Accepted Manuscript

Adverse Effects of Status Epilepticus and the Treatment Strategies - A Literature Review

Maneet Matharu, Samyukta Kumari

To appear in: *Journal of Neoteric Life Science*

Received Date: 06 February 2024

Accepted Date: 13 February 2024

Please cite this article as:

Matharu M., Kumari S. Adverse Effects of Status Epilepticus and the Treatment Strategies - A Literature Review. *JNL*. 2024;2(1):23-48.

Adverse Effects of Status Epilepticus and the Treatment Strategies - A Literature Review

Author name: Matharu M.

Author affiliation: ADI Intellect, 400 Tradecenter Dr, Woburn, MA 01801, United States.

Corresponding author details

Name: Kumari S.

Address: ADI Intellect, 400 Tradecenter Dr, Woburn, MA 01801, United States.

Phone: +91-8876248346

Email: samyuktak98@gmail.com

Abstract

Purpose: Status epilepticus (SE) is a neurological emergency characterized by a prolonged seizure lasting for more than 30 minutes or a person having multiple seizures with no recovery between them. The occurrence of more severe adverse events (AEs) may aggravate the condition and raise the mortality rate. This literature review is focused on reporting the AEs of SE and standard treatment approaches.

Methods: For this literature review, we have identified 78 articles via comprehensive searching using the PubMed database, of which 59 were selected.

Discussion: Neurological dysfunction was reported as the most common outcome among patients with SE. The high mortality rate was mainly due to co-morbidities associated with the disorder. Other AEs reported in the patients with SE were respiratory failure, hypotension, septic shock, renal failure, and rhabdomyolysis. Convulsive SE (CSE) is a life-threatening condition mostly present in pediatric patients, which is characterized by prolonged tonic-clonic seizures and always requires a medical emergency. In terms of seizures, elders are more prone than the younger ones. The refractory SE (RSE) and super-refractory SE (SRSE) conditions increase hospitalization and the risk of mortality.

Conclusion: In conclusion, SE conditions can cause serious AEs, which could lead to a high mortality rate. This review article highlights the need for regular patient follow-ups. Moreover, further research and randomized controlled studies are required to develop an effective treatment for SE.

Keywords: Status epilepticus, adverse effects, neurological, mortality, treatment.

Introduction

Status epilepticus (SE) is a life-threatening neurological disorder in which seizures last for more than 30 minutes, or a person may experience more seizures without recovery between them.[1-2] It is mainly caused by brain trauma, infections, cerebrovascular disorders, epilepsy syndromes, and treatment with low concentrations of the antiepileptic drug.[2]

The symptoms of the SE depend upon its types, i.e., convulsive SE and non-convulsive SE. In convulsive SE, patients mostly experience limb stiffness, jerking motions, drooling, rapid eye movements, and grunting sounds. In contrast, in non-convulsive SE, patients usually experience amnesia, confusion, clouding of consciousness, unusual behavior, daydreaming, and speaking problems.[3-5]

Globally, the incidence of SE is around 50 patients per 100,000 population per year. By age group, SE is more prevalent in neonates and infants than in the elderly adult population. The incidence of SE is around 150 patients per 100,000 population in the age group of below one year, <25 per 100,000 patients in the age group 1-5 years, and >50 patients per 100,000 in the age group of above 40 years. If SE is left unattended or delayed in its course of action, it may result in higher morbidity and mortality rates. Globally, the mortality rate of SE is around 2.5%.[6]

An intravenous lorazepam or an injectable midazolam is an effective early treatment for 64–73% of cases of SE.[7] Although high-class randomized studies are lacking, intravenous clobazam may be a helpful substitute.[8] When it is not possible to administer other benzodiazepines intravenously or intramuscularly to children, buccal midazolam can be used as a substitute.[7]

Around 30% of SE patients show resistance against the primary treatment,[9] and some patients delay the treatment after diagnosis, which increases the chance for the development of adverse

effects (AEs) such as metabolic disorder, thrombotic thrombocytopenic purpura, eclamptic seizures, multi-organ dysfunctions, cardiac issues, and respiratory and permanent neurological damage.[10] Moreover, the AEs associated with SE disorder can lead to morbidity and mortality. Therefore, this literature review summarizes the AEs of SE and known treatment strategies.

Methods

This literature review was performed to describe the AEs of SE and treatment strategies based on already published articles. We identified 78 articles via comprehensive searching using the PubMed database and selected 59 relevant published articles for this review. To create a search strategy, the following terms were used: “status epilepticus OR SE”, “causes AND status epilepticus”, “epidemiology AND status epilepticus”, prevalence AND status epilepticus”, “status epilepticus AND mortality”, “status epilepticus complication”, “adverse effects of status epilepticus”, “guidelines for prevention AND status epilepticus”, “current treatment for status epilepticus”, “future treatment against status epilepticus”, “development of drug for status epilepticus”, and “new treatment for status epilepticus”. The search was not limited by period. All the prospective or retrospective studies were included, where the main focus was epidemiology, prevalence, mortality, AEs, and treatment options or strategies. The crucial data from selected studies were extracted into a separate bibliographic report.

