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REVIEW

Optimal Management of Status Epilepticus in Children in the Emergency Setting: A Review of Recent Advances

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Abstract: Convulsive status epilepticus (CSE) is the most common neurological emergency in children and the second most common neurological emergency in adults. Mortality is low, but morbidity, including neuro-disability, learning difficulties, and a de-novo epilepsy, may be as high as 22%. The longer the duration of CSE, the more difficult it is to terminate, and the greater the risk of morbidity. Convulsive status epilepticus is usually managed using specific national or local algorithms. The first-line treatment is administered when a tonic-clonic or focal motor clonic seizure has lasted five minutes (impending or premonitory CSE). Second-line treatment is administered when the CSE has persisted after two doses of a first-line treatment (established CSE). Randomised clinical trial (RCT) evidence supports the use of benzodiazepines as a first-line treatment of which the most common are buccal or intra-nasal midazolam, rectal diazepam and intravenous lorazepam. Alternative drugs, for which there are considerably less RCT data, are intra-muscular midazolam and intravenous clonazepam. Up until 2019, phenobarbital and phenytoin (or fosphenytoin) were the preferred second-line treatments but with no good supporting RCT evidence. Robust RCT data are now available which has provided important information on second-line treatments, specifically phenytoin (or fosphenytoin), levetiracetam and sodium valproate. Lacosamide is an alternative second-line treatment but with no supporting RCT evidence. Current evidence indicates that first, buccal or intranasal midazolam or intravenous lorazepam are the most effective and the most patient and carer-friendly first-line anti-seizure medications to treat impending or premonitory CSE and second, that there is no difference in efficacy between levetiracetam, phenytoin (or fosphenytoin) or sodium valproate for the treatment of established CSE. Pragmatically, levetiracetam or sodium valproate are preferred to phenytoin (or fosphenytoin) because of their ease of administration and lack of serious adverse side-effects, including potentially fatal cardiac arrhythmias. Sodium valproate must be used with caution in children aged three and under because of the rare risk of hepatotoxicity and particularly if there is an underlying mitochondrial disorder.

Keywords: convulsive, status epilepticus, emergency, anti-seizure medications, anticonvulsants, pediatric, children

Objective

This paper describes the current evidence base for the optimal medical management of convulsive status epilepticus (CSE) in the Accident and Emergency Department (AED) or Emergency Room (ER) setting. The paper will not discuss the management of convulsive seizures in the community, neonatal CSE (as this typically occurs in neonatal intensive or special care baby units) or non-convulsive status epilepticus. It will focus on the management of a child that presents to the AED/ER in prolonged focal or generalised tonic-clonic seizure (referred to as "impending or premonitory CSE"), "established CSE" and, briefly, "refractory CSE". These are the terms used by the International League Against Epilepsy (ILAE) in its definition of status epilepticus published in 2017.[1] "Super-refractory CSE" falls outside the remit of this

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paper because the management of these patients will occur on the intensive care unit (ICU) and not in the AED or ER. The term, anti-seizure medication (ASM), will be used throughout this paper.

Definition and Classification

In 2015, the definition and classification of status epilepticus (SE) was reviewed by the ILAE.[2] This definition highlighted the fact that "prolonged" seizures (which the ILAE defined as lasting about five minutes) could continue and cause significant long-term consequences, particularly if the seizures lasted longer than 30 minutes.[2] Practically, this means that if a tonic-clonic seizure has lasted 4–5 minutes treatment should be given to try and terminate it and stop it from persisting and lasting longer than 30 minutes to prevent or minimise long-term consequences.

