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The effects of adjunctive topiramate therapy on seizure severity and health-related quality of life in patients with refractory epilepsy—a Canadian study

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Although reduction in seizure frequency is the most common endpoint used to assess the antiepileptic efficacy, seizure frequency alone does not provide a complete picture of effectiveness, particularly in patients with refractory epilepsy. The aim of our study was to assess the effects of topiramate on seizure severity and health-related quality of life (HRQL), in addition to standard efficacy measures, in an open, multicentre, 6-month trial of patients with epilepsy uncontrolled on antiepileptic drugs other than topiramate. Two hundred and nine patients were enrolled and received topiramate for up to 6 months (initiated at 50 mg/day and titrated to a recommended dose of 200–400 mg/day) in addition to existing medication. The median reduction in seizure frequency from baseline to the post-titration period was 40.9% ($P < 0.0001$). Patients also demonstrated a mean reduction in the Liverpool Seizure Severity Scale (LSSS) of 5.3 ($P < 0.0001$), which was considered clinically significant. Statistically significant changes in HRQL were not observed with the SF-36, a generic measure. Tolerability of antiepileptic medication was good, with a low incidence of cognitive adverse events. The results indicate that topiramate significantly reduces seizure severity—an important aspect of HRQL—when administered as adjunctive therapy to anticonvulsant therapy.

Key words: topiramate; epilepsy; seizure; quality of life.

INTRODUCTION

Topiramate (TOPAMAX®, JANSSEN-ORTHO Inc.) is a novel antiepileptic drug with multiple mechanisms of action. Its pharmacological properties include blockade of sodium channels[1], enhancement of the activity of GABA at $GABA_A$ receptors[2], and inhibition of kainate-induced currents[3]. Topiramate is indicated for adjunctive therapy in patients with epilepsy who are not controlled on conventional therapy. Investigations of the efficacy and the safety of topiramate (200–1000 mg/day) as adjunctive therapy were performed initially in adults with refractory partial-onset seizures with or without secondarily generalized seizures in six randomized, double-blind, placebo-controlled trials[4–9]. Subsequently, the efficacy and safety of topiramate (6 mg kg^{-1}/day) as adjunctive therapy have been confirmed in children with refractory partial-onset seizures with or without generalized seizures[10]. Efficacy and safety have been further assessed in adults and children with generalized seizures[11] and Lennox–Gastaut syndrome[12]. In addition, a pilot study has suggested that topiramate is a promising new agent for the treatment of infantile spasms[13].

Reduction in seizure frequency is the most common endpoint used to assess the efficacy of new treatments in epilepsy[14]. However, it has become apparent that seizure frequency alone is an inadequate measure[15,16]. This is particularly the case for patients with refractory epilepsy, for whom minimizing side effects of medication, reducing seizure severity and improving psychological well being, may be

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equally valuable therapeutic goals[16, 17]. Consequently, alternative or additional outcome measures to seizure frequency are required. Health-related quality of life (HRQL) measures provide information on the effects of therapies on physical, social and psychological well being from the patient's perspective. Such measures are being used increasingly alongside traditional measures of efficacy and safety as indicators of therapeutic outcome in many diseases[18, 19].

Since conventional clinical trials involve heavily selected target populations and a variety of other constraints, they provide little information on the day-to-day use of a drug[20]. This article presents the results of a multicentre, open 6-month trial of topiramate as add-on therapy for patients with epilepsy not satisfactorily controlled on existing treatment, examining the effects on partial and generalized seizures. This trial, which recruited a broad spectrum of patients and permitted adaptable dosages, enabled topiramate to be investigated under the conditions of actual clinical practice. This was the first trial designed to assess the effects of topiramate on seizure severity and HRQL in addition to standard efficacy and safety measures. Effects on partial and generalized seizures were examined. Since weight gain is often an issue with traditional antiepileptic drugs, and weight loss has been reported with topiramate[4–12], weight change was assessed as part of the safety profile throughout this trial.

MATERIALS AND METHODS

Patient population

The study population included 209 patients with refractory epilepsy. Recruitment was based on eligibility criteria and willingness to participate. Inclusion criteria required patients to be at least 18 years of age, to have been on a stable antiepileptic drug regimen for at least 28 days prior to the baseline visit, and to have reported at least six seizures within the 12-week retrospective baseline period. The principal exclusion criteria included non-epileptic seizures, conditions that might impair a patient's reliable participation or safety in the trial, pregnancy or breast feeding, and use of topiramate during the 12-week retrospective baseline period. Written informed consent was obtained from each patient or legal guardian.

