Adverse Outcomes of Status Epilepticus and the Treatment Strategies: A Literature Review

Matharu M.[1], Kumari S. [1]

[1]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.

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.[1-4] It is mainly caused by brain trauma, infections, cerebrovascular disorders, epilepsy syndromes, and treatment with low concentrations of the antiepileptic drug.[4]

The symptoms of the SE depend upon its types, ie, convulsive SE and non-convulsive SE. In convulsive SE, patients mostly experience limb stiffness, jerking motions, drooling, rapid eye movements, and grunting sounds, while in non-convulsive SE, patients usually experience amnesia, confusion, clouding of consciousness, unusual behavior, daydreaming, and speaking problem.[5-8]

Globally, the incidence of SE is around 50 patients per 100,000 population per year. By age groups, SE is more prevalent in neonates and infants than the elderly adult population. The incidence of SE is around 150 patients per 100,000 population in the age group of 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 delays its course of action, it may result in higher morbidity and mortality rates. Globally, the mortality rate of SE is around 2.5%.[9-14]

Around 30% of SE patients show resistance against the primary treatment[15] and, some patients delay the treatment after diagnosis, which increases the chance for the development of adverse outcomes such as metabolic disorder, thrombotic thrombocytopenic purpura, eclamptic seizures, multi-organ dysfunctions, cardiac issues, and respiratory and permanent neurological damage.[1] Moreover, the adverse outcomes associated with SE disorder can lead to morbidity and mortality. Therefore, this literature review summarizes the adverse outcomes of SE and known treatment strategies.

METHODS

This literature review was performed to describe the adverse outcomes of SE and treatment strategies based on already published articles. We identified 78 articles via comprehensive searching using the PubMed database and selected 74 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 outcome 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 and reviews were included where the main focus was epidemiology, prevalence, mortality, adverse outcomes, and treatment options or strategies. The important data from selected studies were extracted into a separate bibliographic report.

DISCUSSION

Adverse Outcomes of Status Epilepticus

Status epilepticus has become a major public health concern due to the significant morbidity and mortality rates and associated adverse outcomes 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 adverse outcomes are presented below in **Figure1** and summarized in **Table 1** and **Table 2.**

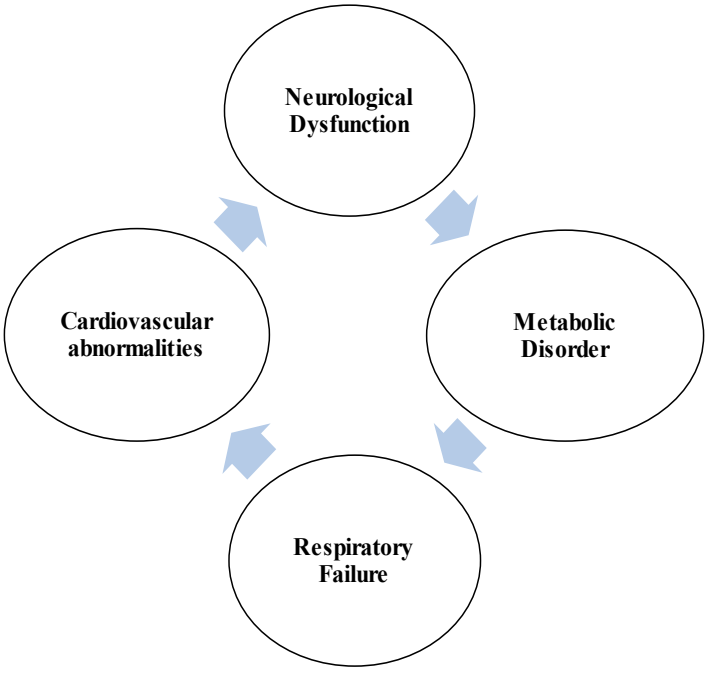


Figure 1. Adverse outcomes associated with SE

Neurological deficit is a very frequent adverse outcome reported in children because seizures directly affect the brain system when they persist for a long time.[16] Cerebral edema occurs when water starts accumulating in the intra or extracellular spaces of the brain which stops the oxygen circulation in the brain and results in brain damage.[17-19] Therefore, cerebral edema increases the fatality in SE patients.[20, 21] 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.[22]

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 did not end immediately. The commonly reported neurological problems (>2%) were epilepsy (4.1%), speech impairment (2.8%), and motor impairment (2.8%; **Figure**).[23]