The ILAE published a comprehensive revised classification of CSE in 2017 which included by age and aetiology and also by duration and the response to anti-seizure medication (ASM).[1] This classification is as follows:

- Impending or premonitory CSE: the seizure has lasted ≥5 minutes
- Established CSE: the seizure has lasted >5 minutes and has not responded to the first-line ASM
- Refractory CSE: the seizure has persisted after failure of a benzodiazepine and a second-line ASM
- Super-refractory CSE: status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases that recur on the reduction or withdrawal of anaesthesia

Most protocols and guidelines used in the management of CSE recommend that an ASM should be administered if the focal clonic or generalised tonic-clonic seizure has lasted five minutes. The reason for this is that approximately 80–90% of tonic-clonic seizures stop spontaneously after four minutes[3] and if it has not, then the likelihood is that it will continue. Furthermore, the longer a seizure continues, the more likely it is that it will be more difficult to terminate with ASMs. A paediatric study showed that, once a convulsive seizure has lasted more than five minutes, it is likely to last at least 30 minutes.[4] Continuing seizures, and particularly generalised tonic-clonic seizures, are associated with an increased risk of morbidity and mortality. The mortality rate increases dramatically if the CSE becomes refractory (15–20%) and can reach over 30% or 60%[5] in super-refractory CSE in adults; there are no equivalent reliable mortality data of super-refractory CSE in children. Neurological morbidity is more common and includes a new and chronic epilepsy, neuro-disability and learning difficulties. The most important factor that determines mortality and morbidity in CSE is its etiology, followed by age, although this is closely linked to the etiology. The duration of CSE is the next most important factor and for obvious reasons, its management is closely linked with its duration.

Epidemiology and Etiology of CSE

The estimated incidence of CSE is approximately 15–25 in 100,000 children a year[6,7] and 15–40 per 100,000 per year across all ages.[8] The highest incidence is in infancy (<3 years of age) and in the elderly (>65 years of age)[8] which predominantly reflects the underlying etiology of CSE.

The etiology of CSE is relevant to its management in that it is important to consider and exclude any potentially treatable causes, and particularly an underlying infection (specifically, meningitis or encephalitis) or metabolic cause. The most common metabolic causes are hypoglycaemia, hypocalcaemia, hypo- or hypernatraemia and hypoxia.

The analysis of CSE by etiology is complicated by the fact that its classification has evolved and changed and not all authors use the same classification. Consequently, the reported prevalence of the different aetiologies is not consistent. The current ILAE classification by etiology is: febrile; epilepsy-related and acute symptomatic (eg during meningitis or encephalitis, hypoglycaemia or hypoxia or following a traumatic brain injury) and these are further divided into specific epilepsy syndromes and aetiologies.[2] Using this definition, a very recent study of 665 children (≤15 years of age) with CSE found that 41.2% had febrile CSE, 55.5% had epilepsy-related CSE and only 2.1% had acute symptomatic seizures.[9] However, an earlier paediatric study found that the acute symptomatic group represented 17% of all causes of CSE.[6]

Infants and Children (1 Month to 18 Years)

The most common cause of CSE in children is febrile and typically during a febrile illness; this accounts for 33–35% of all cases of paediatric CSE. A small minority of these children will have a genetic epilepsy, specifically Dravet syndrome and PCDH19 because these two syndromes typically present between 3 and 12 months of age with 'febrile seizures', including febrile CSE.

Adults (>18 Years)

The most common cause of CSE in adults is acute symptomatic which accounts for 48–60% of all cases of CSE. The most common cause is stroke caused by a haemorrhage or an infarct.[11] Additional acute symptomatic causes include alcohol-related, metabolic (eg hypoglycaemia), hypoxia and infection. The second most common cause of CSE in adults is low or absent blood levels of ASMs in patients with pre-existing epilepsy which reflects poor or no compliance with the ASM they had been prescribed. The most likely cause of non-compliance is a sudden, rather than a gradual discontinuation of the medication.

There is one final but important issue in the etiology of CSE. A very small number of patients, particularly adults but also older children, may present with what appears to be CSE but is actually "pseudo-epileptic CSE" or more appropriately, "psychogenic, non-epileptic CSE". In the Established Status Epilepticus Treatment Trial (ESETT) study, 10% of 384 patients that were enrolled into this double-blind, randomised controlled trial (RCT) were considered to have psychogenic CSE.[10] Treating these patients with ASMs, and certainly escalating treatment to rapid sequence induction with an anaesthetic carries a high risk of iatrogenic complications. This emphasises the importance of the correct diagnosis of CSE.