Study design

This open-label, non-comparative trial was performed in over 40 centres in Canada according to Good Clinical Practice and the guidelines of the International Conference on Harmonization[21]. The protocol was approved by independent ethics committees. Eligible patients received topiramate as adjunctive therapy to existing medication for up to 6 months. Topiramate therapy began at 50 mg/day and patients were titrated to an effective dose over an anticipated period of 8 weeks. The dose increases, guided by clinical outcome, were of 50 mg/day, with increments at weekly intervals. The recommended dose, administered as two divided doses, was 200–400 mg/day. Concomitant antiepileptic medication was adjusted as required during the study, at the discretion of the investigator. Four clinic visits were scheduled: baseline (visit 1), and on-treatment months 1 (visit 2), 3 (visit 3) and 6 (visit 4). Patients discontinuing from the trial early were requested to return to the clinic so that the final assessments could be performed at termination (visit 4).

Evaluations

Seizures were classified according to the recommendations of the International League Against Epilepsy[22] as partial, generalized, or other. Baseline assessments (visit 1) included medical history, and seizure history including seizure frequency over the 12-week retrospective baseline period. Neurological examination, complete blood count (CBC) including differential counts, weight and calculation of body mass index (BMI), and a urinary pregnancy test were also performed.

Patients used diaries to record the date and type of each seizure experienced during the trial. Seizure frequency data were transcribed into the case report form at clinic visits 2, 3 and 4. These data were used to calculate the following efficacy outcomes relative to the seizure frequency during the 12-week retrospective baseline period:

(a) percentage reductions in the average monthly (28-day) seizure rate for the last 8 weeks that the patient was in the trial and for the entire treatment period (from the start of titration through to the last dose on trial);

(b) percentages of patients experiencing $\geq$50% reduction in seizure frequency for the entire trial;

(c) percentage of patients who were seizure free for the last 8 weeks;

(d) change in seizure frequency by seizure type for the last 8 weeks.

Table 1: The components of the Liverpool Seizure Severity Scale.

Sub-scale	No. of items	Description of items
Ictal/post-ictal	12	Loss of consciousness, level of confusion, time to recovery, injury, headaches, incontinence, lip smacking, tongue biting, overall severity
Percept scale	8	Level of perceived control, timing, clusters, aura or warning, prevention of normal activities

For patients participating in the trial for less than 8 weeks, the data for the period that they were included were used and standardized to a 28-day month.

Prior to treatment, patients were asked to complete two questionnaires for the previous 4-week baseline period: the Liverpool Seizure Severity Scale (LSSS)[23], which is a disease-specific measure of seizure severity providing information on an important aspect of HRQL; and the Short-Form 36 (SF-36)[24], which is a generic HRQL scale. Seizure severity and HRQL were re-assessed at the end of treatment (visit 4) using the LSSS and SF-36.

The LSSS, a 20-item patient-based scale, is divided into two subscales: the ictal and post-ictal effects of seizures (comprising 12 items) and the patient's perception of control (comprising eight items). Each item is scored on a simple Likert[1–4] scale. The higher the total score, the greater the seizure severity. The scale has recently been adapted to accommodate individuals who may experience more than one seizure type[25]. This modified, validated scale was used in the present trial, and patients with more than one seizure type were requested to complete a scale for their most severe seizures (major seizures) and another for their least severe seizures (minor seizures). The components of the LSSS are presented in Table 1.

The SF-36 comprises 36 items across eight separate health domains including one item measuring health transition, which encompass the three dimensions of mental health, physical health and perception of general health[24]. Patients' scores on each domain are linearly transformed to a 0–100 scale, with 100 indicating the most favourable and 0 the least favourable health state. The components of the SF-36 are presented in Table 2. A reduction in SF-36 score of 5 points or more is statistically significant[26], and a reduction of 10 points or more implies clinically significant improvement. At the final visit, investigators rated their treatment satisfaction using a global evaluation of improvement on a Likert[1–5] scale (worse, none, minimal, moderate or marked). Similarly, at this visit patients rated their overall assessment of the trial medication on a Likert[1–4] scale (poor, fair, good or excellent).

