient was on TPM monotherapy. The study was performed before TPM was approved for monotherapy in Germany. Seventeen patients were treated with TPM in combination with one additional anticonvulsant, 14 patients in combination with 2 additional anticonvulsants, eight patients had 3 and 2 patients 4 additional anticonvulsants *(table 2)*.

Table 1. Demographic and clinical characteristics of patients (n = 42).

Age, median (y)	36.5
- range	16-70
Gender (M/F)	21/21 patients
Epileptic syndrome	
- focal	n = 36
- generalized	n = 4
- undetermined	n = 2
Etiology of epilepsy	
- symptomatic/cryptogenic	n = 29
- idiopathic	n = 4
- undetermined	n = 9
Seizure (sz) history	**No. of patients**
- focal sz evolving to secondary generalized sz	22
- tonic-clonic sz, undetermined if with or without focal initiation	2
- simple focal sz	2
- complex focal sz	9
- tonic-clonic sz and absences	2
- absences	2
- tonic-clonic sz, complex focal sz, absences	1
- tonic-clonic sz, complex focal sz, absences, drop attacks, head nodding	1
- complex focal sz, absences, drop attacks	1
Compliance during the study (n = 42 patients, n = 109 investigations)	**No (%) of investigations**
- yes	98 (90%)
- no	3 (2.8%)
- uncertain	8 (7.3%)
Age (y) at onset of epilepsy, median (range)	6.5 (0.8 - 35)
Duration (y) of epilepsy at the beginning of the study, median (range)	30 (2 - 57)
Duration (y) of anticonvulsant treatment at the beginning of the study, median (range)	28 (2 - 56)

At the time of the first clinical examination, the duration of TPM treatment was 0.3 – 50 months (median 6 months, mean 10.6 ± 12.3 months).

The mean TPM dosage for 42 patients at the 109 medical examinations performed was 271 ± 155 mg (± SD). The median was 250 mg (range: 25 to 800). The corresponding body weight-related TPM dosage was 3.8 ± 2.3 mg/kg (mean ± SD) and 3.3 mg/kg (median; range: 0.2 to 10.9).

As a rule, changes of dosage were performed slowly (initial dose: 25 mg daily, increase of dosage was undertaken as 25 mg increments weekly). For the inpatients, TPM was determined in morning samples, before drug intake. For outpatients, blood samples had to be taken after the morning dose, because many of the patients attending our specialized outpatient clinic live quite a distance away from the hospital, and so blood examination could not be done before late morning. The mean interval between last drug intake and blood sampling in the whole group was 8.3 ± 5.5 h (± SD), the median was 6 h (range 1.3 to 24 h).

Separate evaluation of outpatients and inpatients was not performed, because the total number of patients was too small. Furthermore, some patients were treated as outpatients as well as inpatients during the study period. The study design does not allow for investigation of the relationship between TPM serum levels (or TPM dosages) and the reduction of seizure frequency caused by TPM, or the withdrawal of TPM due to adverse events.

The efficacy of TPM was not investigated for two reasons: the anticonvulsant efficacy of TPM is well known and, above all, we did not want to exclude those outpatients who did not reliably record seizure frequency.

TPM serum concentrations were determined by fluorescence polarization immunoassay/FPIA) developed by OXIS International Inc. (Portland, USA). The INNOFLOUR™ TPM Assay is for use on TDx or TDxFLx analyzers. The Innofluor assay is a robust procedure for the measurement of TPM in clinical samples (Berry and Patsalos 2002, May *et al.* 2002). The serum concentrations of carbamazepine, phenobarbital, phenytoin and valproic acid were also determined by FPIA; lamotrigine was determined by HPLC.

Statistical analysis: statistical methods included descriptive statistics for specification of the total sample, and the Wilcoxon rank sum test for differences between patients without, respectively with adverse events relating to TPM serum concentrations and TPM dosages. To compare the non-independent TPM serum concentrations at dates with and without adverse events, we used the Wilcoxon signed rank test. For each test we required a minimum of 10 patients.

To examine the influence of the co-medication on the occurrence of adverse events, we performed a logistic regression analysis using the occurrence of the most frequent adverse event "abnormal thinking" as the dependent variable (0 = no/1 = yes). The dose (mg/kg) and the serum concentration of TPM were used as independent variables. In addition, the total number of antiepileptic drugs (model 1) and the number of antiepileptic drugs per substance group (see below, model 2) were included, but not the respective dosages (group 1 – marked sedation: clobazam, clonazepam, phenobarbital, primidone. Group 2 – moderate sedation: carbamazepine, oxcarbazepine, phenytoin. Group 3 – mild sedation: lamotrigine, valproic acid. Group 4 – other anticonvulsants. The last group comprises the anticonvulsants rarely used in this study: acetazolamide, gabapentin, levetiracetam, sulthiame, tiagabine, vigabatrin). The predictor variables were entered simultaneously into the models. All statistical analyses were performed with the SAS System (Version 8.2).