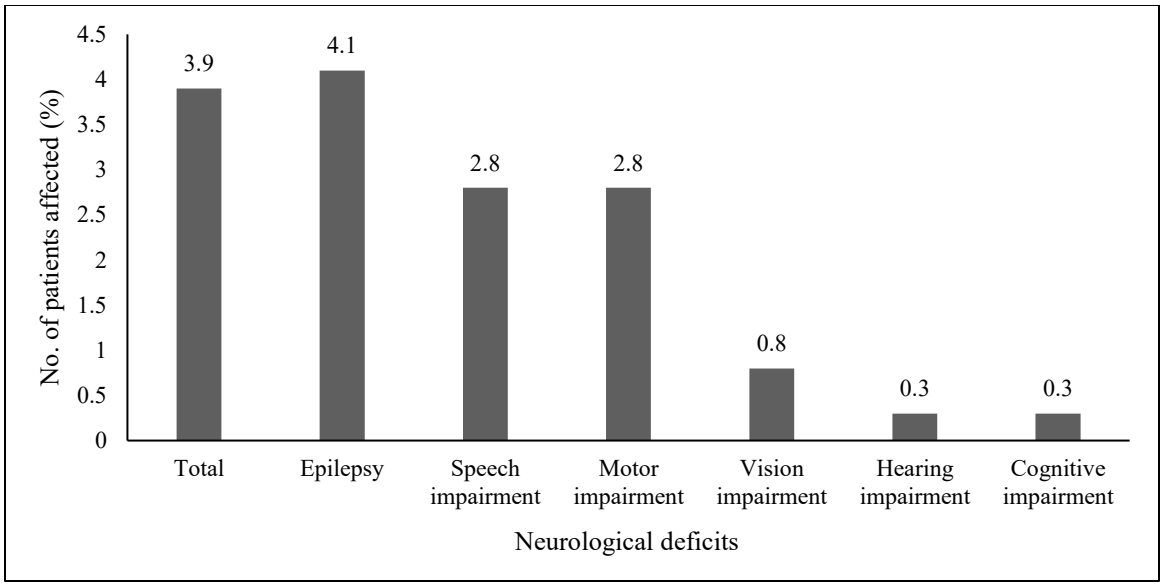


Figure 2. Common neurological problems in children[23]

Including neurological deficit, the risk of neurological deterioration is high in children who have a history of CNS disorder or progressive encephalopathy. This was observed in a retrospective study conducted on 25 patients with SE in a regional hospital in Hong Kong. Of 25 patients, 15 (60%) had a history of neurological abnormality and 11 (44%) had seizure disorders. Neurological deteriorations were observed in 6 children. These included mental retardation or paresis, behavioural problems, learning problems, and memory skills. The duration of SE was more frequent and long in patients who developed adverse outcomes. Adverse outcome was significantly associated with acute or remote aetiology and refractory SE ($p<0.05$). Two patients reported fatalities: one died of wolf syndrome and multiorgan failure, while the second one died of encephalitis.[24]

If seizure activity does not stop within 10 minutes, then it can lead to brain damage and death. A retrospective study aimed to assess the immediate outcome, clinical profile, and risk factors in patients with SE in the tertiary care center, India. Of 30 patients, 9 (30%) died due to >45 minutes of seizure activity ($p<0.001$) and septic shock ($p<0.001$). The most common (>25%) adverse outcomes were generalized tonic-clonic seizure (63%) and partial seizure (27%).[25] Therefore, there is a need to stop the seizure activity as

soon as possible to improve the outcome. In a case study, a 27-year-old woman with SE reported episodes of left facial twitching, decreased sensation to pinprick, neuronal loss, focal perivascular, and intraparenchymal lymphocytic infiltrates. A week later, she died while asleep at home.[26]

Risk factors significantly affect the outcomes of SE or sometimes increase the mortality rate in the patients. A study was conducted to identify the risk factors determining the 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 (5%) developed neurological sequele, and 13 (15%) died mainly due to IE metabolism (50%), acute CNS infection (24%), remote causes (24%), and non-compliances (20%). The risk factors that significantly ($p<0.05$) affected the SE outcome were decompensated shock, hypoxia, acidosis, and respiratory failure.[13, 27-30] 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 ($p<0.0001$).[31, 32]

Convulsive SE (CSE) is a life-threatening condition mostly present in pediatric patients, which is characterized by prolonged tonic-clonic seizures and always require a medical emergency. This was reported by a cohort study conducted on 70 children with SE in the children hospital of Cairo University, Egypt. Twenty-six (37%) patients reported mortality, and 15 (21%) had a severe disability due to refractory CSE. Therefore, the refractory CSE was considered as a significant predictor of morbidity and mortality in the SE patients.[33] Another study reported recurred seizure (16%), mental retardation (16%), and mental retardation along with seizure (16%) in the children with CSE. The mortality rate was 6% due to acute symptomatic (11%), febrile (2%), progressive encephalopathy (7%), and idiopathic (1%).[31] It was also reported that acute bacterial meningitis can be a possible predictor of the first episode of CSE in children.[34] Neuropsychological impairments in the infants started early within 6 weeks and were present later for 1 year post CSE.[35]