Table 2: The components of the Short-Form 36.

Domain	No. of items
Physical functioning	10
Role functioning—physical	4
Bodily pain	2
General health	5
Vitality	4
Social functioning	2
Role functioning—emotional	3
Mental health	5
Reported health transition	1

Safety

Adverse events (AEs), concomitant medications, weight (including calculation of BMI) and CBC (including differential counts) were recorded at clinic visits 2, 3 and 4. Investigators were requested to assess the association of AEs with the use of topiramate. Neurological examination was performed at baseline and at visit 4. Reasons for early termination were recorded.

Statistical methods

The population sample size of approximately 200 patients was based on the intention to perform exploratory subgroup analyses (e.g. by baseline seizure type). This sample size was considered ample to examine the effects of topiramate on overall seizure frequency. Based on clinical experience, it was estimated that 50 patients would be required to demonstrate a mean (±standard deviation) decrease from baseline in monthly seizure rate of 40% (±60) ($P = 0.05$; 99.6% power).

Three populations were used in the analyses. The safety population included all patients who took at least one dose of trial medication. The intent-to-treat (ITT) population included patients in the safety population who provided seizure data at the baseline visit and at least one other clinic visit. It was anticipated that there would be a stable dose period during the trial. However, due to significant dose variations during the trial, it was not possible to establish a stable dose maintenance period. A *post-hoc*

Table 3: Seizure frequency outcomes across all seizure types.

		Population			
		ITT ($n = 201$)		MITT ($n = 160$)	
Outcome	Time frame	%	P-value	%	P-value
Median % reduction in seizure frequency	Last 8 weeks	40.9	<0.0001	50.0	<0.0001
Median % reduction in seizure frequency	Entire trial	29.2	0.0095	41.6	<0.0001
Percentage of patients with ≥50% reduction in seizure frequency	Last 8 weeks	44.3		51.9	
Percentage of patients with ≥50% reduction in seizure frequency	Entire trial	36.8		43.1	
Percentage of patients seizure free	Last 8 weeks	10.0		11.3	

decision was made to examine data over 16 weeks, comprising an 8-week 'titration' period and an 8-week 'post-titration' treatment period. The modified-intent-to-treat (MITT) population included the ITT patients who contributed at least 16 weeks of dose and seizure information.

The Wilcoxon sign rank test was used to detect statistically significant changes from baseline for the following outcomes: percentage reduction in the number of seizures (overall and within each seizure type); change from baseline in the LSSS; change from baseline in the SF-36 (overall, eight domains and three health dimensions). Two-sided P-values of ≤ 0.05 were considered to be statistically significant. Sample size estimations were performed based on a mean ($+/-$ standard deviation) percent decrease from baseline in the frequency of monthly seizures of 40 ($+/-60$). Changes in weight and BMI from baseline to visit 4 were assessed using the paired t-test. The relationship between baseline BMI and change in BMI to visit 4 was explored using a regression analysis.

RESULTS

Patients

The trial examined patients who were not well controlled on existing therapy and whose daily lives were, therefore, affected substantially by their epilepsy. The mean age of the study population was 37 years (range 18–78 years), 92% of patients were Caucasian and 58% were female. Patients had suffered from epilepsy for an average of approximately 23 years (range 1–60 years). Over 70% of the patients were receiving two or more anticonvulsant medications at baseline. The most common concomitant medication was carbamazepine, which was used by 30% of the patients.

A total of 209 patients were enrolled in the trial. The safety population comprised 205 patients; four patients were excluded from the safety analyses because of inadequate documentation of their epilepsy and the study parameters. Four patients in the safety population could not be evaluated for efficacy because of missing seizure diary information, and the ITT (per-protocol) population therefore comprised 201 patients. The MITT population (patients receiving at least 16 weeks of treatment) comprised 160 patients.

During the retrospective 12-week baseline period for patients in the ITT population the number of patients reporting seizures were: simple partial (SP) 60, complex partial (CP) 135 and secondarily generalized (SG) 63. Fewer patients reported experiencing primary generalized seizures during this baseline period. The number of patients in the ITT population who reported generalized seizures were: absence (A) 12, atypical absence (AA) 4, atonic (AT) 2, myclonic (MY) 7, tonic (T) 2 and tonic–clonic (TC) 14.