Table 2. Type of concomitant antiepileptic drugs (AED) Baseline: n = 41 patients, one patient was on TPM monotherapy.

	n	dose (mg, median, range)	serum concentration (µg/mL, median, range)
Phenobarbital (n = 11)	17	PB: 120 (15-325)	PB: 25.3 (5.5-52.8)
and primidone[a] (n = 6)		PRM: 844 (500-1000)	
Carbamazepine	14	1300 (600-2850)	8.4 (4.7-15)
Valproic acid	13	1500 (150-2700)	70 (5-110)
Lamotrigine	10	375 (100-700)	3.8 (1.4-10)
Phenytoin	10	325 (200-450)	16.2 (8.4.-20.8)
Benzodiazepines	(6)	CLB: 10 (10-20)	not determined in most cases
- clobazam	- 3		
- clonazepam	- 3	CZP: 5.5 (1-8)	
Other AEDs (acetazolamide, gabapentin, levetiracetam, oxcarbazepine, sulthiame, tiagabine, vigabatrin)	9		not determined in most cases

CLB = clobazam, CZP = clonazepam. PB = phenobarbital, PRM = primidone.
[a] In patients who were treated with primidone, only the concentration of phenobarbital was determined. In one patient the concentration of phenobarbital was not determined by error.

Results

At the first examination, 29 out of 42 patients (69%) experienced an adverse event, 33 out of 42 patients (79%) had, in at least one out of the 109 examinations, an adverse event *(table 3)*. Adverse events that were observed in at least five (out of 42) patients, were evaluated further. The TPM serum concentration and the TPM dosage at the time of the first registration of these adverse events were compared with the corresponding values of patients who had no adverse event at the first examination (n = 13; *tables 4* and *5*). The differences in TPM serum concentrations and TPM dosages (mg/kg) for patients without an adverse event and patients with a given adverse event were statistically significant for abnormal thinking, impaired concentration, weight loss, dizziness, speech problems, somnolence, ataxia, increased seizure frequency and paresthesia. Only in the case of "fatigue" was the difference not significant.

The comparison of TPM serum concentration and dosage at the first examination of patients with the occurrence of any adverse events resulted in statistically significant differences for the serum concentration and for dosage *(table 6)*.

Figure 1 shows the 109 serum concentrations of all examinations of the 42 patients. Serum concentrations accompanied by an adverse event, and serum concentrations not accompanied by an adverse event are markedly different; however, a vast overlap between these two categories can be seen. This vast overlap can also be demonstrated by comparing the lowest TPM serum concentration of patients with a distinct adverse event, with the highest TPM serum concentration at which the patient did not have this adverse event. The statistical evaluation (Wilcoxon signed-rank test) was done only in those adverse events which were reported by at least ten patients. Only those patients could be included who had the distinct adverse event in at least one but not all examinations. Therefore, the number of patients is small for this comparison of the adverse events "abnormal thinking, impaired concentration and weight loss". There was no statistical difference between TPM serum concentration or dosage and patients with and without these adverse events.

Figure 2 indicates the proportion of patients with and without adverse events at the different examination times. This proportion did not change essentially during the whole study period.

Figure 3 shows that the occurrence of adverse events at the first examination was dependent on TPM serum concentrations. Patients were experiencing adverse events at serum concentrations as low as 0.1 – 4 µg/mL. Above a TPM serum concentration of 4 µg/mL, the predominance of patients with adverse events is even more distinct. *figures 4* and *5* show the occurrence of adverse events to be dependent on absolute dosage or the dosage related to body weight. Only with a TPM dosage of ≤ 100 mg or ≤ 1.5 mg/kg, respectively, do patients appear to be without any adverse events. The 13 patients without any adverse event at the first examination had a mean TPM serum concentration of 3.2 ± 3.6 µg/mL (mean ± SD).

In the logistic regression model 1 (with the total number of antiepileptic drugs) as well as in model 2 (with the number of antiepileptic drugs per substance group), only the TPM dose and not the serum concentration allowed the prediction of the appearance of "abnormal thinking" *(table 7)*. The increase in the dose of 1 mg/kg raises the risk of

Table 3. Adverse events in patients treated with TPM at the first examination (53 adverse events in 29 patients), and during the whole study (123 adverse events in 42 patients).

Adverse events	1st examination		All examinations	
	n	% of 42 pat.	n	% of 42 pat.
Abnormal thinking	10	24	18	43
Impaired concentration	9	21	13	31
Weight loss	5	12	12	29
Dizziness	4	10	8	19
Speech problems	4	10	8	19
Ataxia	4	10	5	12
Fatigue	3	7	6	14
Exhaustion	2	5	4	10
Paresthesia	2	5	5	12
Loss of appetite	2	5	2	5
Somnolence	1	2	8	19
Dysarrythmia	1	2	3	7
Confusion	1	2	2	5
Nausea, vomiting	1	2	2	5
Increased seizure frequency	1	2	5	12
Impaired memory	1	2	3	7
Emotional lability	1	2	2	5
Leucopenia	1	2	2	5
Irritability, aggressiveness	0	0	3	7
Apathia	0	0	2	5
Skin lesion	0	0	2	5
Increased alertness	0	0	1	2
Elevated mood	0	0	1	2
Dyspnoea on exertion	0	0	1	2
Edema of the malleolar region	0	0	1	2
Incontinence of urine	0	0	1	2
Diarrhoea	0	0	1	2
Nervousness	0	0	1	2
Tremor	0	0	1	2

"abnormal thinking" by a factor of 1.5 or 1.6, respectively. The total number of additional anticonvulsants and the number of anticonvulsants per group were not significant.

