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Topiramate in add-on therapy: Results from an open-label, observational study

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on behalf of the TOP-GER-3 investigators

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Summary An open-label, observational prospective study assessed the effectiveness of topiramate (TPM) as add-on therapy. A total of 450 patients aged 12 and above with a diagnosis of epilepsy and at least one epileptic seizure during the 12-week retrospective baseline were to be documented. After baseline evaluation, topiramate was added. Ninety-five percent of patients had at least one baseline AED, most commonly Carbamazepine (53%) or Valproate (34%). In 5% TPM was started in monotherapy. Topiramate dose titration and target dose was determined by clinical response and side effect profile. Patients were intended to be followed for a total of 1 year which included 6 visits during which seizure frequency, adverse events, weight as well as clinical global impression were recorded. During the 12 weeks retrospective baseline, a median of 2.8 seizures per month were recorded which reduced significantly to 0.7 per month during the complete treatment phase ($p < 0.0001$). Seventy-two percent of patients had a $\geq$50% seizure reduction. Ten percent of patients were seizure free during the study. The most commonly reported adverse events were difficulties with memory (4.2%), somnolence (3.6%), and dizziness (2.7%). Overall, topiramate was well tolerated, and only 5% of patients discontinued treatment due to an adverse event. Retention in the study was higher than previously reported during randomized, dose controlled studies and is likely due to individualized doses as well as slower titration used.

Introduction

Less than 50% of patients become seizure-free with the first anticonvulsant drug [1,2] and failure due to lack of efficacy is associated with poor outcome for the

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individual. Excess mortality, cognitive and behavioral dysfunction as well as social and educational disadvantages are negative consequences of uncontrolled epilepsy.[3] A second monotherapy or a combination therapy is frequently unavoidable and an anticonvulsant with few drug—drug interactions is generally preferred. Topiramate (TPM) is a sulfamate-substituted monosaccharide, with multiple mechanisms of action that include blockade of voltage-sensitive sodium channels, potentiation of $GABA_A$-evoked chloride flux, blockade of kainate/AMPA type of glutamate receptors, and reduction of type L-calcium channels activity.[4,5] Various seizure types can be treated effectively. The lack of significant pharmacokinetic interactions, minimal protein binding as well as the long half-life is advantageous in clinical settings.[6]

In early randomized, placebo-controlled trials, topiramate was shown to be highly efficacious demonstrating a significant median reduction in seizure frequency at doses of 200—600 mg/day [7] and seizure freedom in 5% of drug-resistant patients. However, tolerability of the drug was reduced because fixed titration and target doses as well as inability to adjust concomitant AEDs. As a result of this, treatment during drug trials is frequently discontinued due to adverse events. In general, 75% of patients dropping out of from randomized trials will do that within the first 2 months, often during forced titration without reduction of concomitant therapy.[7,8] Therefore, results of these trials are only partially applicable for daily routine, since ease of titration, pharmacokinetic and pharmacodynamic interactions and the patient's individual response to seizure control and medication side effects are important constituents of individualized therapy. Studies reflecting the daily use of topiramate in adult patients with difficult to treat epilepsy add valuable information regarding overall effectiveness of the drug.

In order to assess this further, we conducted a 1-year prospective open-label multicenter study to assess topiramate in add-on therapy in patients with epilepsy who should be diagnosed within the last 3 years and who failed several AEDs due to insufficient efficacy and/or tolerability under the conditions of daily clinical practice. Doses of TPM were determined by the treating physician according to prescribing information based on tolerability and seizure reduction.

Methods

Study design and patients

Patients were to be enrolled in this prospective, open-label multicenter study provided they were at least 12 years of age, had a confirmed diagnosis of epilepsy according to the ILAE 1989 classification,[9] the diagnosis was made within the last 3 years and they were drug-naïve to TPM. In addition, a minimum of one epileptic seizure during the 12-week retrospective baseline was required. Patients were to be followed up for 1 year at 158 study centers in Germany.

Treatment

Target doses and dose escalation of topiramate add-on therapy were based upon the physicians' discretion. However, a starting dose of 25 mg/day with a weekly escalation of 25 mg/day thereafter given b.i.d. was recommended according to the German TPM prescribing information. No upper or lower dose limit was set. Concomitant AEDs could be adjusted upon the physicians' discretion.