The final dose and mean dose for the last 8 weeks of the trial were reasonably consistent within each population (293 vs. 289 mg/day, respectively, for ITT; 324 vs. 321 mg/day, respectively, for MITT). Patients in the ITT and MITT populations received treatment with trial medication for a mean of 151 and 175 days, respectively.

Efficacy and health-related quality of life

Efficacy and HRQL data were derived for both the ITT and MITT populations. Since the ITT and MITT results were very similar, and because the ITT is the more rigorous study population, the following description of results focuses on the ITT population alone. However, data for both the ITT and MITT is presented in the tables and figures.

The seizure frequency outcomes are summarized in Table 3. The median reduction in monthly seizure rate from the baseline period to the last 8 weeks was 40.9% ($P < 0.0001$), and for the entire treatment period

was 29.2% ($P = 0.0095$), in the ITT population (Table 3). Overall, 44.3% of patients experienced a ≥50% reduction in seizure frequency from baseline to the last 8 weeks, compared with 36.8% of patients when assessed from baseline for the entire treatment period. Table 4 shows the pattern of reduction in seizure frequency, where (as stated above) 44.3% of patients experienced a ≥50% reduction, and 28.4% of patients experienced a ≥75% reduction. Freedom from seizures (100% reduction) during the last eight weeks in the trial was experienced by 10.0% of patients (Table 4).

Table 4: Pattern of reduction in seizure frequency from baseline to last 8 weeks.

Percentage reduction in seizure frequency	Population			
	ITT ($n = 201$)		MITT ($n = 160$)	
	n	%	*n*	%
100	20	10.0	18	11.3
≥75	57	28.4	52	32.5
≥50	89	44.3	83	51.9
0	142	70.6	122	76.3

Table 5 presents the numbers of patients experiencing seizures and the reduction in seizure frequency from baseline to the last 8 weeks by seizure type. For the more common types of seizures (CP, SG and SP), substantial percentage reductions in monthly seizure rate were reported from the baseline period to the last 8 weeks: CP $P = 0.0002$, SG and SP $P < 0.0001$. Marked reductions in TC ($P = 0.0002$) and A ($P = 0.0205$) seizures were also reported, but these analyses should be regarded with caution because of the small numbers of patients reporting these types of seizure (Table 5).

The mean reduction in the LSSS score between baseline and end of treatment was 5.3 points for the ITT population (Table 6). This difference was statistically ($P < 0.0001$) and also considered clinically significant. The SF-36 showed reductions in the mean scores for the mental health dimension ($P = 0.0301$) and the mental health domain ($P = 0.0025$) between baseline and the end of treatment for the ITT population (Table 7). Despite the statistical significance of these SF-36 findings, the differences were of insufficient magnitude to be considered clinically significant.

Observations were also made regarding any potential relationship between LSSS and SF-36 scores, and seizure response and continuation/discontinuation status. The reduction in LSSS score by seizure response is shown in Fig. 1. Patients with a 75% or greater reduction in seizure frequency also reported a considerable reduction in the severity of their seizures ($P = 0.0002$). Of all patients, those who continued to the end of the trial achieved a greater reduction in LSSS score and a lower mean LSSS score at endpoint than patients who did not complete treatment (Fig. 2). Of all patients, those who continued to the end of the trial achieved a greater improvement in SF-36 domain scores at the final clinic visit than patients who discontinued treatment prematurely (Fig. 3).

At the final clinic visit, investigators rated improvement in condition as marked or moderate for 53.7% of the ITT population and 65.0% of the MITT population. Similarly, 54.7% of the ITT patients and 65.0% of the MITT patients rated the trial medication as good or excellent.

Safety

Across the entire safety population ($n = 205$), there were 1119 reports of AEs by 186 patients during the 6-month trial period. A total of 757 (67.6%) of the AEs were considered to be drug related. Of these drug-related AEs, fatigue (6.0%), somnolence (5.3%) and headache (4.2%) were the most frequently occurring. The majority of the drug-related AEs, 713 (94%), were mild or moderate in severity; 44 were of marked severity, the most frequent being dizziness and somnolence, which were each reported by three patients. Only one patient developed a kidney stone. There were 18 serious AEs reported by a total of 12 patients; none were considered by the investigators to be drug related.

