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UPDATE

Advances in the management of generalized convulsive status epilepticus: what have we learned?

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Convulsive status epilepticus is the most serious manifestation of an epileptic diathesis. In the early stages (5–30 min), there exists class A evidence to support the efficacy of benzodiazepines as first-line treatment. As status epilepticus progresses into the later stages, the evidence for treatment becomes less robust until we are depending upon short case series and case reports for the treatment of refractory status epilepticus. However, the past year saw the publication of three randomized controlled trials in the setting of benzodiazepine-resistant established convulsive status epilepticus: the EcLiPSE and ConSEPT studies, compared levetiracetam to phenytoin in children; and the ESETT study compared fosphenytoin, levetiracetam and sodium valproate in adults and children. In addition, the emergence of data from the SENSE study, a multicentre multinational prospective cohort study and the publication of a systematic review and meta-analysis of the mortality of status epilepticus over the past 30 years, has brought the treatment of status epilepticus into sharp focus. In this update we provide a detailed analysis of these studies and their impact on clinical practice. We review contentious areas of management in status epilepticus where a consensus is lacking and advance the case for more research on existing and alternative treatment strategies.

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Introduction

Convulsive status epilepticus (CSE) is a medical emergency with a high mortality and morbidity.[1] Yet, it has suffered from a lack of evidence-based medicine other than in the early stages. Over the past 20 years, there have been a growing number of randomized control studies demonstrating that early interventions in prolonged acute seizures with benzodiazepines in the community can successfully stop seizure activity. Moreover, the landmark

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Veterans Affairs Status Epilepticus study[2] established the primacy of the benzodiazepine lorazepam, over phenytoin alone as first-line treatment of early CSE in hospital. Together, these studies have established the initial treatment of status epilepticus (buccal midazolam in the community followed by an intravenous benzodiazepine, usually lorazepam, on hospital admission). The choice of subsequent treatments has been less clear, but phenytoin and its prodrug fosphenytoin were the accepted standard of care.[3]

The emergence of data regarding the potential efficacy of valproate and levetiracetam in CSE have recently challenged the status quo. Smaller studies have supported their candidacy as viable alternatives to phenytoin, but none of these has had the statistical power to determine best practice. With a lack clear-cut evidence, protocols for the treatment of CSE varied between hospitals and countries with little consensus. Indeed, the ease of use and lack of cardiorespiratory compromise with levetiracetam and valproate had even led to the suggestion of using these agents ahead of benzodiazepines.[4] In this review we have chosen to highlight five studies, out of more than 500 clinical reports/reviews published in 2019, that advance knowledge of the current clinical state and management of CSE.

Systemic review of mortality in convulsive status epilepticus

In 2019, a systematic review and meta-analysis of mortality in CSE in high-income countries between 1990 and 2017,[5] placed present circumstances in sharp relief. In total 61 studies were included (five were of refractory status epilepticus), of which 30 were adult studies with a pooled mortality of 15.9% [95% confidence interval (CI) 12.7 to 19.2]. The pooled mortality in seven paediatric studies was 3.6% (95% CI 2.0 to 5.2). There were six population studies (all ages) identified, with an overall pooled estimated mortality of 13.1% (95% CI 7.2 to 19.0). Importantly, however, comparing three different time periods, employing both linear regression and meta-regression analysis in the paediatric and adult studies, did not demonstrate any significant change in mortality over time. Despite confining the included studies from high-income countries and subdividing studies by age group, there was evidence of very high study heterogeneity ($I^2 > 75\%$). Further subanalysis of all studies and by age (paediatric, adult and all-age) using individual meta-regression by region (North America, Europe and Asia/Oceania), definition of status epilepticus used (seizure duration > 5 min versus any other time period), study design (retrospective versus prospective), setting (ICU versus non-ICU) and time period (1990–99, 2000–09 and 2010–17), did not demonstrate any significant difference in estimated pooled mortality. Finally, a multivariate meta-regression analysis combining all variables separately in adult, paediatric and all-age groups, did not result in a significant reduction in the heterogeneity demonstrated ($I^2 > 75\%$). This study highlights two surprising, but critical findings: (i) the evidence indicates that the hospital mortality of CSE has not altered significantly in the past 30 years; and (ii) the epidemiological studies of CSE, despite its clinical impact, are poor and inconsistent.