Discussion

Adverse Effects of Status Epilepticus

Status epilepticus has become a primary public health concern due to the significant morbidity and mortality rates and associated AEs such as cognitive impairment, permanent neurological deficits, and subsequent epilepsy. Various risk factors significantly affect the outcomes of SE or sometimes increase the mortality rate. The AEs are presented below in **Figure1** and summarized in **Table 1** and **Table** 2**.**

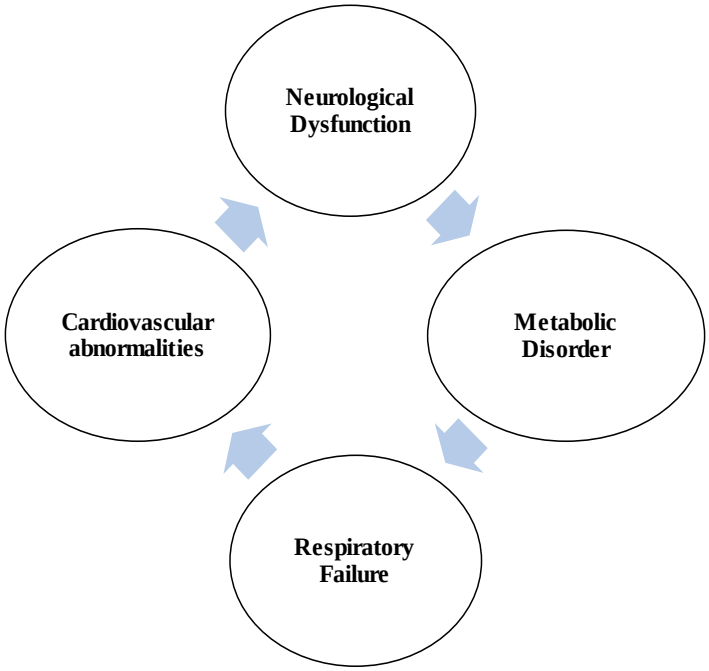

Figure 1 Adverse Effects Associated with Status Epilepticus

Neurological deficit is a persistent AE reported in children because seizures directly affect the brain system when they persist for a long time.[11] Cerebral edema occurs when water starts accumulating in the intra or extracellular spaces, which stops the oxygen circulation in the brain and results in brain damage.[12, 13] Therefore, cerebral edema increases fatality in SE patients.[14]

This was reported in 5 children with SE; 4 children were reported to have brainstem dysfunction and cytotoxic edema with cerebral herniation, while 1 child had laminar necrosis. All children died due to severe brain swelling.[15]

Seizures activity for more than 30 minutes is the first sign of SE condition, which leads to neurological problems or sometimes damages the neurological system if seizures do not end immediately. The commonly reported neurological problems (>2%) were epilepsy (14.5%), speech impairment (10%), motor impairment (10%), and vision impairment (2.7%; **Figure**).[16]

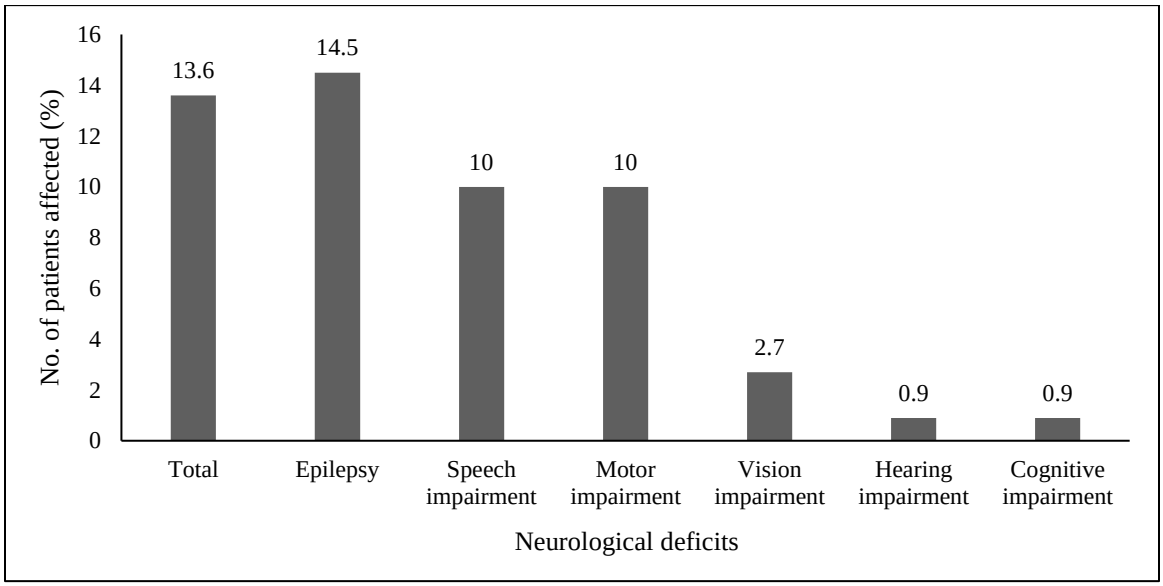

Figure 2 Common Neurological Problems in Children[16]

