Received: 12 July 2019 | Revised: 16 October 2019 | Accepted: 18 October 2019

DOI: 10.1111/epi.16382

Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Treatment of refractory and superrefractory status epilepticus with topiramate: A cohort study of 106 patients and a review of the literature

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Abstract

Objective: Novel treatments are needed to control treatment-resistant status epilepticus (SE). We present a summary of clinical cases where oral topiramate (TPM) was used in refractory SE (RSE) and superrefractory SE (SRSE).

Methods: A review of medical records was carried out to detect TPM administration in SE patients treated in Frankfurt and Marburg between 2011 and 2016. The primary outcome question concerned SE resolution after TPM initiation.

Results: In total, TPM was used in 106 of 854 patients having a mean age of 67.4 ± 18.1 years, 61 of whom were female (57.5%). The median latency from SE onset to TPM initiation was 8.5 days. Patients with SE had previously failed a median of five other antiepileptic drugs. The median initial TPM dose was 100 mg/d, which was uptitrated to a median maintenance dose of 400 mg/d. Treatment with TPM was continued for a median time of 12 days. TPM was the last drug provided to 42 of 106 (39.6%) patients, with a resultant response attributed to TPM observed in 29 of 106 (27.4%) patients. A response was attributed to TPM in 21 (31.8%) of 66 RSE cases and eight (20%) of 40 SRSE cases. Treatment-emergent adverse events were attributed to TPM usage in two patients, one each with pancreatitis and hyperchloremic acidosis, and in 38 patients (35.8%), hyperammonemia was seen. Thirty-four of these patients received a combination of TPM and valproate and/or phenobarbital. The intrahospital mortality rate was 22.6% (n = 24).

Significance: The rate of SE cessation attributed to TPM treatment (27.4%) represents a relevant response given the late treatment position of TPM and the treatment latency of more than 8 days. Based on these results and in line with the findings of other case series, TPM can be considered an alternative option for treating RSE and SRSE.

KEYWORDS

anticonvulsant, antiepileptic drug, epilepsy, seizure

1 | INTRODUCTION

Status epilepticus (SE) is a medical emergency associated with high morbidity and mortality. It requires instant medical intervention and is accompanied by prolonged hospital stays and increased health care costs.[1–5] Refractory SE (RSE) and superrefractory SE (SRSE) are characterized by the failure of first-, second-, and third-line therapy and, in the latter case, anesthetic therapy.[1,6] There are few controlled or randomized study data on RSE and SRSE, so that the basis of therapeutic management frequently relies on expert opinion, clinical reports, and pathophysiological assumptions arising from experimental data.[6–8]

Topiramate (TPM) is a second-generation antiepileptic drug (AED) known to be effective against a wide range of seizure types with pleiotropic effects on different receptors and ion channels. The potential of TPM in second- or third-line therapy in RSE and SRSE has not been evaluated in larger cohorts to date. Pathophysiological studies have suggested that TPM blocks voltage-sensitive sodium channels and high-voltage calcium channels, potentiates the activity of γ-aminobutyric acid (GABA) at $GABA_A$ receptors, inhibits excitatory transmission by antagonizing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors, and inhibits carbonic anhydrase isoenzymes. Furthermore, the enhancement of $GABA_A$-receptor activity seems to be independent of the binding sites of benzodiazepines, so TPM may help to overcome benzodiazepine resistance in SE.[9] Neuroprotective effects of TPM have previously been identified in animal models due to it preventing delayed neuronal death by reducing neuronal injury after prolonged SE duration.[10,11] Other advantages of TPM include a high oral bioavailability, low protein binding, and fast absorption. Although an intravenous solution of TPM is not yet available on the market, it is under investigation.[9,12–14] So far, there exists only limited evidence on the use of TPM in RSE and SRSE.[15]

The aim of our multicenter study was to assess the usage of, efficacy of, and tolerability to TPM in patients with RSE and SRSE.

