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Epileptic Disorders

ORIGINAL ARTICLE

Eslicarbazepine acetate for the treatment of status epilepticus

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Abstract

Objective: Due to the high mortality of patients with refractory status epilepticus (SE), new antiseizure medications (ASMs) are needed to improve long-term outcomes. In this study, we evaluated the efficacy and safety of eslicarbazepine acetate (ESL), a new sodium channel blocker, based on the data from a large epilepsy register.

Methods: Data on the efficacy and safety of ESL for the treatment of refractory SE were gathered from the Mainz Epilepsy Registry (MAINZ-EPIREG). Logistic regression was applied to identify predictors of status interruption.

Results: In total, 64 patients with remote symptomatic refractory SE were treated with ESL. No cases of idiopathic generalized epilepsy were included. The average age was 61.4 ± 11.0 years. The median number of administered ASMs before the start of ESL was three. On average, 2 days had elapsed since the onset of SE before the administration of ESL. The initial dose of 800 mg/day was increased up to a maximum daily dose of 1600 mg in case of nonresponse. In 29 of 64 patients (45.3%), the SE could be interrupted within 48 h of ESL therapy. In patients with poststroke epilepsy, the control of SE was achieved in 62% of patients (15/23). The earlier initiation of ESL therapy was an independent predictor of control of SE. Hyponatraemia occurred in five patients (7.8%). Other side effects were not observed.

Significance: Based on these data, ESL may be used as an adjunct therapy for the treatment of refractory SE. The best response was found in patients with poststroke epilepsy. In addition, early initiation of ESL therapy appears to result in better control of SE. Besides a few cases of hyponatraemia, no other adverse events were detected.

KEYWORDS

efficacy, eslicarbazepine acetate, hyponatraemia, poststroke epilepsy, safety, status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is a neurological emergency causing both high morbidity and mortality unless prompt and effective treatment is administered.[1] Excessive neuronal discharges lead to epileptiform potentials inducing brain damage and secondary systemic complications. Alterations at the molecular, cellular, synaptic, and

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The preliminary data of five patients from this cohort were presented at the 4th Congress of the European Academy of Neurology (EAN) in 2018.

network levels occur, leading to self-sustaining, abnormal excitability with prolonged discharges and seizure prolongation, resulting in irreversible inflammatory, metabolic, and apoptotic processes.[2] An additional prolongation of the SE is facilitated by the failure of several mechanisms involved in ceasing abnormal brain activity during the seizure.[3] During SE, excitatory NMDA-mediated synaptic currents increase and the inhibitory GABAergic synaptic transmission decreases simultaneously.[4] This hyperexcitability in the neuronal circuits continuously increases along with the increase in the threshold to modulate this pathological brain state as the SE is prolonged. Thus, the SE requires early treatment to reduce progression to a refractory and super-refractory state.[5] Evidence for the recommended treatments for this neurological emergency is surprisingly thin, especially in benzodiazepine-refractory cases and for super-refractory SE.[6]

New antiseizure medications (ASMs) may provide an urgently needed avenue for the successful treatment of SE. In the cohort presented, eslicarbazepine acetate (ESL), a novel sodium channel blocker, was administered for refractory SE. The mechanism of action of ESL involves the slow inactivation of sodium channels.

Key Points

- ESL may be considered as adjunctive therapy for refractory status epilepticus.
- Relative to other aetiologies of status epilepticus, the highest rate of cessation in response to ESL was reported in cases of poststroke epilepsy.
- Regular laboratory controls for possible hyponatraemia are required if status epilepticus is treated with ESL.

2 | METHODS

The data of patients with refractory SE treated with ESL were gathered from the Mainz Epilepsy Registry (MAINZ-EPIREG) and analyzed. The epileptic activity within the first 48 h of ESL therapy and the side effects of ESL therapy were assessed.