Assessments and documentation

On the initial visit, demographic data, a thorough medical and epilepsy history was documented and a comprehensive physical and neurological examination was conducted. Further visits at 1, 2, 3, 6, 9, and 12 months were documented. During each visit, seizure diaries were reviewed and number and type of seizures were recorded. In addition, adverse events including seriousness, causality with TPM treatment, and outcome were noted. AEDs and other concomitant medications, medical and neurological findings were documented. At the final visit the patients and physicians were asked to assess the efficacy of the treatment using a 5-point rating scale (very good, good, reasonable, unchanged, worsened) and the tolerability using a 4-point rating scale (very good, good, moderate, poor).

Analysis and statistics

Safety data were analyzed for the entire study period in all subjects who had received topiramate at least once. In the intent-to-treat population for effectiveness all patients who received TPM at least once and with at least one post-baseline observation were included. The maintenance phase was determined for each single patient: it was defined as the period starting from the individual study end backwards where a stable dose of TPM within the range of $\pm$50 mg was applied over at least 12 weeks. Thus, patients in whom the study was prematurely terminated before 12 weeks or in whom the dose was changed for more than 50 mg/day during the last 12 week-observation period do not have a maintenance phase.

The 4-week seizure frequency during treatment was determined per patient based on the seizures cumulatively counted over the whole treatment period and the maintenance phase if applicable, respectively. Mean ± standard deviation (S.D.) and median values were calculated and the change versus baseline was assessed, using the Wilcoxon signed-rank test, two sided at the 5% significance level. Responder rates were defined as the proportion of patients achieving ≥50- (primary endpoint), ≥75- and 100% reduction in mean monthly seizure frequency from study entry to endpoint compared to the 12-weeks retrospective baseline. Change in body weight was assessed at each visit and the finally observed weight compared to baseline using the Wilcoxon signed-rank test, two-sided at the 5% significance level. For comparisons between subgroups the two-sided Mann—Whitney *U* test or the Chi square test was used depending on the scale level. All inferential tests were performed without adjustment of the significance level for multiple testing.

Results

Patient characteristics

Documentation was available for a total of 454 patients; 4 of these never received topiramate therapy and were excluded from all analyses, which are based on 450 patients. These 450 patients were followed up for a median time of 364 days. In 60 patients, topiramate therapy was prematurely discontinued due to various reasons which were noted by the investigator on the case record form.

In several patients the selection criteria were not fulfilled (multiple violations possible): three patients were younger than 12 years, 21 patients had no AED at start of observation, 173 patients had a history of epilepsy of more than 3 years. Naturally, these patients were all included into both the safety- and ITT analyses.

Out of 450 safety and intention-to-treat-patients, 232 (52%) were male, mean age was 40.3 years in a range of 10—93 years (Table 1).

One hundred and seventy-six patients (39%) were classified as having idiopathic epilepsy, 66 (15%) had cryptogenic epilepsy and the remainder had symptomatic epilepsy except for four patients (1%) in whom the epilepsy was not classified. Most commonly listed underlying etiologies were vascular causes, infections and dysplasias. In 128 patients, the neurological examination was abnormal (often due to a preexisting hemiparesis) and 34% had concomitant diseases, most frequently listed were hypertension and diabetes.

Ninety-five percent of patients had at least one baseline AED, most commonly Carbamazepine (53%) or Valproate (34%). In 5%, TPM was started in monotherapy. Other concomitant medications were listed in 27.5% patients and included psychotropics, antidiabetic medication, antihypertensives and platelet inhibitors.

Table 1a Patient demographics and disease description ($n = 450$)