Key Points

- The effect of topiramate on cessation of refractory and superrefractory status epilepticus was investigated in 106 patients
- A median initial topiramate dose of 100 mg/d and high median maintenance dose of 400 mg/d were used
- Topiramate was used as the last drug in 42 patients (39.6%), with a response attributed in 29 cases (27.4%)
- Hyperammonemia was a frequent adverse event in 38 patients (35.8%), mainly in combination with the administration of valproate

2 | MATERIALS AND METHODS

2.1 | Study settings and design

We reviewed the medical records of a cohort of SE patients treated at the Frankfurt (population: 736 414 as of December 31, 2016; www.statistik-hessen.de) and Marburg (population: 74 675) university hospitals between January 2011 and December 2016 (evaluation period of 6 years) for TPM administration. Both hospitals offer a full range of neurological care services with expertise in epileptology and intensive care medicine. Whereas Frankfurt serves primarily an urban area, Marburg provides care as the only neurological department for the city and surrounding rural areas, managing a population of >500 000. Due to its representative population structure, the area around Marburg was earlier used for a population-based estimate of the incidence and cost of illness of SE in Germany.[16–18] The detailed evaluation of all SE patients is part of a study on SE outcomes; this study was registered at the German Clinical Trials Register (DRKS00008718) and was approved by both local ethics committees. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

2.2 | Definition of SE

The classifications of seizure type, epilepsy type and syndrome, and SE were adopted based on the latest definitions proposed by the International League Against Epilepsy (ILAE).[20–22] Regarding seizure duration, we followed the SE ILAE definition and considered all tonic-clonic seizures lasting for >5 minutes as well as focal seizures with impaired consciousness or absence seizures lasting for >10 minutes as SE.[22] SRSE was defined as when SE continues or recurs at 24 hours or more after treatment initiation with anesthetic drugs, whereas RSE refers to recurrent seizure activity notwithstanding the administration of two AEDs appropriately selected and dosed, including a benzodiazepine.[1,6] Patients younger than 18 years and patients with hypoxic-ischemic encephalopathy were excluded from this investigation.

2.3 | Data entry and outcome parameters

Data on etiology, semiology, clinical diagnosis, demographics, history of seizures or SE, total length of stay (LOS) in hospital, ventilation time, modified Rankin Scale (mRS) score, Charlson Comorbidity Index, and the SE Severity

Score (STESS)[23] were systematically collected in all patients. Four experienced physicians (S.K., K.M., F.R., A.S.) board-certified to perform electroencephalography (EEG) interpreted the EEG data. SE duration before TPM initiation and the number of AEDs previously used were analyzed. Additionally, information on the timing of TPM in relation to SE onset and cessation and the presence of adverse events was collected. A response to TPM was assumed to exist in patients who showed SE cessation after TPM administration, when TPM was the last drug added with no further changes to the AED regimen before SE cessation, and when the last changes to the AED regimen were made >24 hours before the initiation of TPM. The SE cessation time was defined as the time when the seizure symptoms ceased and the patient returned to baseline, or, in equivocal cases, as the time of the first EEG recording that showed that EEG signs of SE had ceased. Patients in whom TPM was the last drug applied but in whom other interventions precluded an unambiguous classification were considered to be nonresponders. Secondary outcomes included the number of AEDs, LOS, and mRS score at discharge as well as disposition (eg, home, rehabilitation, nursing home, other hospital, hospice, or death).

2.4 | Review of the literature

To identify studies that evaluated the use of TPM in SE, we performed a systematic literature search in the MEDLINE, the Cochrane Central Register of Controlled Trials, and Excerpta Medica databases from 1996 until December 2018, using a combined search strategy including the following keywords: "topiramate," "epilepsy," "seizure," and "status epilepticus." We included studies only reporting on more than five patients, to minimize reporting bias from case reports and small case series. We examined the reference lists of all identified studies and review articles on TPM[15,24] for additional studies that might be relevant.

2.5 | Statistical analysis

Data were analyzed using the IBM SPSS Statistics version 25.0 software program. Patients were categorized into two groups to compare responders and nonresponders to TPM, as defined above. Among these groups, univariate comparisons of proportions were performed with Pearson chi-square or Fisher exact tests. For analyses with continuous variables, normal and abnormal distributions were distinguished by the Shapiro-Wilk test. A Student *t* test was applied for the comparison of variables with normal distribution, whereas the Mann-Whitney *U* test was applied for comparisons of variables with nonnormal distribution. Two-sided *P* values of <.05 were considered to be significant. To adjust the *P* values for multiple comparisons, we applied the Bonferroni-Holm method.