2.1 | Study design and clinical evaluation

All patients included in this observational study were treated at the Comprehensive Epilepsy Center Mainz, which is integrated into the Department of Neurology of the University Medical Center of the Johannes Gutenberg University Mainz. MAINZ-EPIREG is focused on the prospective evaluation of the disease course and health-related quality of life of patients with epilepsy. During the period from January 1, 2016, to December 31st, 2021, we identified all patients with refractory SE who were being treated with ESL, as the last ASM administered prior to cessation of SE or prior to initiation of anesthesia. In these patients, ESL was considered to have failed if SE was not terminated within 48 h of ESL administration. In the case of ESL failure, anesthesia was initiated. Refractory SE was defined as SE persisting despite adequate treatment with benzodiazepines and at least one ASM, with doses for both being insufficient. In order to estimate the efficacy of ESL, EEG and clinical data from before and after the administration of ESL were analyzed (Figure 1). All patients underwent one EEG daily. The cessation of SE was proved both clinically and with EEG. All patients with nonconvulsive SE had continuous epileptiform discharges on EEG with a frequency of >2.5 per second. ESL was administered orally as a single daily bolus. In patients with impaired consciousness or dysphagia, ESL was administered via nasogastric tube ($n = 46$). Because ESL reaches its steady state after several days, we used a rapid titration approach. The initial dose of ESL was 800 mg/day. If the status was not interrupted with this dose, then the ESL dose was increased up to the maximum daily dose of 1600 mg on the next day. The maximum daily dose (800 or 1600 mg/day) was continued as the maintenance dose. We determined the plasma concentration of ESL and (R)-licarbazepine in all patients using chiral, high-performance liquid chromatography. The approximate time of the quantification of plasma concentration was 10–12 h after the administration of ESL.

The safety data were documented as side effects determined based on laboratory parameters and clinical observations during monitoring over the course of the treatment. Patients in whom SE was not interrupted by ASMs were treated by intubation and sedation. This study was approved by the local ethics committee. All patients gave their informed consent to participate and are included in the MAINZ-EPIREG, either before the onset of SE or after successful treatment. This study has been registered at ClinicalTrials.gov with the registration number NCT05267405.

2.2 | Statistics

The statistical analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp.). Data were presented as mean and standard deviation (SD) or median and range.

