Treatment of Super-Refractory Status Epilepticus: A Review

Juan G. Ochoa, MD[1*], Michelle Dougherty, MD[2],
Alex Papanastassiou, MD[3], Barry Gidal, PharmD[4],
Ismail Mohamed, MD[5], and David G. Vossler, MD[6,7]

[1] University of South Alabama, Mobile, AL, USA
[2] Neurotech LLC, Waukesha, WI, USA
[3] UT Health San Antonio, TX, USA
[4] University of Wisconsin, Madison, WI, USA
[5] Department of Pediatrics, University of Alabama, Birmingham, USA
[6] University of Washington, Seattle, WA, USA
[7] Treatments Committee, American Epilepsy Society, Chicago, IL, USA
*Correspondence: Juan G. Ochoa, University of South Alabama, University Hospital 2451 USA Medical Center Drive, Mobile, AL 36617, USA; e-mail: jochoa@health.southalabama.edu

Abstract

Purpose: Super-refractory status epilepticus (SRSE) presents management challenges due to the absence of randomized controlled trials and a plethora of potential medical therapies. The literature on treatment options for SRSE reports variable success and quality of evidence. This review is a sequel to the 2020 American Epilepsy Society (AES) comprehensive review of the treatment of convulsive refractory status epilepticus (RSE). Methods: We sought to determine the effectiveness of treatment options for SRSE. We performed a structured literature search (MEDLINE, Embase, CENTRAL, CINAHL) for studies on reported treatments of SRSE. We excluded antiseizure medications (ASMs) covered in the 2016 AES guideline on the treatment of established SE and the convulsive RSE comprehensive review of the 2020 AES. Literature was reviewed on the effectiveness of vagus nerve stimulation, ketogenic diet (KD), lidocaine, inhalation anesthetics, brain surgery, therapeutic hypothermia, perampanel, pregabalin (PGB), and topiramate in the treatment of SRSE. Two authors reviewed each therapeutic intervention. We graded the level of the evidence according to the 2017 classification scheme of the American Academy of Neurology. Results: For SRSE (level U; 39 class IV studies total), insufficient evidence exists to support that perampanel, PGB, lidocaine, or acute vagus nerve stimulation (VNS) is effective. For children and adults with SRSE, insufficient evidence exists to support that the KD is effective (level U; 5 class IV studies). For adults with SRSE, insufficient evidence exists that brain surgery is effective (level U, 7 class IV studies). For adults with SRSE insufficient, evidence exists that therapeutic hypothermia is effective (level C, 1 class II and 4 class IV studies). For neonates with hypoxic-ischemic encephalopathy, insufficient evidence exists that therapeutic hypothermia reduces seizure burden (level U; 1 class IV study). For adults with SRSE, insufficient evidence exists that inhalation anesthetics are effective (level U, 1 class IV study) and that there is a potential risk of neurotoxicity. Conclusion: For patients with SRSE insufficient, evidence exists that any of the ASMs reviewed, inhalational anesthetics, ketogenic diet, acute VNS, brain surgery, and therapeutic hypothermia are effective treatments. Data supporting the use of these treatments for SRSE are scarce and limited mainly to small case series and case reports and are confounded by differences in patients' population, and comedications, among other factors.

Keywords

super-refractory status epilepticus, SRSE, treatment effectiveness, children, adults

Introduction

Status epilepticus (SE) is part of a continuum of seizure activity that is classified based on response to treatment. Established SE is defined as one seizure lasting longer than 5 minutes or 2 or more seizures happening back to back with no return to baseline.[1] Refractory status epilepticus (RSE) is defined as SE that does not respond to an adequate dose of a benzodiazepine and administration of one other appropriately chosen antiseizure medication (ASM). Super-refractory status epilepticus (SRSE) is defined as seizure activity greater than 24 hours despite treatment with an anesthetizing ASM.[2] This includes cases in which seizures recur with an attempted withdrawal of the anesthetics.[3,4]

Super-refractory status epilepticus is a neurological emergency with high potential for morbidity and mortality if not recognized early. Approximately 23% to 48% of established patients with SE progress to RSE, and 22% of patients with RSE transition to SRSE.[5] In some cases, SRSE may develop because of inadequate treatment of RSE, but in others, the progression to SRSE is due to the underlying etiology such as infection, inflammatory, or anatomical/structural cause.[4] A small retrospective study of SRSE in children found that 47% had immune-mediated encephalitis.[6]

Super-refractory status epilepticus carries a substantial risk of poor neurological outcomes. In a review of 596 cases, 35% returned to baseline, 13% had a severe neurological deficit, 13% had mild neurological deficit, 4% had undefined deficit, and 35% died.[7] One study found progressive brain atrophy in 19 patients with SRSE who underwent serial imaging.[8]

Uncontrolled seizure activity upregulates N-methyl-D-aspartic acid (NMDA) receptors, resulting in glutamate-mediated increased in intracellular calcium that has been associated with increased excitation, apoptosis, and necrosis of neurons. In addition, γ-aminobutyric acid (GABA) receptors are internalized from the extracellular membrane to the cytosol, reducing the effectiveness of the GABA agonists that target them, such as benzodiazepines and barbiturates.[4]

The treatment of SE was unchanged for decades and included the use of benzodiazepines plus phenytoin/fosphenytoin.[9] The current guidelines include other intravenous (IV) medications such as levetiracetam and valproic acid.[10,11] The treatment of RSE and SRSE is more heterogeneous and lacks support from controlled studies[2,12,13] and American Epilepsy Society (AES) treatment of RSE comprehensive review.[14] This is a very important topic to review since mortality and health care cost is significantly higher for SRSE than RSE and non-RSE due to prolonged hospital stay requiring intensive care unit (ICU) level care.[15]

Methods

Group Constituents

Members of the AES Treatments Committee formed the Super Refractory Status Epilepticus Taskforce to conduct this literature review and assessment.

Scope

In 2016, the AES Guidelines Committee published the revised guidelines for the treatment of SE, which focuses on the initial management of SE.[11] Subsequently, the AES Treatments Committee published the comprehensive review on the treatment of RSE.[14] The current work was conducted as a sequel to these recent publications in order to analyze the existing literature supporting the use of treatments of SRSE not covered in our earlier guidelines and published review and to identify areas for future research. We specifically review the studies on effectiveness of hypothermia, ketogenic diet (KD), vagus nerve stimulation (VNS), brain surgery, inhalational anesthetics, and other ASMs such as topiramate, pregabalin (PGB), lidocaine, and perampanel.