A study was conducted to ascertain an appropriate dosage of ganaxolone for patients with refractory SE (RSE) and to gather preliminary information regarding its safety and effectiveness. The study involved the enrolment of 17 patients in total. 15 (88%) reported 61 AEs, 23 (38%) of which were thought to be related to the treatment. Sedation was one of the two serious AEs of the treatment. There were 10 serious AEs reported by 6 (35%) patients. Two were considered to be related to the treatment (sedation). The eight serious AEs that were not related to treatment included single events in 2 (12%) patients (sepsis and perforated bowel), two events (respiratory

depression and death from life support withdrawal) in 1 (6%) patient, and four events (multiple fractures, fall, loss of consciousness, and pneumothorax) in 1 (6%) patient.[17]

A study was conducted to identify the risk factors determining outcomes in 92 children with SE aged 1 month to 12 years. Of 92 patients, 87 cases were analyzed, of which 74 (85%) recovered, 5 (6%) developed neurological sequelae, 13 (14%) died, and 5 (6%) were discharged with medical help. Of these patients, 25 (27%) had remote causes linked to SE, 18 (20%) had acute CNS infection, 17 (19%) had febrile seizure, and 15 (16%) had cryptogenic or idiopathic SD. The risk factors that significantly ($p<0.05$) affected the SE outcome were decompensated shock, hypoxia, acidosis, and respiratory failure.[18] Few other studies also reported risk factors associated with the poor functional outcome of SE, such as acute symptomatic etiology ($p<0.001$), old age ($p=0.036$), seizure ($p=0.043$), burst suppression ($p=0.016$), and periodic discharge during initial EEG ($p<0.0001$).[19, 20]

Convulsive SE (CSE) is a life-threatening condition mostly present in pediatric patients, which is characterized by prolonged tonic-clonic seizures and always requires a medical emergency. This was reported by a cohort study conducted on 70 children with SE in the children's hospital at Cairo University, Egypt. Twenty-six (37%) patients reported mortality, and 15 (21%) and 17 (24%) had a severe and moderate disability due to refractory CSE, respectively. Therefore, the refractory CSE was considered a significant predictor of morbidity and mortality in SE patients.[21] Another study reported recurred seizure (16%), mental retardation (16%), and mental retardation along with seizures (16%) in the children with CSE. The mortality rate was 22% due to acute symptomatic (11%), febrile (3%), progressive encephalopathy (7%), and idiopathic (1%).[19] It was also reported that acute bacterial meningitis can be a possible predictor of the first

episode of CSE in children.[22] Neuropsychological impairments in the infants started early, within 6 weeks, and were present later for 1 year post CSE.[23]

In non-convulsive SE (NCSE), patients have an absence of prolonged seizures. De novo SE patients are more likely to develop NCSE and have poorer outcomes. This was observed in a retrospective study, which aimed to assess the AEs of 87 patients with SE admitted to intensive care units (ICU) of two hospitals in Hong Kong. Mortality was reported in 18% of patients, and 46% of patients reported poor outcomes on discharge. The most commonly reported effects (>11%) with various etiologies were breakthrough seizure (21%), encephalitis/meningitis (18%), idiopathic (15%), and cerebrovascular accident (12%).[24] In a case study, a 46-year-old male developed new-onset refractory SE (NORSE) due to primary angiitis of the central nervous system (PACNS), which is a very rare form of vasculitis (inflammation of blood vessels). The early diagnosis of PACNS and treatment with immunotherapy can improve the outcome of NORSE. The patient also reported neurophysiological effects such as a state of confusion and frequent non-convulsive seizures. Cerebrospinal fluid (CSF) analysis was proven helpful in diagnosing PACNS, and the findings showed an increased level of protein.[25]

The incidence of SE or prolonged seizures is higher in older than younger populations, which carry a high risk of mortality and morbidity. This was observed in a study that aimed to assess the outcome of SE in 121 patients and risk factors, including age, pre-existing epilepsy, and co-morbidities during the follow-up. The mortality rate was statistically significant among the older population (54%; $p<0.0001$), mainly due to co-morbidities such as stroke, tumor, and infection. Focal, generalized & combined types of epilepsy were reported in 67 (50%), 47 (35%), and 21 (16%) patients, respectively, and 9 (7%) patients had NCSE.[26]

In refractory status epilepticus (RSE) condition, seizures do not respond to treatment therapy and persist for longer than 60 minutes.[27] A retrospective cohort study was conducted on adult patients with NORSE. Eight (40%) of the 20 NORSE patients experienced potential AEs. Super-refractory SE (SRSE) occurred in 15 (75%) patients. Three patients died during SRSE; the median SE duration for the remaining 17 patients was 10 days (IQR 7–25 days). Two patients died within six months of being discharged from the hospital, and five patients died while they were in the hospital.[28]

In SRSE condition, SE continues for more than 24 hours after the onset of treatment. The SRSE condition increases mortality and morbidity rates and requires immediate treatment.[29-32] A retrospective analysis was conducted in 5 patients with SRSE to assess the clinical symptoms and associations between clinical characteristics of patients in India. Out of 5 patients, 4 had ventilator-associated pneumonia, 2 had metabolic disturbance, 2 died due to increased cerebrospinal fluid (CSF) protein, and another 1 died due to sepsis.[33] A few other cases of SRES revealed morbidities like pneumonia, sepsis, bilateral brain abnormalities, 5-8 seizures per day, and residual neurological deficits.[34, 35]

Rhabdomyolysis (severe muscle damage) was also observed in the patients with SE. This was confirmed by one case study of a 21-year-old man who was hospitalized for SE and had increased uric acid in his blood. He was diagnosed with rhabdomyolysis due to SE and developed acute kidney failure later.[36]