Current Management

The current management of CSE in children and adults is largely based on international or national guidelines. Local guidelines for individual hospitals may also be used but these are still likely to be predominantly based on national guidelines. Finally, there will be those people with epilepsy who will have individual or personalised rescue (emergency) plans because of a known allergy or resistance to one or more ASMs.

In the United Kingdom (UK), protocols and guidelines are derived from the Advanced Life Support (ALS) and Advanced Paediatric Life Support (APLS) groups and the Resuscitation Council of the UK. The National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) review, and subsequently usually endorse these guidelines.

In the United States (US), the protocols and guidelines are based on those recommended by the American Epilepsy Society. A specific US pediatric status epilepticus research group (pSERG) found that the status epilepticus pathways used within its many constituent hospitals were consistent with the AES status epilepticus guideline with regard to the choice of anti-seizure medications, but generally recommended a more rapid escalation in therapy than the guideline.[12]

This paper will address the evidence-base of the protocol and ASMs that are used in the current APLS[13] and new Resuscitation UK[14] Guidelines; the latter's new algorithm is shown in Figure 1. The new and updated APLS algorithm to be published in late 2022 is Figure S1 in the Supplementary Material; this algorithm is very similar to that of the Resuscitation UK algorithm.

General

All patients that present to the AED or ER in impending or established CSE should undergo the basic assessment of airway patency (A), breathing (B) and circulation (C). Many children will also require measurements of blood gases, glucose, urea, creatinine, calcium, electrolytes and a full blood count and particularly if it is their first presentation with either a convulsive seizure or CSE. These are important not only to identify a potentially treatable etiology but also to exclude any metabolic factor that might be contributing to the episode of CSE and/or preventing it from being successfully stopped with ASMs; this is particularly likely with low levels of blood glucose, calcium and sodium.