3 | RESULTS

3.1 | Patient characteristics at admission

During the evaluation period, 854 patients with SE were treated at both hospitals. TPM was used for SE treatment in 106 of these patients, or 12.4% of the total SE cohort. None of the patients was admitted twice during the study period with TPM treatment of SE. The mean age of the study cohort was 67.4 years (standard deviation [SD] = 18.1 years, median = 73 years, range = 18-95 years), and 61 patients were female (57.5%). Admissions were attributed to an acute symptomatic etiology in 37 patients (35%), remote symptomatic SE without previous history of epilepsy in 19 patients (18%), a remote symptomatic SE accompanied by a previous history of epilepsy in 37 patients (35%), a progressive cause in 12 patients (11.3%), and a genetic generalized epilepsy in one patient. Main etiological factors were remote (n = 35) and acute (n = 17) cerebrovascular injury and brain tumor in 16 cases. TPM was used for the treatment of 66 patients with RSE (62.3%) and 40 patients with SRSE (37.7%). Generalized tonic-clonic SE was present in 34 cases, whereas 17 cases had nonconvulsive SE with coma as their predominant symptom, 54 patients presented with focal SE with impaired consciousness or focal motor SE, and one patient had absence SE. Disability at the time of admission, as measured by the mRS, was present in 64 patients (mRS score = 3-5 points; 60.4%). A favorable STESS score of 0-3 points was present in 68 (64.2%) of the patients. Charlson Comorbidity Index showed no comorbidities in eight patients (7.5%), whereas 98 patients had a score of between one and six points (92.5%), reflecting a low to moderate number of comorbidities.

Out-of-hospital emergency treatment with benzodiazepines was given to 32 patients (30.2%), including in six cases by a layperson and in 26 cases by the ambulance service. In total, 59 patients (55.7%) had a previous history of epilepsy and 51 (48.1%) were taking AEDs at the time of their admission. Patients on AEDs were taking a mean number of 1.9 ± 1.0 AEDs (median = 2 AEDs, range = 1-5 AEDs) before admission due to SE. Levetiracetam (n = 36/51, 70.6%), valproate (VPA; n = 20/51, 39.2%), and lacosamide (n = 14/51, 27.5%) were the most frequently prescribed drugs prior to SE.

3.2 | Treatment of SE with TPM

From SE onset to first TPM administration, the median latency was 8.5 days, ranging between the first 24 hours and 30 days. Before TPM application, a median number of five AEDs had been administered (range = 1-10 AEDs, premorbid AEDs not included). In 50 patients, at least one episode of general anesthesia for at least 24 hours with an EEG-proven burst-suppression pattern had occurred; here, in 42 cases,

TPM was given during or after anesthesia, whereas in eight cases, TPM was given before anesthesia. Initial TPM dosage varied from 25 to 500 mg (median = 100 mg) with titration up to maintenance daily doses of 25 to 900 mg (median = 400 mg). Treatment with TPM was continued over a median of 12 days (range = 1-70 days).

Cessation of SE was attributed to TPM in 29 patients (29/106; overall success rate = 27.4%) within a median time of 26.5 hours, ranging between the first hour and 432 hours. In 14 patients, SE ceased within 24 hours after the first administration of TPM and after >24 hours in the other 15 patients. A response was attributed to TPM in 21 (31.8%) of 66 patients with RSE and in eight (20%) of 40 patients with SRSE. Overall, TPM was the last anticonvulsant to be added to the therapeutic regimen for 42 patients (39.6%); however, in 13 patients, other interventions precluded an unambiguous classification of TPM as the AED terminating SE. Among the TPM nonresponders, SE cessation was attributed to lacosamide in eight cases, phenytoin in eight cases, VPA in eight cases, and anesthetic agents in six cases ahead of other AEDs in 21 patients.

3.3 | Outcome and predictors of response

The clinical characteristics of all patients, including both responders and nonresponders, are presented in Table 1. Visualization of TPM response in relation to the number of AEDs taken before TPM is provided in Figure 1. When comparing the mRS scores before SE and after SE, only 23 (21.7%) patients were observed to have returned to their baseline clinical condition at the time of discharge from the hospital (Figure 2). The final disposition was discharge to home for 11 patients (10.4%), to a rehabilitation facility for 46 patients (43.4%), to a nursing home for 15 patients (14.2%), to other hospitals for four patients (3.8%), and to palliative care for three patients (2.8%), whereas 24 patients (22.6%) died at the hospital.

3.4 | Treatment-emergent adverse effects

Prehospital-acquired and in-hospital–acquired infections were present in 77 patients (72.6%) and included 49 respiratory infections and 30 urinary tract infections (some patients presented with both). These cases required treatment with antibiotics, complicating intensive care treatment regimens. Transient liver enzymes and creatinine elevation were also seen. None of these was attributed to TPM use.