Table 1 Adverse Effects Associated with Status Epilepticus

Study Author	No of patients	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
Myers KA, et al[15]	388	Neurological deficit (4.1%)	N/A	N/A	N/A	N/A	2.3%
Prins A, et al[16]	5	Cerebral edema (100%)	N/A	N/A	N/A	N/A	100%
Vaitkevicius H[17]	17	N/A	N/A	Respiratory depression, pneumothorax	N/A	Sedation, sepsis, perforated bowel, multiple fractures, fall, loss of consciousness	5.9%
Thandavarayan M, et al[18]	92	Neurological sequels (14%)	N/A	Hypoxia, respiratory failure	Decompensated shock	N/A	14%
Uzair M, et al[19]	73	Mental retardation along with seizures (17%), seizure recurrent (16%)	N/A	N/A	N/A	N/A	22%
Kang BS, et al[20]	120	Simple partial and complex partial seizures, absence, myoclonic seizure type (40%), generalized convulsive (40%), non-convulsive SE in coma (20%)	N/A	N/A	N/A	N/A	30.7%
Halawa EF, et al[21]	70	Refractory CSE	N/A	N/A	N/A	N/A	37%
Martinos MM, et al[23]	54	Prolonged febrile seizures (50%), non-febrile CSE (50%)	N/A	N/A	N/A	N/A	N/A
Lui HK, et al[24]	87	Breakthrough seizure (21.0%), encephalitis/meningitis (18.3%), cerebrovascular accident (11.5%), hypoxic brain damage (6.9%), traumatic, subdural hemorrhage / subarachnoid hemorrhage	Metabolic cause (10.3%)	Idiopathic (17.8%)		Sepsis (4.6%)	18%
Horváth L , et al[26]	121	Focal (49.6%), generalized (34.8%) & combined types of epilepsy (34.8%)	N/A	N/A	N/A	N/A	53.7%

CSE = convulsive status epilepticus; N/A = not applicable: SE = status epilepticus

Table 2 Adverse Effects Associated with Status Epilepticus – Case Studies

Study Author	Patient's Age (Year)	Adverse Effects					
		Neurological	**Metabolic**	**Respiratory**	**Cardiovascular**	**Other**	**Fatality rate**
Matar RK, et al[25]	46	State of confusion, frequent non-convulsive seizures	N/A	N/A	N/A	N/A	N/A
Valappil AMN, et al[34]	13	Five to eight seizure, bilateral brain abnormalities, visual hallucinations, progressive cerebellar atrophy	N/A	N/A	N/A	Nausea and abdominal pain, small tumor on adrenal gland	N/A
Aroor S, et al[35]	7	Persisting seizures, CSE, residual neurological deficits	N/A	N/A	N/A	N/A	N/A
	7	Spastic quadriparesis, dystonia and choreo-athetoid movements, generalized tonic-clonic, focal seizures	N/A	N/A	N/A	N/A	N/A
	6	Generalized tonic-clonic seizures, cognitive dysfunction, mutism and orokinetic dyskinesia, autoimmune encephalitis	N/A	N/A	N/A	N/A	N/A
Wang L, et al[36]	21	N/A	Rhabdomyolysis, acute kidney failure	N/A	N/A	N/A	N/A

CSE = convulsive status epilepticus; N/A = not applicable

Treatment Options for Status Epilepticus

SE requires rapid treatment to prevent systemic and neurologic pathology.[6] For this, anti-seizure drugs are effective against SE conditions. Including treatment options, initial management of the SE condition is also necessary, which includes checking airway status, blood pressure, cardiac rhythm, circulatory support, maintaining adequate ventilation, and securing IV access in large veins during seizure activity to prevent future medical complications.[37] As various studies identified anti-seizure drugs for the management of SE, discussed below:

Treatment for SE:

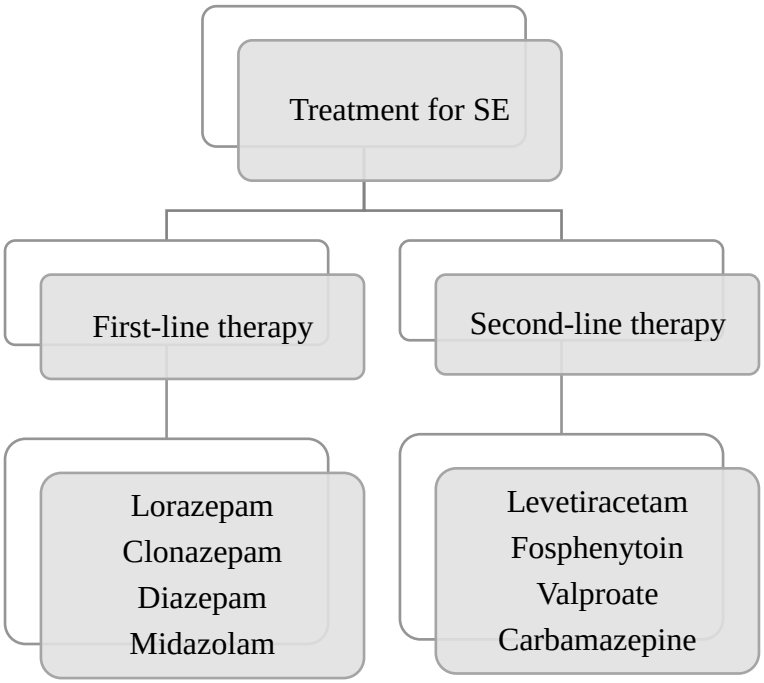

Figure 3 Treatment Option for Status Epilepticus Patients

First-Line Treatment: Benzodiazepines (BZD) such as lorazepam, clonazepam, diazepam, and midazolam are effective drugs used as first-line treatment for prolonged seizures in patients with SE.[38, 39] However, inadequate doses of BZD can lead to the progression of RSE or may increase the tendency of coma in NCSE patients (**Table 3**).[40]