Parameter	Value
Demographic characteristics	
Gender, male/female, *n* (%)	232 (52)/218 (48)
Mean age, years (±S.D.)	40.3 (±S.D. 16.7)
Age range, years (3 patients <12 years)	10—93
At least one concomitant disease, *n* (%)	153 (34)
At least one concomitant medication, *n* (%)	124 (28)
AED started during the observation (other than TPM), *n* (%)	55 (12)
Epilepsy characteristics	
Duration of epilepsy, months	
Mean (±S.D.)	87.8 (±128.4)
Median (range)	30.9 (0.2—848.5)
Patients with duration of epilepsy ≤3 years, *n* (%)	272 (60)
Patients with duration of epilepsy >3 years, *n* (%)	173 (39)
Patients with no information on duration of epilepsy *n* (%)	5 (1)
Ethiology, *n* (%)	
Idiopathic, *n* (%)	176 (39)
Cryptogen, *n* (%)	66 (15)
Symptomatic, *n* (%)	204 (45)
Thereof (multiple answers possible)	
Vascular, *n* (%)	50 (11)
Tumor, *n* (%)	34 (8)
Others, *n* (%)	128 (28)
Unknown	4 (1)
Seizure classification, *n* (%)	
Focal	262 (58)
Generalized	156 (35)
Other	14 (3)
Unclear	18 (4)
Number of AEDs at start of observation	
0 AED, *n* (%)	21 (5)
1 AED, *n* (%)	297 (66)
2 AEDs, *n* (%)	127 (28)
3 AEDs, *n* (%)	5 (1)

Table 1b Anticonvulsive therapy at study start

Type of AED	Number of patients[a] (%)
Carbamazepine	240 (53)
Valproate	152 (34)
Phenytoin	40 (9)
Lamotrigine	37 (8)
Oxcarbazepine	27 (6)
Gabapentin	17 (4)
Primidone	13 (3)
Other	38 (8)
No AED treatment	21 (5)

[a] Multiple AEDs possible.

Table 2 Topiramate maintenance doses

Maintenance dose (mg/day)	Number of patients (%)
25–50	16 (4)
51–100	64 (15)
101–200	165 (39)
201–300	94 (22)
301–400	56 (13)
>400	26 (6)

In 421 patients with a maintenance phase of at least 12 weeks.

Topiramate dose

In the ITT-sample, patients took on average 235mg/day (median 200 mg/day) topiramate at the end of the study with a wide range of 25–1200 mg/day. Approximately 94% of all patients ($n = 421$) reached a maintenance phase which was defined as a stable dose of topiramate within the range of ±50 mg over at least 12 weeks. About 75% of these patients were treated with maintenance doses between 100 and 400 mg/day (Table 2). The mean dose during the maintenance phase was 237 mg/day (median 200 mg/day) with a wide range of 25–800 mg/day.

Seizure response rate

Seizure frequency and response rates were analyzed in 450 patients for the ITT population and separately for the 421 patients with a 12-week maintenance phase (see Table 3). In the latter group, the mean seizure frequency was 11.4 ± 39.4 per month during the 12-week retrospective baseline (median 3, range: 0.3–463; Table 3a). During the TPM maintenance phase, median monthly seizure frequency reduced significantly to 0.4 seizures (range 0–246; $p < 0.0001$ versus baseline). Seventy-six (18%) patients were seizure free during the maintenance phase which lasted at least 3 months with a median duration of about 10 months (see Table 3b).

As already mentioned, patients were to have had epilepsy for less than 3 years in this study. Actually, however, 173 (38.4%) patients with a history of epilepsy of more than 3 years were included by the physicians. Since the patient population thus falls somewhere between ''recent onset'' epilepsy and the very refractory patients typically enrolled in blinded trials, a post hoc subgroup-analysis was performed contrasting patients with an epilepsy history of ≤36 versus patients with an epilepsy history of >36 months. The results of this subgroup-analysis can be summarized as follows:

In both subgroups a significant reduction in seizure frequency (retrospective baseline versus seizure frequency during the whole observation period) was observed (Wilcoxon-tests: $p < 0.0001$). Mean seizure frequency during the retrospective baseline was smaller in the '≤36 months'-group (8.50 ± 27.64 sei-

Table 3a Seizure frequency before and during treatment of topiramate

	Seizure frequency per 4 weeks	All patients $n = 450$	Patients with a maintenance phase of at least 12 weeks ($n = 421$)
12-weeks retrospective baseline	Mean ± S.D. Median (range)	11.3 ± 39.3 2.8 (0.3–462.7)	11.4 ± 39.4 3.0 (0.3–462.7)
Treatment period		Complete treatment phase	Maintenance phase
	Mean ± S.D. Median (range)	4.3 ± 18.5 0.7 (0–258.7)	2.9 ± 15.0 0.4 (0–245.7)
Pre–post change	Mean ± S.D. 95%-CI (mean) Median (range)	−7.0 ± 28.7 (−9.65, −4.35) −1.6 (−331–32.8)	−8.2 ± 31.4 (−11.20, −5.20) −1.9 (−362–35.8)
Pre–post change %	Mean ± S.D. 95%-CI (mean) Median (range)	−53.8 ± 117.6 (−64.67, −42.93) −73.7 (−100–1672.7)	−67.6 ± 119.0 (−78.97, −56.23) −86.5 (−100–1672.7)
Wilcoxon pre–post	p	<0.0001	<0.0001

CI, confidence interval.