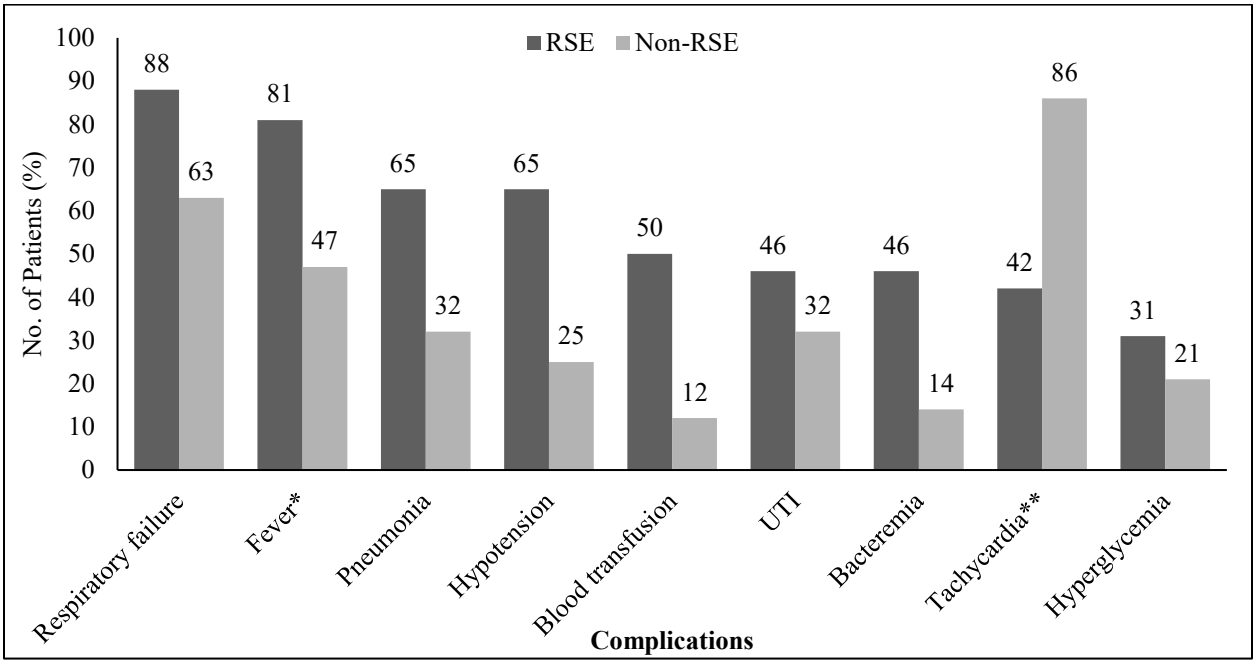
In non-convulsive SE (NCSE), patients have an absence of prolonged seizures. De novo SE patients are more likely to develop NCSE and have poorer outcomes. This was observed in a retrospective study, which aimed to assess the adverse outcomes of 87 patients with SE admitted to ICU of two hospitals in Hong Kong. Mortality was reported in 18% of patients and 46% of patients reported poor outcomes on discharge. The most commonly reported outcomes (>11%) with various etiologies were breakthrough seizure (21%), encephalitis/meningitis (18%), and cerebrovascular accident (12%).[36] In a case study, a 46-year-old male developed new-onset refractory status epilepticus (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 outcomes such as a state of confusion and frequent non-convulsive seizures. Cerebrospinal fluid (CSF) analysis was proven useful in the diagnosis of PACNS, and the findings showed an increased level of protein.[37]

The incidence of SE or prolonged seizures is more in older than younger populations, which carry a high risk of mortality and morbidity. This was observed in a study which 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 (53.7%; $p<0.0001$) 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.[27]

In refractory status epilepticus (RSE) condition, seizures do not respond to treatment therapy and persist for longer than 60 minutes.[1, 38] The RSE condition increases hospitalization and mortality rates. A retrospective cohort study conducted in New York, United States, enrolled 74 patients with SE to assess the incidence, risk factors, and effect on the outcome of RSE. Of 74 patients, 26 (35.1%) were RSE, and 57 (77.0%) were non-

RSE. Seizure duration, length of hospital stay, and the mortality rate was higher in the patients with RSE than non-RSE (20.1 hours vs 2.5 hours; p<0.001, 32.5 days vs. 1.0 days; p<0.001, and 23% vs. 14%; p = 0.31, respectively). The most commonly reported complications (>50%) in patients with RSE were respiratory failure (88%; p = 0.02), fever (81%; p = 0.004), pneumonia (65%; p = 0.004), and hypotension (65%; p < 0.001; **Figure 3**) and in patients with non-RSE were respiratory failure (63%; p = 0.02) and tachycardia (86%; p = 0.56).[39]



*Temperature>38.3°C; **Heart rate>120/min

Figure 3. Commonly reported complications in RSE (%)[39]