SENSE registry for status epilepticus: a prospective observational study

Also in 2019, the SENSE study,[4] a prospective cohort study of status epilepticus between January 2011 and June 2015, included 1049 patients with 1179 status epilepticus episodes of whom 457 were diagnosed as having CSE. Treatment was initiated within 30 min in less than half of the CSE patients. On multivariate analysis, younger age [hazard ratio (HR) 0.89; 95% CI 0.82 to 0.97; $P = 0.01$], lower Rankin score before status epilepticus onset (HR 0.89; 95% CI 0.8 to 0.99; $P = 0.05$), the use of benzodiazepines as initial treatment (HR 9.62%; 95% CI 1.34 to 69.3; $P = 0.04$), a higher cumulative dose of anti-convulsants given within the first 30 min of treatment (HR 1.02; 95% CI 1.01 to 1.03; $P = 0.002$) and shorter latency from status epilepticus onset to treatment initiation (HR 0.89; 95% CI 0.82 to 0.97; $P = 0.04$) independently predicted a shorter time to status epilepticus cessation within the first hour of treatment. Overall mortality was 9.4% (43), of whom 93% (40) had status epilepticus non-cessation within 60 min of treatment initiation ($P < 0.001$). This study highlighted and reaffirmed that CSE needs to be treated early and that benzodiazepines remain the first treatments of choice. Indeed, the large number who were treated late and with non-benzodiazepines may, in part, contribute to the failure to detect a fall in mortality in the past 30 years.

Randomized control trials in convulsive status epilepticus: EcLiPSE, ConSEPT and ESETT

The year 2019 saw the publication of three major randomized trials to address the question of treatment after benzodiazepines. Two, EcLiPSE[6] and ConSEPT,[7] were paediatric open label multicentre studies in which levetiracetam went head-to-head with phenytoin, for the management of established status CSE (30–60 min) and the third, ESETT,[8] was a large, long-awaited, multicentre study in which valproate, levetiracetam and fosphenytoin were compared in CSE in children and adults at 57 centres in the USA.

In the EcLiPSE study,[6] 152 children (aged 6 months to 18 years) were randomized to levetiracetam (40 mg/kg, maximum dose 2.5 g, over 5 min) and 134 to phenytoin (20 mg/kg, maximum dose 2 g, with a maximum infusion rate of 1 mg/kg/min over at least 20 min). The primary outcome was time from randomization to cessation of all visible signs of clinical convulsive activity. Research without prior consent (also known as deferred consent) was used because of the time-crucial management of convulsive status epilepticus—the process of research without prior consent was formally assessed and evaluated in a nested consent study. Final outcome was recorded 14 days after enrolment. The primary analysis was based on a modified intention to treat (mITT).

Status epilepticus was terminated in 106 (70%) in the levetiracetam group and 86 (64%) in the phenytoin group with a median time from randomization to seizure cessation of 35 min in the levetiracetam group and 45 min in the phenytoin group (HR 1.20; 95% CI 0.91 to 1.60; $P = 0.20$). Median time from randomization to start of infusion was 11 min [interquartile range (IQR) 8–15] for levetiracetam and 12 min (8–17) for phenytoin. Secondary outcomes measures such as need for further anticonvulsants for the presenting status epilepticus were comparable [24 (15.8%) in the levetiracetam group, 20 (14.9%) in the phenytoin group; relative risk 1.06 (0.61–1.83); $P = 0.84$; 145 (95%) in the levetiracetam group and 130 (97%) in the phenytoin group had been discharged]. The time from seizure onset to infusion initiation was not given. The study additionally demonstrated that research without prior consent is acceptable and successful with 95% of those randomized and 92% of those treated providing consent.

