

Topiramate in refractory status epilepticus: a systematic review

 Hamide Arvan¹, Asieh Mehramiri^{2*} , Mitra Ansari Dezfouli^{3*} 

1. Neurology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

2. Department of Neurology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

3. Hearing Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ABSTRACT

Epilepsy is a chronic neurological disease characterized by recurrent seizures and is caused by abnormal electrical activity in neuronal circuits. Refractory status epilepticus is a life-threatening condition that does not respond to first- and second-line anticonvulsant medications. Topiramate is a powerful antiseizure medication that is used in various types of epilepsy. This study aimed to investigate the effect of topiramate in treatment of refractory status epilepticus. We have developed search strategies to identify articles related to the effect of topiramate on refractory status epilepticus. Our searches encompassed validated databases, including PubMed / MEDLINE, Scopus, Google Scholar, and Cochrane Library, from 2012 to May 2026.

Of the 896 articles found in the preliminary search, 10 clinical studies were selected for structured review. The results of this study indicated that refractory status epilepticus occurs in about 38% of patients with status epilepticus and causes more mortality and disability. Acute symptomatic seizures tend to be resistant to treatment. Topiramate treatment ameliorated epileptic seizures in 194 cases out of 317 patients. Adverse effects, including pancreatitis and metabolic acidosis, and allergic reactions have been reported in rare cases. In conclusion, the available evidence suggests that topiramate may be a potentially useful adjunctive therapy for refractory status epilepticus, especially when administered early. However, reported studies are limited and most of them are based on observational data. Further well-designed prospective studies are required to evaluate its efficacy and safety.

Keywords:

Topiramate

Refractory status epilepticus

Epilepsy

Seizures

Introduction

Epilepsy is one of the most important conditions of the nervous system, characterized by long-term intermittent

seizure attacks. These seizures occur due to the sudden, sporadic, and excessive electrical discharge of the neurons (Jehi 2025). The diagnosis of epilepsy is based on

* Corresponding authors: Asieh Mehramiri, mehramiri.ac@gmail.com

Mitra Ansari Dezfouli, mitraansari84@gmail.com

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the history of clinical findings and the results of electroencephalography (Santamarina et al., 2019). There is a possibility of epilepsy in any age, gender, race, or social class; however, it is more observed in children and the elderly. Additionally, epilepsy is reported slightly more common in men than in women (Tanaka et al., 2024).

Status epilepticus refers to cases in which a patient experiences seizures lasting more than five minutes or repeated attacks during which the patient does not regain his state of consciousness before the seizure (Asadi-Pooya et al., 2015). Refractory status epilepticus (RSE) is a life-endangering neurological state characterized by recurrent seizures despite initial intravenous benzodiazepine treatment and subsequent administration of an additional intravenous anticonvulsant drug (Fisher et al., 2017; Rohrer et al., 2018; Scheffer et al., 2018). Nonconvulsive status epilepticus and focal motor seizures have been mentioned as a risk factor for RSE (Orlandi et al., 2022). A meta-analysis of refractory status epilepticus found that acute symptomatic factors such as infections and inflammation are the most common causes in RSE cases (Schubert-Bast et al., 2019). Mortality of RSE has been mentioned in different studies up to 37.5% and 39.5% (Kellinghaus et al., 2019). The treatment of this condition is challenging, and various methods have been proposed to control it. General anesthesia is recommended for RSE that is not adequately controlled with first-line and second-line antiseizure medications (ASMs), regardless of seizure duration (Kortland et al., 2016). However, this method carries the potential risks of cardiac and respiratory depression.

Administration of topiramate has been mentioned as one of the most useful treatment strategies for controlling RSE in most centers (Brigo et al., 2017). Topiramate is a strong ASM that is used as a single drug or together with other ASMs to treat different types of epilepsy (Löscher and Soul 2025). Topiramate is a molecule with the chemical formula $C_{12}H_{21}NO_8S$. Neurochemical and neurophysiological studies, as well as animal studies, have shown that topiramate exerts at least five different types of effects and, therefore, creates a wide spectrum of clinical effects. These effects include inhibition of sodium channels, effects on GABA receptors, blocking of glutamate receptors, reduction of calcium passage through high-voltage calcium channels, and inhibition of carbonic anhydrase (Fariba and Saadabadi

2024; Lim et al., 2021).