In super-refractory SE (SRSE) condition, SE continues for more than 24 hours after the onset of treatment. The SRES condition increases mortality and morbidity rate and requires immediate treatment.[40-43] A retrospective analysis was conducted in 5 patients with SRSE to assess the clinical symptoms and associations between clinical characteristics patients in India. Out of 5 patients, 4 had ventilator-associated pneumonia, 2 had metabolic disturbance, and 2 died due to increased cerebrospinal fluid (CSF) protein and sepsis.[44] A few other cases of SRES revealed morbidities like pneumonia, sepsis, bilateral brain abnormalities, 5-8 seizures

per day, and residual neurological deficits.[45, 46] Acid-base abnormalities are also observed in patients with SE. It occurs when acids and bases in the human body become abnormal that alters the normal pH of the blood. In a retrospectively study conducted in 38 patients with SE, acid-base abnormalities were observed in 32 (84%) patients. The most commonly reported acid-base abnormality was respiratory acidosis (42%).[47]

Rhabdomyolysis (severe muscle damage) was also observed in the patients with SE. This was confirmed by one case study of a 21-year 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.[48]

Table 1. Adverse outcomes associated with Status Epilepticus

Study Author	No of patients	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
Prins A, et al[23]	5	Cerebral edema (100%)	N/A	N/A	N/A	N/A	100%
Myers KA, et al[22]	388	Neurological deficit (4.1%)	N/A	N/A	N/A	N/A	2.3%
Kwong KL, et al[24]	25	Recurrent seizures, mental retardation or paresis, school or learning problems, behavioral problems, difficulty with concentration, memory or linguistic skills	N/A	N/A	N/A	N/A	8%
Gulati S, et al[25]	30	Tonic clonic seizure (63.3%), partial seizure (26.6%), myoclonic seizure (6.6%), not defined (3.3%)	N/A	N/A	Septic shock	N/A	30%
Thandavarayan M, et al[28]	92	Neurological sequels (14%)	N/A	Hypoxia, respiratory failure	Decompensated shock	N/A	14%
Uzair M, et al[31]	73	Mental retardation along with seizures (17%), seizure recurrent (16%)	N/A	N/A	N/A	N/A	22%
Kang BS, et al[32]	120	Simple partial and complex partial	N/A	N/A	N/A	N/A	30.7%

Study Author	No of patients	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
		seizures, absence, myoclonic seizure type (40%), generalized convulsive (40%), non-convulsive SE in coma (20%)					
Halawa EFalawa, et al[33]	70	Refractory CSE	N/A	N/A	N/A	N/A	37%
Martinos MM, et al[35]	54	Prolonged febrile seizures (50%), non-febrile CSE (50%)	N/A	N/A	N/A	N/A	N/A
Lui HK, et al[36]	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[27]	121	Focal (49.6%), generalized (34.8%) & combined types of epilepsy (34.8%)	N/A	N/A	N/A	N/A	53.7%
Mayer SA, et al[39]	83	RSE (35.1%), non-RSE (77.0%)	N/A	Respiratory failure	Hypotension (65%), tachycardia (86%)	Pneumonia (65%)	18.9%
Balakrishnan S, et al[44]	5	N/A	Metabolic disturbance (50%)	N/A	N/A	Ventilator associated pneumonia (80%)	40%
Wijdicks EF, et al[47]	38	N/A	Acid-base abnormality (84%)	Respiratory acidosis (42%)	N/A	N/A	N/A

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

Table 2. Adverse outcomes associated with Status Epilepticus – Case Studies

Study Author	Patient's Age (Year)	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
Liu X, et al[26]	27	Left facial twitching, decreased sensation to pinprick, neuronal loss, focal perivascular and intraparenchymal lymphocytic infiltrates	N/A	N/A	N/A	N/A	N/A
Matar RK, et al[37]	46	State of confusion, frequent non-convulsive seizures	N/A	N/A	N/A	N/A	N/A
Valappil AMN, et al[45]	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[46]	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[48]	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.[9] For this, anti-seizure drugs are effective against SE conditions. Including treatment options, initial management of the SE condition is also necessary which include checking airway status, blood pressure, cardiac rhythm, circulatory support,

maintaining adequate ventilation, and secure IV access in large veins during seizure activity to prevent future medical complication.[49] As various studies identified anti-seizure drugs for the management of SE, discussed below:

Treatment for SE:

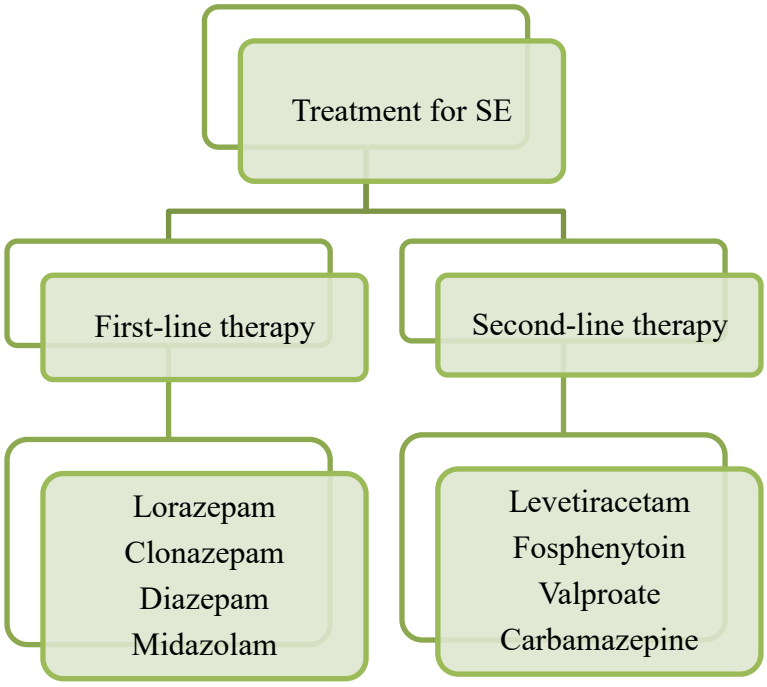


Figure 4. Treatment option for SE patients

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.[50, 51] However, inadequate dose of BZD can lead to the progression of RSE or may increase the tendency of coma in NCSE patients (Table 3).[52] Emergency medical service protocols in California define a few guidelines about the doses of benzodiazepines.

The guidelines suggest that a dose of the BZD drugs (0.1 mg/kg) to be administered to the SE patients should be as per their body weight.[53]

Table 3. The FDA-approved medications among benzodiazepines for SE

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 ie, levetiracetam (LEV), fosphenytoin (FPHT), valproate (VPA), and carbamazepine (CBZ). The LEV drug is reported more effective and safer for the prevention of recurrent seizures in SE patients than FPHT after following the BZD treatment.[54-56] A 20-year-old male with SE was initially treated with IV BZD, ie, 10 mg IV diazepam and IV lorazepam 4 mg (repeated after 5 minutes). When the administration of IV BZD became ineffective then alternative anticonvulsant treatments, ie, phenobarbital and phenytoin were given for the treatment of continuing seizures.[57]

Intravenous phenytoin is used as a second-line treatment against SE, but intramuscular fosphenytoin was well tolerated and delivered faster than IV phenytoin for the treatment of acute seizures and tonic-clonic SE.[58] Including this, IV midazolam is also used as a second-line treatment for pediatric SE. But, when midazolam is compared with FPHT, then both drugs have similar efficacy. Although midazolam therapy treats SE in pediatric population without barbiturate coma therapy (BCT) while FPHT requires BCT. Mechanical ventilation is more frequently reported in midazolam treatment than FPHT therapy (32.0% vs. 4.7%, $p = 0.01$).[59] Including this, fosphenytoin can be given as a maintenance medication at a dose of 18 to 20 mg/kg to the patients with SE. Phenobarbital at a dose of 10 to 20 mg/kg, up to 100 mg/min can be given to the SE

patients with cardiac rhythm disturbances.[47]

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 was improved and at 3 months follow-up, the patient showed signs of recovery.[60]

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 that 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.[61]

Seizure activity in RSE patients can be improved with parenteral phenobarbital (dose 5 to 19.8 mg/kg) without causing any significant complications.[62] In addition, treatment with phenobarbital improved the short-term outcome and decreased the hospital stay of neonates with SE.[63] 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.[64] Hypothermia (temperature: 31-35°C) using an endovascular cooling system appears to be promising as an alternative to other agents as it has demonstrated a marked reduction in seizure activity in RSE patients. However, a further study is required to better understand its safety and efficacy due to the observed adverse events such as shivering and coagulopathy.[65]

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.[66] 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.[67]

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.[68]

Epilepsy Foundation-Recommended Guideline for SE Management[47]

The Epilepsy Foundation has recommended guidelines for the management of SE which are discussed below:

- Make sure diagnosis of SE should be right because SE condition sometimes may be confused with myoclonuscccc, decerebrate posturing, nonepileptic seizures, and other movement disorders. A blood test and electroencephalogram (EEG) may be helpful for the diagnosis of SE.