In the ConSEPT study,[7] carried out at 13 centres in Australia and New Zealand, 234 children aged between 3 months and 16 years with CSE, were enrolled. After failure of appropriate benzodiazepine therapy, patients were randomized to receive phenytoin 20 mg/kg over 20 min or levetiracetam 40 mg/kg over 5 min. The primary outcome was clinical cessation of seizure activity 5 min after the completion of infusion of the first trial drug, assessed at 25 min (phenytoin) and 10 min (levetiracetam), repeated with levetiracetam and phenytoin infusions at 35 min if necessary. If possible, the primary outcome assessment was video-recorded to assess the tone and the presence of jerking, limb, face or eye movements.

The mean age of patients was 3.9 years, with the median length of time of seizure activity before infusion was 73 min (IQR 52–99). Primary outcome was achieved 5 min after infusion in 68 (60%) in the phenytoin group compared to 60 (50%) in the levetiracetam group, $P = 0.16$. There was no evidence of a differential effect of the study drugs in the prespecified subgroups. At 2 h, 62 (54%) in the phenytoin group and 61 (51%) in the levetiracetam group maintained seizure control and did not require further treatment. In the phenytoin group, 42 (37%) received levetiracetam and 48 (40%) of the levetiracetam group received phenytoin for seizure control. Seizure control at 2 h after administration of one or both study drugs was achieved in 89 (78%) in the phenytoin group and 86 (72%) in the levetiracetam group [risk difference –5.8% (95% CI –16.9 to 5.3); $P = 0.31$]. Fifty-three (22%) underwent rapid sequence induction of anaesthesia, 21 (18%) in the phenytoin group and 31 (26%) in the levetiracetam group [risk difference 7.6% (95% CI –3.0% to 18.3%); $P = 0.16$]. Rate and length of intensive care unit (ICU) admission and hospital duration were comparable in both groups. Seizure duration data were available for 196 (84%) of the 233 participants. The median time to seizure cessation was 22 min (IQR 9–49) in the phenytoin group and 17 min (5–30) in the levetiracetam group [difference –5.0 min (95% CI –13.5 to 3.5); $P = 0.25$]. One participant died in the phenytoin group. At 1-month follow-up, outcome measures were comparable in both groups.

In the ESETT Trial,[8] the efficacy and safety of levetiracetam, fosphenytoin and sodium valproate were evaluated in the management of benzodiazepine-resistant status epilepticus. The trial was conducted under the exception from informed-consent requirements for emergency research (FDA regulation). Eligible patients were aged >2 years, and had been treated with a generally accepted cumulative dose (minimal specified dose given) of benzodiazepines for CSE lasting more than 5 min and continued to have persistent or recurrent convulsions in the emergency department (ED) at least 5 min after the last dose of benzodiazepine, and no more than 30 min after the last dose. Patients were randomized to receive either levetiracetam 60 mg/kg (max 4500 mg), fosphenytoin 20 mg phenytoin equivalent (PE)/kg (max 1500 mgPE) or sodium valproate 40 mg/kg (max 3000 mg)—the trial drug was administered by an infusion pump programmed with a determined rate over a period of 10 min.

The primary outcome was an absence of clinical apparent seizures and improving responsiveness at 60 min after the start of trial-drug infusion, without additional anti-seizure medications including medication used for endotracheal intubation. Secondary efficacy outcomes included time to termination of seizures, as determined in the subgroup of patients with audio recordings that made accurate determination of times possible; admission to the ICU, and the length of ICU and hospital stays. The time to termination of seizures was defined as the interval from the start of infusion of the trial drug to the cessation of clinically apparent seizures.

The study design was a response-adaptive comparative-effectiveness design, with patients randomly assigned to receive one of the three trial drugs, initially in a 1:1:1 ratio. After 300 patients, response-adaptive randomization was initiated with the goal of maximizing the likelihood of identifying the most effective treatment. The study could be stopped early for success or futility after planned interim analyses. The maximal sample was 795 patients, with randomization stratified by age (2–17, 18–65, and >65 years).