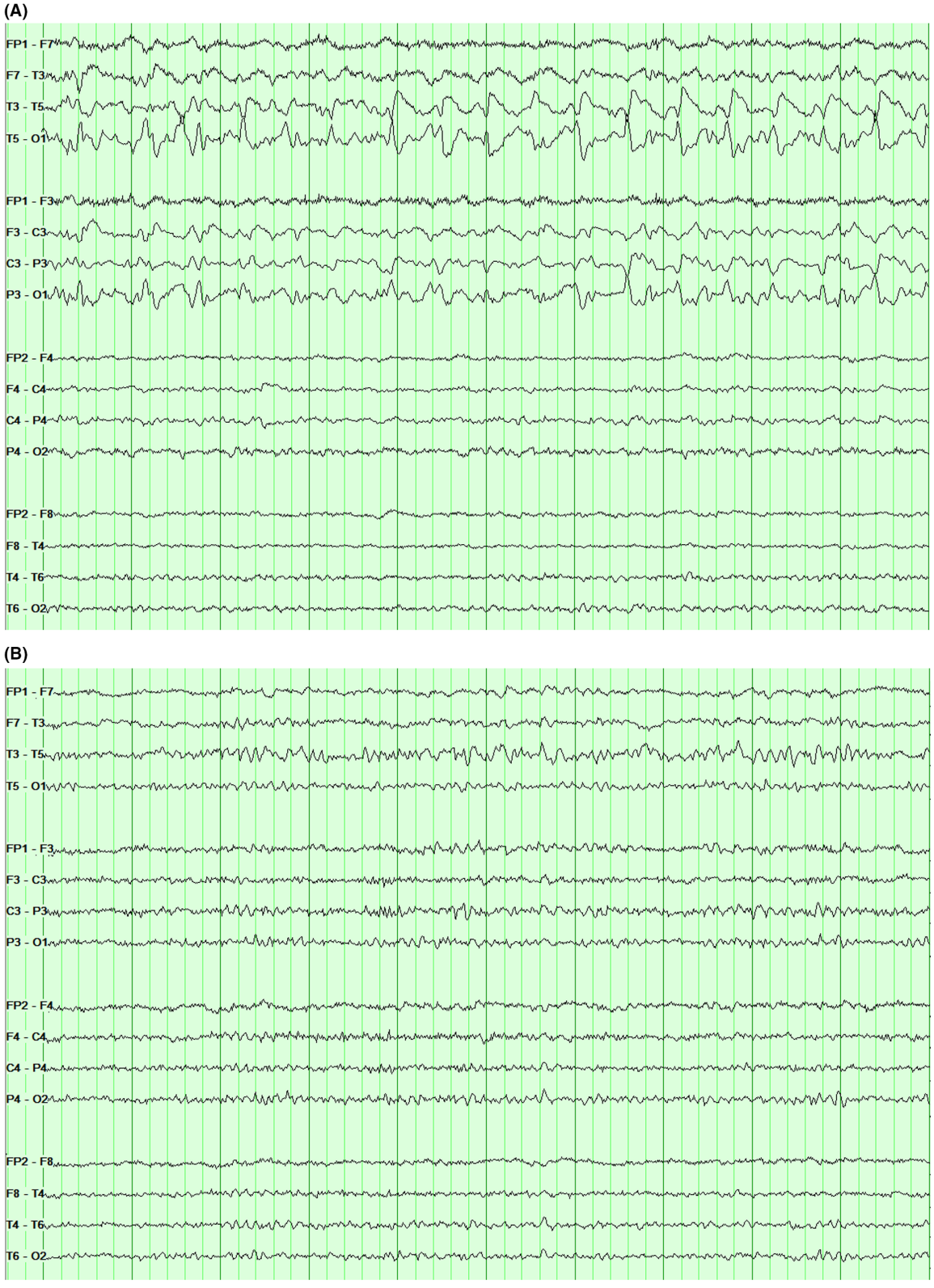

FIGURE 1 EEG of a patient with status epilepticus responding to eslicarbazepine acetate therapy. (A) EEG recorded before the administration of eslicarbazepine acetate (ESL) showing rhythmic sharp wave activity, maximum in the left temporo-occipital region. After initial benzodiazepine therapy, the patient received levetiracetam (3000 mg) and valproate (2400 mg). (B) EEG recorded 24 h after initiation of ESL at 800 mg/day showing cessation of status epilepticus and only single theta waves in the left temporal region.

We used the Kolmogorov–Smirnov test to assess data distribution. A *t*-test was applied for comparisons of normally distributed variables. For non-normal distributions, the Mann–Whitney *U*-test (two independent groups), the Kruskal-Wallis test (more than two independent groups), or the Wilcoxon rank test (two dependent groups) were applied. Logistic regression analysis was performed to identify independent factors affecting the control of SE. Data were presented using regression coefficient (*B*) and 95% confidence intervals (CI). Statistical significance was assumed at a *p* value of <.05.