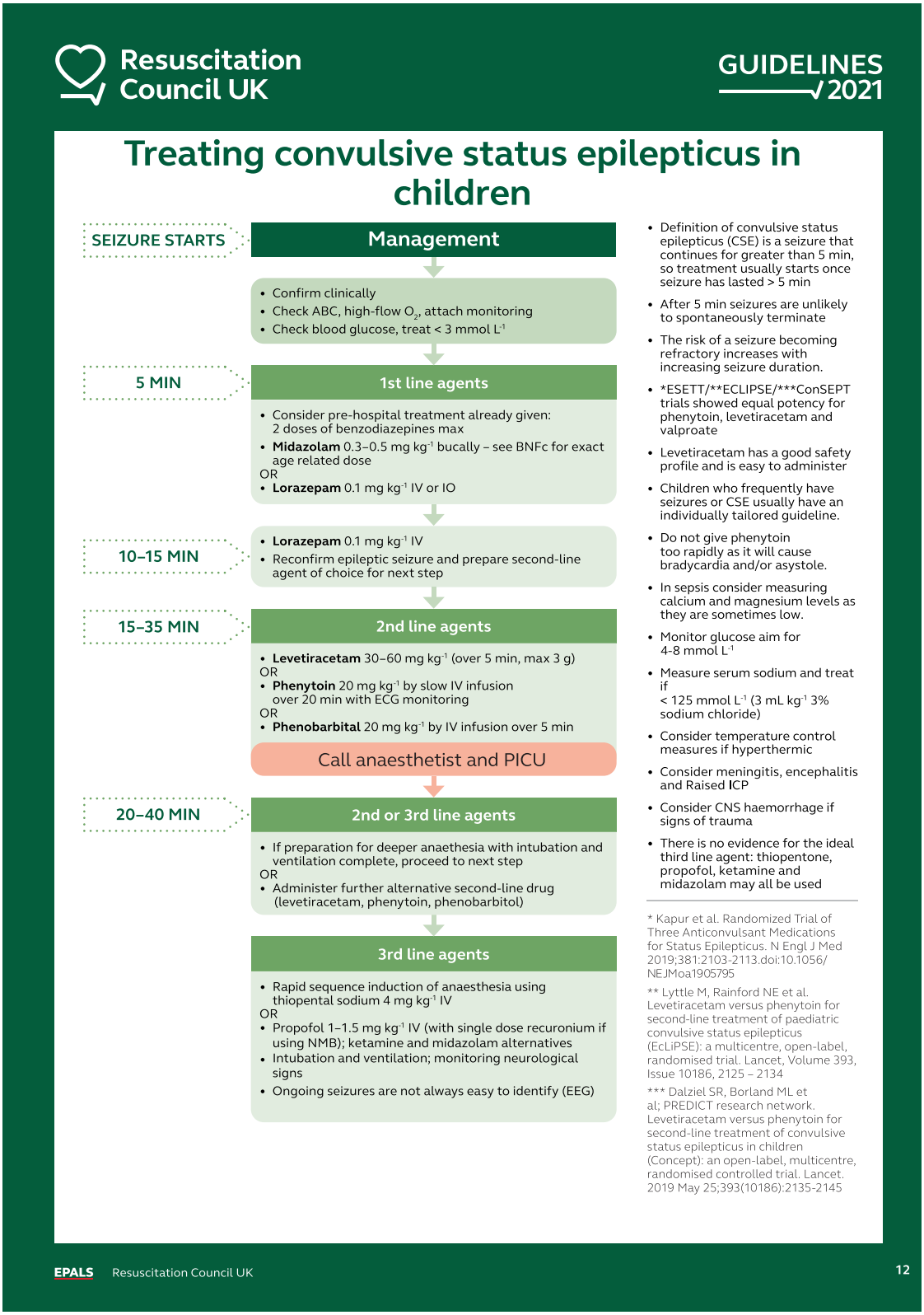

Figure 1 Status Epilepticus Algorithm. Resuscitation Council UK: Paediatric emergency algorithms and resources. 2022. Version 1 (Reproduced with the kind permission of the Resuscitation Council UK).[14]

Abbreviations: ABC, Airway, Breathing, Circulation; BNFc, British National Formulary for Children; IV, Intravenous; IO, Intraosseous; ICP, Intracranial Pressure; CNS, Central Nervous System; ECG, Electrocardiogram; PICU, Paediatric Intensive Care Unit; NMB, Neuromuscular Block; EEG, Electroencephalogram.

Blood levels of ASMs must also be measured in any patient with a known diagnosis of epilepsy and being treated with an ASM and these should be done on admission and not many hours later.

Specific Anti-Seizure Medications for Impending and Established CSE

There is little difference in the use of specific ASMs between children aged four years and over and adults. In children aged less than three and certainly less than two years, and particularly where there is no immediately identified cause for the CSE or the child's underlying and refractory epilepsy, many algorithms and guidelines exclude sodium valproate. This is to avoid the rare possibility of hepatotoxicity if the child might have an underlying metabolic, and specifically, a mitochondrial disorder which might be un-masked by sodium valproate.

The use of specific ASMs in the treatment of CSE may vary depending on the country. For example, intravenous clonazepam is used in France because lorazepam is unavailable and there is very limited or no availability of intravenous lacosamide, levetiracetam and sodium valproate in many developing countries.

The doses and routes of administration of the most commonly used ASMs used in the management of the first two stages of CSE are shown in Table 1.

First-Line ASMs

Benzodiazepines

Benzodiazepines are currently the first-line ASM in the treatment of status epilepticus.[13–15] In the UK the initial, first-line step is a maximum of two doses of a rapid onset but short-acting benzodiazepine. The most commonly used are lorazepam, midazolam and diazepam. In France, intravenous clonazepam is used as intravenous lorazepam is not available. There is a lack of consensus regarding the specific drug, dose and route of administration.[16–18] Intravenous (IV), intramuscular (IM) buccal, rectal and intranasal (IN) have all been used as potentially effective routes of administration with a range of reported efficacies and adverse events.[15–19] The choice of benzodiazepine in the AED/

Table 1 Anti-Seizure Medications Used in the Management of CSE (Listed in Alphabetical Order)