Discussion

The proportion of patients with adverse events likely to be related to TPM was high in our study. At the first clinical examination, 29 out of 42 patients (69%) showed at least one adverse event; 33 out of 42 patients (79%) had an adverse event at least once during the study period. According to the different reports in the literature regarding children and adult patients with epilepsy, the frequency of at least one adverse event with TPM as add-on-therapy ranges from 17% (Schreiner 2003b) to 73% of patients (Rosenfeld *et al.* 1997). Cognitive or behavioural side effects were reported in almost 50% of patients in the study of Kellett *et al.* (1999), and most of these patients were receiving combination therapy. Kellett *et al.* (1999) supposed that their figures could be an underestimation of the true incidence of side effects as they did not specifically enquire about adverse events in all patients. The observation of Diaz-Obregon *et al.* (Diaz-Obregon *et al.* 2002) that neuropsychological function is not influenced by treatment with TPM is in contradiction with other results in the literature (Kockelmann *et al* 2004, Ortinski and Meador 2004). The frequency of adverse events with TPM monotherapy is lower than with combination therapy (Reife *et al.* 2000, Ben-Menachem *et al.* 2003, Gilliam *et al.* 2003, Privitera *et al.* 2003, Schreiner 2003a, Schreiner 2003b); however, the spectrum of adverse events seems to be identical (2003). In the TPM monotherapy studies of Gilliam *et al.* (2003), the number of adverse events occur-

Table 4. TPM serum concentration at the first observation of an adverse event. Comparison with a TPM serum concentration from 13 patients without adverse events at the first examination.

Adverse event	Serum concentration of the patients with a given adverse event (µg/mL)	Serum concentration of the 13 patients without adverse events (n = 13) (µg/mL)	Wilcoxon rank sum test
Abnormal thinking	n = 18 7.2 ± 4.9	3.2 ± 3.6	W = 138. p = 0.003
Impaired concentration	n = 13 6.7 ± 4	3.2 ± 3.6	W = 228. p = 0.004
Weight loss	n = 12 7.3 ± 5.1	3.2 ± 3.6	W = 202. p = 0.0067
Dizziness	n = 8 5.5 ± 4.7	3.2 ± 3.6	W = 115. p = 0.03
Speech problems	n = 8 6.4 ± 4.9	3.2 ± 3.6	W = 113. p = 0.04
Somnolence	n = 8 6.9 ± 5.	3.2 ± 3.6	W = 113. p = 0.04
Fatigue	n = 6 3.8 ± 3.5	3.2 ± 3.6	W = 73. p = 0.14
Ataxia	n = 5 7.1 ± 5.2	3.2 ± 3.6	W = 69. p = 0.02
Increased seizure frequency	n = 5 6.7 ± 4.1	3.2 ± 3.6	W = 68. p = 0.02
Paresthesia	n = 5 6.8 ± 3.8	3.2 ± 3.6	W = 68. p = 0.02

Table 5. Dosage at the first observation of the adverse event. Comparison with TPM dose of 13 patients without adverse events at the first examination.

Adverse event	TPM dose of the patients with a given adverse event	TPM dose of the 13 patients without adverse events (mg/kg)	Wilcoxon rank sum test
Abnormal thinking	n = 18 5.2 ± 2.8	2.1 ± 1.8	W = 134.5 p = 0.002
Impaired concentration	n = 13 4.4 ± 2.2	2.1 ± 1.8	W = 225. p = 0.006
Weight loss	n = 12 5.1 ± 2.4	2.1 ± 1.8	W = 211. p = 0.002
Dizziness	n = 8 5.1 ± 2.5	2.1 ± 1.8	W = 121.5 p = 0.008
Speech problems	n = 8 4.5 ± 3	2.1 ± 1.8	W = 117. p = 0.02
Somnolence	n = 8 5.3 ± 2.6	2.1 ± 1.8	W = 123.5 p = 0.006
Fatigue	n = 6 2.9 ± 2.5	2.1 ± 1.8	W = 70. p = 0.2
Ataxia	n = 5 5.2 ± 1.7	2.1 ± 1.8	W = 72.5 p = 0.008
Increased seizure frequency	n = 5 4.4±1.7	2.1 ± 1.8	W = 69. p = 0.02
Paresthesia	n = 5 5.1 ± 1.4	2.1 ± 1.8	W = 71. p = 0.01

Table 6. Comparison of TPM serum concentration and dose for patients with versus without adverse events at the first examination.

	Without adverse events (n = 13 pat.)	With adverse events (n = 29 pat.)	Wilcoxon rank sum test
TPM serum concentration (µg/mL)	3.2 ± 3.6	5.2 ± 4.2	W = 199. p = 0.02
TPM dose (mg/kg)	2.1 ± 1.8	4.2 ± 2.8	W = 185. p = 0.006

ring in more than 10% of the patients was considerable however, (paresthesia in 13% of patients with a low TPM dosage, and in 35% of patients with a higher TPM dose).

Some studies report a relationship between the frequency of adverse events caused by TPM and the duration of the TPM treatment; the adverse events occurring at the beginning of the treatment are assumed to disappear, at least partially with time (Reife *et al.* 1995b, *et al.* 1997, Gilliam *et al.* 2003). We did not observe this effect in our patients; at the first clinical examination they had been treated with TPM for six months (median, range 0.3 to 50 months), the percentage of patients with any adverse event did not decrease during the subsequent study period *(figure 2)*.

In our study, the most frequent adverse events, *i.e.* adverse events occurring in at least 10% of the patients, were, at the first examination (in alphabetical order): ataxia, impaired concentration, dizziness, speech problems, abnormal thinking, and weight loss. During the whole study, the most frequent adverse events were (in alphabetical order): ataxia, impaired concentration, dizziness, exhaustion, increased seizure frequency, speech problems, paresthesia, somnolence, abnormal thinking, fatigue, weight loss. Obviously, during the course of the study, complaints of a sedating effect of TPM became more frequent. The most frequent adverse events at the first examination – abnormal thinking, impaired concentration, weight loss – remained the most frequent adverse events during the whole observation period.