Table 3b Seizure response rates comparing retrospective baseline with complete observation period and maintenance phase, respectively

Seizure response rates (%)	All patients $n = 450$	Patients with a maintenance phase of at least 12 weeks ($n = 421$)
	Complete treatment phase	Maintenance phase
≥50	323 (72%)	350 (83%)
≥75	217 (48%)	274 (65%)
100	46 (10%)	76 (18%)

seizures/4 weeks) than in the '>36 months'-group (15.98 ± 52.78 seizures/4 weeks); the differences was, however, not significant (Mann—Whitney *U* test: $p = 0.098$). Mean pre-post- reduction of seizure frequency between retrospective baseline and the whole observation period was 4.69 ± 15.64 seiseizures/4 weeks in the ≤36 months'-and 10.75 ± 41.76 seizures/4 weeks in the '>36 months'-group (*U* test: $p = 0.951$).

There was a significant difference (Chi square test: $p = 0.011$) between the distributions of the classified relative pre—post changes: derived from these distributions we found a ≥50% response-rate of 77.21% in the '≤36 months'- and of 63.58% in the '>36 months'-group.

In 82% of the 450 cases efficacy of treatment was judged by the physician as very good or good, in 12% as reasonable, unchanged or worsened, and in 6% no assessment was available. The corresponding percentages for the patients' assessments were 78, 14 and 8%, respectively.

Tolerability and safety

Tolerability data from all 450 patients exposed to TPM were analyzed. In 64 patients (14.2%) a total number of 181 treatment-emergent adverse events (TEAE) were documented. The most common TEAEs were difficulties with memory ($n = 19$; 4.2%), somnolence ($n = 16$; 3.6%), and dizziness ($n = 12$; 2.7%). Details of the adverse events are provided in Table 4. In 23 patients (5.1%) TPM was discontinued due to an adverse event, in 11 patients (2.4%) due to insufficient efficacy, and in 26 patients due to other reasons, mainly loss of follow-up. Adverse events leading to discontinuation of TPM encompassed cognitive adverse events including speech disturbance in five patients (1.1%). Overall, 12 serious adverse events occurred in five patients; these are listed in Table 4.

Although not very common under topiramate therapy, one patient developed skin problems: while on 25 mg/day topiramate treatment for 8 days, this individual developed vesicles at elbows and chest which ceased after 12 days treatment with chamomile crème; 4 days later, he developed efflorescenses at the lower leg and after other 19 days the topiramate therapy was stopped. The causal relationship was assessed by the investigator as possible and later as probable, respectively.

Twelve serious adverse events in five patients were reported. Four serious adverse events occur-

Table 4 Most frequent adverse events and main reasons for withdrawal

Number of patients (% of 450) with adverse events		
	Patients (%)	Reason for dropout [number of patients (% based on patients with adverse events)][a]
At least one adverse event	64 (14.2)	23 (36)
At least one adverse event with causal relationship	52 (11.6)	19 (30)
Memory difficulties	19 (4.2)	4 (6)
Somnolence	16 (3.6)	2 (3)
Dizziness	12 (2.7)	4 (6)
Weight decrease	9 (2.0)	5 (8)
Depressive symptoms	9 (2.0)	2 (3)
Nausea	8 (1.8)	1 (2)
Gastrointestinal problems	8 (1.8)	1 (2)
Paresthesia	6 (1.3)	2 (4)
Speech disturbances	6 (1.3)	1 (2)
Skin problems	1 (1.6)	1 (2)

[a] Multiple reasons possible.

ring in the same patient were thought to be causally related to topiramate treatment. Listed were depression (twice), strong weight loss and perceptual disorder. Serious adverse events without a causal relationship to Topiramate were: recurrence of brain tumor leading ultimately to death, depression in the context of borderline personality disorder, cold, forced hospitalization by patient by ingestion of high doses of topiramate, hypercalcemia, seizures, drowsiness, alcohol delirium.