Databases Searched

The group reviewed numerous guidelines published in epilepsy and other areas of neurology and discussed the bibliographic databases, which would likely yield the largest numbers of publications. In order to minimize bias, the Cochrane Handbook of Systematic Reviews of Interventions was used to guide this systematic review.[16] Cochrane Library review authors are encouraged to use MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. The present study used not only MEDLINE, Embase, and the Cochrane Library but also CINAHL (Cumulative Index to Nursing and Allied Health Literature) in order to identify articles published in other journals that might not be captured in the first 3 databases. Embase database search dates include 1974 to May 2020; MEDLINE from May 1, 2020; Cochrane Database from 2005 to May 2020; and Cochrane Central Register of Controlled Trials from 2014 to May 2020.

Search Strategies

Search strategies included "Status Epilepticus"[Major]) AND (super [tiab] OR super-refractory [tiab] OR superrefractory [tiab] OR benzodiazepine-resistant [tiab] OR Midazolam-Resistant [tiab] OR lorazepam-resistant [tiab] OR LOR-resistant [tiab] OR refractory* [tiab] OR prolonged [tiab] OR intractable [tiab] OR treatment-resistant [tiab] OR treatment-refractory [tiab])) OR SRSE [ti] OR RSE [ti]) OR (((epilep* [ti] OR seizure* [ti]) AND (super [tiab] OR super-refractory [tiab] OR superrefractory [tiab] OR benzodiazepine-resistant [tiab] OR Midazolam-Resistant [tiab] OR lorazepam-resistant [tiab] OR LOR-resistant [tiab] OR refractory* [tiab] OR prolonged [tiab] OR intractable [tiab] OR treatment-resistant [tiab] OR treatment-refractory [tiab])) NOT medline [sb])) NOT ((animals[mh] NOT humans[mh]))) NOT ((comment[pt] OR editorial[pt] OR letter[pt] OR in vitro techniques[mh] OR news[pt] OR "Introductory Journal Article" [Publication Type] OR "Ephemera" [Publication Type] OR "Newspaper Article" [Publication Type] OR "Congresses" [Publication Type] OR

Table 1. Evidence of Therapeutic Interventions for SRSE.

Therapeutic intervention	Level of evidence	Comment
Therapeutic hypothermia	Level C: 1 Class II study 3 Class IV studies 13 Case reports	Risk of serious complications including venous thrombosis, pulmonary embolism, infection, and paralytic ileus
Vagus nerve stimulation	Level U: 27 Class IV studies	Potential bias in the systematic review publication
Ketogenic diet	Level U: Children 5 Class IV studies Level U: Adults: 3 Class IV studies	Retrospective and small sample size studies
Lidocaine	Level U: 5 Class IV studies	Most studies are focused on neonatal seizures
Inhalational anesthetics	Level U: 16 Class IV studies	Risk of potential neurotoxicity
Brain surgery	Level U: 7 Class IV studies	Focal resection of a well-localized ictal zone in noneloquent cortex is recommended
Perampanel	Level U: 4 Class IV	Possible role in the treatment of postanoxic SRSE
Pregabalin	Level U: 3 Class IV studies	Risk of induction of myoclonic status epilepticus
Topiramate	Level U: 1 Class IV 6 Case reports	Enteral administration is well tolerated

Abbreviation: SRSE, super-refractory status epilepticus.

comment [ti]))) AND (("2018/09/01"[Date - Entry]: "3000"[Date - Entry]) AND (english[Filter])) Filters: English.

Evidence Classification

Articles were classified as class I (prospective, randomized controlled trials), class II (prospective matched group cohort study), class III (all other controlled trials), or class IV (evidence from uncontrolled studies, case series or reports, or expert opinions) according to the 2017 Edition Clinical Practice Guideline Process Manual of the American Academy of Neurology.[17] Each article was adjudicated by 2 authors or, in the case of disagreement, by 3 authors.

Results

Database searches identified no class I, 1 class II, and multiple class IV studies on the use of other therapeutic trials in the treatment of SRSE. Table 1 depicts a summary of evidence of therapeutic interventions for SRSE.

Therapeutic Hypothermia

Therapeutic hypothermia has been proposed as a therapy for SRSE based on data from animal studies, showing that hypothermia has protective effects against the edema and inflammatory reaction associated with SE and prevented SE-induced neuronal injury in most animals.[18-20] Mild hypothermia has also shown an increase in latency of onset of seizures and SE, as well as decrease in spike frequency in

the rat pilocarpine model.[21] Another experiment on rats with spontaneous SE after electrical stimulation demonstrated a significant reduction of duration and severity of motor of seizures after external cooling enhanced by low-dose benzodiazepine.[22]

Efficacy in SRSE. The HYBERNATUS study was the only randomized controlled trial of therapeutic hypothermia for patients with SRSE.[23] This was a class II study of 268 adults with propofol-resistant SRSE conducted at 11 centers across France. Patients were randomly assigned to receive hypothermia at 32 °C to 34 °C or normothermia plus standard treatment. This study was designed to compare the functional outcome as measured by the Glasgow Outcome Scale after 90 days between the 2 groups. There was no significant difference in the outcomes between the 2 treatment groups. Also, there was a higher number of reported adverse effects in the hypothermia group without significant difference in the 90-day mortality and functional impairment.[23]

One study reviewed 13 articles of case reports with a limited number of patients. There was inconsistent evidence to support the efficacy of hypothermia for SRSE.[24] In a series of 4 adults with SRSE refractory to midazolam or barbiturate, infusions were treated with endovascular cooling to a target temperature. The authors felt that therapeutic hypothermia was successful in aborting SE in all 4 patients. Adverse effects were shivering, coagulopathy, and venous thromboembolism.[25]

A case series of 5 children reported that 1 patient died and 4 children successfully recovered after hypothermia therapy.[26] Another retrospective study included 31 cases of neonates with

hypoxic-ischemic encephalopathy (HIE) who underwent continuous electroencephalogram (EEG) monitoring. About half of them received cooling therapy. There was a significant reduction of the electrographic seizure burden in cooled neonates with moderate HIE.[27]

Therapeutic hypothermia has been associated with serious complications including venous thrombosis, pulmonary embolism, infection, and paralytic ileus.[20] In order to minimize complications, the recommended temperature target has been between 32 °C and 35 °C, and hypothermia duration should be limited to 24 to 48 hours.[28] In patients with SRSE, insufficient evidence exists to support the efficacy of therapeutic hypothermia (level C,1 class II study, 3 class IV studies, and 13 case reports).