The spectrum of adverse events associated with TPM in our study, corresponds, to a high degree, to the results of other studies in adults and children with TPM both as add-on-therapy and as monotherapy (Kellett *et al.* 1999, Sziklas *et al.* 1999, Thompson *et al.* 1999, Abou-Khalill *et al.* 2000, Arroyo *et al.* 2000, Biton *et al.* 2001, Contin *et al.* 2002, Guberman *et al.* 2002, Jette *et al.* 2002, Christensen *et al.* 2003, Dlugos *et al.* 2003, Dodson *et al.* 2003, Gilliam *et al.* 2003, Krakow *et al.* 2003, Mikaeloff *et al.* 2003, Reith *et al.* 2003); this is especially true for the comparison with the results of Reife *et al.* (1995b, 2000) in 5, double-blind, placebo-controlled parallel group studies. Their results were the basis of our list of questions regarding adverse events. In the study of Reife *et al.* (Reife *et al.* 1995b), adverse events related to the CNS were also the most frequent adverse events. In particular, "abnormal thinking" was also the most frequent adverse event. In the study of Krakow and Schreiner (2003) in patients on polytherapy however, adverse events related to the CNS were much less frequent.

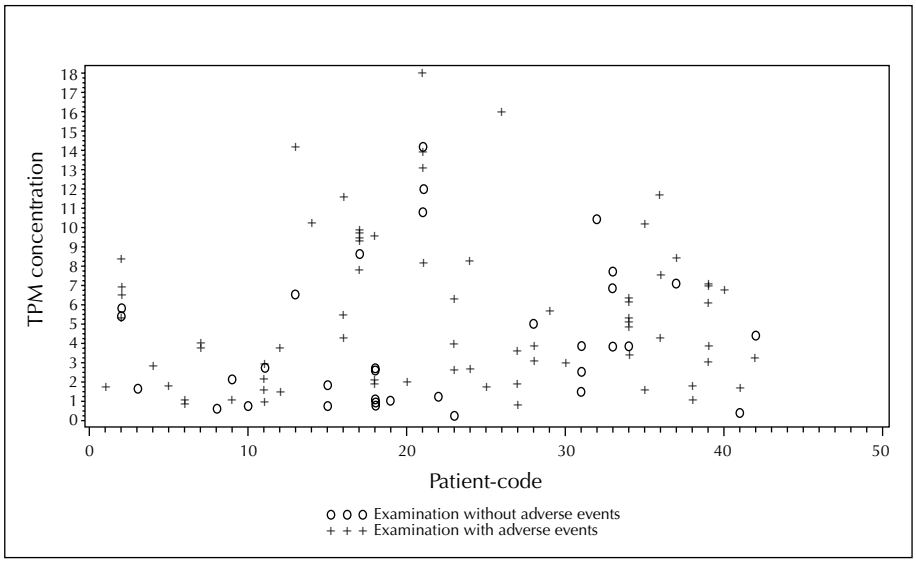

Figure 1. TPM serum concentration of 42 patients in 109 examinations.

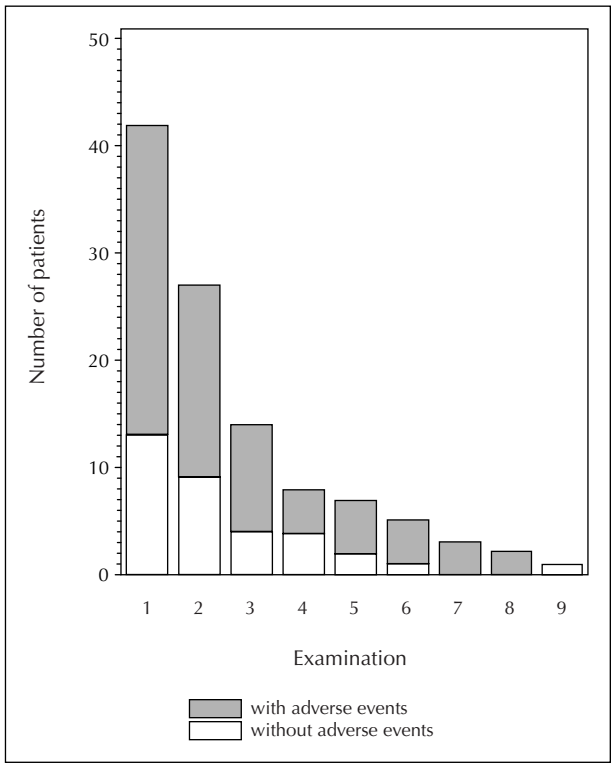

Figure 2. Relationship between the number of patients with and without adverse events at the different investigation times during the whole study.