Table 3 FDA-approved Medications among Benzodiazepines for Status Epilepticus

Benzodiazepine	FDA approved for SE	FDA approved for treatment of seizures	Formulation (route)	Recommended Dose
Clonazepam	No (off-label use)	Yes	Disintegrating tablet (oral)	0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg
Diazepam	Yes (rectal gel)	Yes	Gel (rectal)	Children <2 years: Safety and efficacy have not been studied Children 2-5 years: 0.5 mg/kg Children 6-11 years: 0.3 mg/kg Children 12 years or above: 0.2 mg/kg
Lorazepam	Ye; (parenteral only)	No – off-label use (focal seizures)	Parenteral	N/A
Midazolam	No (off-label use)	No – only for sedation	Solution (IV, IM, buccal), Syrup, and Buccal	13-40 kg: 5 mg once >40 kg: 10 mg once

IV = intravenous; IM = intramuscular; N/A = not applicable; FDA = Food and Drug Administration; SE = status epilepticus

Second-Line Treatment: After first-line treatment with BZD drugs, SE patients are treated with second-line therapies, i.e., levetiracetam (LEV), fosphenytoin (FPHT), valproate (VPA), and carbamazepine (CBZ).[41-43] The LEV drug is reported to be more effective and safe for the prevention of recurrent seizures in SE patients than FPHT after following the BZD treatment.[41] It has been demonstrated that intramuscular midazolam, intravenous lorazepam, intravenous diazepam, and intravenous phenobarbital are effective as initial therapies (Level A) in adults with convulsive SE.[44] Including this, IV midazolam is also used as a second-line treatment for pediatric SE. But, when midazolam is compared with FPHT, both drugs have similar efficacy. However, midazolam therapy treats SE in the pediatric population without barbiturate coma therapy (BCT), while FPHT requires BCT. Mechanical ventilation is more frequently reported in midazolam treatment than in FPHT therapy (32.0% vs. 4.7%, $p = 0.01$).[45]

A 21-year-old male diagnosed with SE associated with Wilson disease was admitted to the ICU and treated with lorazepam (0.1 mg/kg IV) and phenytoin (20 mg/kg bolus IV followed by 6 mg/kg

IV as maintenance dosages). The condition improved, and at the 3 month follow-up, the patient showed signs of recovery.[46]

Treatment for RSE:

Benign epilepsy with centrotemporal spikes (BECTS) is a common form of childhood epilepsy, and usually, it can be cured before 16 years. A case study of a 16-year-old girl reported propofol medication-induced RSE in patients with BECTS. Her prolonged seizure, which lasted for about 14 hours, was controlled with diazepam (4 mg/h), propofol (6 mg/kg/h), and VPA (2400 mg/d IV injection). Then, she received VPA (800 mg/d po), oxcarbazepine (600 mg/d po), and LEV (1000 mg/d po). On Day 17, she was discharged without any seizure recurrence during 3 months of follow-up.[47]

Seizure activity in RSE patients can be improved with parenteral phenobarbital (dose 5 to 19.8 mg/kg) without causing any significant complications.[48] In addition, treatment with phenobarbital improved the short-term outcome and decreased the hospital stay of neonates with SE.[49] Phenobarbital terminated the seizure activity faster than parenteral phenytoin ($p<0.0001$). Therefore, phenobarbital can be safely & effectively given to infants for the management of refractory CSE.[50]

Treatment for SRSE:

The SRSE patients who did not respond to IV VPA, LEV, lacosamide, thiopental, and midazolam can be improved with 4 mg or 8 mg dose of perampanel.[51] A case study of a 28-year-old female diagnosed with SRSE recovered with 3 cycles of midazolam (3 mg/kg/hr), 2 cycles of thiopentone (6 mg/kg/hr), methylprednisolone, IV immunoglobulin, and acyclovir.[52]

A female with generalized tonic status epilepticus (TSE) initially failed to respond to the anti-seizure drug therapy (LEV and VPA), and later, her seizure was controlled with lacosamide.[53]

Potential Treatment Options for Future Recommendation

The future-recommended treatment options for the treatment of SE condition are discussed below and presented in **Table 4**.