We observed hyperammonemia during treatment with TPM in 38 patients (35.8%; mean ammonia level = 100.4 μg/L, SD = 39.9 μg/L, median = 95.8 μg/L, range = 56-250.16 μg/L, upper reference limit = 53 μg/L). Among these, 31 concurrently received VPA (mean ammonia level = 100.4 μg/L, SD = 41.7 μg/L, median = 95.6 μg/L), and three received VPA and phenobarbital (PB; mean ammonia level = 119.7 μg/L, SD = 39.9 μg/L, median = 104 μg/L) in addition to TPM. Only four of the 38 patients with hyperammonemia (mean ammonia level = 86.6 μg/L, SD = 23.5 μg/L, median = 83.7 μg/L) received TPM without VPA or PB as a complementary medication. The percentage of patients who developed hyperammonemia was not different between the responders (n = 10/29, 34.5%) and the nonresponders to TPM (n = 28/77, 36.4%; $P = 1.0$). Further treatment-emergent adverse effects attributed to TPM included pancreatitis in one patient and hyperchloremic acidosis in another patient.

4 | DISCUSSION

The reported group of 106 patients treated with TPM is the largest cohort of such published to date, with SE cessation attributed to TPM in 27.4%.

The presented results are in line with the majority of previous studies[15,25–34] published on TPM use in SE; the results of available studies are summarized in Table 2. Previous publications report a wide range for TPM efficacy of between 0%[27,30] and 100%,[31] with some publications suggesting a possible efficacy of TPM of up to 63%[25] or 80%.[30] The wide reported range of efficacy and the disagreement with the attribution of possible efficacy itself both highlight the underlying problem of correctly assigning the efficacy of AEDs in SE,[35] which is even more important in the context of orally administered AEDs like TPM. In our study, we chose a very conservative classification[35] that attributes response to TPM as occurring only in patients with SE cessation after TPM administration, when TPM was the last drug added with no further changes to AED regimen before SE cessation, and when the last changes to the AED regimen were made >24 hours before the initiation of TPM. These strict criteria might have lowered the efficacy rate to 27.4%; in a further of 12.2% of the patients in whom TPM was the last drug, other interventions precluded an unambiguous classification.

Although the TPM Summary of Product Characteristics[36] recommends uptitration from an initial daily dose of 25-50 mg in adults with weekly or biweekly increases of 25-50 mg/d with a target dose of 200-400 mg/d, higher therapeutic levels of TPM are required more immediately to control SE; thus, a higher median initial dose of 100 mg/d and loading of up to 500 mg in selected cases were not unexpected. The daily dose was uptitrated to a median of 400 mg/d with a maximum of 900 mg/d. Such an approach is consistent with other case series of TPM treatment of SE that used median maintenance doses of between 400 and 600 mg/d with a maximum of up to 1600 mg/d.[28–31] Only one recently published case series[27] used a lower median maintenance dose of 225 mg/d. In none of the cases was the efficacy attributed to TPM, which could possibly be

TABLE 1 Baseline demographics and clinical characteristics of patients with status epilepticus treated with topiramate

		Total n = 106	Responders n = 29 (27.4%)	Nonresponders n = 77 (72.6%)	*P*
Age	Mean ± SD, y	67.4 ± 18.1	66.9 ± 17.2	67.6 ± 18.5	.602
Gender	Female/male, n	61/45	17/12	44/33	.891
Previous history of seizures	n	59 (55.7%)	13 (44.8%)	46 (59.7%)	.168
Status severity					
RSE	n	66 (62.3%)	21 (72.4%)	45 (58.4%)	.185
SRSE	n	40 (37.7%)	8 (27.6%)	32 (41.6%)	
Etiology					
Acute symptomatic	n	37 (35%)	9 (31%)	28 (36.4%)	.608[a]
New onset	n	19 (18%)	8 (27.6%)	11 (14.3%)	
Remote symptomatic	n	37 (35%)	7 (24.1%)	30 (39%)	
Progressive	n	12 (11.3%)	5 (17.2%)	7 (9.1%)	
Other	n	1 (1%)	0 (0%)	1 (1.3%)	
mRS at admission					
mRS score of 0-2	n	42 (39.6%)	10 (34.5%)	32 (41.5%)	.507
mRS score of 3-5	n	64 (60.4%)	19 (65.5%)	45 (58.4%)	
Comorbidities					
CCI score of 0	n	8 (7.5%)	4 (13.8%)	4 (5.2%)	.135
CCI score of 1-6	n	98 (92.5%)	25 (86.2%)	73 (94.8%)	
STESS at admission					
STESS score of 0-3	n	68 (64.2%)	19 (65.5%)	49 (63.6%)	.857
STESS score of 4-6	n	38 (35.8%)	10 (34.5%)	28 (36.4%)	
Characteristics of SE treatment					
Preclinical treatment	n	32 (30.2%)	9 (31%)	23 (29.9%)	.907
Treatment with anesthesia					
No	n	56 (52.8%)	20 (69%)	36 (46.8%)	.041
Yes, before TPM	n	42 (39.6%)	7 (24.1%)	35 (45.5%)	
Yes, after TPM	n	8 (7.5%)	2 (6.9%)	6 (7.8%)	
Characteristics of TPM use					
Maintenance dose	Median, mg	400	400	400	.750
Number of AEDs prior to TPM	Median (range)	5 (1-10)	4 (1-9)	5 (1-10)	.799
Latency from SE to TPM	Median, d	8.5	8	9	.698
Duration of TPM administration	Median, d	12	11	12.5	.744
Hyperammonemia during TPM	n	38 (35.8%)	10 (34.5%)	28 (36.4%)	.857
mRS at discharge					
mRS score of 0-2	n	2 (1.9%)	1 (3.4%)	1 (1.3%)	.468
mRS score of 3-6	n	104 (98.1%)	28 (96.6%)	76 (98.7%)	
mRS = 6 (death, mortality rate)	n	24 (22.6%)	4 (13.8%)	20 (26%)	.181