Fifty-four patients (26.3%) were withdrawn from the trial prematurely. Of these, 28 patients (13.7%) reporting a total of 66 AEs withdrew because of AEs. Anorexia, memory difficulties, nervousness, paraesthesia and increased number or intensity of seizure were the most frequent reasons for early termination. Contrary to previous studies of topiramate which have suggested that cognitive problems lead to high dropout rates[5,27,28], in the present trial, only nine patients (4.4%) withdrew because of cognitive AEs, which accounted for a small proportion of the AEs which led to withdrawal, and included memory difficulties (6.1%), concentration difficulties (4.5%), cognitive problems (3.0%), confusion (3.0%), and amnesia (1.5%). Other reasons for withdrawal from the trial included poor seizure control (4.4%), investigator's decision (2.4%), patient's choice (2.0%), protocol violation (1.0%) and loss to follow up (0.5%).

A consistent statistically significant decrease in bodyweight was seen during the trial ($P < 0.0001$). The mean weight loss over the course of the study was approximately 3.5 kg. These findings were reflected in the BMI values. Regression analysis indicated that higher baseline BMI was associated with a greater reduction in BMI from baseline to the final visit ($P = 0.0001$); however, firm conclusions

Table 5: Change in seizure frequency from baseline to the last 8 weeks by seizure type.

Seizure type	ITT population No. of patients	ITT population Median % reduction	ITT population Wilcoxon *P*-value	MITT population No. of patients	MITT population Median % reduction	MITT population Wilcoxon *P*-value
Partial seizures						
Simple partial (SP)	60	70.58	< 0.0001	45	71.15	< 0.0001
Complex partial (CP)	135	38.89	0.0002	106	52.50	< 0.0001
Secondarily generalized (SG)	63	96.25	< 0.0001	51	91.67	< 0.0001
Primary generalized						
Absence (A)	12	91.06	0.0205	10	91.06	0.0430
Atypical absence (AA)	4	28.53	0.6250	4	28.53	0.6250
Atonic (AT)	2	−537.50	1.0000	2	−537.50	1.0000
Myclonic (MY)	7	100.0	0.5781	6	100.0	1.0000
Tonic (T)	2	46.00	1.0000	2	46.00	1.0000
Tonic–clonic (TC)	14	100.0	0.0002	12	100.0	0.0010
Unclassified (UC)	2	100.0	0.5000	1	100.0	1.0000

cannot be drawn because the analysis was *post-hoc* and exploratory, the study population was large, and the slope of the regression line was not steep. Investigators were asked to record any clinically significant laboratory findings which emerged during the trial and were asked to report any clinically significant haematological findings during the trial as an AE. Only one case of reduced white blood cell count (2.4×10^9 L^{-1}) was reported as an AE and this was classified as being of mild severity and not related to treatment with topiramate. No clinically significant changes were reported at the final neurological examination.

Table 6: Liverpool Seizure Severity Scale score (baseline vs. end of treatment).

Population and stage of trial	Mean	Standard deviation	No. of patients	*P*-value
ITT:				
Baseline	23.1	7.6	182	
End of treatment	17.8	10.0	180	<0.0001
MITT:				
Baseline	23.2	7.8	155	
End of treatment	17.5	10.3	153	<0.0001

DISCUSSION

This open, multicentre trial was designed to provide a better understanding of subjects with refractory epilepsy in a standard care setting. Past studies of patients with epilepsy have been criticized for focusing on a narrow spectrum of patients[29], which can lead to an unexpectedly high proportion of patients with an unfavourable outcome. Therefore, the present study was performed at over 40 centres under actual clinical practice conditions, and included a broad spectrum of patients experiencing a range of seizure types. Subjects who, for at least 28 days prior to the start of the study, were uncontrolled by existing stable antiepileptic therapy were included. During the trial, the dose of existing concomitant antiepileptic therapy could be adjusted at the discretion of the investigator, akin to normal clinical practice.

The patients in the present trial were severely affected by their epilepsy, as reflected in the number of concomitant anticonvulsant medications in use and the poor control of their condition. However, despite this, patients responded well to treatment. The seizure response and safety data in this trial are consistent with those obtained in other clinical trials with topiramate. In six previous multicentre, randomized, double-blind, placebo-controlled trials using doses between 200 and 1000 mg/day[4–9], 44% of patients responded to adjunctive topiramate treatment with at least a 50% reduction in seizure rate. In the present trial, 44% of patients in the ITT population and 52% of patients in the MITT population experienced at least a 50% reduction in seizure rate from the baseline period to the last 8 weeks in the trial. When assessed over the entire treatment period, 37% of patients in the ITT population and 43% of patients in the MITT population had at least a 50% reduction in seizure rate. Topiramate was generally well tolerated, with the most common AEs being related to the central nervous system. As in previous trials[11], most AEs in the present trial were mild or moderate in severity.