Vagus Nerve Stimulation

Vagus nerve stimulation was approved in 1997 by the US Food and Drug Administration (FDA) for adjunctive treatment of drug-resistant focal epilepsy.[29] Experimental studies demonstrated that VNS was capable of seizure termination.[30] Electrical stimulation of the human hippocampus at a rate of 30 Hz produced a significant decrease in the occurrence of epileptiform discharges compared to baseline.[31] There are few case reports and case series in which VNS was implanted acutely for the treatment of SRSE. A recent systematic review of 26 articles and abstracts included 38 patients and demonstrated a lack of evidence for efficacy of VNS in this scenario.[32] Seizure cessation occurred in 28 of 38 cases; the patients were implanted within an average of 18 days. The average time for "response" was 1 week after implantation.[33] This review is problematic as all publications were retrospective and poorly controlled, the concomitant treatment was vaguely described, the electrographic outcome is not available in many cases, and the main author in this review has a significant conflict of interest. Another review article in 2015 reported similar findings with only 2 cases of seizure cessation within 24 hours of stimulation.[33] In conclusion, insufficient evidence exists to support that VNS is effective for the treatment of SRSE (level U, 27 class IV studies).

Ketogenic Diet

Ketogenic diet has been used in the treatment of medically refractory epilepsy in children since 1921 in the United States.[34] How the diet exerts its antiseizure effect is not entirely known, but a number of possible mechanisms of action have been proposed. Ketogenic diet appears to modulate glutamate release[35] and has anti-inflammatory[36,37] and neuroprotective effects,[38] which is of particular importance to its use in SRSE. The largest experience using KD therapy for the treatment of SRSE has been in children, but it has also recently been used in adults.

As the diet involves an energy shift from the use of carbohydrates to lipids, it might induce deterioration in some patients with disorders of fat metabolism. Screening for metabolic disorders as a possible etiology of SRSE and potentially exacerbated by KD is recommended, particularly in children without a clear underlying etiology for RSE.[39]

Enteral feeding is typically used for initiation and maintenance of KD,[40-43] although IV administration of the KD has also been described in patients who would not tolerate enteral feeding, secondary to ileus, or reduced gastrointestinal motility due to coma-inducing medications.[44-46]
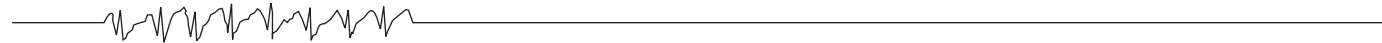
There are several challenges when attempting to achieve ketosis in critically ill patients secondary to concomitant medications. For example, carbohydrate contents from concomitant medications may prevent or delay the onset of ketosis, some IV ASMs contain propylene glycol (ie, IV phenytoin and IV lorazepam), which can produce lactic acidosis, making it difficult to induce ketosis. The use of steroids may delay the onset of ketosis, and propofol infusion in combination with or within 24 hours of KD administration is considered relatively contraindicated due to increased risk of propofol infusion syndrome.[39,47]

Early side effects include metabolic acidosis, hypoglycemia, hyponatremia, and hyperlipidemia, and careful monitoring of blood glucose, serum lipids, liver functions, acid–base status, electrolytes, urine, and serum ketones is recommended.[41,42,48]

Efficacy in SRSE in adults. There is only 1 prospective multicenter study investigating the feasibility, safety, and efficacy of a KD for SRSE in adults. The diet was initiated via gastrostomy tube in 15 patients, with a median duration of SRSE of 10 days before KD initiation. There was no control group. Ketosis was achieved with a median of 2 days after initiation. Of the 14 patients who completed KD treatment, 11 had resolution of SRSE, with a median of 5 days.[48] Thakur et al described 10 adult patients initiated on KD treatment. The median duration of SE before initiation of KD was 21.5 days, and the median number of ASMs used before initiation of KD was 7. Nine patients achieved ketosis, and SE ceased in all patients achieving ketosis, with a median of 3 days. Two patients developed hypertriglyceridemia and 1 had transient acidosis that resolved without interrupting dietary treatment.[47] Data from case reports, case series, and 2 other retrospective studies demonstrated similar efficacy.[46,49,50]

Efficacy of KD in SRSE in children. There are no prospective or randomized trials assessing the efficacy of KD in SRSE in children. Data are available from several retrospective studies and case series in children with SRSE of different etiologies.[41,42,51,52] There is no consensus on the timing of initiation of KD in SRSE, although typically started via the enteral route after days of failed anesthetic treatment. Of particular interest is its use in febrile infection–related epilepsy syndrome (FIRES) where there are several studies suggesting its efficacy.[53,54] Park et al reported 16 children with SRSE, including 10 patients with FIRES who were treated with KD. The patients were in SRSE with a median of 23 days (range, 3-420 days) prior to KD initiation. Ketosis was achieved within 2 to 6 days. Of the 16 patients, 9 achieved seizure freedom, 6 had >50% seizure reduction, and 1 had <50% seizure improvement. Eleven patients reported side effects, with the most common being gastrointestinal

disturbances. Other early side effects included lipid aspiration pneumonia, hypercholesterolemia, elevated liver enzymes, and hypoproteinemia.[53] Nabbout et al reported 10 patients with RSE and SRSE due to FIRES. In 7 patients, seizures stopped within 2 to 4 days following the onset of ketonuria and 4 to 6 days following the onset of the diet. Patients recovered consciousness within 24 to 48 hours following seizure cessation.[52]

The KD has also been used for the treatment of SRSE of different etiologies, including patients with preexisting epilepsy and immune-mediated encephalitis.[51,55] Appavu et al reported on KD treatment in 10 children with SRSE. Median duration of SE prior to KD was 18 days. Nine patients had resolution of SRSE, with a median of 7 days after diet initiation, and 8 patients were weaned off anesthesia within 15 days of diet initiation and within 1 day of achieving ketonuria.[51]

In conclusion, for children with SRSE (level U, 5 class IV studies) and adults (level U, _3_ class IV studies), insufficient evidence exists to support that the KD is effective. Studies are limited by their retrospective nature, small sample size, and concomitant use of other agents, although KD was utilized. The optimal timing for KD initiation remains unknown. The effectiveness of KD with some treatment agents compared to others or for specific etiologies is also unknown. Prospective trials are needed to determine the effectiveness of KD for SRSE.

Lidocaine

Lidocaine, a class Ib anti-arrhythmic and local anesthetic agent, reversibly binds a specific receptor site in the pore of sodium channels of axons, blocking ion movement through the pore. This is not to be confused with ASMs, which enhance the rapid phase of sodium channel inactivation in the central nervous system (eg, phenytoin, carbamazepine, lamotrigine, and others), or lacosamide, which enhances slow inactivation of sodium channels in neurons. The reason for this additive effect of lidocaine likely stems from the drug's amine chain, not present in other commonly used sodium channel–based antiepileptic drugs.[56] Literature on the use of lidocaine in the treatment of SE is focused on its use for neonatal seizures and is beyond the scope of this review.[57] Yamamoto et al[58] in a survey of 194 neonatal ICUs at university hospitals in Japan found that lidocaine was useful in the treatment of neonatal SE.