Anti-Seizure Medication	Single Dose	Route of Administration	Duration of Administration
First-line			
Clonazepam	0.04mg/kg (max: 1mg)	IV	Bolus
Diazepam	0.5mg/kg (max: 10mg)	Rectal	
	0.3–0.5mg/kg (max: 10mg)	IV	3–4 minutes
Lorazepam	0.1mg/kg (max: 4mg)	IV/IO	Bolus
Midazolam	0.2–0.3mg/kg (max: 10mg)	Buccal/IN	
	0.2–0.3mg/kg (max: 10mg)	IV	Bolus
	0.2–0.3mg/kg (max: 10mg)	IM	
Second-line			
Fosphenytoin[a]	20mgPE/kg (max: 1500mg)	IV/IO	10–15 minutes
Levetiracetam[a]	30–60mg/kg (max: 4500mg)	IV/IO	5 minutes
Phenobarbital	10–20mg/kg	IV/IO	20 minutes
Phenytoin[a]	20mg/kg (max: 2000mg)	IV/IO	20 minutes (minimum)
Sodium valproate[a]	30–40mg/kg (max: 3000mg)	IV/IO	10 minutes

Notes: [a]Doses cited in most trials, and specifically the "EcLiPSE", "ConSEPT" and "ESETT" trials. There are insufficient data to give the most appropriate loading dose of intravenous lacosamide used in the management of CSE.
Abbreviations: IV, intravenous; IN, intranasal; IM, intramuscular; IO, intraosseous; PE, phenytoin equivalents.

ER depends on the specific clinical situation and availability of intravenous access. Intravenous administration is generally regarded as the most important route in many clinical treatment algorithms.[13,14,18,19]

First-line treatment may begin in the community (including home) setting before arrival at the hospital and usually with one, or, rarely, two doses of a benzodiazepine. Treatment with more than two doses of benzodiazepines is considered to be associated with an increased risk of respiratory depression and other side effects without substantial benefits.[16] A network meta-analysis in 2016[17] and Cochrane review in 2018[15] showed no clear difference in efficacy and safety between diazepam, lorazepam and midazolam. These studies also assessed three other first-line ASMs, lidocaine, paraldehyde and sodium valproate, but the data were poor and consequently no conclusions could be made about their efficacy compared to benzodiazepines. Both studies concluded that midazolam by any route (intravenous, buccal or intranasal) is more efficacious at terminating a seizure than intravenous or rectal diazepam but that intravenous lorazepam has a better adverse event profile than rectal diazepam and was at least as effective as non-intravenous midazolam. Overall, the recommendations were that non-intravenous midazolam for prehospital treatment and IV lorazepam for AED/ER treatment were the most effective and safest benzodiazepines. In the UK, the first-choice benzodiazepine is intravenous lorazepam (when intravenous access is available), or buccal midazolam (when intravenous access is difficult or unavailable).[13–15]

Midazolam can be given IV, IM, buccally, rectally, and IN. It has a rapid onset of action. Intranasal midazolam is often used in the procedural sedation of pediatric patients and has been used in the AED/ER for many years.[20] Its intranasal administration in the management of CSE is not established in routine practice and is not included in the UK guidelines.[13,14] Intranasal and buccal midazolam are listed as last choice in the American Epilepsy Society guidelines of pediatric CSE.[19] In 2019, the Food and Drug Administration (FDA) approved Nayzilam®, an intranasal preparation of midazolam licensed for use in children aged 12 years and above. In January 2022, the European Medicines Agency (EMA) recommended the authorisation of Nasolam® (midazolam nasal spray). A marketing authorisation will be granted in the Netherlands, Denmark, Germany, Finland, Ireland, Norway Sweden, and the UK for Nasolam® in the near future.[21] Intranasal administration clearly offers another treatment option particularly in the community setting.