Topiramate is quickly and easily absorbed, and its highest level in the blood happens about 2 to 4 hours after use. After oral consumption, its bioavailability is at least 81%. The half-life of the drug is about 19 to 25 hours, and it is distributed in all tissues, including the central nervous system. Topiramate is mostly unchanged and is excreted through the kidneys (Orlandi et al., 2021). The most common side effects are central nervous system problems and weight loss. Paresthesia is also one of the problems that occur with less prevalence (Chimakurthy et al., 2021). Most of these side effects are mild to moderate. The most common complications of the central nervous system include drowsiness, anorexia, fatigue, nervousness, concentration and attention problems, aggressive behaviors, and memory impairment. Hematologic abnormalities associated with topiramate are infrequent. Several studies have been conducted on the effects of topiramate in the treatment of different types of seizures in children and adults, either as a single treatment or in addition to other therapeutic drugs. Most of these studies have shown the positive effect of the drug in reducing seizures, the number of seizures and, and different types of epilepsy (Panda et al., 2021).

Recently, the use of topiramate as an adjunctive therapy for RSE has been increased, and several studies have attempted to summarize the available evidence. However, most previous literature, has been limited by smaller evidence bases, the inclusion of heterogeneous study designs, or the lack of recently published clinical data. In addition, previous studies have focused less on systematic evaluation of clinical data and response rates and adverse events. Addressing these gaps may help to better interpret the role of topiramate in the management of RSE. Therefore, the present study was conducted with the aim of reviewing the effect of topiramate on RSE.

Materials and Methods

In the present review, we systematically reviewed all studies evaluating the effect of topiramate in refractory status epilepticus from 2012 to May 2026.

Literature search

The data presentation method in this study, including defining the study problem, collecting data, and analyzing and interpreting the findings, was based on the Pre-

ferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The aforementioned protocol applied as a principle for examining the studies. Studies conducted within the time range 2012 to May 2026 were included. To obtain relevant information, search databases including Cochrane Library, PubMed/MEDLINE, Scopus, and Google Scholar by keywords including "Topiramate" and "Refractory Status Epilepticus" or "Topiramate" and "Status Epilepticus".

Inclusion and exclusion criteria

Original English-language articles related to topiramate in RSE were included in the study. Inclusion criteria included primary clinical studies evaluating topiramate in RSE, studies with full text available, and studies reporting clinical outcomes. Exclusion criteria included review articles, editorials, case reports, and conference abstracts. Studies focusing on chronic drug-resistant epilepsy without RSE and articles lacking adequate clinical outcome data and duplicate publications were excluded. The study population included patients of any age diagnosed with RSE. The intervention was topiramate as part of treatment. Seizure cessation or control, clinical outcomes, mortality, and adverse events were assessed as treatment outcomes. Clinical studies included prospective studies, retrospective observational studies, and clinical trials. In order to enhance the comprehensiveness of the study, the reference lists of relevant articles were efficiently searched to find other possible sources. If there were multiple reports of one research study, the most complete one was selected. In cases where the article did not present sufficient information, that article was excluded from the study. For study selection and information extraction, two contributors reviewed all article titles. Duplicate entries were removed, and then the titles and abstracts of the remaining studies were thoroughly examined, with any articles not meeting the criteria for this structured review excluded. Ultimately, the full texts of potentially relevant reports were reviewed; eligible studies were included and irrelevant ones were excluded. As a result, 10 studies relevant to the inclusion and exclusion criteria were found and analyzed. Information was obtained regarding study characteristics, including seizure cessation/control, clinical outcomes, and adverse events.