Response rates in each of the treatment groups (all initially considered to be the most or least effective) were modelled independently with the use of Bayesian analysis, with the probability that each treatment was the most or least effective treatment was calculated. Intention to treat analysis was used. Four hundred enrolments of 384 patients were carried. The enrolment was discontinued after planned interim analysis met the predefined futility criteria. Of those enrolled, 39% were aged between 2 and 17 years, 48% between 18 and 65 years, and 13% were >65 years of age. Approximately 87% had a final diagnosis of status epilepticus (10% dissociative seizures) in all three groups. Approximately two-thirds (66.6%) had a prior history of epilepsy.

In the efficiency analysis, primary outcome was achieved in 68 of 145 (47%) in the levetiracetam group, 53 of 118 (45%) in the fosphenytoin group and 56 of 121 (46%) in the valproate group. The median duration of seizure at enrolment was ~61.0 min (IQR 38.5–94.0). Of those patients in the levetiracetam group, 89 (61.4%) received benzodiazepines prior to arrival in the ED compared to 68 (57.6%) in the fosphenytoin and 62 (51.2%) in the valproate group.

The median time from the start of trial-drug infusion to seizure termination (among patients with an audio recording) was 10.5 min (IQR 5.7–15.5) in the levetiracetam group, 11.7 min (IQR 7.5–20.9) in the fosphenytoin group and 7.0 min (IQR 4.6–14.9) in the valproate group. Thirty patients in the levetiracetam group (20.0%) required intubation within 60 min after start of trial-drug infusion compared to 33 (26.4%) in the fosphenytoin group and 21 (16.8%) in the valproate group. Seven patients (4.7%) died in the levetiracetam group compared to three (2.4%) in the fosphenytoin group and two (1.6%) in the valproate group. In the per-protocol population, valproate had the highest probability of being the most effective (0.36) compared to fosphenytoin (0.34) and levetiracetam (0.31), whilst in the adjudicated outcome population, the probabilities of being the most effective were valproate (0.48), fosphenytoin (0.35) and levetiracetam (0.17).

A further analysis was published in 2020 with an additional 78 cases [total 478 cases (462 patients)], consisting of 225 children (aged <18 years), 186 adults (18–65 years) and 51 older adults (>65 years). The primary outcome was met in 52% (95% CI 41 to 62) of children, 44% (95% CI 41 to 62) of adults and 37% (95% CI 19 to 59) of those receiving levetiracetam compared to 49% (95% CI 38 to 61) of children, 46% (95% CI 34 to 59) of adults and 35% (95% CI 17 to 59) of those receiving fosphenytoin, and 52% (95% CI 41 to 63) of children, 46% (95% CI 34 to 58) of adults, and 47% (95% CI 25 to 70) of older adults receiving valproate, with no evidence of a statistical significant difference in primary outcome between the treatment groups.[9]

These studies are a welcome addition to the status epilepticus corpus. Three salient findings emerge. First, we now have class A evidence for the effectiveness of levetiracetam, phenytoin and sodium valproate in the management of established status epilepticus with seizure cessation in approximately two-thirds of patients. Second, EcLiPSE, ConSEPT and ESETT have shown that large multicentre randomized controlled trials in established status epilepticus are possible with the achievement of clear procedural and diagnostic advances. In particular, these have established that the concept of research without prior consent or exception from informed-consent (FDA regulation 21 CFR 50.24) in emergency conditions such as status epilepticus is feasible and broadly acceptable to patients and family. In addition, these studies have established the feasibility of audio-visual recordings to ascertain the exact timing of seizure cessation in relation to drug infusions. Lastly, all studies underpinned the absolute need for prospective studies of status epilepticus with accurate recording of the timing of status epilepticus onset and cessation, an issue that has plagued the status epilepticus literature.[5,10]

Where do these studies leave us with treatment recommendations?