Intramuscular midazolam provides another route of administration when intravenous access is unavailable. A randomised controlled trial (RCT) of 150 children aged 4.5 months to 14 years that presented with an acute seizure to the AED showed seizure-cessation within five minutes of administration of the randomised medication in 61% of the intramuscular and 46% of the buccal treatment groups.[22] The authors concluded that IM rather than buccal midazolam should be the preferred route for the treatment of acute seizures in the emergency setting based on efficacy and safety.[22] Clearly, IM administration may cause some pain although many would consider this of little significance or concern in view of the seriousness of CSE. Others have proposed a practice change towards a wider use of IM and IN midazolam where IV access is unavailable or difficult.[16,23]

Diazepam is commonly used in US for the acute management of acute seizures and CSE. It is unclear why rectal diazepam is preferred to buccal (or intranasal) midazolam in the US. It may be given intravenously and rectally. In 2020, an intranasal preparation (Valtoco®) was approved by the FDA for use in children aged 6 years and over.[24] A large systematic review and meta-analysis undertaken in 1602 patients (1573 of whom were aged <16 years) showed that non-intravenous midazolam was as effective and as safe as intravenous or rectal diazepam in terminating early SE in children and probably also in adults.[25] The only exception was the comparison between buccal midazolam and rectal diazepam, where midazolam was more effective in terminating SE but only when results were expressed as an odds ratio. Finally, and interestingly, although the times from arrival in the AED/ER to administration of the ASM were shorter with non-intravenous midazolam than with intravenous or rectal diazepam, this did not result in better seizure control. There was no difference in the frequency of reported adverse effects.[25]

Diazepam is also more likely to cause respiratory depression than lorazepam or midazolam,[15] which may be important in the community or in the AED/ER that has no immediate anaesthetic support.

Lorazepam has a slower onset of action than diazepam but longer anticonvulsant activity as it is less lipophilic.[16] An RCT undertaken in the US by the Pediatric Emergency Care Applied Research Network (PECARN) found no statistically significant difference between IV diazepam (0.2 mg/kg, maximum dose, 8 mg) and IV lorazepam (0.1 mg/kg, maximum

dose 4 mg) in seizure-termination at 10 minutes (diazepam 72.1% vs IV lorazepam 72.9%).[26] Zhao et al reviewed data from 16 RCTs involving 1821 patients and concluded that non-IV midazolam and IV lorazepam were superior to IV or non-IV diazepam and that IV lorazepam was at least as effective as non-IV midazolam in terminating CSE in children.[17] They concluded that midazolam had the highest probability of achieving seizure cessation and that lorazepam had the highest probability of causing less respiratory depression.[17]

A randomized open-label study compared IV lorazepam to IN lorazepam in 141 children aged 6–14 years (70 receiving IV and 71 IN treatment). The primary outcome measure was cessation of seizure activity within 10 minutes of drug administration. The results were similar with seizure control in 80% of the IV and 83.1% of the IN group. The authors concluded that IN lorazepam 0.1 mg/kg (maximum 4 mg) was not inferior to IV lorazepam for the termination of seizures in children aged 6–14 years and also that it was not inferior for continued seizure remission after one hour.[23] A specific theoretical benefit of a non-IV route (either IN or buccal) is that it is likely to be quicker to administer and therefore quicker to take effect because it obviates the need for securing intravenous access which may take several minutes.

Paraldehyde

Paraldehyde has been used as an anticonvulsant for over 60 years. It is sometimes used when other ASMs, including benzodiazepines or phenytoin and phenobarbital, have failed to stop a tonic–clonic convulsion.[27] Despite the accepted role of paraldehyde in the management of tonic–clonic convulsions, there are almost no published data on its effectiveness and safety, and what data there are have focused on its intramuscular route of administration. Paraldehyde is not used in the management of CSE in adults in the UK or, as far as the authors are aware, in the management of CSE outside the UK. An open study of 160 paediatric patients that presented to the emergency department in CSE showed no significant difference in seizure cessation at 10 minutes, time to seizure cessation or seizure recurrence at 24 hours between intranasal lorazepam (0.1mg/kg) and IM paraldehyde (0.2mls/kg) (75% versus 61%).[28] However, rather paradoxically, the study showed that patients treated with IM paraldehyde were more likely to require two or more additional doses of ASM (intranasal lorazepam, 10%; IM paraldehyde, 26%; $p = 0.007$).[28] Intramuscular paraldehyde can be very painful and may potentially damage the sciatic nerve. A small, retrospective study published in 2008 reported the use of rectal paraldehyde in a dose of 0.4mls/kg mixed with an equal volume of olive oil in 53 episodes in 30 children with an acute, prolonged tonic-clonic convulsion.[29] Paraldehyde was the first rescue medication to be used in 19 (35.9%) episodes (seven of the 30 children) and in the remaining 34 episodes, it was used after either a benzodiazepine or phenytoin, or both. Overall, it terminated the seizure in 33 (62.3%) of the 53 episodes. There were no reports of respiratory depression. The rationale behind its use in the UK's current (6th edition) APLS CSE algorithm[13] is that the preparation and administration of intravenous phenytoin is likely to take at least 20–25 minutes and during this time rectal paraldehyde should be given simultaneously to try and terminate the status. However, its use was optional and many had not used it in routine practice because of the concern that it might cause respiratory suppression in those children that had already received benzodiazepines,[30] or delay the administration of phenytoin. Rectal paraldehyde is not included as a therapeutic option in the Resuscitation UK algorithm[14] or the next APLS algorithm to be published in late 2022. In part, this reflects the concern over respiratory suppression but also the emergence of intravenous levetiracetam as a first choice ASM in the second-line management of CSE which can be administered over five minutes and which clearly obviates the need for rectal paraldehyde. However, a number of specialists in pediatric emergency medicine and also pediatric neurology in the UK feel that the drug should still be available for those children in refractory CSE in whom intravenous access is very difficult.