Data extraction

We reported this systematic review using the PRISMA guidelines. The studies were identified using the following PICOS principle. To avoid subversion, two independent researchers extracted and evaluated the quality of the articles. If the reports were excluded, the details for exclusion were documented. If there was a disagreement between the two reviewers, a third reviewer conducted the review. Then, information about the included reports was prepared, including the name of the first author, year and location of the study, sample size, doses administered, study method, and results. The form has been pre-registered. The included studies were primarily retrospective, non-randomized observational studies (rather than randomized trials). Thus domains specific to randomized trials such as random sequence generation and allocation concealment were not applicable. Consequently, study quality was assessed using the Newcastle-Ottawa Scale (NOS), which is designed for non-randomized studies, and randomized trial domains were excluded from the methods and limitations sections.

The resulting risk-of-bias classification for each study is reported in Table 1. As most of the included studies were single-arm and lacked an internal comparison group, the comparability domain could not be fully assessed; this factor was taken into account when rating those studies. Studies with limited sample sizes, retrospective data collection, or incomplete reporting were rated as having a moderate risk of bias. Risk of bias particularly arising from confounding and selection is mentioned as a major limitation of the current evidence in the discussion section, and our conclusions have been formulated accordingly. This assessment included selection (representation of the study population and case ascertainment), comparability (control of confounding factors), and outcome measurement (adequacy of follow-up and completeness of outcome data). Studies were excluded based on inclusion criteria limited to the English language and only original papers with free full-text access, as illustrated in Fig. 1.

Results

In the primary search, 896 reports were found, and following assessment of the titles and the abstracts and excluding duplicate and irrelevant data, 18 potentially relevant reports remained. Of these, eight articles were excluded due to lack of sufficient information. Finally,