Data in adults are limited to case reports with mixed efficacy. Cervenka et al[59] reported on the use of IV lidocaine, coadministered with other ASMs including IV anesthesia in a 49-year-old with SRSE. Lidocaine was ineffective in controlling SE. Lidocaine was effective in a case report of a 15-year-old with FIREM. Lidocaine was started at a dose of 1.25 mg/kg/h, resulting in a progressive resolution of SE and EEG improvement from the first day of administration allowing the barbiturate coma to be completely removed in the subsequent days.[60] Lidocaine was also effective in a 23-year-old after failure of pentobarbital coma.[61]

For children and adults with SRSE, insufficient evidence exists to support that the lidocaine is effective (level U, 5 class IV studies).

Inhalational Anesthetics

Inhalational anesthesia (in decades past halothane, and in recent years isoflurane) has been used occasionally for the treatment of SRSE when other treatments have failed. The exact mechanism by which these agents suppress seizures is not completely understood, but clinical experience has demonstrated a very rapid suppression of seizure activity under EEG monitoring. The most common complication is hypotension that may require the use of pressors.[62-64] Isoflurane is highly effective in stopping epileptic activity in up to 92.9% and 94.4% of adult and pediatric patients, respectively. In most patients, the seizures returned after cessation of inhalational anesthetics. In all, 30% inhaled Xenon has been associated with 100% seizure control in all neonates with seizures due to asphyxia.[65] There is a concern for potential toxicity associated with the use of inhalation anesthetics. A case-controlled study reported 8 patients with SRSE treated with anesthetic agents and matched with similar patients not receiving isoflurane. Isoflurane cases showed more magnetic resonance imaging (MRI) hippocampal signal abnormalities compared to control.[66] A case report of 2 patients treated with isoflurane for over 30 days was associated with MRI abnormalities, suggesting a potential neurotoxic effect after prolonged use.[67]

In conclusion, for children and adults with SRSE (level U, 16 class IV studies), insufficient evidence exists to support that anesthetic agents are effective. There is also a concern for potential neurotoxicity, which makes this therapeutic approach less desirable. Indeed, the main goal to treat SRSE aggressively is to prevent potential brain damage.

Brain Surgery

Surgical approaches in the management of SRSE have been reported when first-, second-, and third-line pharmacological management of seizures are ineffective. Different surgical procedures have been used for SRSE, including focal resection, lobar or multilobar resection, functional/anatomical/modified hemispherectomy, corpus callosotomy, and multiple subpial transections with or without focal resection.[68] Surgical interventions have been performed at least 2 weeks after persistent SE in all but one case who was operated within 8 days of the onset.[68,69] Resection has been used primarily in the setting of Rasmussen encephalitis with epilepsia partialis continua.[70,71] In patients with seizure focus in eloquent cortex, such as motor or language areas, resection is not ideal and will result in postoperative neurological deficit. In these cases, it has been shown that multiple subpial transections are effective at decreasing clinical seizure activity.[72] Multiple subpial transection is thought to be effective due to decreased synchronization through the transected cortex preventing spread of seizure from the foci to adjacent cortex.[73] Ma et al reported a case of a 25-year-old woman who had partial anterior callosotomy who presented with persistent generalized SE lasting over 1 month and was finally treated with completion of the corpus callosotomy. She returned to baseline following the procedure.[72]

In summary, focal surgical resection is recommended for patients with a well-localized ictal zone in noneloquent cortex and persistence of convulsive or nonconvulsive SRSE and failure of proper pharmacological therapy (level U, 7 class IV studies). There is no evidence to recommend the use of corpus callosotomy for SRSE.

Perampanel

Perampanel is a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. Increased trafficking of NMDA and AMPA receptor subunits to the synaptic membrane contributes to increased glutamate-mediated excitatory activity. Therefore, targeting AMPA receptors may offer alternative treatments for patients with SRSE.[1] Perampanel is available only as an oral (PO) formulation that can be administered via nasogastric tube in patients with SRSE. The gastrointestinal absorption and consequent bioavailability of perampanel given by enteral feeding tube could be reduced by slowed gastric emptying, impaired intestinal blood flow, and reduced intestinal motility.[74] The literature describing the use of perampanel is limited to small retrospective studies and a few case reports.

Strzelczyk et al described the use of perampanel, administered via nasogastric tube, in 23 patients with SRSE; 6 patients responded. Resolution of SRSE on EEG occurred with a median time of 3 days, with a median dose of 6 mg.[75] Rohracher et al described 12 patients, including 5 patients with SRSE treated with perampanel. Perampanel was given after a median number of 4 ASMs (range: 2-7). Median initial dose was 4 mg titrated up to a median of 12 mg in increments of 2 to 4 mg/d. Of the 12 patients, 2 responded. No adverse cardiorespiratory changes or changes in laboratory parameters related to the administration of perampanel were observed.[76,77]

Beretta et al[78] described 8 postanoxic patients with SRSE. Patients were treated with a single daily dose of perampanel, administered via nasogastric tube. Perampanel was started with a median initial dose of 6 mg (range 6-12 mg). In 6 patients, SRSE resolved within 72 hours following administration of perampanel without changes in comedications. A mild cholestatic injury was observed in 5 patients. Similarly, there are case reports describing resolution of postanoxic SRSE following administration of perampanel.[79,80] It should be recognized that with a very long half-life of approximately 105 hours, if only maintenance dosing is provided once daily (ie, with no loading dose), it will take approximately 525 hours (3 weeks) to achieve a steady-state plasma concentration of perampanel. This makes it hard to interpret studies reporting resolution of SRSE after only 72 hours.

In conclusion, the current data supporting the use of perampanel in the treatment of SRSE are scarce and limited to small case series and case reports and confounded by differences in patients' population, comedications, timing of administration, and dosages of perampanel. Preliminary data suggest it may have a role in the treatment of postanoxic SRSE, although larger prospective studies are needed to assess its utility in this population. For adults and children with SRSE, insufficient evidence exists to support the efficacy of perampanel (level U, 4 class IV studies).