3 | RESULTS

In total, 64 patients (34 females) with remote symptomatic refractory SE were treated with ESL. No patients with idiopathic generalized epilepsies were included. The average age was 61.4 ± 11.0 years. The median number of previously administered ASMs before the use of ESL was three. On average, 2 days had elapsed since the onset of SE before the administration of ESL. The etiology of SE in patients was poststroke epilepsy in 36% ($n = 23$), temporal lobe epilepsy in 37% ($n = 24$), epilepsy after encephalitis in 16% ($n = 10$), tumor in 2% ($n = 1$), post-traumatic in 5% ($n = 3$), and neurodegenerative in 5% ($n = 3$). All cases were remotely symptomatic according to the classification of ILAE Task Force on SE.[3] Data on demographics, clinical parameters, etiology, and semiology are shown in Table 1. Patients with temporal lobe epilepsy consisted of both those with nonlesional temporal lobe epilepsy ($n = 14$, 58%) and those who had undergone temporal lobe epilepsy surgery in the past but had not remained seizure-free ($n = 10$, 42%). Benzodiazepines were administered as the first ASM to treat SE. The second administered ASMs were levetiracetam ($n = 35$, 65%), valproate ($n = 14$, 22%), phenytoin ($n = 9$, 14%), and others ($n = 6$, 9%).

In 29 of 64 patients (45.3%), the SE could be interrupted within 48 h of ESL therapy (Table 1). In 21 patients (32.8%), SE was interrupted after the application of 800 mg/day of ESL. The rest of the study population required a dose of 1600 mg/day. The mean dose of ESL was 1020 ± 567 mg/day in responders and 1600 ± 803 mg/day in nonresponders. The mean plasma levels of ESL and (R)-licarbazepine were 19.8 ± 4.2 and 1.3 ± .3 μg/mL, respectively. The mean plasma levels of ESL and (R)-licarbazepine were lower in responders than in nonresponders because, in the majority of responders, ESL did not have to be titrated up to 1600 mg/day (ESL: 16.3 ± 8.6 vs. 22.6 ± 11.36 μg/mL; (R)-licarbazepine: 1.1 ± .6 vs. 1.5 ± .7 μg/mL for responders vs. nonresponders, respectively).

TABLE 1 Data on demographics and clinical parameters of patients with status epilepticus and eslicarbazepine acetate therapy.

	***n* = 64**
Age (years)	
Mean (±SD)	61 (±11)
Median (range)	60 (34–83)
Gender, *n* (%)	
Male	30 (46.9)
Female	34 (53.1)
Days of SE before ESL	
Mean (±SD)	2.31 (±.9)
Median (range)	2 (1–4)
Control of SE with ESL, *n* (%)	
Yes	29 (45.3)
No	35 (54.7)
Number of ASMs before ESL	
Mean (±SD)	3.08 (±1.0)
Median (range)	3 (2–5)
Etiology, *n* (%)	
Poststroke epilepsy	23 (35.9)
Temporal lobe epilepsy	24 (37.5)
Postencephalitic epilepsy	10 (15.6)
Tumor	1 (1.6)
Post-traumatic epilepsy	3 (4.7)
Neurodegenerative epilepsy	3 (4.7)
Semiology, *n* (%)	
Focal onset evolving into bilateral convulsive	5 (7.8)
Focal motor	40 (62.5)
Nonconvulsive	19 (29.7)

Abbreviations: ASM, antiseizure medication; ESL, eslicarbazepine acetate; SD, standard deviation; SE, status epilepticus.

In 65% of patients with poststroke epilepsy (15 of 23 patients), SE could be interrupted by ESL (Table 2). In 10 of 24 (42%) patients with temporal lobe epilepsy, control of SE was also achieved by starting therapy with ESL (Table 2). However, in patients with postencephalitic epilepsy, interruption of SE by ESL was achieved only in one of 10 patients (10%) (Table 2).

A logistic regression analysis showed that days of SE before initiation of therapy with ESL was an independent predictor of interruption of SE ($p = .004$) (Table 3). The other variables, such as age, gender, and number of previously administered ASMs, were not independent predictive factors (Table 3). The level of sodium was measured at least every second day. Hyponatraemia (sodium level below 136 mmol/L) occurred in five patients (7.8%). In these cases, hyponatraemia was mild, with the lowest level of sodium at 125 mmol/L. Other side effects were not observed.

TABLE 2 Clinical parameters of patients with status epilepticus and eslicarbazepine acetate therapy relative to etiology.