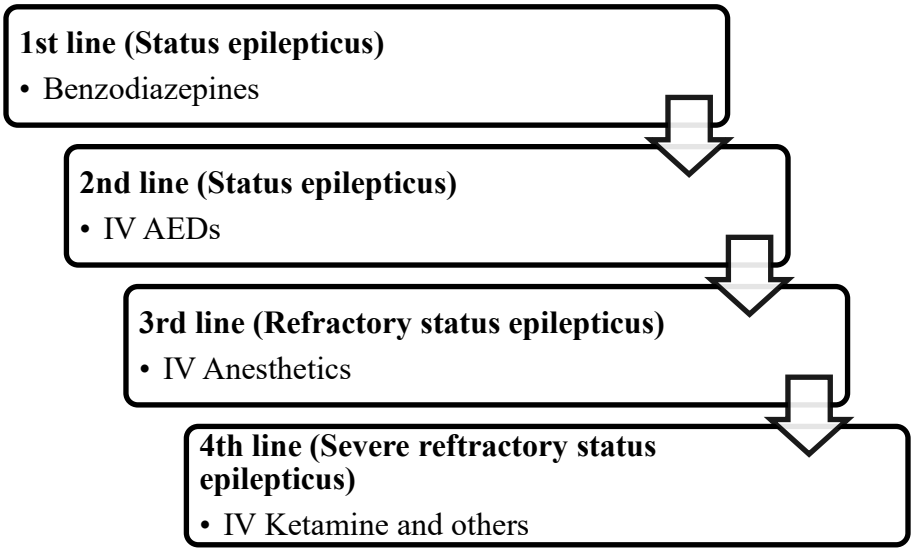


Figure 5. Treatment vision for SE patients

- If SE lasts for more than 30 minutes, BZD drugs are administered. If seizures are continuous then phenytoin or phenobarbital infusions are administered. If seizures reoccur, then lorazepam 4 to 8 mg (0.1-0.2 mg/kg) is given.
- Fosphenytoin can be used as a maintenance therapy with saline at 150 mg PE/min. If patients develop blood pressure and cardiogram, then the dose of fosphenytoin is reduced to 18 to 20 mg/kg. If all the above mentioned treatments are unsuccessful then patients should be admitted to the hospital. The definitive

treatments (midazolam, propofol, or pentobarbital) are administered and EEG is continuously monitored for any neurological complication given and the blood pressure is maintained with inotropic medications.

- Anaesthetic doses are given to the patient for the required time if seizure activity is not controlled. The EEG is monitored for seizure recurrence.

Potential Treatment Options for Future Recommendation

There are various drugs available against SE but are effective only when patients are treated immediately after the seizure activity because prolonged seizure activity can increase neurological dysfunction or permanently damage it. Even after successful treatment, SE can be recurrent, or sometimes, patients do not respond to standard treatment. Therefore, it is necessary to develop an effective treatment against SE, which prevents the recurrence of SE as well as rapidly abrupt seizure activity. For this, few preclinical studies have identified some drugs against refractory SE, which effectively cease the seizure activity. 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 the developing stage (Phase 3) as adjunctive therapy for the treatment of SRSE condition. It effectively controls seizure in SRSE patients without causing any serious side effects.[69, 70] Ketamine is a strong N-methyl-d-aspartate glutamate receptor antagonist which is in Phase 3 for the treatment of refractory CSE, which may be completed by April 2020.[71, 72]

Few preclinical studies also suggested drugs against SE conditions. Moreover, patients are already treated with LEV as a second-line treatment. But in the preclinical study, when LEV was given via rectal mode to the dogs, then this drug showed good control on seizure activity than standard treatments (IV/rectal diazepam and IV phenobarbital).[73] 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.[74]

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[70]	Phase 1/2	Super-RSE	Brexanolone	N/A	N/A
Rosati A, et al[71]	Phase 3	Refractory CSE	Ketamine	Initial bolus of 2–3 mg/kg Continuous infusion of 10 µg/kg/min Preceded by a bolus of 1–2 mg/kg	N/A 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[73]	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[74]	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 adverse outcomes, which could lead to a high mortality rate. The neurological complications were considered the most common adverse outcome in patients with SE. Other adverse outcomes reported were respiratory failure, hypotension, septic shock, renal failure, and rhabdomyolysis. All these complications occur when there is delay in the treatment after diagnosis or patients are unable to 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 follow-up of

patients. Additionally, further research and randomized controlled studies are required to develop effective treatment of SE.

CONFLICT OF INTEREST

The author declares conflict of interest due to being part of the editorial board at the Journal of Neoteric Life Sciences. To mitigate this conflict, the author will abstain from participating in any decision-making processes related to this manuscript and agree to comply with any approach outlined by the Journal of Neoteric Life Sciences to manage this conflict.

DATA AVAILABILITY STATEMENT

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

ACKNOWLEDGEMENT

Not applicable.

REFERENCES

1. Cherian A, Thomas SV. Status epilepticus. Annals of Indian Academy of Neurology. 2009;12(3);140-153.
2. Wylie T, Sandhu DS, Murr N. Status epilepticus. [Updated 2021 Aug 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430686/
3. Treiman DM, Walker MC. Treatment of seizure emergencies: convulsive and non-convulsive status epilepticus. Epilepsy research. 2006;68:77-82
4. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia. 2012;53;127-38.
5. John Hopkins Medicine. Status epilepticus. Conditions and Diseases. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/status-epilepticus
6. Prasad M, Krishnan PR, Sequeira R, et al. Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews. 2014(9).
7. Scholtes FB, Renier WO, Meinardi H. Non-convulsive status epilepticus: causes, treatment, and outcome in 65 patients. Journal of Neurology, Neurosurgery & Psychiatry. 1996;61(1):93-5.
8. 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.
9. Al-Sofyani K. An insight into the current understanding of status epilepticus: From concept to management. Neurology Research International. 2021;2021.
10. Bashiri F, Hamad M, Amer Y, Abouelkheir M. Management of convulsive status epilepticus in children: An adapted clinical practice guideline for pediatricians in Saudi Arabia. Neurosciences. 2017;22(2):146-155
11. Gunawan P, Noviandi R, Samosir S. The correlation between long-lasting serum lactate and brain MRI abnormality in children with status epilepticus. 2022.