Second Line

Phenobarbital

Phenobarbital (PHB) has been used as an alternative second-line ASM to phenytoin or fosphenytoin in the management of CSE for many decades.[31,32] One recent pediatric study suggested that it was more efficacious than phenytoin in terminating both established and refractory CSE and, perhaps predictably therefore, was associated with fewer admissions to pediatric intensive care.[33] Its current use in CSE is mainly limited to neonatal CSE, in children and adults who

are already receiving phenytoin as a regular, oral maintenance ASM, or where phenytoin (PHY) and fosphenytoin (FOS) are contra-indicated because of a previous serious adverse reaction. Some also use phenobarbital in preference to phenytoin in children and young people with Dravet syndrome (DS), in which episodes of CSE are common. This is because phenytoin is a sodium channel blocker and, as with other ASMs with a similar mechanism of action, may exacerbate seizures in these patients.[34] Although this may be true for oral, maintenance ASMs, there is no evidence that IV phenytoin or fosphenytoin exacerbates or prolongs CSE in DS. In terms of efficacy, a study of 99 patients with DS from Japan showed that IV phenytoin was less effective at terminating episodes of ongoing status epilepticus (15–21% success) than IV barbiturates (75–100% success) or IV benzodiazepines (54–69% success).[35] This would suggest that it would be more appropriate to use phenobarbital rather than phenytoin in the management of CSE in individuals with DS. A small Chinese study of 73 adults with benzodiazepine-resistant SE showed that intravenous phenobarbital was successful in 81.1%, and intravenous valproate in 44.4% of patients ($p < 0.05$). Fewer patients in the phenobarbital compared to the valproate group showed a relapse in SE within 24 hours (6.7% vs 31.3%). The total number of adverse events did not differ significantly between the two groups ($p > 0.05$).[36] High dose phenobarbital is a therapeutic option in refractory CSE but only when patients can be safely monitored in intensive care because of the respiratory depression associated with the drug. Finally, phenobarbital's recognised efficacy, inexpensive cost and therefore easy availability is clearly important in the management of CSE in resource-poor countries.

Phenytoin

Historically, phenytoin or its pro-drug, fosphenytoin which is primarily used in the US, has been the standard second-line ASM when benzodiazepines have failed to terminate the episode of impending CSE. This is despite very limited RCT and mostly open data on its use in this situation.[37,38] The literature suggests that phenytoin is effective in terminating CSE in between 50 and 96% of patients.[37,39] It has several disadvantages including a narrow therapeutic index, long infusion time, numerous drug interactions, and a poor adverse events profile. The latter is characterised by acute and profound hypotension, cardiac arrhythmias (including irreversible asystole), Stevens-Johnson syndrome, hepatotoxicity and pancytopenia.[40] Although fosphenytoin can be infused more rapidly, it may still be associated with a similar toxicity to phenytoin. The authors of a review of the drug stated the following: "Published literature shows that intravenous fosphenytoin has a similar adverse effect profile than phenytoin when it is administered as recommended. There is no evidence of clear benefit that would justify the higher price of the fosphenytoin compared to phenytoin".[41]

However, within the past few years three large RCTs have been published that have provided much-needed evidence on not only the efficacy and safety of phenytoin (or fosphenytoin), but also on two additional ASMs, levetiracetam (LEV) and sodium valproate (SVP), in the management of CSE. The RCTs were the "EcLiPSE",[42] "ConSEPT"[43] and "ESETT"[44] studies.