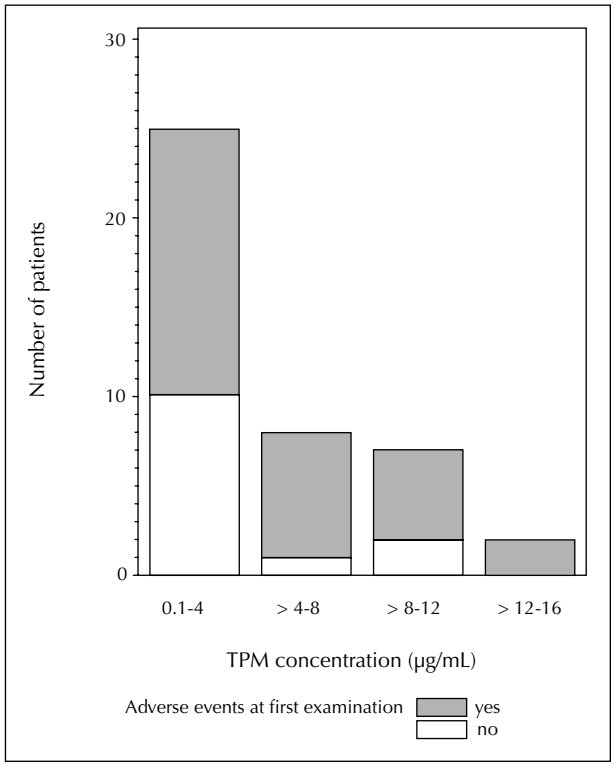

Figure 3. Number of patients with and without adverse events depending on the range of the TPM serum concentration (µg/mL).

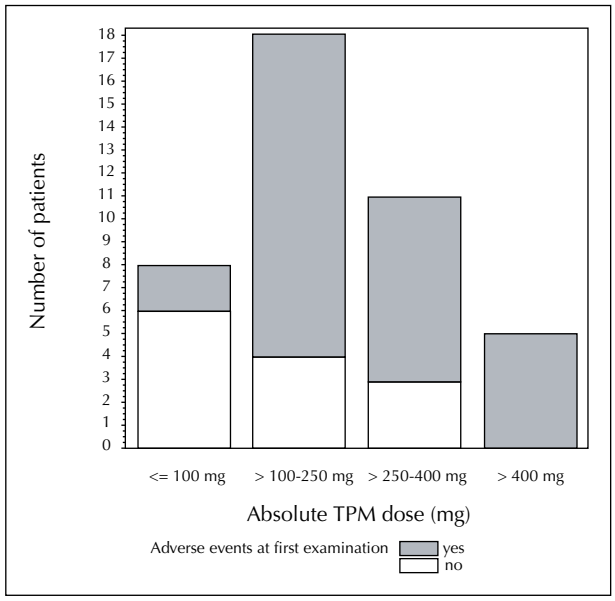

Figure 4. Number of patients with and without adverse events depending on the range of the absolute TPM dose (mg).

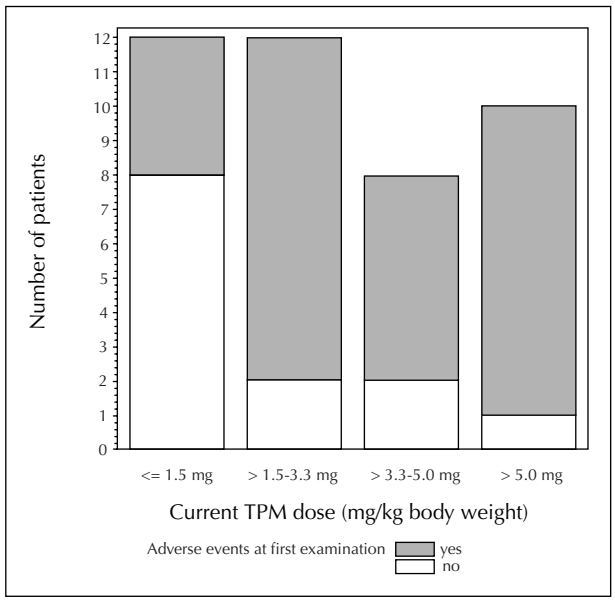

Figure 5. Number of patients with and without adverse events depending on the range of the TPM dose (mg/kg).

Table 7. Results of the logistic regression analysis to examine the influence of the co-medication on the emergence of "abnormal thinking" (the anticonvulsive co-medication, the TPM serum concentration and the TPM dose were used as effects).

	Odds ratio	95%-CI-Limits
Model 1		
Total number of anticonvulsants	0.8	0.2 – 2.2
TPM serum concentration	1.0	0.8 – 1.3
TPM dose (mg/kg)	1.5	1.03 – 2.2
Model 2		
Number of markedly sedating anticonvulsants	2.2	0.4 – 10.6
Number of moderately sedating anticonvulsants	0.8	0.2 – 3.5
Number of mildly sedating anticonvulsants	0.6	0.1 – 3.1
Number of remaining anticonvulsants	0.2	0.01 – 2.5
TPM dose (mg/kg)	1.6	1.03 – 2.6
TPM serum concentration	1.0	0.79 – 1.4