12. Huang TH, Lai MC, Chen YS, Huang CW. Status epilepticus mortality risk factors and a correlation survey with the newly modified STESS. Healthcare 2021;9(1570)
13. Gaínza-Lein M, Fernández I, Ulate-Campos A, Loddenkemper T, Ostendorf A. Timing in the treatment of status epilepticus: From basics to the clinic. Seizure. 2019;68:22-30
14. Lu M, Faure M, Bergamasco A, Spalding W, Benitez A, Moride Y, Fournier M. Epidemiology of status epilepticus in the United States: A systematic review. Epilepsy & Behavior. 2020;112:107459.
15. Singh SP, Agarwal S, Faulkner M. Refractory status epilepticus. Ann Indian Acad Neurol. 2014;17(Suppl 1):S32-S36.
16. Holmes GL. Cognitive impairment in epilepsy: the role of network abnormalities. Epileptic Disord. 2015;17(2):101-116.
17. Jha SK. Cerebral Edema and its Management. Med J Armed Forces India. 2003;59(4):326-331.
18. Nehring SM, Tadi P, Tenny S. Cerebral edema. Statpearls. 2019
19. Mahajan S, Bhagat H. Cerebral oedema: pathophysiological mechanisms and experimental therapies. Journal of Neuroanaesthesiology and Critical Care. 2016;3(04):S22-8.
20. Dibué M, Spoor JKH, Dremmen M, et al. Sudden death in epilepsy: There is room for intracranial pressure. Brain Behav. 2020;10(11):e01838.
21. Fontaine C, Jacq G, Perier F, Holleville M, Legriel S. The role of secondary brain insults in status epilepticus: a systematic review. Journal of Clinical Medicine. 2020;9(8):2521.
22. 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.
23. 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 research and treatment. 2014;2014.
24. Kwong KL, Chang K, Lam SY. Features predicting adverse outcomes of status epilepticus in childhood. Hong Kong Medical Journal. 2004;10(3):156-9.

25. Gulati S, Kalra V, Sridhar MR. Status epilepticus in Indian children in a tertiary care center. The Indian Journal of Pediatrics. 2005;72(2):105-8.

26. Liu X, Fortin K, Mourelatos Z. MicroRNAs: biogenesis and molecular functions. Brain pathology. 2008;18(1):113-21.

27. Horváth L, Fekete I, Molnár M, Válóczy R, Márton S, Fekete K. The outcome of status epilepticus and long-term follow-up. Frontiers in Neurology. 2019;10:427.

28. 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. International Journal of Contemporary Pediatrics. 2017; 4(4): 1289-1295.

29. Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, Kothare SV, Alshekhlee A, Koubeissi MZ. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. PloS one. 2012;7(10):e47474.

30. Aydin S, Özdemir C, Gündüz A, Kiziltan ME. Seizures in patients with respiratory disease-a retrospective single center study. Arquivos de Neuro-Psiquiatria. 2020;78:247-54.

31. Uzair M, Ibrahim A, Zafar F, Sultan T. Etiology and outcomes of convulsive status epilepticus in children. Pakistan Journal of Medical Sciences. 2019;5(3):620.

32. 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. Critical Care. 2015;20(1):1-8.

33. Halawa EF, Draz I, Ahmed D, Shaheen HA. Predictors of outcome of convulsive status epilepticus among an Egyptian Pediatric tertiary hospital. Journal of child neurology. 2015;30(13):1736-42.

34. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. The Lancet. 2006;368(9531):222-9.

35. Martinos MM, Yoong M, Patil S, et al. Early developmental outcomes in children following convulsive status epilepticus: a longitudinal study. Epilepsia. 2013;54(6):1012-9.

36. Lui HK, Hui KF, Fong WC, et al. De novo status epilepticus is associated with adverse outcome: an 11-year retrospective study in Hong Kong. Seizure. 2016;40:42-5.

37. Matar RK, Alshamsan B, Alsaleh S, Alhindi H, Alahmedi KO, Khairy S, Baz S. New onset refractory status epilepticus due to primary angiitis of the central nervous system. Epilepsy & behavior case reports. 2017;8:100-4.

38. Abend NS, Bearden D, Helbig I, et al. Status epilepticus and refractory status epilepticus management. Semin Pediatr Neurol. 2014;21(4):263-274.

39. Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Archives of neurology. 2002;59(2):205-10.

40. Rai S, Drislane FW. Treatment of refractory and super-refractory status epilepticus. Neurotherapeutics. 2018;15(3):697-712.

41. Samanta D, Garrity L, Arya R. Refractory and super-refractory status epilepticus. Indian Pediatrics. 2020;57(3):239-53.

42. Vasquez A, Farias-Moeller R, Tatum W. Pediatric refractory and super-refractory status epilepticus. Seizure. 2019;68:62-71.

43. 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):1-1.