	Poststroke epilepsy	Temporal lobe epilepsy	Postencephalitic epilepsy	Others (tumor, post-traumatic, neurodegenerative)
Age, mean ± SD	69.5 ± 9.1	58.5 ± 5.9	46.7 ± 7.4	65.9 ± 9.3
Gender, *n* (%)				
Male	10 (43.5)	11 (45.8)	6 (60.0)	3 (42.9)
Female	13 (56.5)	13 (54.2)	4 (10.0)	4 (57.1)
Days of SE before ESL, mean ± SD	2.1 ± .9	2.3 ± .8	3.0 ± .9	1.9 ± .7
Control of SE with ESL, *n* (%)				
Yes	15 (65.2)*	10 (41.7)*	1 (10)*	3 (42.9)*
No	8 (34.8)*	14 (58.3)*	9 (90)*	4 (57.1)*
Number of ASMs before ESL, mean ± SD	2.4 ± .7	3.1 ± 1	4.2 ± .9	3.4 ± .8
STESS, mean ± SD	2.3 ± 1.0	1.9 ± 1.4	2.9 ± 1.5	3.0 ± 2.2

Abbreviations: ASM, antiseizure medication; ESL, eslicarbazepine acetate; SD, standard deviation; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

*Statistically significant difference at $p < .05$ in the group comparison between different aetiologies.

TABLE 3 Logistic regression analysis of control of status epilepticus in patients with eslicarbazepine acetate therapy.

	B	95% CI	*p* value
Female gender	−.02	−.28; 3.47	.979
Age	.14	.07; 1.11	.315
Days of SE before ESL	−1.58	−2.71; −.60	.004
Number of ASMs before ESL	−.45	−.90; 1.36	.244
Constant	2.47		.418

Abbreviations: ASMs, antiseizure medications; *B*, regression coefficient; CI, confidence interval; ESL, eslicarbazepine acetate; SE, status epilepticus.

4 | DISCUSSION

Based on the data presented herein, ESL may be considered as an adjunct therapy in the treatment of refractory SE. In the cohort, hyponatraemia identified by daily laboratory examinations was rare and no other side effects could be detected.

The evidence supporting treatments of SE is growing; however, data on new ASMs for the treatment of this neurological emergency are scarce.[7] Intravenous phenytoin has been the ASM of choice for benzodiazepine-refractory SE since the 1970s.[7] In addition to cardiac arrhythmia and hypotension, which may require close monitoring of heart and blood pressure in an intensive care unit, intravenous administration of phenytoin may be associated with reactions at the site of infusion and the metabolism of many drugs (including other antiseizure medications) increases due to the induction of liver enzymes. Accordingly, the replacement of phenytoin by other ASMs with more favorable pharmacokinetics and side effect profiles is desirable.

Systematic review of three relatively small randomized controlled trials (RCTs), comparing intravenous phenytoin with levetiracetam for benzodiazepine-refractory SE, confirmed similar efficacy at onset and functional outcomes at hospital discharge.[8] Even though an evaluation of the data was not possible due to the small sample sizes, levetiracetam is often preferred for SE.[9] In the Established Status Epilepticus Trial, 384 patients were randomly assigned to receive levetiracetam, fosphenytoin, or valproate. All of these ASMs led to seizure cessation and improved alertness in half of the treated patients.[10]

Like phenytoin, carbamazepine and valproate, as well as other newer ASMs such as lamotrigine[11] and topiramate, suppress abnormal neuronal excitability by inhibiting sodium channels. Lamotrigine and phenytoin bind with greater affinity to both open and inactivated channels as compared to channels at rest.[11,12] This voltage-dependent block is an important prerequisite for the selective suppression of epileptiform activity during epileptic seizures.[13] Inhibition of neural sodium ion flow, similar to phenytoin and carbamazepine, has been shown for several newer ASMs such as lamotrigine,[11,14] topiramate,[15,16] and brivaracetam.[17] The inhibition of sodium ion flow is an effective antiseizure mechanism.[11,18]