Brexanolone (SAGE-547) is a formulation of allopregnanolone (neuroactive steroid) which was under development (Phase 3) as adjunctive therapy for the treatment of SRSE condition. It effectively controls seizures in SRSE patients without causing any serious side effects.[54, 55] Ketamine is a strong N-methyl-d-aspartate glutamate receptor antagonist, which was in Phase 3 for the treatment of refractory CSE. The study was completed on 31 March 2020.[56, 57]

Few pre-clinical studies also suggested drugs against SE conditions. Moreover, patients are already treated with LEV as a second-line treatment. However, in a pre-clinical study, when LEV was given via rectal mode to the dogs, this drug showed reasonable control on seizure activity than standard treatments (IV/rectal diazepam and IV phenobarbital).[58] Another pre-clinical study evaluated novel anticonvulsant/neuroprotectant drugs such as scopolamine, memantine, and phenobarbital in the BZD refractory nerve agents-induced SE. This study found that scopolamine terminated the seizure activity more effectively than memantine, while phenobarbital delayed the seizure termination.[59]

Table 4 Future-Recommended Treatment Options for Status Epilepticus

Study Author	Stage of drug development	SE Condition Type	Treatment	Dose	Frequency
Rosenthal ES, et al[55]	Phase 1/2	Super-RSE	Brexanolone	N/A	N/A
Rosati A, et al[56]	Phase 3	Refractory CSE	Ketamine	Initial bolus of 2–3 mg/kg	N/A
				Continuous infusion of 10 µg/kg/min Preceded by a bolus of 1–2 mg/kg	N/A
			MDZ	2–4 µg/kg	Per minute
			BZD	Reduced from 6 to 2 µg/kg Reduced from 6 to 3–4 µg/kg/min	Per minute
Cagnotti G, et al[58]	Pre-clinical	SE	LEV	40 mg/kg rectally	N/A
			IV/rectal diazepam and IV phenobarbital	N/A	Every 8 hours
Jackson C, et al[59]	Pre-clinical	RSE	Scopolamine, memantine, and phenobarbital.	N/A	20 min after SE onset
			Atropine, 2-Pralidoxime, and midazolam	N/A	5, 20, or 40 min after SE onset

BZD = benzodiazepine; CSE = convulsive status epilepticus; LEV = levetiracetam IV = intravenous; MDZ = midazolam; N/A = not applicable; RSE = refractory status epilepticus; SE = status Epilepticus

Conclusion

Status epilepticus can cause severe AEs, which could lead to a high mortality rate. Neurological complications were considered the most common AEs in patients with SE. Other AEs reported were respiratory failure, hypotension, septic shock, renal failure, and rhabdomyolysis. All these complications occur when there is a delay in the treatment after diagnosis or patients cannot respond to the primary treatment. The worst outcomes of SE are linked to old age, etiology, NCSE, and focal status epilepsy. This review article highlights the need for regular patient follow-ups. Additionally, further research and randomized controlled studies are required to develop an effective treatment of SE.

Conflict of interest

The authors whose names are listed in the paper have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this paper.

Data availability statement

The data can be made available upon request from the author.

Acknowledgement

Not applicable.

References

1. Wylie T, Sandhu DS, Murr N. Status Epilepticus. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; May 8, 2023.
2. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. *Epilepsia*. 2012;53 Suppl 4:127-138. doi:10.1111/j.1528-1167.2012.03622.x
3. John Hopkins Medicine. Status epilepticus. hopkinsmedicine.org. Accessed November 20, 2023. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/status-epilepticus
4. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev*. 2014;2014(9):CD003723. doi:10.1002/14651858.CD003723.pub3
5. Sutter R, Rüegg S, Kaplan PW. Epidemiology, diagnosis, and management of nonconvulsive status epilepticus: Opening Pandora's box. *Neurol Clin Pract*. 2012;2(4):275-286. doi:10.1212/CPJ.0b013e318278be75
6. Al-Sofyani KA. An Insight into the Current Understanding of Status Epilepticus: From Concept to Management. *Neurol Res Int*. 2021;2021:9976754. doi:10.1155/2021/9976754
7. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366(7):591-600. doi:10.1056/NEJMoa1107494
8. Madžar D, Geyer A, Knappe RU, et al. Effects of clobazam for treatment of refractory status epilepticus. *BMC Neurol*. 2016;16(1):202. doi:10.1186/s12883-016-0724-y
9. Singh SP, Agarwal S, Faulkner M. Refractory status epilepticus. *Ann Indian Acad Neurol*. 2014;17(Suppl 1):S32-S36. doi:10.4103/0972-2327.128647

10. Cherian A, Thomas SV. Status epilepticus. *Ann Indian Acad Neurol*. 2009;12(3):140-153. doi:10.4103/0972-2327.56312
11. Holmes GL. Cognitive impairment in epilepsy: the role of network abnormalities. Epileptic Disord. 2015;17(2):101-116.
12. Nehring SM, Tadi P, Tenny S. Cerebral Edema. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; July 3, 2023.
13. Mahajan, S. and Bhagat, H. Cerebral oedema: Pathophysiological mechanisms and experimental therapies. *JNACC*, 2016;3(4):pp.S22-S28. doi:10.4103/2348-0548.174731
14. Dibué M, Spoor JKH, Dremmen M, et al. Sudden death in epilepsy: There is room for intracranial pressure. *Brain Behav*. 2020;10(11):e01838. doi:10.1002/brb3.1838
15. Myers KA, McMahon JM, Mandelstam SA, et al. Fatal Cerebral Edema With Status Epilepticus in Children With Dravet Syndrome: Report of 5 Cases. *Pediatrics*. 2017;139(4):e20161933. doi:10.1542/peds.2016-1933
16. Prins A, Chengo E, Mung'ala Odera V, et al. Long-term survival and outcome in children admitted to kilifi district hospital with convulsive status epilepticus. *Epilepsy Res Treat*. 2014;2014:643747. doi:10.1155/2014/643747
17. Vaitkevicius H, Ramsay RE, Swisher CB, Husain AM, Aimetti A, Gasior M. Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial. *Epilepsia*. 2022;63(9):2381-2391. doi:10.1111/epi.17343
18. Thandavarayan M, Ramaswamy S, Bose P, Thirumalaikumarasamy S. Immediate outcome and risk factors determining the outcome of status epilepticus in children attending tertiary care centre. *IJCP*. 2017;4(4):1289-1295. doi:10.18203/2349-3291.ijcp20172516