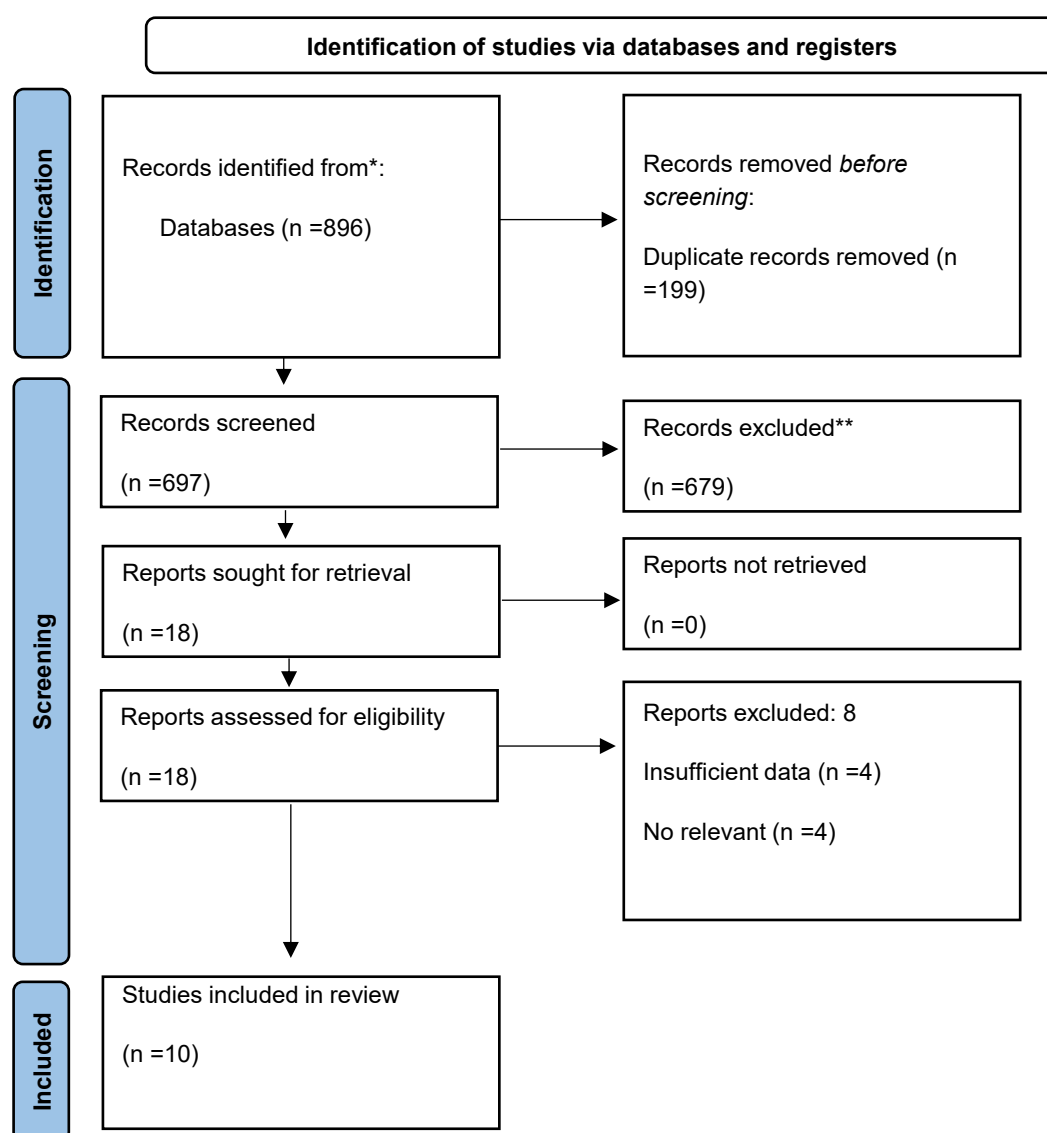


FIGURE 1. The PRISMA Flowchart

10 clinical reports were included in the study (Figure 1). According to the results of the study, the use of topiramate in the treatment of RSE has positive results in 194 cases out of 317 patients. Since the decrease in the number of seizures in cases with RSE improves the outcome and mortality, it is suggested that this drug could be used in the treatment of patients with RSE. Because many of the ASMs that are commonly used have many side effects, combination therapies require careful administration.

The causes of refractory status epilepticus varied significantly across and within investigations. Contributing factors included infections, intracranial bleeding, insufficient levels of ASMs, metabolic disturbances,

overdose or withdrawal from drugs or alcohol, physical traumatic injuries, stroke, brain tumors, congenital brain anomalies, and conditions such as Lennox-Gastaut syndrome.

Demographically, the investigations showed no major disparities in participant age or sex distribution, with the exception of one study that focused solely on children. Most research included individuals with a range of seizure types: generalized clonic, generalized tonic-clonic, simple partial, complex partial, nonconvulsive, and focal motor seizures. However, Fechner and colleagues did not specify seizure types among their subjects, while Asadi-Pooya et al. exclusively included individuals with generalized convulsive status epilepticus (Asadi-Pooya