There have been reports of worsening of seizures after treatment with some antiepileptic drugs, particularly after initial use[30,31]. However, topiramate has been shown to be an effective adjunctive therapy that does not cause a worsening of seizures and is well tolerated by patients[11]. In the present trial, which included patients with both partial and generalized seizures, there was no deterioration in the frequency of any seizure type following treatment with topiramate, apart from an increase in the frequency of atonic seizures which was of questionable significance as

Table 7: SF-36 score (baseline vs. end of treatment).

	ITT population				MITT population			
Category	Mean baseline score (SD)	Mean end of treatment score (SD)	No. of patients (end of treatment)	*P*-value	Mean baseline score (SD)	Mean end of treatment score (SD)	No. of patients (end of treatment)	*P*-value
Domain								
Physical functioning	81.0 (23.1)	78.2 (25.3)	185	0.5736	80.7 (23.1)	78.4 (26.3)	156	0.8752
Role functioning—physical	59.7 (39.4)	59.5 (42.7)	186	0.9553	60.2 (39.9)	65.3 (41.2)	157	0.1548
Bodily pain	68.6 (27.2)	72.6 (27.6)	185	0.1035	68.6 (27.2)	74.3 (26.9)	157	0.0154
General health	62.8 (23.0)	63.3 (21.0)	183	0.7485	63.1 (23.6)	65.2 (21.1)	154	0.3622
Vitality	52.0 (20.6)	49.5 (22.5)	183	0.2814	51.6 (21.2)	52.6 (21.8)	155	0.4753
Social functioning	68.7 (23.1)	65.7 (27.5)	186	0.2347	69.1 (23.4)	70.0 (26.7)	157	0.6633
Role functioning—emotional	66.2 (40.2)	60.7 (43.5)	185	0.0811	66.2 (40.5)	65.8 (41.5)	157	0.9871
Mental health	65.9 (20.4)	60.8 (22.2)	183	0.0025	65.9 (21.2)	62.6 (22.0)	155	0.0620
Dimension								
Mental health	66.9 (23.6)	62.4 (26.6)	186	0.0301	67.0 (24.2)	66.2 (25.6)	157	0.6451
General health	57.4 (19.5)	56.3 (18.5)	185	0.4580	57.3 (19.9)	58.7 (18.3)	156	0.4132

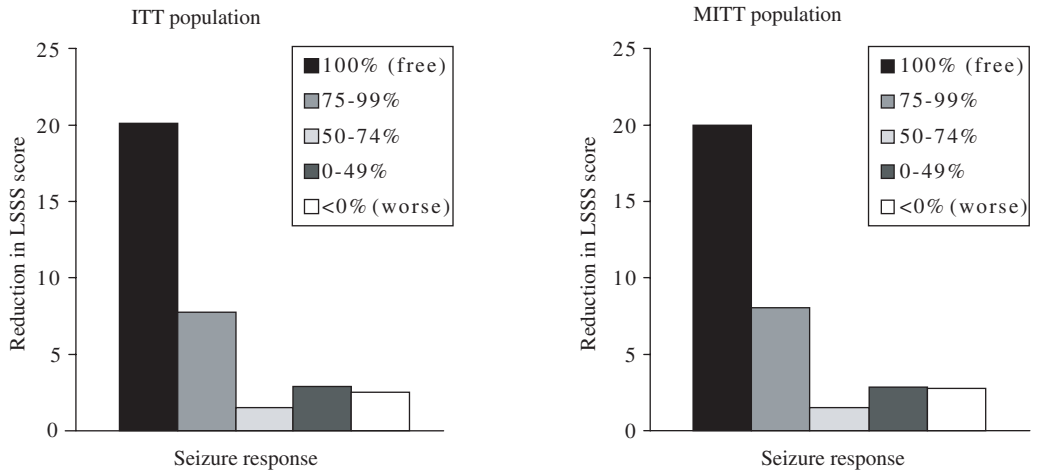

Fig. 1: Reduction in Liverpool Seizure Severity Scale score by seizure response.