Note: P values indicate the testing between the responder and nonresponder group.

Abbreviations: AED, antiepileptic drug; CCI, Charlson Comorbidity Index; mRS, modified Rankin Scale; RSE, refractory SE; SD, standard deviation; SE, status epilepticus; SRSE, superrefractory SE; STESS, SE Severity Score; TPM, topiramate.

[a]Acute symptomatic etiology vs nonacute symptomatic etiology.

ascribed to the low maintenance dose used.[27] Based on our data and the other case series, an initial as well as a daily maintenance dose of at least 400 mg/d seems to be advisable. The route of drug administration is another important consideration, in terms of rapid attainment of therapeutic drug levels, and the practicalities of administration while SE is ongoing and patients are potentially under general anesthesia requires further investigation. Nasogastric delivery

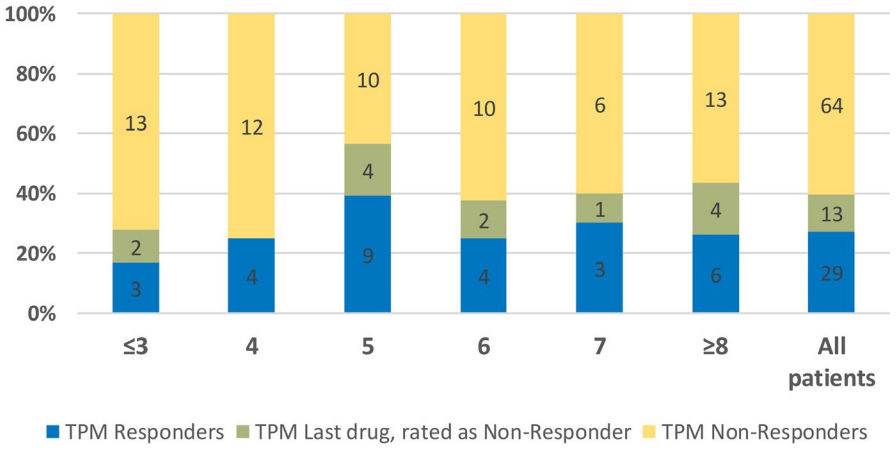

FIGURE 1 Number of administered antiepileptic drugs before the use of topiramate (TPM). Patients are separated as responders and nonresponders to topiramate, and among the latter, patients in whom topiramate was the last drug added before the cessation of status epilepticus but where other interventions precluded an unambiguous classification are indicated in light green