TABLE 1: The Main Characteristics of Studies Included in the systematic review

Reference	Study design	Population	Operational Definition of “Amelioration”	Loading Dose /Maintenance Dose	Main Outcomes (Seizure Cessation % / Time to Cessation)	Risk of Bias *
(Fechner et al., 2019)	Retrospective cohort study	106 patients with RSE and SRSE	Cessation of seizures following topiramate administration	Loading: 100 mg/day (start) Maintenance: 400 mg/day median with a maximum of 1600 mg/day for 12 days	- Seizure Cessation: 27.4% -Time to Cessation: Not reported Hyperammonemia: 35.8%	Low
(Asadi-Pooya et al., 2015)	Prospective open-label non-randomized clinical trial	20 patients with refractory GCSE (≥18 years)	Successful: termination of seizure; Possibly successful: clinical improvement without full cessation	Loading: 400 mg (start) Maintenance: 225 mg.	-Seizure Cessation: 25% (full) -Partial response: 55% -Time to Cessation: 24 h	Low
(Madzar et al., 2016)	Retrospective study	17 patients with RSE	Seizure control following topiramate administration	Loading dose: 100mg/day (IQR, 50–400 mg/day) Maintenance: 225mg/day (IQR, 150–1000 mg/day).	-Seizure control was achieved in 100% of patients. -Seizure Cessation: Not reported -Time to Cessation: Not reported	Moderate
(Brigo et al., 2017)	Systematic review with individual patient data analysis	35 patients with generalized convulsive SE	Control of status epilepticus after topiramate	Loading dose: N/A Maintenance dose: 200–1,000 mg/day	-Status epilepticus was controlled in 68.6% of patients receiving topiramate. -Seizure Cessation: 40 % -Time to Cessation: range from 1 to 4 days	Low
(2021) (Welling et al., 2021)	Systematic review	261 patients with RSE	Hospital discharge within 72 hours of topiramate administration	Loading dose: N/A Maintenance dose: 200–1000 mg/day	-Seizure Cessation: 27%–100%(range) -Time to Cessation: Within 72 hours	Low
(Synowiec et al., 2012)	Retrospective study	35 adult patients with RSE	Discontinuation of RSE after topiramate	Loading dose: N/A Maintenance dose: 100–800 mg/day	-Seizure Cessation: 40% -Time to Cessation: 3 days	Low
(Suttichaimongkol et al., 2012)	Retrospective study	8 patients with RSE	Complete cessation of SE	Loading: 400 mg Maintenance: 100 mg/day	-Seizure Cessation: 87.5% (7/8) -Time to Cessation: Not reported -No adverse effects reported	Moderate
(Keskin-Güler et al., 2025)	Retrospective, multicentre study	60 patients with convulsive or non-convulsive SE	Successful: seizure termination; Possibly successful: partial response	Loading dose: 400–500 mg Maintenance dose: 100 mg/day (titrated down 50 mg/2days)	-Seizure Cessation: 36% (successful) Partial response: 38% -Time to Cessation: Not reported. -20% of cases showed adverse effects including metabolic acidosis, renal calculi, hyponatremia and allergic reaction.	Low
(Hottinger et al., 2012)	Observational cohort study	35 patients with RSE	Seizure termination within 72 hours of Topiramate administration	Loading: N/A Maintenance: 200–800 mg/day	-Seizure Cessation: 71% (within 72 h) -Time to Cessation: 72 hours -No adverse effects reported.	Low

Abbreviations: RSE = Refractory Status Epilepticus; SRSE = Super-Refractory Status Epilepticus; GCSE = Generalized Convulsive Status Epilepticus; * NOS scores are estimated based on available information in each study. The systematic reviews by Brigo et al. (2017) and Welling et al. (2021) are listed as sources through which primary clinical reports were identified.

et al., 2015; Fechner et al., 2019). Epilepsy prevalence has been recorded by Synowiec et al., Hottinger et al., and Asadi-Pooya et al., with rates of 45.7%, 31.4%, and 20%, respectively (Asadi-Pooya et al., 2015; Fechner et al., 2019; Hottinger et al., 2012; Synowiec et al., 2012).

Topiramate treatment was administered to 317 patients with persistent refractory epilepsy, and seizure improvement was observed in 194 patients (simple cumulative ratio: 61.5%; 95% confidence interval: 56.1%-66.9%). This figure represents the crude ratio pooled across all considered studies and has not been adjusted for differences in study size, design, or population heterogeneity; therefore, it should be interpreted accordingly. The prescribed topiramate dosage differed widely across studies. A maximum daily dose ranged from 400 mg to 1600 mg per day, while minimum daily doses were between 50 mg and 200 mg. Even in individual investigations, substantial dosage variability was observed among participants. Adverse effects were generally mild or absent in the majority of investigations, with reported side effects including metabolic acidosis, elevated blood ammonia (hyperammonemia), nephrolithiasis (noted in one patient, 63 days after starting topiramate, which led to sepsis). Fechner et al. reported that 35.8% of participants experienced hyperammonemia following topiramate therapy (Fechner et al., 2019)h.