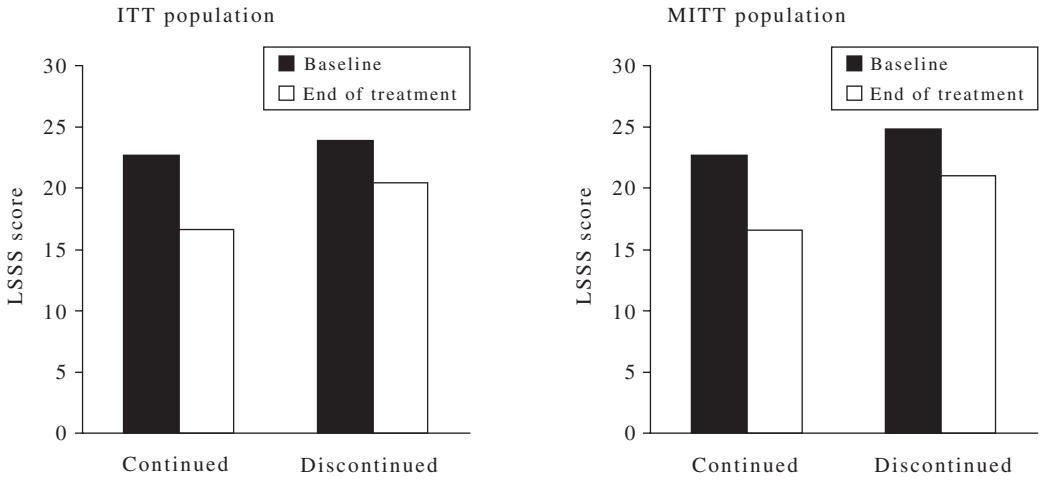

Fig. 2: Liverpool Seizure Severity Scale score by continuing status.

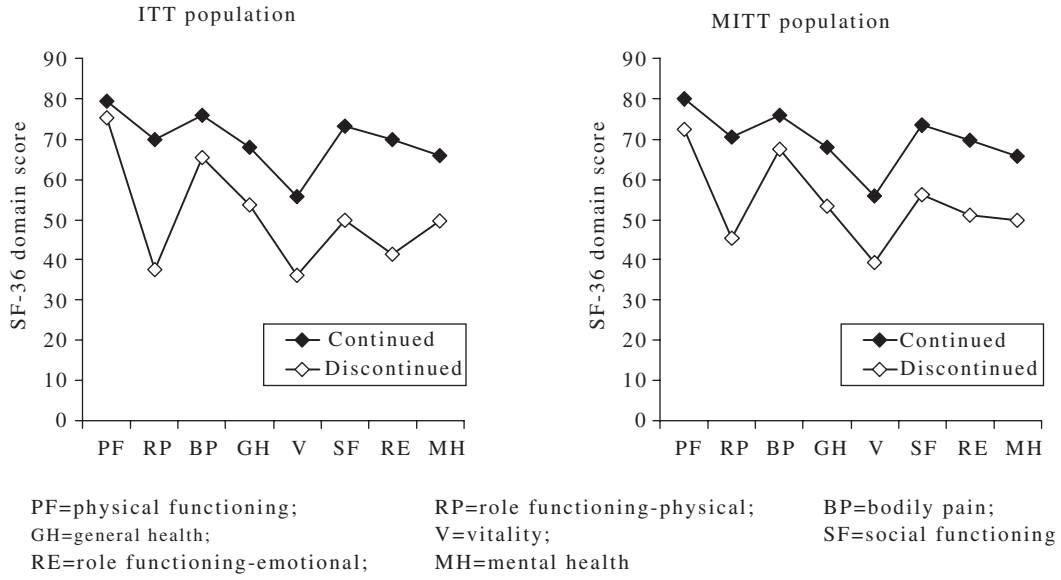

Fig. 3: SF-36 domain scores at final clinic visit by continuing status.

it involved just two patients. The majority of investigators and patients provided positive assessments of the trial medication. Overall, topiramate led to a reduced seizure frequency and seizure severity without compromising patients' perceived health status, as assessed by the SF-36.