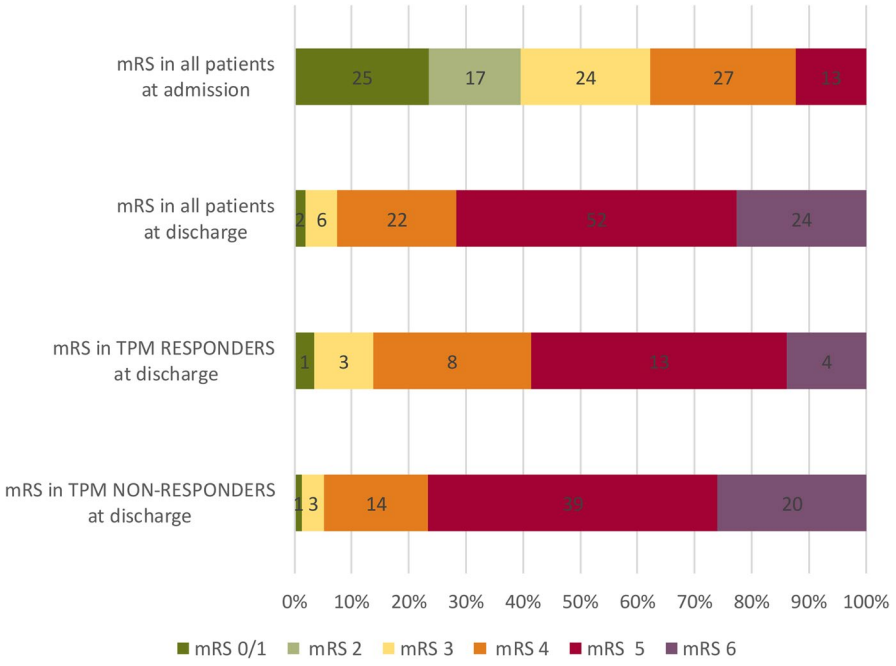

FIGURE 2 Modified Rankin Scale (mRS) scores at admission and discharge, and in responders and nonresponders to topiramate (TPM)

of TPM has previously been reported in SE,[28,31] and successful intravenous delivery of the same has been achieved in healthy volunteers and patients with epilepsy and migraine.[13,14] In healthy volunteers, oral TPM was bioequivalent to intravenous TPM, and an infusion of 50-100 mg over 15 minutes was determined as safe.[13] Among our cases, nasogastric delivery of ground TPM tablets was performed in patients unable to swallow. Instructions for the preparation of oral TPM suspensions of up to 20 mg/mL are available[37] but were not used in our patients.

Patients in the current study had failed a median of five other AEDs prior to TPM initiation, representing a particularly refractory population. The SE cessation attributed to TPM in 29 of 106 (27.4%) patients therefore represents a relevant response. Even among patients with SRSE, eight of 40 showed a response (20%) in this difficult-to-treat population. The latency from SE onset to TPM initiation is unlikely to account for differences in the response to TPM, given the similarity in treatment latencies between the responders (median = 8 days) and nonresponders (median = 9 days). There were also no differences in the median maintenance dose of 400 mg/d between responders and nonresponders. In a prospective open-label nonrandomized clinical trial reported by Asadi-Pooya et al,[27] TPM was always administered as the third AED due to financial or other limitations of the hospital. TPM was effective in 25% (5/20) of patients within 42 minutes after administration, which is comparable with the effectiveness of TPM in our and other retrospective studies.

Previous studies have described varied outcomes with other AEDs used off-label for the treatment of SE. A systematic review of intravenous lacosamide for SE demonstrated an overall efficacy of 57% across 522 episodes of SE.[38] In cases of RSE treated with lacosamide or phenytoin after failure of two previous AEDs, SE ceased in seven