The fact that the results of Reife *et al.* (Reife *et al.* 1995b) are similar to ours is probably caused by our choice of questions concerning the adverse events; the frequent adverse events shown in their study were also investigated systematically in our own study, whereas other possible adverse events (*e.g.* irritability, elevated mood, nausea or upper respiratory infection), which had a relatively high frequency in other studies (Arroyo *et al.* 2000, Montouris *et al.* 2000, Ritter *et al.* 2000, Arroyo *et al.* 2002, Gilliam *et al.* 2003) were not investigated systematically, and therefore were probably underestimated. The percentage of reported adverse events depends, to a high degree, on the specificity of questions (Grudzinski *et al.* 1998, Cramer *et al.* 1999, Kellett *et al.* 1999, Donati *et al.* 2000, Gilliam *et al.* 2004). The dosage schedule in our study was different however, from those in the studies reviewed by Reife *et al.* (1995b); the initial dosage of TPM and the dosage increments were lower in our study. This is important because it was demonstrated that the frequency of adverse events, and especially of adverse events related to the CNS, depends, to a greater degree, on the starting dose and the escalation regimen rather than the maintenance dosage (Biton *et al.* 2001, Mula *et al.* 2003). While Reife *et al.* (1995b) reported on daily dosages of 200 to 1,000 mg, the median daily dosage in our patients was 250 mg (range 25 to 800 mg), and the increase of dosage was not performed in 200 mg/d increments at weekly intervals, but in 25 (- 50) mg increments at weekly intervals. It should be underlined that in some other studies (Reith *et al.* 2003, Trimble *et al.* 2003) there was no clear correlation between adverse events and starting dose or titration schedule.

The determination of the serum concentration of TPM was aimed at finding a better correlation between TPM serum concentration and adverse events than could be expected between such adverse events and TPM dosage.

In our study, the adverse events "abnormal thinking, impaired concentration, weight loss, dizziness, speech problems, somnolence, ataxia, increased seizure frequency and paresthesia" showed a significant positive correlation with the serum concentration as well as with the dosage of TPM. Only the correlation with fatigue was not significant; the possible reason for this result might be the small number of patients. The positive correlation was at least as strong in the case of the dosage as in the serum concentration of TPM. Therefore, the predictability of adverse events is probably not much improved by the availability of the serum concentration of TPM. This assumption is supported by the broad overlapping of TPM serum concentrations accompanied by adverse events and serum concentrations not accompanied by adverse events. This was demonstrated graphically *(figure 1)*, and by comparing the lowest TPM serum concentration (all dosage) of patients with the adverse events "abnormal thinking, impaired concentration, weight loss" with the highest TPM serum concentration at which the patients did not have these adverse events.

In our study with a TPM serum concentration of up to 4 µg/mL, 15 out of 25 patients (60%) complained of adverse events, with a serum concentration above 4 µg/mL 14 out of 17 patients (82%) complained of adverse events. Therefore, we recommend starting treatment with TPM, with the aim of obtaining a serum concentration below 4 µg/mL, while checking the efficacy of this relatively low serum concentration.

Some authors report on the positive correlation of dosages of TPM and adverse events, *e.g.* a significant dependence of weight loss on the TPM dosage (monotherapy and/or combination therapy) was demonstrated (Nagel *et al.* 2001, Widmann *et al.* 2002, Gilliam *et al.* 2003); an analogous dependence was demonstrated in case of par-

esthesia, diarrhea and upper respiratory infections (Gilliam *et al.* 2003). A dependence on the TPM dosage was also demonstrated with the adverse events "difficulty with concentration/attention, speech problems, confusion, nausea, abdominal pain" (Privitera *et al.* 2003); the degree of statistical significance was not reported.

The dependence of "abnormal thinking" and "somnolence" on the TPM dosage has to be underlined, as it is in contrast to the statement that cognitive impairment (particular verbal fluency, working memory and speed of information processing) appears to be more an idiosyncratic feature of TPM than a dose-dependent one (Kockelmann *et al.* 2002).

Up to a dosage of 100 mg or 1.5 mg/kg, respectively, the majority of patients did not complain of adverse events (6 out of 8, or 8 out of 12 patients respectively, without adverse events), above this dosage the majority of patients did complain of adverse events *(figures 4, 5)*. With regard to the adverse events, patients should be treated with low dosage TPM. This well-tolerated, low dosage is below the dosage that is usually recommended in the literature. The dosage for seizure prevention is typically given as between 25 and 900 mg (in TPM monotherapy, higher dosages are recommended than when given in combination with enzyme inducing drugs (Mula *et al.* 2003, Chadwick *et al.* 1999, Topamax®-Fachinformation/Product monograph 2003, Sander *et al.* 2003). In the case of TPM as an add-on drug, 200 to 400 mg is the usual recommended daily maintenance dosage (Stefan 2003).

Our recommendation of a target dosage of 100 mg TPM or less (1.5 mg/kg or less) with respect to possible adverse events is not unrealistic. A daily dose of 50 to 100 mg TPM as monotherapy, or as combination therapy has proved to be effective in different studies (Arroyo *et al.* 2000, Kelly *et al.* 2002, Privitera 2003, Privitera *et al.* 2003, Dodson *et al.* 2003, Prange 2004). Our recommendations are limited by the relatively small number of patients.

The problem of adverse events occurring already at low doses of TPM indicates a narrow therapeutic range. Occasionally, the treatment with TPM has to be stopped because of adverse events, although a high dosage might be very effective in seizure prevention. This situation is similar to the situation with phenobarbital, which seems to be as effective as TPM and whose sedative effect is comparable or equal to that of TPM (Lathers *et al.* 2003).

Our results indicate that the correlation of several adverse events with TPM dosage seems to be comparable to that with TPM serum concentration. However, this does not mean that monitoring of serum concentration of TPM is superfluous. Nevertheless, it reduces the relevance of the knowledge of the TPM serum concentration for dosage titration. Primarily dosage titration is based on the clinical situation (occurrence of seizures, occurrence of adverse events) Trimble *et al.* 2003. □

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References

Abou-Khalil B, Topiramate YOL Study Group. Topiramate in the long-term management of refractory epilepsy. *Epilepsia* 2000; 41 (suppl 1): S72-S76.