Discussion

Pharmacological treatment serves as the primary approach to managing epilepsy. The use of ASMs is highly effective at stopping or lessening seizure frequency (Kanner and Bicchi 2022). Core ASMs include phenytoin, levetiracetam, and valproic acid, alongside additional options such as lacosamide, tiagabine, gabapentin, and topiramate. Topiramate is a versatile ASMs that addresses various seizure types, likely due to its multifaceted mechanism of action. Topiramate demonstrates favorable oral absorption, linear pharmacokinetics, minimal protein binding, and lacks active metabolites. For individuals with critical illness, topiramate can be rapidly titrated and is recognized as a potential treatment option for super-refractory status epilepticus (SRSE) (Brigo et al., 2017).

More recently introduced ASMSs, such as fosphenytoin, phenytoin, levetiracetam, valproic acid, phenobarbital, and lacosamide, are generally better tolerated by users, though potential unintended long-term

consequences must still be considered (Hakami 2021). Studies indicate that ASM like topiramate and levetiracetam can trigger lipid peroxidation and weaken antioxidant defenses in laboratory rats, while in patients and experimental epilepsy models, these drugs show therapeutic effects with antioxidative properties (Sarang et al., 2016; Shishmanova-Doseva et al., 2021). Detailed protocols documented the sequence and extent of ASMS administration, though systematic monitoring of serum levels and side effects was not consistently conducted. Levetiracetam showed comparable efficacy to phenytoin and fosphenytoin in seizure control (Klowak et al., 2021). Mortality rates were comparable between treatment options. Regarding intubation safety, phenobarbital was preferable to phenytoin in pediatric cases, levetiracetam outperformed fosphenytoin, and valproate was more favorable than both phenobarbital and fosphenytoin (Besli et al., 2020). Additionally, valproate was associated with reduced cardiovascular instability in comparison with phenytoin.

Phenobarbital and high-dose levetiracetam were notably more effective than phenytoin at stopping seizures within a 60-minute timeframe. Based on network analysis, phenobarbital ranked as the most likely to be the top-performing treatment among the interventions studied, followed closely by high-dose levetiracetam and high-dose valproate (Brigo et al., 2019; Zhang et al., 2021). The strongest available evidence for second-line treatment of benzodiazepine-resistant convulsive status epilepticus, from the Established Status Epilepticus Treatment Trial, indicates that fosphenytoin at 20 mg/kg, valproate sodium at 40 mg/kg, and levetiracetam at 60 mg/kg are equally successful in controlling status epilepticus, achieving a success rate of approximately 50% (Cock and Group 2011; Kapur et al., 2019). Similar effectiveness has been reported in earlier research with lacosamide at 400 mg and fosphenytoin at 20 mg/kg (Niquet et al., 2019).

Rather than acting as a substitute for anesthetic therapy in RSE, topiramate could be an adjunctive non-anesthetic option that can be considered before or in addition to continuous intravenous sedation. This treatment strategy could be particularly important in patients at risk for anesthetic complications (Au et al., 2024). Additionally, one investigation that evaluated episodes treated with and without topiramate found a significantly higher likelihood of terminating RSE when topiramate was includ-

ed in the baseline ASMs treatment (Madžar et al., 2016). Ferlisi and Shorvon noted that the results of topiramate interventions in super-refractory status epilepticus are limited to 60 cases across ten reports (Shorvon and Ferlisi 2011). This scarcity of data arises from the considerable variability in clinical profiles in “refractory status epilepticus” studies, which often include both super RSE cases and those resistant to first- and second-line therapies without anesthetic administration (Akyıldız and Kumandaş 2011). Therefore, the number of super RSE cases treated with topiramate remains insufficient to make definitive conclusions about its specific significance in managing this condition (Asadi-Pooya et al., 2015; Madžar et al., 2016; Stojanova and Rossetti 2012; Tarulli and Drislane 2004).