Pregabalin

No class I, II, or III studies have been performed on PGB as a treatment for SRSE. A literature search identified only 3 original articles on this subject. Review articles were excluded. Novy and Rossetti[81] retrospectively found 10 of 230 patients with RSE treated with PO PGB at their center over a 3.5-year span. One patient was treated twice daily (bid) for a total of 11 episodes. Pregabalin was used after other ASMs had failed in all cases, and 9 of 11 episodes were considered refractory. Pregabalin was given PO for simple partial SE via nasogastric tube for patients in stupor/coma. Episodes were very likely controlled in 5 patients, possibly controlled in 3, and not controlled in 3.[81]

Swisher et al reported a retrospective review in which they identified 23 patients with SE related to primary or metastatic brain tumors. In all patients, phenytoin and levetiracetam were used initially, then PGB was given. After administration of all 3 ASMs, SE was controlled in 16 (70%) of 23 patients an average of 24 hours after the addition of the third drug.[82] This same group reported a series of 21 patients who received PGB for the treatment of nonconvulsive SE or seizures. They found PGB was more effective in aborting seizures than nonconvulsive SE (2 patients, 18%). Of the 9 patients with brain tumors, 6 responded, whereas all 4 with posthypoxic seizures did not.[83]

One concern is that de novo myoclonic SE has been reported in patients without epilepsy treated with PGB. Knake et al[84] reported 2 patients with chronic pain with PGB-induced myoclonic SE. Likewise, Baysal Kirac et al[85] described 2 chronic pain patients treated with PGB who developed myoclonic SE.

In conclusion, for the treatment of SRSE, insufficient data exist to support the efficacy of PGB (level U, 3 class IV studies). Induction of myoclonic SE has been reported in patients without epilepsy following administration of PGB.

Topiramate

Topiramate was approved by the FDA in 1997 for both focal and generalized seizures in patients aged 2 years and older. This agent appears to have multiple mechanisms of action that may contribute to its antiseizure activity, including rapid inactivation of voltage-gated sodium channels, augmentation of GABA currents (independent of benzodiazepine receptors), inhibition of carbonic anhydrase, and blockade of excitatory postsynaptic AMPA/kainate receptors.[86]

Several studies have evaluated topiramate use in both neonatal seizures and RSE and SRSE in adult patients. In neonates, Perry et al reported that in infants with EEG confirmed SE, seizures were terminated within 24 hours following an enteral loading dose of 5 mg/kg bid for 2 days. Patients were then started on a maintenance dose of 2.5 mg/kg bid.[87] Lower initial and target maintenance doses of 2 to 3 and 5 to 6 mg/kg/d,

respectively, have also been reported to be efficacious.[88] Although limited anecdotal data suggest benefit in preterm infants (maintenance doses of 3.5-8 mg/kg/d),[89] this ASM is not without potential serious adverse effects in these patients, including irritability, feeding problems, metabolic acidosis, and, more recently, necrotizing enterocolitis.[90] In adults, although several small retrospective reviews and/or case series have evaluated topiramate in RSE, evidence is sparse for SRSE.[91]

For the treatment of RSE, data have been conflicting, with Hottinger and colleagues reporting in a retrospective study that topiramate successfully terminated RSE in over 70% of patients when topiramate was given as the fourth to seventh ASM at doses ranging from less than 400 to 799 mg/d.[92]

Conversely, Madzar et al[93] did not observe any meaningful efficacy of topiramate in RSE.

In one of the largest published data sets, Fechner and colleagues retrospectively evaluated adjunctive use of topiramate, given both PO and via nasogastric tube, in n = 106 patients classified as either RSE (n = 66) or SRSE (n = 40). The authors denoted a positive response to topiramate in those patients whose SE terminated when topiramate was the last ASM added with no additional changes to background ASMs. Using this criterion, the median time from the onset of SE to initiation of topiramate was about 8 days (1-30 days). Initial topiramate doses ranged from 25 to 500 mg, with a median initial dose of 100 mg. Treatment duration ranged between 1 and 70 days, with a median of 12 days and with a median maintenance dose of 400 mg (25-900 mg/d).[86]

Overall, these authors reported a positive response to TPM in 32% of patients with RSE and 20% in patients with SRSE.

Although generally well tolerated, hyperammonemia has been commonly observed. Fechner et al noted this in 35.8% of treated patients, and particularly in those concomitantly receiving valproic acid. Similarly, Hottinger and colleagues reported hyperammonemia in 20% of treated patients.

Mild hyperchloremic acidosis has also been noted, and rarely, pancreatitis. In summary, limited data suggest that enteral administration of topiramate to patients with SRSE may be of some value. Importantly, this agent seems to be generally well tolerated. In conclusion, for the treatment of SRSE insufficient, data exist to support the efficacy of topiramate (level U, 1 class IV study and 6 case reports).

Discussion

Super-refractory status epilepticus is the end of a continuum of sustained seizure activity that is increasingly difficult to treat. The overall approach to SRSE should be similar to that of typical SE and RSE, with the addition of therapy not previously used up to that point. Similar to RSE, no guidelines exist for the treatment of SRSE. Current data derive from retrospective studies, where selection bias likely affected the results. Treatment options are selected at the clinician's discretion based upon their training, personal experience, expert opinion, and published case reports or small uncontrolled studies. To our knowledge, no evidence-based review discussed the broad range of treatments for SRSE and no guidelines exist regarding the optimal approach to treatment of this serious condition. Similar to recent review of RSE by the AES Treatments Committee, we systematically reviewed the world's literature regarding the treatment of SRSE.

When SE persists after the first 24 hours and fail typical treatments, the evidence is more diluted. In desperation to offer a therapy for these patients, clinicians have explored multiple unconventional treatments that lack evidence of efficacy or safety. Among the therapies reviewed here, we found mostly class IV studies. Some therapies carry a significant health risk. For example, therapeutic hypothermia may cause venous thrombosis and pulmonary embolism; inhalation anesthetics may cause neurotoxicity. Other therapies such as lidocaine, PGB, perampanel, and VNS had very little data to support their use. Ketogenic diet has been used mainly in children with class IV evidence. Brain surgery may be reserved for patients with a well-defined super-refractory seizure focus in a noneloquent cortex after other treatments have failed.

Similar to the recent review of RSE by the AES Treatments Committee, we systematically reviewed the world's literature regarding the treatment of SRSE. The methodology used for this comprehensive review has limitations. We used a librarian to search for publications about SRSE and assigned a small number of taskforce members to conduct independent searches for each therapy. As a result, it is possible that each small group did not conduct identical search strategies. In addition, some groups did not track the exact number of articles identified nor catalog the reasons for excluding them beyond relying on the inclusion and exclusion criteria listed in section "Methods." Our methodology and reporting meet most of the Institute of Medicine and PRISMA standards, but given these limitations, we consider this a review rather than a systematic review.