First, these studies demonstrate, where timing of CSE was recorded, that a majority of patients in CSE still face significant

Table 1 Summary of the principal findings of the five key studies

Authors	Methodology	Primary outcome/finding	Secondary outcomes/ findings	Comments
Kellinghaus *et al.*[4] (SENSE study)	Prospective incident multicentre study of SE over 4.5 years	1049 patients of whom 457 had GCSE with a median age of 65 years (IQR 49–78) and in-hospital mortality of 9%	48% treated within ⩽30 min of SE onset. Shorter latency to treatment initiation, use of BDZ within 30 min, were predictive of shorter time to cessation	Accurate prospective timing of SE onset, initiation of treatment and SE cessation 10% were treated with non-BDZ as initial treatment (associated with poorer outcome)
Lyttle *et al.*[6] (EcLiPSE study)	Open-label multicentre RCT comparing the use of IV LEV to IV PHY as second-line treatment of paediatric CSE	CSE was terminated in 70% in LEV group and 64% in PHY group.	15.8% in LEV group and 14.9% in PHY group needed further anticonvulsant Successful discharge at 14 days follow-up [95% (LEV) and 97% (PHY)]	Successful demonstration of the acceptability of the use of research without prior consent with 92% of those randomized and treated providing consent
Dalziel *et al.*[7] (ConSEPT study)	Open-label multicentre RCT comparing the use of IV LEV to IV PHY as second-line treatment of paediatric CSE	Clinical cessation of CSE was achieved 5 min after infusion in 50% in LEV group and 60% in PHY group	Seizure control at 2 h after administration of one or both drugs was achieved in 78% in PHY group and 86 72% in LEV group	Use of visual confirmation of clinical seizure cessation Demonstration of the efficacy of the combination of IV LEV and IV PHY in paediatric CSE when the initial drug fails
Neligan *et al.*[5]	Systematic review and meta-analysis/meta-regression analysis of CSE in high income countries	Pooled mortality ratio of 15.9% in adults, 13.0% in all-age population studies and 3.6% in paediatric studies	No evidence of a difference in SE mortality following subanalysis by study time period, region, SE definition employed, study design and study setting (ICU versus non-ICU)	Use of multivariate meta-regression analysis to try to reduce the very high study heterogeneity Critical appraisal of the SE epidemiology literature
Kapur *et al.*[8] (ESETT study)	Multicentre randomized blinded comparative-effective of three drugs (IV LEV, IV SVP and IV FOS) in BDZ-resistant CSE in children and adults	Absence of seizures and improvement in responsiveness at 60 min was achieved 47% of LEV group, 45% of FOS group and 46% of SVP group	Seizure termination from start of infusion was 10.5 min with LEV, 11.7 min with FOS group and 7.0 min with SVP group. 20.0% in LEV group required intubation within 60 min; 26.4% in FOS group and 16.8% in SVP group	Use of audio recording to determine timing of seizure cessation Successful demonstration of exception from informed-consent requirement for emergency research Adaptive study design allowing for interim analysis and early study termination

BDZ = benzodiazepines; FOS = fosphenytoin; ICU = intensive care unit; IV = intravenous; LEV = levetiracetam; PHY = phenytoin; SE = status epilepticus; SVP = sodium valproate.

time delays before treatment initiation for both early and established CSE, despite the long-established advocacy of the need for early and aggressive treatment in status epilepticus. The additional finding of suboptimal benzodiazepine dosing is a further concern, albeit one that is remediable. One frequently cited fear is the risk of drug-induced respiratory distress, yet the RAMPART study[11] demonstrated that this is more likely to occur with ongoing seizure activity, and in that context is associated with a poorer prognosis,[12] rather than due to the effects of benzodiazepines. The median latency to treatment in established status epilepticus was 60 min in ESETT and 73 min (IQR 52–99) in ConSEPT. In light of increasing refractoriness with time in status epilepticus, these findings underscore the need for ongoing awareness and education for swift intervention following onset, adequate initial benzodiazepine dosing and the timely initiation of second-line treatment in benzodiazepine-resistant cases.