The LSSS is a valid and reliable measure of seizure severity designed for use in patients with epilepsy[23], and was developed as part of a HRQL model[17]. In the present trial, statistically significant reductions in seizure severity, an important aspect of HRQL, were observed between baseline and end of treatment ($P < 0.0001$). These improvements in LSSS score were also considered to be of clinical significance, since a reduction in score of more than 5 points was obtained. In the present study, the improvement observed was far greater than reported previously in a similar study of lamotrigine which employed the same criteria for measuring HRQL[32].

Post-hoc exploratory analyses showed that only patients experiencing a reduction in seizure frequency of 75% or more also reported a notable reduction in seizure severity (by LSSS score). Similar but less robust findings were reported for lamotrigine as add-on therapy in partial epilepsy, where simple correlation and multiple-regression analysis indicated that effects on seizure frequency, seizure severity, and psychological well being were independent of each other[32]. Thus, the reduction in seizure severity may be considered an additional, independent effect of treatment.

In epilepsy, the SF-36 has been used as a valid and reliable health status measure in its own right[33,34], and as the generic core measure for two epilepsy-specific measures, the Epilepsy Surgery Inventory (ESI-55)[35] and the Quality of Life in Epilepsy Inventory (QOLIE-89)[19]. HRQL data obtained using the SF-36 have been collected for over 5000 patients with epilepsy across Europe[34]. Side effects of therapy and poor control of seizures contribute to poor HRQL in patients with epilepsy as was reported by patients at the baseline of the present trial. In the UK, SF-36 scores have been found to be lower in all domains for patients with epilepsy compared with the general population, and in all but three domains (role functioning—physical, vitality and general health) compared with a population of patients with some other long-standing illness, such as clinical depression and type 2 diabetes[26,33]. In the present study, the SF-36 results for the ITT and MITT populations differed slightly. Reductions between baseline and end of treatment were observed in the SF-36 scores for the mental health domain and mental health dimension for the ITT population. For the MITT population, there was improvement between baseline and end of treatment for the bodily pain domain. However, due to the generic nature of the tool, all these changes in SF-36 scores were small and were not considered clinically significant. Further research work is required to confirm any treatment-related effects on HRQL.

In the present trial, patients received the recommended starting dose of topiramate and were titrated to an effective dose over an 8-week period, where possible. Tolerability was good and only 14% of patients discontinued because of AEs during the entire 6-month treatment period. Approximately half of these patients discontinued during the initial 8-week period. Recent clinical experience suggests

that low initial doses, gradual titration and the use of topiramate as monotherapy can improve tolerability[20, 36, 37]. To even further minimize adverse cognitive events, a starting dose of 25 mg/day is often advised, with weekly increases in the daily dose of 25 mg[38]. While the incidence of AEs tends to be highest during titration, many resolve with continued topiramate treatment[36]. Some antiepileptic drugs are known to cause significant weight gain[39, 40]. However, in the present study of topiramate as adjunctive therapy, patients experienced on average a 3.5 kg weight loss.

Since this was not a randomized, controlled, clinical trial, and statistical analyses were intra-group analyses, caution is needed in the interpretation of the results. Some patients may have reported benefits after topiramate treatment, although these improvements might have resulted from better care as a result of participating in a clinical trial or period effects. However, the improvements in seizure frequency were consistent with the results of controlled trials with topiramate[4–9]. Many patients (64%), including some who did not achieve a significant reduction in seizure frequency, continued with topiramate therapy beyond the 6-month treatment period of the trial. This suggests that there may have been some additional clinical benefits. Reduction in seizure frequency and severity and improvement in perceptions of health may have contributed to patients deciding to continue with treatment. Since the patients involved in this trial were refractory to treatment, care should be taken in the interpretation of the data and extrapolation to individuals who are more responsive to antiepileptic drugs.

In conclusion, the adjunctive use of topiramate in a broad spectrum of patients was associated with a significant reduction in seizure frequency and severity, without appearing to compromise patients' perceived health status. At least 10% of patients were seizure free during the last 8 weeks of the trial. Topiramate was well tolerated, with a low incidence of cognitive AEs, no serious idiosyncratic reactions and a low drop-out rate. The majority of investigators and patients rated the medication well, and 64% of patients chose to continue with topiramate therapy after the trial. There was a statistically significant decrease in bodyweight during the trial. Randomized clinical trials are currently in progress to further examine the HRQL changes associated with topiramate.

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