In conclusion, mostly insufficient evidence exists on the efficacy of alternative treatments for SRSE besides the treatments reported in recent comprehensive review of RSE and no guidelines exist regarding the optimal approach to treatment of this serious condition.

research support from Marinus Pharmaceuticals; travel compensation as sub-PI for research study meeting for UCB GmBH. D. Vossler: PI with research support to institution for Accorda, Biogen, Eisai, Pfizer, SK Life Science, UCB, and Vertex; consultant or speaker's bureau for Greenwich Biosciences, Neurelis, Otsuka, SK Life Sciences, Sunovion, and UCB Biosciences.

Funding

ORCID iD

David G. Vossler ⓘ https://orcid.org/0000-0003-4823-0537

References

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus – report of the ILAE task force on classification of status epilepticus. *Epilepsia*. 2015;56(10): 1515-1523. doi:10.1111/epi.13121

2. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134(10):2802-2818. doi:10.1093/brain/awr215

3. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012; 17(1):3-23. doi:10.1007/s12028-012-9695-z

4. Bayrlee A, Ganeshalingam N, Kurczewski L, Brophy GM. Treatment of super-refractory status epilepticus. *Curr Neurol Neurosci Rep*. 2015;15(10). doi:10.1007/s11910-015-0589-2

5. Dubey D, Kalita J, Misra UK. Status epilepticus: refractory and super-refractory. *Neurology India*. 2017;65(7):12. doi:10.4103/neuroindia.NI_958_16

6. Arayakarnkul P, Chomtho K. Treatment options in pediatric super-refractory status epilepticus. *Brain Dev*. 2019;41(4): 359-366. doi:10.1016/j.braindev.2018.11.011

7. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*. 2012;135(pt 8):2314-2328. doi:10.1093/brain/aws091

8. Hocker S, Nagarajan E, Rabinstein AA, Hanson D, Britton JW. Progressive brain atrophy in super-refractory status epilepticus. *JAMA Neurol*. 2016;73(10):1201-1207. doi:10.1001/jamaneurol.2016.1572

9. Fellman DM. Treatment of status epilepticus. *JAMA*. 1994; 271(13):980-981. doi:10.1001/jama.1994.03510370032016

10. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103-2113. doi:10.1056/NEJMoa1905795

11. 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

12. Holtkamp M. Pharmacotherapy for refractory and super-refractory status epilepticus in adults. *Drugs*. 2018;78(3): 307-326. doi:10.1007/s40265-017-0859-1

13. 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

14. Vossler DG, Bainbridge JL, Boggs JG, et al. Treatment of refractory convulsive status epilepticus: a comprehensive review by the American Epilepsy Society Treatments Committee. *Epilepsy Curr*. Published online August 21, 2020. doi:10.1177/1535759720928269

15. Strzelczyk A, Ansorge S, Hapfelmeier J, et al. Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. *Epilepsia*. 2017;58(9): 1533-1541. doi:10.1111/epi.13837

16. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions, 2020. Version 6.1. https://handbook-5-1.cochrane.org/

17. Gronseth GS, Cox J, Gloss D, et al. 2017 Edition clinical practice guideline process manual. *Am Acad Neurol*. Published online 2017.

18. Niquet J, Gezalian M, Baldwin R, Wasterlain CG. Neuroprotective effects of deep hypothermia in refractory status epilepticus. *Ann Clin Translat Neurol*. 2015;2(12):1105-1115. doi:10.1002/acn3.262

19. Wang Y, Liu P-P, Li L-Y, Zhang H-M, Li T. Hypothermia reduces brain edema, spontaneous recurrent seizure attack, and learning memory deficits in the kainic acid treated rats. *CNS Neurosci Ther*. 2011;17(5):271-280. doi:10.1111/j.1755-5949.2010.00168.x

20. Motamedi GK, Lesser RP, Vicini S. Therapeutic brain hypothermia, its mechanisms of action, and its prospects as a treatment for epilepsy. *Epilepsia*. 2013;54(6):959-970. doi:10.1111/epi.12144

21. Yu L, Zhou Y, Chen W, Wang Y. Mild hypothermia pretreatment protects against pilocarpine-induced status epilepticus and neuronalapoptosis in immature rats. *Neuropathology*. 2011;31(2): 144-151. doi:10.1111/j.1440-1789.2010.01155.x

22. Schmitt FC, Buchheim K, Meierkord H, Holtkamp M. Anticonvulsant properties of hypothermia in experimental status epilepticus. *Neurobiol Dis*. 2006;23(3):689-696. doi:10.1016/j.nbd.2006.05.008

23. Legriel S, Lemiale V, Schenck M, et al. Hypothermia for neuroprotection in convulsive status epilepticus. *New Engl J Med*. 2016;375(25):2457-2467. doi:10.1056/NEJMoa1608193

24. Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. Therapeutic hypothermia for refractory status epilepticus. *Can J Neurol Sci*. 2015;42(4):221-229. doi:10.1017/cjn.2015.31

25. Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refractory status epilepticus. *Neurocrit Care*. 2008;9(2):189. doi:10.1007/s12028-008-9092-9

26. Guilliams K, Rosen M, Buttram S, et al. Hypothermia for pediatric refractory status epilepticus. *Epilepsia*. 2013;54(9):1586-1594. doi:10.1111/epi.12331

27. Low E, Boylan GB, Mathieson SR, et al. Cooling and seizure burden in term neonates: an observational study. *Arch Dis Child*

Fetal Neonatal Ed. 2012;97(4):F267-F272. doi:10.1136/archdis-child-2011-300716

28. Rossetti AO. What is the value of hypothermia in acute neurologic diseases and status epilepticus? *Epilepsia*. 2011;52(s8):64-66. doi:10.1111/j.1528-1167.2011.03241.x

29. Morris GL, Gloss D, Buchhalter J, et al. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy. *Neurology*. 2013;81(16):1453-1459. doi:10.1212/WNL.0b013e3182a393d1

30. Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. *Epilepsia*. 1990;31(suppl 2):S7-S19. doi:10.1111/j.1528-1157.1990.tb05852.x

31. Olejniczak PW, Fisch BJ, Carey M, et al. The effect of vagus nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes. *Epilepsia*. 2001;42(3):423-429. doi:10.1046/j.1528-1157.2001.10900.x

32. Dibué-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus – a systematic review. *Brain Stimulat*. 2019;12(5):1101-1110. doi:10.1016/j.brs.2019.05.011

33. Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. VNS for refractory status epilepticus. *Epilepsy Res*. 2015;112:100-113. doi:10.1016/j.eplepsyres.2015.02.014

34. Geyelin HR. Fasting as a method for treating epilepsy. *Medical Recodrs*. 1921;(99):1037-1039.

35. Juge N, Gray JA, Omote H, et al. Metabolic control of vesicular glutamate transport and release. *Neuron*. 2010;68(1):99-112. doi:10.1016/j.neuron.2010.09.002