Body weight

Body weight was documented in 411 patients (91.3%) both at first and last visit. The mean body weight at baseline was 73.4 ± 14.5 kg with mean height of 170.9 ± 9.0 cm. At endpoint, the mean body weight decreased to 71.8 ± 13.60 kg, which represents a significant weight loss of 1.6 ± 4.7 kg ($p < 0.0001$). A total of 210 patients (51.1%) experienced a weight decrease. However, only in 9 patients (2%) weight decrease was reported as an adverse event.

Global tolerability assessment

At the end of the observation, the treating physician as well as the patient rated the tolerability of topiramate on a 4-point rating scale. Physicians rated the tolerability of TPM as 'good' or 'very good' in 88% of patients which was comparable to 82% of patients who rated the tolerability of TPM as 'very good' or 'good'. Eighty-five percent of patients completed an observation period of at least 48 weeks.

Discussion

The main aim of this study was to explore effectiveness of TPM as add-on therapy in patients seen in neurology and epilepsy private practices. The addition of TPM to a regimen of 1—2 concomitant anticonvulsants resulted in a $\geq$50% seizure reduction in 72% of patients during the complete treatment phase. In addition, 10% achieved seizure-freedom during the treatment phase and 18% during the maintenance phase which was defined to last for at least 12 weeks without change of TPM dose for more than 50 mg/day. This response rate is substantially higher than reported during the placebo-controlled, fixed-dose regulatory trials.[7] In Reife's meta-analysis a $\geq$50% seizure reduction occurred in 24—44% of patients taking doses between 200 and 600 mg/day of topiramate. Responder rates in our study are higher which is likely due to the fact that less severe patients were documented in this study. This is confirmed by the additional subanalyses differentiating between recent onset epilepsy ($\leq$36 months) and longer duration epilepsy showing that the 50% responder rate is higher in the first group though mean seizure reduction are not different between the two groups.

Comparisons with other add-on therapy trials published recently are hampered by differences in patient selection, trial design and types of epilepsy studied. In Guberman's study,[10] which was a placebo-controlled double-blind study, median percent reduction in seizure frequency from baseline to endpoint was 44% with topiramate which contrasts to 74% in our study and 20% in the placebo arm. There, a significant therapeutic effect was seen at 2 weeks with a dose of 100 mg/day of topiramate despite patients were on an enzyme inducing concomitant AED (Carbamazepine). The median seizure frequency/month was 7 contrasting to our patient population (baseline median seizure frequency was 2.8), however, supporting that even with lower doses of topiramate a clinically relevant seizure reduction can be achieved. Our study supports this finding furthermore since the median dose of topiramate found to be clinically useful and tolerated was 200 mg/day.

The patient retention rate in the present study was 85% with only 5.1% terminating the observation early due to an adverse event. The number of withdrawals due to adverse events is lower than frequencies from randomized controlled trials which range between 7 and 16%.[11] Individualized dosing as well as dose adjustments when needed may have contributed to the low drop-out rate. Adverse events reported during this study were the ones known occurring with TPM therapy. Reports of dizziness, difficulties with memory or somnolence were rare and occurred considerably less frequently than reported before. Somnolence for instance was reported considerably less often (3.6%) than in Reifés pooled analysis (30%) which at least in part can be attributed to a lower starting dose and slower titration rate compared to early controlled TPM studies.[11]

The results of this study suggest that topiramate 100—200 mg/day is an appropriate initial target dose for add-on therapy. In most of the patients in this study, TPM was added to an enzyme inducing antiepileptic drug (Carbamazepine in 53% of patients). This indicates that even lower doses might be considered when TPM is used in patients without an enzyme-inducing co-medication.

In conclusion, in an open naturalistic setting topiramate used in low dose and individualized

titration was effective and well tolerated in add-on therapy. In line with controlled studies, good seizure response rates, high patient retention and good tolerability were observed. The results of this study is supported by findings of a recent controlled study [10] which showed that 100—200 mg/day is an appropriate initial target dose in the add-on therapy for treatment-resistant epilepsy.

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