Second, the ConSEPT study demonstrated that a strategy of successive use of intravenous anti-seizure medications (in this case, phenytoin and levetiracetam) in children, where associated morbidity and mortality is extremely low, should be considered before recourse to anaesthetic agents. The extent to which this approach is feasible in adults, where mortality is higher, merits consideration. This strategy is often used in the setting of non-convulsive and focal status epilepticus where cardiorespiratory compromise is less of a concern and the desire to avoid intubation, unless absolutely necessary, is strong. Although phenytoin and levetiracetam were trialled in ConSEPT, valproate, lacosamide and even phenobarbital are additional options.

Third, ESETT, ConSEPT and EcLiPSE have demonstrated that levetiracetam is a viable alternative to phenytoin. Its speed of administration, absence of adverse cardiovascular effects, simpler pharmacokinetics along with its increasing familiarity in emergency settings will, in our view, result in its superseding phenytoin to become the default treatment in benzodiazepine-resistant cases. However, an uncritical move in this direction would be remiss; in head-to-head comparisons, levetiracetam has not shown a clear advantage over phenytoin and its ascendency in the pharmacological hierarchy, is largely predicated on the perceived unfavourable safety profile of its rival. Nevertheless, the frequency of significant side-effects was not significantly higher in the fosphenytoin group [four (3.2%) of life-threatening hypotension within 60 min of drug infusion; zero life-threatening cardiac arrhythmia within 60 min of drug infusion] compared to the levetiracetam group [one (0.7%) hypotension; one (0.7%) cardiac arrhythmia] in the ESETT study. Moreover, it is possible, although speculative, that certain aetiologies may be more responsive to one and not the other. Thus, an open mind and some latitude when designing treatment algorithms is required.

Despite the widespread use of phenytoin as the default option in CSE, there is surprisingly little evidence to support the perception of its superiority over valproate. Several studies, including a few randomized/non-randomized clinical trials, have shown valproate to be at least as effective as phenytoin.[13] A meta-analysis of five anti-seizure medications in benzodiazepine-resistant status epilepticus indicated a trend towards valproate being the most effective. Levetiracetam and phenobarbital were similarly effective, but the evidence did not support the first-line use of phenytoin; there was insufficient data to support the routine use of lacosamide.[14] In the case of the ESETT study, if any anti-seizure medication was to be favoured, it would be valproate which was associated with the shortest duration to seizure cessation and lowest mortality. Moreover, the Bayesian analysis used[15] favoured valproate with the highest probability of being the most effective therapy.

A recent study of the use of newer anti-seizure medications (principally levetiracetam and lacosamide) in over 800 episodes of status epilepticus in ~700 patients[16] delivers a sobering conclusion; the use of newer anti-seizure medications was associated with a higher degree of refractoriness in status epilepticus and increasing morbidity. Much of the clinical research into status epilepticus in recent years has focused on newer anti-seizure medications. However, reappraisal of the role of phenobarbital is justified; once a staple of status epilepticus treatment algorithms, but recently fallen into disfavour. Its efficacy is arguably superior to that of phenytoin's with the landmark Veteran's Affairs SE study demonstrating a similar efficacy to lorazepam and a trend favouring it over phenytoin alone. There has been some renewed interest in its use, with positive results[17–19] and a recent head-to-head comparison with valproate favouring phenobarbital.[20] 'Supra' normal doses of phenobarbital have also been used successfully in the setting of refractory status epilepticus.[21–23] Its safety profile, principally cardiorespiratory depression continues to militate against wider use.

Finally, in light of the absolute need for timely pharmacological intervention, there is a growing argument to shift the focus even more to the pre-hospital setting whereby both benzodiazepine and intravenous second-line anti-seizure medications could potentially be given prior to arrival in the ED, along the lines of the recent SAMUKeppra study[24] in which one arm of the study involved the addition of intravenous levetiracetam to clonazepam for the pre-hospital management of status epilepticus. Although the addition of levetiracetam conferred no advantage over clonazepam alone, the study highlighted the high response rate with early treatment and the feasibility of using non- benzodiazepine intravenous anti-seizure medications in a pre-hospital setting. Preclinical studies indicate that there may be more suitable adjunctive therapies that demonstrate synergy with benzodiazepines such as valproate or NMDA receptor antagonists.[25]