TABLE 2 Efficacy data from studies on topiramate in status epilepticus

	Fechner et al, current study	Brigo et al[15] Drugs 2017	Madžar et al[27] Seizure 2016	Asadi-Pooya et al[28] Seizure 2015	Hottinger et al[25] CNS Drugs 2012	Stojanova and Rossetti[26] Acta Neurol Scand 2012	Synowiec et al[30] Epilepsy Res 2012	Kim et al[29] J Epilepsy Res 2011	Akyildiz and Kumandas[32] Childs Nerv Syst 2011	Towne et al[31] Neurology 2003
Study design	Multicenter, r	Review[a]	Monocenter, r	Monocenter, p	Monocenter, r	Monocenter, r	Multicenter, r	Monocenter, r	Monocenter, r	Multicenter, r
Year of recruitment	2011-2016	2004-2014	2001-2013	2013-2014	2004-2011	2006-2010	2003-2010	2006-2008	2007-2009	Not provided
Country (city) of study	Germany (Frankfurt, Marburg)	Not applicable	Germany (Erlangen)	Iran (Shiraz)	Switzerland (Basel)	Switzerland (Lausanne)	USA (Philadelphia, Pittsburgh)	Korea (Seoul)	Turkey (Kayseri)	USA (Richmond)
Number of patients	106	35	17	20	35	11	35	16	14	6
Age, y[b] (range)	67.4 ± 18.1 (18-95)	Median 40 (16-92)	53 (37-70)	44.45 ± 23.15 (18-92)	Median 60.5	Median 60 (16-80)	57.7 ± 21.7	50.4 ± 18.3 (14-79)	5.3 ± 4	52.16
Female, n (%)	61 (57.5%)	16 (46%)	12 (71%)	6 (30%)	16 (46%)	8 (73%)	20 (57%)	8 (50%)	6 (43%)	5 (83%)
Patients with previous history of seizures, n (%)	59 (55.7%)	7 (20%)	11 (65%)	4 (20%)	11 (31%)	6 (55%)	17 (49%)	0 (0%)	—	—
Etiology, n (%)										
Acute symptomatic	37 (35%)	24 (68.6%)	—	7 (35%)	20 (57%)	7 (63.63%)	16 (46%)	—	6 (43%)	5 (83%)
New onset	19 (18%)	4 (11.4%)	—	—	—	—	—	—	—	—
Remote symptomatic	37 (35%)	4 (11.4%)	—	1 (5%)	8 (23%)	3 (27.3%)	—	—	8 (57%)	1 (17%)
Other	13 (12%)	3 (8.6%)	—	12 (60%)	7 (20%)	1 (9.1%)	19 (54%)	—	—	—
RSE, n (%)	66 (62.3%)	29 (83%)	—	—	35 (100%)	—	—	—	—	6 (100%)
SRSE, n (%)	40 (37.7%)	6 (17%)	—	—	0 (0%)	—	—	—	—	0 (0%)
AEDs prior to TPM, n	Mean 5 Median 5 Range 1-10	Median 2 Range 1-5	Median 6 Range 4-8	Mean 2 Median 2 Range 2-2	Median 4 Range 1-6	Range 2-5	—	—	—	—
First administration of TPM, d	Mean 10.5 Median 8.5 Range 1-30	—	—	—	Median 2 Range 2-23	Median 2 Range 0-28	—	—	—	—
Duration of TPM treatment, d	Mean 15.5 Median 12 Range 1-70	—	—	—	Median 3 Range 1-24	—	—	—	—	—

(Continues)

TABLE 2 (Continued)

	Fechner et al, current study	Brigo et al[15] Drugs 2017	Madžar et al[27] Seizure 2016	Asadi-Pooya et al[28] Seizure 2015	Hottinger et al[25] CNS Drugs 2012	Stojanova and Rossetti[26] Acta Neurol Scand 2012	Synowiec et al[30] Epilepsy Res 2012	Kim et al[29] J Epilepsy Res 2011	Akyildiz and Kumandas[32] Childs Nerv Syst 2011	Towne et al[31] Neurology 2003
TPM loading dose, mg	Mean 139 Median 100 Range 25-500	—	Median 100 Range 50-400	Mean 400 Median 400 Range 400-400	—	—	Mean 360 Median 400 Range 200-400	Mean 637.5 Median 700 Range 300-1000	—	—
TPM maintenance dose, mg	Mean 364 Median 400 Range 25-900	—	—	Mean 400 Median 400 Range 400-400	—	Median 400 Range 50-800	Mean 485.71 Median 600 Range 100-800	Mean 637.5 Range 300-1000	—	—
TPM maximum daily dosage, mg	—	Median 400 Range 200-1000	Median 225 Range 150-1000	Mean 400 Median 400 Range 400-400	—	Mean 381.8 Median 400 Range 50-800	—	—	—	Mean 950 Median 900 Range 300-1600
Adverse events (%)	Hyperammonemia (35.8%) Pancreatitis (0.9%) Hyperchloremic acidosis (0.9%)	—	—	—	Hyperchloremic acidosis Hyperammonemia	Nephrolithiasis (9%)	—	—	Metabolic acidosis (21%)	Lethargy
Efficacy rate of TPM										
Yes, n (%)	29 (27.4%)	6 (17%)	—	5 (25%)	3 (9%)	2 (18%)	—	6 (36.5%)	9 (64.3%)	6 (100%)
Probable, n (%)	13 (12.2%)	8 (23%)	1 (5.9%)	11 (55%)	22 (63%)	2 (18%)	28 (80%)	—	3 (21.4%)	—
No, n (%)	64 (60.4%)	21 (60%)	16 (94.1%)	4 (20%)	10 (29%)	7 (64%)	7 (20%)	10 (63.5%)	2 (14.3%)	—
Mortality, n (%)	24 (22.6%)	14 (40%)	1 (5.9%)	7 (35%)	11 (31%)	4 (36%)	6 (17%)	11 (69%)	—	—

Abbreviations: AED, antiepileptic drug; CNS, central nervous system; p, prospective; r, retrospective; RSE, refractory status epilepticus; SRSE, superrefractory status epilepticus; TPM, topiramate.