19. Uzair M, Ibrahim A, Zafar F, Sultan T. Etiology and outcomes of convulsive status epilepticus in children. *Pak J Med Sci*. 2019;35(3):620-623. doi:10.12669/pjms.35.3.120
20. Kang BS, Kim DW, Kim KK, et al. Prediction of mortality and functional outcome from status epilepticus and independent external validation of STESS and EMSE scores. *Crit Care*. 2016;20:25. doi:10.1186/s13054-016-1190-z
21. Halawa EF, Draz I, Ahmed D, Shaheen HA. Predictors of Outcome of Convulsive Status Epilepticus Among an Egyptian Pediatric Tertiary Hospital. *J Child Neurol*. 2015;30(13):1736-1742. doi:10.1177/0883073815579706
22. Heydarian F, Ashrafzadeh F, Rostazadeh A. Predicting factors and prevalence of meningitis in patients with first seizure and fever aged 6 to 18 months. *Neurosciences (Riyadh)*. 2014;19(4):297-300.
23. Martinos MM, Yoong M, Patil S, et al. Early developmental outcomes in children following convulsive status epilepticus: a longitudinal study. *Epilepsia*. 2013;54(6):1012-1019. doi:10.1111/epi.12136
24. Lui HK, Hui KF, Fong WC, Ip CT, Lui HT. De novo status epilepticus is associated with adverse outcome: An 11-year retrospective study in Hong Kong. *Seizure*. 2016;40:42-45. doi:10.1016/j.seizure.2016.06.006
25. Matar RK, Alshamsan B, Alsaleh S, et al. New onset refractory status epilepticus due to primary angiitis of the central nervous system. *Epilepsy Behav Case Rep*. 2017;8:100-104. doi:10.1016/j.ebcr.2017.07.005
26. Horváth L, Fekete I, Molnár M, Válóczy R, Márton S, Fekete K. The Outcome of Status Epilepticus and Long-Term Follow-Up. *Front Neurol*. 2019;10:427. doi:10.3389/fneur.2019.00427

27. Abend NS, Bearden D, Helbig I, et al. Status epilepticus and refractory status epilepticus management. *Semin Pediatr Neurol*. 2014;21(4):263-274. doi:10.1016/j.spen.2014.12.006
28. Gugger JJ, Husari K, Probasco JC, Cervenka MC. New-onset refractory status epilepticus: A retrospective cohort study. *Seizure*. 2020;74:41-48. doi:10.1016/j.seizure.2019.12.002
29. Rai S, Drislane FW. Treatment of Refractory and Super-refractory Status Epilepticus. *Neurotherapeutics*. 2018;15(3):697-712. doi:10.1007/s13311-018-0640-5
30. Samanta D, Garrity L, Arya R. Refractory and Super-refractory Status Epilepticus. *Indian Pediatr*. 2020;57(3):239-253. doi:10.1007/s13312-020-1759-0
31. Vasquez A, Farias-Moeller R, Tatum W. Pediatric refractory and super-refractory status epilepticus. *Seizure*. 2019;68:62-71. doi:10.1016/j.seizure.2018.05.012
32. Tong X, Cai Q, Cao D, Yu L, Sun D, Yang G, Wang J, Li H, Li Z, Wang J, Huang S. Chinese expert recommendations on ketogenic diet therapy for super-refractory status epilepticus. *Acta Epileptologica*. 2022;4(1):1-11. doi:10.1186/s42494-021-00078-6
33. Balakrishnan S, Balasubramanian V. A short case series of super refractory status epilepticus (P3. 381). 2016.
34. Valappil AMN. Case Study: The surprising cause of a case of super-refractory pediatric status epilepticus. consultqd.clevelandclinic.org. Published August 17, 2015. Accessed November 22, 2023. Available at: https://consultqd.clevelandclinic.org/case-study-the-surprising-cause-of-a-case-of-super-refractory-pediatric-status-epilepticus/
35. Aroor S, Shravan K, Mundkur SC, Jayakrishnan C, Rao SS. Super-Refractory Status Epilepticus: A Therapeutic Challenge in Paediatrics. *J Clin Diagn Res*. 2017;11(8):SR01-SR04. doi:10.7860/JCDR/2017/25811.10485

36. Wang L, Hong S, Huang H, Yang M. Rhabdomyolysis following status epilepticus with hyperuricemia: A case report and literature review. *Medicine (Baltimore)*. 2018;97(26):e11281. doi:10.1097/MD.0000000000011281