Our findings may enhance the understanding of patient outcomes with status epilepticus treated with specific ASMs like topiramate. This research holds clinical significance, particularly since practical and ethical constraints prevent the conduction of clinical trials assessing topiramate’s effectiveness for status epilepticus. The literature presented contributes to the existing body of evidence from prior case series and animal studies, suggesting that topiramate may be a viable treatment alternative for refractory status epilepticus and super-refractory status epilepticus when standard treatment protocols are ineffective (Rosenthal et al., 2017). Topiramate exhibited good tolerance and demonstrated a favorable safety profile. RSE is characterized by increased excitability of neuronal circuits and alterations in excitatory and inhibitory receptors, including internalization of synaptic GABA-A receptors and upregulation of NMDA and AMPA receptors. These changes are involved in drug resistance, particularly to benzodiazepines and other GABAergic treatments. Topiramate enhances GABA-mediated neuronal inhibition and simultaneously inhibits glutamate receptors, thereby reducing neuronal excitability. This dual action may modulate the excitatory-inhibitory imbalance that characterizes epileptic pathways. In addition, blockade of voltage-gated sodium and high-voltage-activated calcium channels may reduce neuronal depolarization. Inhibition of carbonic anhydrase by topiramate may cause mild metabolic acidosis in neurons, which alters neuronal pH and reduces excitability (Bai et al., 2022).

The design of large clinical trials with blinding is required to reduce the risk of bias in topiramate efficacy

against RSE. Topiramate doses prescribed for RSE patients vary in different studies and range from 50 mg to 1600 mg per day. It seems that a standard protocol for selecting the dose and duration of topiramate treatment in RSE is needed. In one study that reported favorable outcomes, Suttichaimongkol et al showed that a loading dose of 400 mg per day followed by a maintenance dose of 100 mg per day resulted in seizure cessation in 7 of 8 patients (Suttichaimongkol et al., 2012). In contrast, Fechner et al. reported that 100 mg/d, up-titrated to a median maintenance dose of 400 mg/d in 12 days, resulted in seizure cessation in 27.4% of patients (Fechner et al., 2019). Based on these observations, starting topiramate with an initial dose of 400 mg followed by a target maintenance dose of 200 to 400 mg/day, adjusted according to seizure control, tolerability, and renal function, can be considered in future studies. It is necessary to provide guidelines based on prospective studies and clinical trials for standardizing topiramate dosage in the clinic.

The high incidence of hyperammonemia (35.8%) among RSE patients receiving topiramate reported by Fechner et al. highlights the importance of biochemical monitoring in topiramate treatment (Fechner et al., 2019). Topiramate inhibits carbonic anhydrase and may disrupt the hepatic urea cycle, predisposing patients to elevated serum ammonia levels at high doses or with prolonged use (Tantikittichaikul et al., 2015). Although hyperammonemia in this setting is often asymptomatic, it may contribute to encephalopathy and may interfere with clinical assessment of seizure control in critically ill patients. Therefore, monitoring of serum ammonia is particularly important in patients receiving high doses of topiramate (≥ 400 mg/day) or those receiving long-term treatment (>7 days). Increased monitoring frequency is required in patients with pre-existing liver impairment and those receiving concomitant valproic acid. Early detection of hyperammonemia allows for timely dose adjustment, drug discontinuation, and minimizing the risk of further damages in patients.

Conclusion

Topiramate could be effective in the management of refractory status epilepticus, with response rates comparable to or better than current third-line treatments for the condition, while mortality rates appeared to be lower. Although assessing the side effects of adjuvant drugs

in critically ill patients presents challenges, topiramate was generally well tolerated and did not cause severe side effects, making it a promising option for third-line treatment of refractory status epilepticus. However, reported studies are limited, and most of them are based on observational data. Further well-designed prospective studies are required to evaluate the exact efficacy and safety of topiramate.

Conflicts of Interest

The authors report no conflict of interest.

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