Conclusions

The crystallization of robust evidence-based current practice in status epilepticus is paramount in informing treatment algorithms. Yet, more needs to be done. Aside from the advent of immunomodulatory treatment in suspected autoimmune cases of status epilepticus, there has been little expansion of the effective therapeutic armamentarium. Until we have a better understanding of the biological mechanisms that maintain status epilepticus[26] and more importantly the different biological processes that can lead to status epilepticus termination, a cascade that includes, *inter alia*, neurotransmitter depletion, ATP depletion, ionic changes, increased GABAergic drive and release of adenosine and peptides and which of these predominate,[27] any treatment regimens used are likely to be suboptimal. The intersection of these seminal studies in a single year should lend impetus to refocus efforts on what research should to be prioritized and pursued in order to address some of the most sobering aspects of status epilepticus, a lack of a decline in mortality, the significant long-term sequelae and often poor functional outcome.

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Competing interests

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References

1. Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. *Arch Neurol*. 2010;67:931-940.
2. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998;339:792-798.
3. Meierkord H, Boon P, Engelsen B, et al. European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol*. 2010;17:348-355.
4. Kellinghaus C, Rossetti AO, Trinka E, et al. Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). *Ann Neurol*. 2019;85: 421-432.
5. Neligan A, Noyce AJ, Gosavi TD, et al. Change in mortality of generalized convulsive status epilepticus in high-income countries over time: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:897-905.
6. Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive

status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. *Lancet*. 2019;393:2125-2134.
7. Dalziel SR, Borland ML, Furyk J, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet*. 2019;393:2135-2145.
8. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381:2103-2113.
9. Chamberlain JM, Kapur J, Shinnar S, et al. Pediatric Emergency Care Applied Research Network. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020;395:1217-1224.
10. Leitinger M, Trinka E, Zimmermann G, et al. Epidemiology of status epilepticus in adults: apples, pears, and oranges—a critical review. *Epilepsy Behav*. 2020;103:106720.
11. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366:591-600.
12. Uppal P, Cardamone M, Lawson JA. Outcomes of deviation from treatment guidelines in status epilepticus: a systematic review. *Seizure*. 2018;58:147-153.
13. Trinka E, Hofler J, Zerbs A, et al. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. *CNS Drugs*. 2014;28:623-639.
14. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure*. 2014; 23:167-174.
15. Connor JT, Elm JJ, Broglio KR. ESETT and ADAPT-IT Investigators. Bayesian adaptive trials offer advantages in comparative effectiveness trials: an example in status epilepticus. *J Clin Epidemiol*. 2013;66:S130-S137.
16. Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs in status epilepticus: prescription trends and outcomes in comparison with traditional agents. *CNS Drugs*. 2017;31:327-334.
17. Brigo F, Del Giovane C, Nardone R, et al. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis. *Epilepsy Behav*. 2019;101:106466.
18. 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.
19. Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. *Epilepsia*. 2018;59 (Suppl 2):S193-S197.
20. Su Y, Liu G, Tian F, et al. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults: a prospective randomized controlled trial in China. *CNS Drugs*. 2016;30: 1201-1207.
21. Byun JI, Chu K, Sunwoo JS, et al. Mega-dose phenobarbital therapy for super-refractory status epilepticus. *Epileptic Disord*. 2015; 17:444-452.
22. Crawford TO, Mitchell WG, Fishman LS, et al. Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology*. 1988;38:1035-1040.
23. Lee WK, Liu KT, Young BW. Very-high-dose phenobarbital for childhood refractory status epilepticus. *Pediatr Neurol*. 2006;34: 63-65.
24. Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol*. 2016;15:47-55.
25. Niquet J, Baldwin R, Norman K, et al. Simultaneous triple therapy for the treatment of status epilepticus. *Neurobiol Dis*. 2017; 104:41-49.
26. 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;56:1515-1523.
27. Walker MC. Pathophysiology of status epilepticus. *Neurosci Lett*. 2018;667:84-91.