[a]Review included patients from Kim et al,[29] Hottinger et al,[25] Asadi-Pooya et al,[28] and Stojanova and Rossetti.[26]

[b]Mean ± standard deviation

(33.3%) patients receiving lacosamide and six (40.0%) patients receiving phenytoin, respectively.[39] Case series on the treatment of RSE and SRSE with intravenous brivaracetam show SE cessation rates of between 27%[40] and 57%.[41–43] Two recent case series reported on the use of oral perampanel in patients with various stages of SE, reporting response rates between 17%[44] and 37%.[45] Use of oral oxcarbazepine in SE was reported in 13 patients with a median treatment latency of 81 hours.[46] Oxcarbazepine was the last drug in eight patients (62%); however, hyponatremia was seen in three of these individuals.[46]

With regard to treatment-emergent adverse effects, our study contradicts the results reported by several other authors[27–30] who did not observe any adverse effects. In our study, hyperammonemia was present in 38 patients (35.8%), with a trend toward higher levels of ammonia in patients who received concurrent treatment with VPA and PB.[47] Hottinger et al[25] described hyperammonemia in seven of 35 patients (20%) and mild hyperchloremic acidosis in all patients. We did observe pronounced hyperchloremic acidosis in one patient and pancreatitis in another patient. Overall, TPM seems not to be associated with any serious or life-threatening side effects. The in-hospital mortality rate was 22.6%, which is in line with the findings of other studies on RSE and SRSE.[3,8,48]

It is important to consider inherent limitations associated with a noncontrolled study design and retrospective review format. The SE cases reported here make up a heterogeneous population having varying ages, diagnoses, and causes and severity levels of SE; individual cases may therefore respond differently to treatments and have contrasting prognoses. The specific order of administered AEDs and their duration were protocolled in detail, but there was no systematic recording of serum levels or treatment-emergent adverse effects. Despite these limitations, we report here, to our knowledge, the largest number of cases of patients with SE treated with TPM. Our results may allow better delineation of outcomes in patients with SE following treatment with specific AEDs such as TPM. Our research may be of clinical value, given that practical and ethical issues preclude clinical trials being conducted for the evaluation of TPM as a treatment for SE. As SE is a potentially fatal medical emergency, high-class, randomized, controlled trials have only been carried out in patients with early stages of SE, although a recent phase III trial assessed an experimental treatment with brexanolone that failed as a third-line therapy for SRSE despite encouraging open-label results.[49]

5 | CONCLUSION

Although TPM is not currently licensed for the treatment of SE, the cases described here add to evidence from previous case series and animal studies that TPM might be a therapeutic option for RSE and SRSE when other approved therapy protocols fail. TPM was well tolerated and has a good safety profile. However, although we present a larger patient cohort, there is still a need for a prospective, randomized clinical study of TPM in the treatment of SE following a determined regimen.

ACKNOWLEDGMENTS

We are grateful to all of our colleagues and the staff at the study centers in Frankfurt and Marburg for their assistance in conducting this study.

CONFLICT OF INTEREST

A.F., K.H., K.J., and M.W.R. do not report any conflicts of interest. S.K. reports honoraria for speaking engagements from Desitin and UCB as well as educational grants from AD Tech, Desitin Arzneimittel, Eisai, GW, Medtronic, Novartis, Siemens, and UCB. J.K. reports personal fees from Aesculap, Brainlab, and Carl Zeiss Meditec Vertriebsgesellschaft and grants from the medical department of Goethe University. K.M. reports honoraria as an advisory board member from Eisai and UCB. F.R. reports personal fees from Eisai, grants and personal fees from UCB, grants and personal fees from Desitin Pharma, personal fees and other from Novartis, personal fees from Medtronic, personal fees from Cerbomed, personal fees from ViroPharma and Shire, grants from the European Union, and grants from the Deutsche Forschungsgemeinschaft. A.S. reports personal fees and grants from Desitin Arzneimittel, Eisai, GW Pharmaceuticals, LivaNova, Marinus Pharmaceuticals, Medtronic, Sage Therapeutics, UCB Pharma, and Zogenix. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: A cohort study of 106 patients and a review of the literature. *Epilepsia*. 2019;60:2448–2458. https://doi.org/10.1111/epi.16382