44. Balakrishnan S, Balasubramanian V. A short case series of super refractory status epilepticus (P3. 381).

45. Valappil AMN. Case Study: The surprising cause of a case of super-refractory pediatric status epilepticus. Neurosciences. 2015

46. Aroor S, Shravan K, Mundkur SC, et al. Super-refractory status epilepticus: a therapeutic challenge in paediatrics. Journal of clinical and diagnostic research: JCDR. 2017;11(8):SR01.

47. Wijdicks EF, Hubmayr RD. Acute acid-base disorders associated with status epilepticus. InMayo Clinic Proceedings 1994;69(11):1044-1046.

48. Wang L, Hong S, Huang H, et al. Rhabdomyolysis following status epilepticus with hyperuricemia: A case report and literature review. Medicine. 2018; 97(26).

49. Drislane FW. Convulsive status epilepticus in adults: Management. 2022. Available at: https://www.uptodate.com/contents/convulsive-status-epilepticus-in-adults-management

50. Trinka E, Höfler J, Leitinger M, Brigo F. Pharmacotherapy for status epilepticus. Drugs. 2015;75(13):1499-1521.

51. Ochoa JG, Kilgo WA. The role of benzodiazepines in the treatment of epilepsy. Current treatment options in neurology. 2016;18(4):1-1.

52. 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 Disorders. 2018; 20(4): 265-9.

53. Westafer LM. Benzodiazepine dosing for status epilepticus in emergency departments. Acad Emerg Med. 2019;[e-pub].

54. Nakamura K, Inokuchi R, Daidoji H, Naraba H, Sonoo T, Hashimoto H, Tokunaga K, Hiruma T, Doi K, Morimura N. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. Medicine. 2017; 96(25).

55. Itoh K, Taniguchi R, Matsuo T, Oguro A, Vogel CF, Yamazaki T, Ishihara Y. Suppressive effects of levetiracetam on neuroinflammation and phagocytic microglia: a comparative study of levetiracetam, valproate and carbamazepine. Neuroscience letters. 2019;708:134363.

56. Friedman JN. Emergency management of the paediatric patient with generalized convulsive status epilepticus. Paediatr Child Health. 2011;16(2):91-7.

57. Graham CA, Gordon MW. Status epilepticus in accident and emergency: a difficult case. Emergency Medicine Journal. 2001;18(6):492-3.

58. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus. Drug safety. 2000;22(6):459-66.

59. Nishiyama M, Nagase H, Tomioka K, Tanaka T, Yamaguchi H, Ishida Y, Toyoshima D, Fujita K, Maruyama A, Kurosawa H, Uetani Y. Fosphenytoin vs. continuous midazolam for pediatric febrile status epilepticus. Brain and Development. 2018;40(10):884-90.

60. Chakrabarti S, Pan K. A case of status epilepticus: A giant panda dropped the hint. West African Journal of Radiology. 2015;22(1):39.

61. 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. 2019;98(27):e16257.

62. Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. Epilepsia. 2018;59:193-7.

63. Harris ML, Malloy KM, Lawson SN, Rose RS, Buss WF, Mietzsch U. Standardized treatment of neonatal status epilepticus improves outcome. Journal of child neurology. 2016;31(14):1546-54.

64. Burman RJ, Ackermann S, Shapson-Coe A, et al. 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.

65. Corry JJ, Dhar R, Murphy T, et al. Hypothermia for refractory status epilepticus. Neurocritical care. 2008;9(2):189-97.

66. Rahbani A, Adwane G, Jomaa N. Oral Perampanel for the Treatment of Super-Refractory Status Epilepticus. Case reports in neurological medicine. 2019; 2019

67. Vyas DD, Dash GK. Supra-recommendation treatment of super-refractory status epilepticus. Journal of epilepsy research. 2016;6(1):39.

68. Fernández-Torre JL, Riancho J, Martín-García M, Martínez-de las Cuevas G, et al. Tonic status epilepticus in a centenarian woman. Epileptic Disorders. 2019;21(1):92-6.

69. Sage Therapeutics. A study with SAGE-547 for super-refractory status epilepticus. ClinicalTrials.gov Identifier: NCT02477618. 2022. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02477618

70. Rosenthal ES, Claassen J, Wainwright MS, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. Annals of neurology. 2017;82(3):342-52.

71. 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.

72. Meyer Children's Hospital. Ketamine in Refractory Convulsive Status Epilepticus (KETASER01). Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02431663

73. Cagnotti G, Odore R, Bertone I, et al. Open-label clinical trial of rectally administered levetiracetam as supplemental treatment in dogs with cluster seizures. Journal of Veterinary Internal Medicine. 2019;33(4):1714-8

74. Jackson C, Ardinger C, Winter KM, et al. Validating a model of benzodiazepine refractory nerve agent-induced status epilepticus by evaluating the anticonvulsant and neuroprotective effects of scopolamine, memantine, and phenobarbital. Journal of pharmacological and toxicological methods. 2019;97:1-2.