Eslicarbazepine acetate is administered as an additional ASM for the treatment of partial epileptic seizures with or without secondary generalization.[19,20] The effects are believed to be due to the inhibition of voltage-gated sodium channels by stabilization of the inactive form of the sodium channels and thus, suppression of repetitive discharges.[21] The mechanism of action of ESL involves slow inactivation processes that

can modulate the availability of sodium channels in a membrane-potential-dependent manner by changing the availability of channels within seconds to minutes. The rearrangement of the channel's pores regulates excitability[22] and reduces the availability of voltage-gated sodium channels. The slow inactivation and recovery are mainly due to either prolonged depolarization shifts or to high-frequency activity. The effect of slow inactivation is retained in chronic epilepsy.[23]

Through this mechanism of slow inactivation of sodium channels, ESL could therefore also have an advantage in the treatment of SE. To our knowledge, this is the first, detailed study examining the treatment of SE with ESL.

We were able to show that ESL offers a useful, additional therapy for SE with minimal side effects. In our cohort, interruption of SE was achieved in 45% of patients. SE was most frequently controlled in patients with poststroke epilepsy (65%). A significantly better response to ESL therapy has already been shown in patients with poststroke epilepsy compared with non-poststroke epilepsy but without SE.[24] This relates to a higher responder rate, which is defined as a seizure reduction of ≥50%, as well as a more frequent seizure freedom rate at ≥3 months in patients with poststroke epilepsy and ESL therapy.[24] The mechanism of action of ESL, i.e., slow inactivation of sodium channels, may play a role in an improved response of patients with poststroke epilepsy.[25] Interestingly, this observation was also made for lacosamide, which has the same mechanism of action.[25] These findings may lead to improved treatment of poststroke epilepsy and to a significant increase in patients' health-related quality of life.[26,27]

A logistic regression analysis of our data showed that the number of days spent with SE before the start of ESL is an independent predictor of interruption of SE, with better outcomes in the case of earlier initiation of ESL. Thus, an earlier start of this therapy leads to a higher probability of successful interruption of SE. A better response of SE when therapy is started early has already been shown for other ASMs, such as lacosamide.[28,29]

Our study has several limitations. The data presented are based on a moderate sample size from a large epilepsy register. This limitation is due to the challenge of recruiting patients with SE. Recent studies investigating novel ASMs have generally included a similar or even lower number of patients.[28,29] Subgroup analysis of other aetiologies, excluding poststroke epilepsy, temporal lobe epilepsy, and epilepsy after encephalitis, could not be performed due to the small size of the cohort. In addition, residual confounding by unmeasured variables in the logistic regression analysis was possible. In our study, only remote symptomatic aetiologies of SE were included. Therefore, the results cannot be extrapolated to the treatment of acute symptomatic SE, which is a prevalent condition. Future studies on a more heterogeneous population are needed.

5 | CONCLUSION

Eslicarbazepine acetate may be considered as adjunctive therapy for the treatment of refractory SE, especially in patients with poststroke epilepsy. If this decision is made early, the chances to interrupt SE are possibly higher. In patients receiving ESL for the treatment of SE, regular laboratory controls are required to detect possible hyponatraemia. To achieve a higher level of evidence for the effect and safety of ESL in controlling SE, further studies on larger patient populations with randomized double-blind designs are necessary.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. What is the mechanism of action of eslicarbazepine?
   A. SV2A agonist
   B. Sodium channel blocker
   C. AMPA antagonist
2. Which antiseizure medications act via slow inactivation of sodium channels?
   A. Levetiracetam and brivaracetam
   B. Lamotrigine and phenytoin
   C. Lacosamide and esclicarbazepine
3. What is the level of evidence for eslicarbazepine in the treatment of status epilepticus?
   A. Level of randomized control studies (level A/B)
   B. Level of observational studies (level C)
   C. Level of expert opinion (level D)

Answers may be found in the supporting information.