Arroyo S, Squires L, Twyman R. Topiramate (TPM) monotherapy in newly diagnosed epilepsy: effectiveness in dose-response study. *Epilepsia* 2000; 43 (suppl 8): 47-8.

Arroyo S, Squires L, Wang S, Twyman R. Topiramate effective as monotherapy in dose-response study in newly diagnosed epilepsy. *Epilepsia* 2002; 43 (suppl 7): 241.

Ben-Menachem E, Squires L, Wang S, Thienel U. Topiramate as first-line monotherapy: tolerability and safety in 1000+ epilepsy patients. *Epilepsia* 2003; 44 (suppl 8): 152-3.

Berry DJ, Patsalos PN. Comparison of topiramate concentrations in plasma and serum by fluorescence polarization immunoassay. *Ther Drug Monit* 2002; 22: 460-4.

Biton V, Edwards KR, Montouris GD, *et al.* Topiramate titration and tolerability. *Ann Pharmacother* 2001; 35: 173-9.

Burcet-Dardé J. Use of topiramate in monotherapy and evaluation of plasma levels. *Epilepsia* 2002; 43: 146.

Chadwick DW, Wu SC, Pledger G. Post-titration seizure control with topiramate (TPM) as early/initial monotherapy. *Epilepsia* 1999; 40 (suppl 7): 111.

Christensen J, Andreasen F, Poulsen JH, Dam M. Randomized, concentration-controlled trial of topiramate in refractory focal epilepsy. *Neurology* 2003; 61: 1210-8.

Contin M, Riva R, Albani F, Avoni P, Baruzzi A. Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2002; 24: 332-7.

Cramer JA, Fisher R, Ben-Menachem E, French J, Mattson RH. New antiepileptic drugs: comparison of key clinical trials. *Epilepsia* 1999; 40: 590-600.

Diaz-Obregon MD, Bathal H, Santiago R. Cognitive function in epilepsy patients controlled on monotherapy with topiramate. *Epilepsia* 2002; 43 (suppl 8): 169.

Dlugos DJ, Squires L, Wang S. Neurobehavioural adverse events (AES) with topiramate monotherapy in children and adolescents. *Epilepsia* 2003; 44 (suppl 8): 91-2.

Dodson WE, Kamin M, Kraut L, Olson WH, Wu SC. Topiramate titration to response: analysis of individualized therapy study (TRAITS). *Ann Pharmacother* 2003; 37: 615-20.

Donati F, Pfaeffli C, Ramelli GP. Adverse events due to antiepileptic drugs: results depending on the method of questioning. *Epilepsia* 2000; 41: 108.

Ferrari AR, Guerrini R, Gatti G, Alessandrimg, Bonanni P, Perucca E. Influence of dosage, age, and co-medication on plasma topiramate concentrations in children and adults with severe epilepsy and preliminary observations on correlations with clinical response. *Ther Drug Monit* 2003; 25: 700-8.

Fröscher W, Krämer G, Schmidt D, Stefan H. Serumkonzentration von Antiepileptika – praktische Richtlinien zur Messung und sinnvollen Interpretation (Serum concentration of antiepileptic drugs: guidelines for therapeutic monitoring and appropriate interpretation). *Nervenarzt* 1999; 70: 172-7.

Fröscher W, Schier KR, Hoffmann M, *et al.* Topiramat: Prospektive Untersuchung zur Frage der Korrelation von Serumkonzentration, Dosis und Nebenwirkungen. *Z Epileptol* 2004; 17: 160-1.

Gilliam FG, Veloso F, Bomhof MAM, *et al.* A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy. *Neurology* 2003; 60: 196-202.

Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects – a randomized trial. *Neurology* 2004; 62: 23-7.

Glauser TA, Pippenger CE. Controversies in blood-level monitoring: reexamining its role in the treatment of epilepsy. *Epilepsia* 2000; 41 (suppl 8): S6-S15.

Grudzinski AN, Hakim Z, Coons SJ, Labiner DM. Use of the QOLIE-31 in routine clinical practice. *J Epilepsy* 1998; 11: 34-47.

Guberman A, Neto W, Gassmann-Mayer C. the EPAJ-119 Study Group. Low-dose topiramate in adults with treatment-resistant partial-onset seizures. *Acta Neurol Scand* 2002; 106: 183-9.

Jette NJ, Marson AG, Hutton JL. Topiramate add-on for drug-resistant partial epilepsy. The Cochrane database of symptomatic reviews (electronic resource) (3); p CD001417/2002.

Kellett MW, Smith DF, Stockton PA, Chadwick DW. Topiramate in clinical practice: First year's post-licensing experience in a specialist epilepsy clinic. *J Neurol Neurosurg Psychiatry* 1999; 66: 759-63.

Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Topiramate in patients with learning disability and refractory epilepsy. *Epilepsia* 2002; 43: 399-402.

Kockelmann E, Helmstaedter C, Elger CE. Comparative cognitive effects of topiramate and lamotrigine. Evidence for idiosyncratic and not serum level dependent cognitive impairment on TPM patients with epilepsy. *Akt Neurol* 2002; 29 (suppl 2): S190.

Kockelmann E, Elger CE, Helmstaedter C. Cognitive profile of topiramate as compared with lamotrigine in epilepsy patients on antiepileptic drug polytherapy: Relationships to blood serum levels and comedication. *Epilepsy Behav* 2004; 5: 716-21.