37. Drislane FW. Convulsive status epilepticus in adults: Management. uptodate.com. Updated March 10, 2022. Accessed November 23, 2023. Available at: https://www.uptodate.com/contents/convulsive-status-epilepticus-in-adults-management

38. Trinka E, Höfler J, Leitinger M, Brigo F. Pharmacotherapy for Status Epilepticus. *Drugs*. 2015;75(13):1499-1521. doi:10.1007/s40265-015-0454-2

39. Ochoa JG, Kilgo WA. The Role of Benzodiazepines in the Treatment of Epilepsy. *Curr Treat Options Neurol*. 2016;18(4):18. doi:10.1007/s11940-016-0401-x

40. Rao SK, Mahulikar A, Ibrahim M, Shah A, Seraji-Bozorgzad N, Mohamed W. Inadequate benzodiazepine dosing may result in progression to refractory and non-convulsive status epilepticus. *Epileptic Disord*. 2018;20(4):265-269. doi:10.1684/epd.2018.0987

41. Nakamura K, Inokuchi R, Daidoji H, et al. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. *Medicine (Baltimore)*. 2017;96(25):e7206. doi:10.1097/MD.0000000000007206

42. Itoh K, Taniguchi R, Matsuo T, et al. Suppressive effects of levetiracetam on neuroinflammation and phagocytic microglia: A comparative study of levetiracetam, valproate and carbamazepine. *Neurosci Lett*. 2019;708:134363. doi:10.1016/j.neulet.2019.134363

43. Friedman J. Emergency management of the paediatric patient with generalized convulsive status epilepticus. *Paediatr Child Health*. 2011;16(2):91-104. doi:10.1093/pch/16.2.91

44. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61. doi:10.5698/1535-7597-16.1.48
45. Nishiyama M, Nagase H, Tomioka K, et al. Fosphenytoin vs. continuous midazolam for pediatric febrile status epilepticus. *Brain Dev*. 2018;40(10):884-890. doi:10.1016/j.braindev.2018.08.001
46. Chakrabarti S & Pan K. A case of status epilepticus: A giant panda dropped the hint. *WAJR*. 2015;22(1):39. doi:10.4103/1115-1474.146150
47. Lu L, Xiong W, Zhang Y, Xiao Y, Zhou D. Propofol-induced refractory status epilepticus at remission age in benign epilepsy with centrotemporal spikes: A case report and literature review. *Medicine (Baltimore)*. 2019;98(27):e16257. doi:10.1097/MD.0000000000016257
48. Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. *Epilepsia*. 2018;59 Suppl 2:193-197. doi:10.1111/epi.14488
49. Harris ML, Malloy KM, Lawson SN, Rose RS, Buss WF, Mietzsch U. Standardized Treatment of Neonatal Status Epilepticus Improves Outcome. *J Child Neurol*. 2016;31(14):1546-1554. doi:10.1177/0883073816664670
50. Burman RJ, Ackermann S, Shapson-Coe A, Ndondo A, Buys H, Wilmshurst JM. A Comparison of Parenteral Phenobarbital vs. Parenteral Phenytoin as Second-Line Management for Pediatric Convulsive Status Epilepticus in a Resource-Limited Setting. *Front Neurol*. 2019;10:506. doi:10.3389/fneur.2019.00506
51. Rahbani A, Adwane G, Jomaa N. Oral Perampanel for the Treatment of Super-Refractory Status Epilepticus. *Case Rep Neurol Med*. 2019;2019:8537815. doi:10.1155/2019/8537815

52. Vyas DD, Dash GK. Supra-recommendation Treatment of Super-refractory Status Epilepticus. *J Epilepsy Res*. 2016;6(1):39-41. doi:10.14581/jer.16008

53. Fernández-Torre JL, Riancho J, Martín-García M, Martínez-de Las Cuevas G, Bosque-Varela P. Tonic status epilepticus in a centenarian woman. *Epileptic Disord*. 2019;21(1):92-96. doi:10.1684/epd.2019.1031

54. Sage Therapeutics. A study with SAGE-547 for super-refractory status epilepticus. clinicaltrials.gov. Updated January 28, 2022. Accessed November 24, 2023. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02477618

55. Rosenthal ES, Claassen J, Wainwright MS, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. *Ann Neurol*. 2017;82(3):342-352. doi:10.1002/ana.25008

56. Rosati A, Ilvento L, L'Erario M, et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01). *BMJ Open*. 2016;6(6):e011565. Published 2016 Jun 15. doi:10.1136/bmjopen-2016-011565

57. Rosati A. Ketamine in Refractory Convulsive Status Epilepticus (KETASER01). clinicaltrials.gov. Updated October 08, 2020. Accessed November 24, 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT02431663

58. Cagnotti G, Odore R, Bertone I, et al. Open-label clinical trial of rectally administered levetiracetam as supplemental treatment in dogs with cluster seizures. *J Vet Intern Med*. 2019;33(4):1714-1718. doi:10.1111/jvim.15541

59. Jackson C, Ardinger C, Winter KM, McDonough JH, McCarren HS. Validating a model of benzodiazepine refractory nerve agent-induced status epilepticus by evaluating the

anticonvulsant and neuroprotective effects of scopolamine, memantine, and phenobarbital. *J Pharmacol Toxicol Methods*. 2019;97:1-12. doi:10.1016/j.vascn.2019.02.006