36. Dupuis N, Curatolo N, Benoist J-F, Auvin S. Ketogenic diet exhibits anti-inflammatory properties. *Epilepsia*. 2015;56(7):e95-98. doi:10.1111/epi.13038

37. Youm Y-H, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med*. 2015;21(3):263-269. doi:10.1038/nm.3804

38. Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. *Neuroscience*. 2007;145(1):256-264. doi:10.1016/j.neuroscience.2006.11.065

39. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open*. 2018;3(2):175-192. doi:10.1002/epi4.12225

40. Arya R, Peariso K, Gaínza-Lein M, et al. Efficacy and safety of ketogenic diet for treatment of pediatric convulsive refractory status epilepticus. *Epilepsy Res*. 2018;144:1-6. doi:10.1016/j.eplepsyres.2018.04.012

41. Nam SH, Lee BL, Lee CG, et al. The role of ketogenic diet in the treatment of refractory status epilepticus. *Epilepsia*. 2011;52(11):e181-e184. doi:10.1111/j.1528-1167.2011.03289.x

42. O'Connor SE, Ream MA, Richardson C, et al. The ketogenic diet for the treatment of pediatric status epilepticus. *Pediatr Neurol*. 2014;50(1):101-103. doi:10.1016/j.pediatrneurol.2013.07.020

43. McDonald TJW, Cervenka MC. Ketogenic diets for adults with highly refractory epilepsy. *Epilepsy Curr*. 2017;17(6):346-350. doi:10.5698/1535-7597.17.6.346

44. Chiusolo F, Diamanti A, Bianchi R, et al. From intravenous to enteral ketogenic diet in PICU: a potential treatment strategy for refractory status epilepticus. *Eur J Paediatr Neurol*. 2016;20(6):843-847. doi:10.1016/j.ejpn.2016.08.004

45. Lin J-J, Lin K-L, Chan O-W, Hsia S-H, Wang H-S; CHEESE Study Group. Intravenous ketogenic diet therapy for treatment of the acute stage of super-refractory status epilepticus in a pediatric patient. *Pediatr Neurol*. 2015;52(4):442-445. doi:10.1016/j.pediatrneurol.2014.12.008

46. Strzelczyk A, Reif PS, Bauer S, et al. Intravenous initiation and maintenance of ketogenic diet: proof of concept in super-refractory status epilepticus. *Seizure*. 2013;22(7):581-583. doi:10.1016/j.seizure.2013.03.007

47. Thakur KT, Probasco JC, Hocker SE, et al. Ketogenic diet for adults in super-refractory status epilepticus. *Neurology*. 2014;82(8):665-670. doi:10.1212/WNL.0000000000000151

48. Cervenka MC, Hocker S, Koenig M, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. *Neurology*. 2017;88(10):938-943. doi:10.1212/WNL.0000000000003690

49. Francis BA, Fillenworth J, Gorelick P, Karanec K, Tanner A. The feasibility, safety and effectiveness of a ketogenic diet for refractory status epilepticus in adults in the intensive care unit. *Neurocrit Care*. Published online November 27, 2018. doi:10.1007/s12028-018-0653-2

50. Wusthoff CJ, Kranick SM, Morley JF, Christina Bergqvist AG. The ketogenic diet in treatment of two adults with prolonged nonconvulsive status epilepticus. *Epilepsia*. 2010;51(6):1083-1085. doi:10.1111/j.1528-1167.2009.02388.x

51. Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. *Seizure*. 2016;41:62-65. doi:10.1016/j.seizure.2016.07.006

52. Nabbout R, Mazzuca M, Hubert P, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). *Epilepsia*. 2010;51(10):2033-2037. doi:10.1111/j.1528-1167.2010.02703.x

53. Park EG, Lee J, Lee J. The ketogenic diet for super-refractory status epilepticus patients in intensive care units. *Brain Dev*. Published online January 9, 2019. doi:10.1016/j.braindev.2018.12.007

54. Peng P, Peng J, Yin F, et al. Ketogenic diet as a treatment for super-refractory status epilepticus in febrile infection-related epilepsy syndrome. *Front Neurol*. 2019;10:423. doi:10.3389/fneur.2019.00423

55. Cobo NH, Sankar R, Murata KK, et al. The ketogenic diet as broad-spectrum treatment for super-refractory pediatric status epilepticus: challenges in implementation in the pediatric and neonatal intensive care units. *J Child Neurol*. 2015;30(2):259-266. doi:10.1177/0883073813516192

56. Yang Y-C, Huang C-S, Kuo C-C. Lidocaine, carbamazepine, and imipramine have partially overlapping binding sites and additive inhibitory effect on neuronal Na+ channels. *Anesthesiology*. 2010;113(1):160-174. doi:10.1097/ALN.0b013e3181dc1dd6

57. Zeiler FA, Zeiler KJ, Teitelbaum J, et al. Lidocaine for status epilepticus in pediatrics. *Can J Neurol Sci*. 2015;42(6):414-426. doi:10.1017/cjn.2015.278

58. Yamamoto H, Aihara M, Niijima S, Yamanouchi H. Treatments with midazolam and lidocaine for status epilepticus in neonates. *Brain Dev*. 2007;29(9):559-564. doi:10.1016/j.braindev.2007. 02.003

59. Cervenka MC, Hartman AL, Venkatesan A, Geocadin RG, Kossoff EH. The ketogenic diet for medically and surgically refractory status epilepticus in the neurocritical care unit. *Neurocritical Care*. 2011;15(3):519-524. doi:10.1007/s12028-011-9546-3

60. Capizzi G, Vittorini R, Torta F, et al. Lidocaine treatment in refractory status epilepticus resulting from febrile infection-related epilepsy syndrome: a case report and follow-up. *Neuropediatrics*. 2015;46(1):65-68. doi:10.1055/s-0034-1389898

61. De Giorgio CM, Altman K, Hamilton-Byrd E, Rabinowicz AL. Lidocaine in refractory status epilepticus: confirmation of efficacy with continuous EEG monitoring. *Epilepsia*. 1992;33(5): 913-916.

62. Kofke WA, Young RS, Davis P, et al. Isoflurane for refractory status epilepticus: a clinical series. *Anesthesiology*. 1989;71(5): 653-659.

63. Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. Modern inhalational anesthetics for refractory status epilepticus. *Can J Neurol Sci*. 2015;42(02):106-115. doi:10.1017/cjn.2014.121

64. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol*. 2004;61(8):1254-1259. doi:10. 1001/archneur.61.8.1254

65. Azzopardi D, Robertson NJ, Kapetanakis A, et al. Anticonvulsant effect of xenon on neonatal asphyxial seizures. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(5): F437-439. doi:10.1136/archdischild-2013-303786

66. Ikeda KM, Connors R, Lee DH, et al. Isoflurane use in the treatment of super-refractory status epilepticus is associated with hippocampal changes on MRI. *Neurocrit Care*. 2017;26(3):420-427. doi:10.1007/s12028-016-0340-0

67. Fugate J, Burns J, Wijdicks EF, et al. Prolonged high-dose isoflurane for refractory status epilepticus. *Anesthesia Analgesia*. 2010;111(6):1520-1524. doi:10.1213/ANE.0b013e3181f6da34

68. Lhatoo SD, Alexopoulos AV. The surgical treatment of status epilepticus. *Epilepsia*. 2007;48(s8):61-65. doi:10.1111/j.1528-1167.2007.01353.x

69. Gorman DG, Shields WD, Shewmon DA, et al. Neurosurgical treatment of refractory status epilepticus. *Epilepsia*. 1992;33(3): 546-549. doi:10.1111/j.1528-1157.1992.tb01707.x

70. Honavar M, Janota I, Polkey CE. Rasmussen's encephalitis in surgery for epilepsy. *DevelopMed Child Neurol*. 1992;34(1): 3-14. doi:10.1111/j.1469-8749.1992.tb08558.x

71. Vining EPG, Freeman JM, Brandt J, Carson BS, Uematsu S.Progressive unilateral encephalopathy of childhood (Rasmussen's syndrome): a reappraisal. *Epilepsia*. 1993;34(4):639-650. doi: 10.1111/j.1528-1157.1993.tb00441.x

72. Ma X, Liporace J, O'Connor MJ, Sperling MR. Neurosurgical treatment of medically intractable status epilepticus. *Epilepsy Res*. 2001;46(1):33-38. doi:10.1016/s0920-1211(01)00252-2

73. Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. *J Neurosurg*. 1989;70(2):231-239. doi:10.3171/jns.1989.70.2.0231

74. Brigo F, Lattanzi S, Rohracher A, et al. Perampanel in the treatment of status epilepticus: a systematic review of the literature. *Epilepsy Behav*. 2018;86:179-186. doi:10.1016/j.yebeh.2018. 07.004

75. Strzelczyk A, Knake S, Kälviäinen R, et al. Perampanel for treatment of status epilepticus in Austria, Finland, Germany, and Spain. *Acta Neurol Scand*. 2019;139(4):369-376. doi:10.1111/ ane.13061

76. Rohracher A, Höfler J, Kalss G, et al. Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit. *Epilepsy Behav*. 2015;49:354-358. doi:10. 1016/j.yebeh.2015.04.005

77. Rohracher A, Kalss G, Neuray C, et al. Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit: a single-center audit of 30 patients. *Epilepsia*. 2018;59(suppl 2):234-242. doi:10.1111/epi.14494

78. Beretta S, Padovano G, Stabile A, et al. Efficacy and safety of perampanel oral loading in postanoxic super-refractory status epilepticus: a pilot study. *Epilepsia*. 2018;59(suppl 2):243-248. doi: 10.1111/epi.14492

79. Newey CR, Mullaguri N, Hantus S, Punia V, George P.Super-refractory status epilepticus treated with high dose perampanel: case series and review of the literature. *Case Rep Crit Care*. 2019; 2019:3218231. doi:10.1155/2019/3218231

80. Santamarina E, Sueiras M, Lidón RM, et al. Use of perampanel in one case of super-refractory hypoxic myoclonic status: case report. *Epilepsy Behav Case Rep*. 2015;4:56-59. doi:10.1016/j. ebcr.2015.06.007

81. Novy J, Rossetti AO. Oral pregabalin as an add-on treatment for status epilepticus. *Epilepsia*. 2010;51(10):2207-2210. doi:10. 1111/j.1528-1167.2010.02646.x

82. Swisher CB, Doreswamy M, Gingrich KJ, Vredenburgh JJ, Kolls BJ. Phenytoin, levetiracetam, and pregabalin in the acute management of refractory status epilepticus in patients with brain tumors. *Neurocrit Care*. 2012;16(1):109-113. doi:10.1007/ s12028-011-9626-4

83. Swisher CB, Doreswamy M, Husain AM. Use of pregabalin for nonconvulsive seizures and nonconvulsive status epilepticus. *Seizure*. 2013;22(2):116-118. doi:10.1016/j.seizure.2012.11.004

84. Knake S, Klein KM, Hattemer K, et al. Pregabalin-induced generalized myoclonic status epilepticus in patients with chronic pain. *Epilepsy Behav*. 2007;11(3):471-473. doi:10.1016/j.yebeh. 2007.06.012

85. Baysal Kirac L, Aydogdu I, Acarer A, et al. Myoclonic status epilepticus in six patients without epilepsy. *Epilepsy Behav Case Rep*. 2013;1:10-13. doi:10.1016/j.ebcr.2012.10.003

86. Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. *Epilepsia*. 2019; 60(12):2448-2458. doi:10.1111/epi.16382

87. Perry MS, Holt PJ, Sladky JT. Topiramate loading for refractory status epilepticus in children. *Epilepsia*. 2006;47(6):1070-1071. doi:10.1111/j.1528-1167.2006.00564.x

88. Kahriman M, Minecan D, Kutluay E, Selwa L, Beydoun A. Efficacy of topiramate in children with refractory status epilepticus. *Epilepsia*. 2003;44(10):1353-1356. doi:10.1046/j.1528-1157. 2003.11803.x

89. Riesgo R, Winckler MI, Ohlweiler L, et al. Treatment of refractory neonatal seizures with topiramate. *Neuropediatrics*. 2012; 43(06):353-356. doi:10.1055/s-0032-1327771

90. Courchia B, Kurtom W, Pensirikul A, Del-Moral T, Buch M. Topiramate for seizures in preterm infants and the development of necrotizing enterocolitis. *Pediatrics*. 2018;142(1):e20173971. doi:10.1542/peds.2017-3971

91. Brigo F, Bragazzi NL, Igwe SC, Nardone R, Trinka E.Topiramate in the treatment of generalized convulsive status epilepticus in adults: a systematic review with individual Patient Data Analysis. *Drugs*. 2017;77(1):67-74. doi:10.1007/s40265-016-0672-2

92. Hottinger A, Sutter R, Marsch S, Rüegg S. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. *CNS Drugs*. 2012;26(9):761-772. doi:10.2165/11633090-000000000-00000

93. Madžar D, Kuramatsu JB, Gerner ST, Huttner HB. Assessing the value of topiramate in refractory status epilepticus. *Seizure*. 2016; 38:7-10. doi:10.1016/j.seizure.2016.03.003