Krakow K, Schreiner A. Efficacy and tolerability of topiramate as an early add-on therapy in 450 patients with epilepsy. *Epilepsia* 2003; 44 (suppl 8): 172.

Langtry HD, Gillis JC, Davis R. Topiramate. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy. *Drugs* 1997; 54: 752-73.

Lathers CM, Schraeder PK, Claycamp HG. Clinical pharmacology of topiramate versus lamotrigine versus phenobarbital: comparison of efficacy and side effects using odds ratios. *J Clin Pharmacol* 2003; 43: 491-503.

May TW, Rambeck B, Jürgens U. Serum concentrations of topiramate in patients with epilepsy: influence of dose, age, and comedication. *Ther Drug Monit* 2002; 24: 366-74.

Mikaeloff Y, de Saint-Martin A, Mancini J, *et al.* Topiramate: efficacy and tolerability in children according to epilepsy syndromes. *Epilepsy Res* 2003; 53: 225-32.

Montouris GD, Biton V, Rosenfeld WE, Topiramate YTC/YTCE Study Group. Nonfocal generalized tonic-clonic seizures: response during long-term topiramate treatment. *Epilepsia* 2000; 41 (suppl 1): S77-S81.

Mula M, Trimble MR, Lhatoo SD, Sander JWAS. Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia* 2003; 44: 659-63.

Nagel BJ, Brewer VR, Phelphs SJ. Cognitive and behavioural side effects associated with topiramate. *J Pediatr Pharmacol Ther* 2001; 6: 258-70.

Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. *Epilepsy Behav* 2004; 5: S60-S65.

Patsalos PN. New antiepileptic drugs. *Ann Clin Biochem* 1999; 36: 10-9.

Perucca E. Is there a role for therapeutic drug monitoring of new anticonvulsants? *Clin Pharmacokinet* 2000; 38: 191-204.

Prange E. Epilepsie bei älteren Patienten. *Psychoneuro* 2004; 30: 66.

Privitera MD. Evidence-based use of topiramate in epilepsy. Lecture. 25th Int Epilepsy Congress. October 14, 2003, Lisbon (Symposium "Challenges to the traditional paradigms of epilepsy management").

Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S. for the EPMN 105 Study Group. Topiramate, carbamazepine and valproate monotherapy: a double-blind comparison in newly diagnosed epilepsy. *Acta Neurol Scand* 2003; 107: 165-75.

Reife RA, Pledger G, Doose D, Lim P, Ward C. Topiramate: PK/PD Analyses. *Epilepsia* 1995; 36 (suppl 3): S152.

Reife RA, Lim P, Pledger G. Topiramate: side effect profile in double-blind studies. *Epilepsia* 1995; 36 (suppl 4): 34.

Reife R, Pledger G, Wu SC. Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults. *Epilepsia* 2000; 41 (suppl 1): S66-S71.

Reith D, Burke C, Appleton DB, Wallace G, Pelekanos J. Tolerability of topiramate in children and adolescents. *J Pediatr Child Health* 2003; 39: 416-9.

Ritter F, Glauser TA, Elterman RD, Wyllie E, Topiramate YP Study Group. Effectiveness, tolerability, and safety of topiramate in children with partial-onset seizures. *Epilepsia* 2000; 41 (suppl 1): S82-S85.

Rosenfeld WE, Kanner A, Jacobson M, Kretschmar P, PADS Investigator Group. Topiramate and concomitant weight loss. *Epilepsia* 1997; 38 (suppl 8): 98.

Sachdeo RC. Topiramate. Clinical profile in epilepsy. *Clin Pharmacokinet* 1998; 34: 335-46.

Sander JWAS, Arroyo S, Privitera M, Squires L, Wang S, Twyman R. Topiramate in newly diagnosed epilepsy: 100mg/day as initial target dose. *Epilepsia* 2003; 44 (suppl 8): 82.

Schreiner A. Efficacy and tolerability of topiramate as first-line add-on therapy for epilepsy. *Epilepsia* 2003; 44 (suppl 8): 173.

Schreiner A. Efficacy and tolerability of topiramate as early add-on therapy in 450 patients with epilepsy. *Epilepsia* 2003; 44 (suppl 9): 103-4.

Stefan H. Neue Antikonvulsiva: Zweite Generation. *Arzneimitteltherapie* 2003; 21: 373-84.

Stephen LJ, Sills GJ, Brodie MJ. Topiramate in refractory epilepsy: a prospective observational study. *Epilepsia* 2000; 41: 977-80.

Sziklas VG, Montour-Proulx I, Andermann F, Dubeau F, Jones-Gotman M. Cognitive effects of topiramate therapy in patients with intractable partial epilepsy. *Epilepsia* 1999; 40 (suppl 7): 56.

Thompson PJ, Baxendale SA, Duncan JS, Sander LJWA. Changes in intellect and verbal processing in association with topiramate treatment. *Epilepsia* 1999; 40 (suppl 7): 50.

Topamax®-Fachinformation/Product monograph. Janssen-Cilag, July 2003.

Trimble M, Mula M, Sander J, Thompson P. Word-finding difficulties and topiramate. *Epilepsia* 2003; 44 (suppl 9): 298.

Widmann G, Bien CG, Scherrmann J, Elger CE. Klinische Erfahrungen mit Topiramat. Eine offene, retrospektive Untersuchung an 154 Patienten. *Z Epileptol* 2002; 15: 17-22.