Levetiracetam

The first study, "EcLiPSE", was an open-label RCT of intravenous levetiracetam versus phenytoin in the management of benzodiazepine-resistant CSE in the UK.[42] A total of 286 children, aged six months to 18 years were recruited, 152 receiving levetiracetam and 134 receiving phenytoin. Levetiracetam was infused over five minutes in a dose of 40mg/kg and phenytoin was infused over 20 minutes in a dose of 20mg/kg. The primary end point was time from randomisation to seizure cessation. Although there was no statistically significant difference between the two groups, levetiracetam was found to be associated with higher (70% vs 64%) and faster (35 mins vs 45 mins) rates of seizure cessation than phenytoin. There was no statistically significant difference in the rates of RSI or admission to PICU between the two treatment groups. Neither drug was associated with any severe adverse reactions.[42]

The second study, "ConSEPT", was undertaken in New Zealand and Australia and involved 233 children, aged two months to 16 years.[43] This open-label RCT compared levetiracetam and phenytoin and used an almost identical protocol to that of EcLiPSE; this included the same drug doses and rates of infusion. The primary outcome was seizure cessation at five minutes after the completion of the study drug. Levetiracetam was not found to be superior to phenytoin but there was an opposite trend to that seen in EcLiPSE. The primary outcome was achieved in 60 patients (50%) in the levetiracetam and in 68 patients (60%) in the phenytoin-treated group. In "ConSEPT", the authors used the alternative

study drug when the first treatment failed if the child was seizing after two hours. This resulted in seizure control without the requirement for further intervention in 27 patients who received phenytoin first (64% of those receiving phenytoin, then levetiracetam) and 25 who received levetiracetam first (52% of those receiving levetiracetam, then phenytoin). Therefore, seizure control two hours after administration of one or both drugs was achieved in 89 (78%) participants in the phenytoin and 86 (72%) in the levetiracetam group. Neither drug was associated with any severe adverse reactions.[43]

Finally, levetiracetam has been shown to be well tolerated. Specifically, it has not been reported to be associated with cardiac arrhythmias (including irreversible asystole), Stevens-Johnson syndrome or acute hepatotoxicity.[18,42–44]

Sodium Valproate

The third study, "ESETT",[44] was a double-blind RCT which compared levetiracetam, fosphenytoin (FOS) and sodium valproate (SVP) in 255 children (two to 17 years) and 237 adults.[10,44] Patients were randomised to levetiracetam 60mg/kg, fosphenytoin 20mg/kg or sodium valproate 40mg/kg; all three drugs were infused over 10 minutes. The primary outcome was the absence of clinically evident seizure activity with improving responsiveness at one hour without additional anti-epileptic medication. In children, this outcome was achieved in 52% in the levetiracetam, 49% in the fosphenytoin and 52% in the sodium valproate-treated groups. In adults aged 18–65 years, the primary outcome was achieved in 44% with levetiracetam, 46% with fosphenytoin and 46% with sodium valproate. In the 52 adults aged over 65 years, the primary outcome was achieved in 37% with levetiracetam, 35% with fosphenytoin and 47% with sodium valproate. None of these differences reached statistical significance. The results largely mirrored those of "EcLiPSE" and "ConSEPT". However, an important finding seen in "ESETT" was that statistically more children in the fosphenytoin-treated group required intubation and respiratory support; this was not seen in adults. The authors were unable to explain this finding. Other secondary safety outcomes did not significantly differ by drug within each age group.[44]

An earlier meta-analysis suggested that sodium valproate was being increasingly used in the management of CSE, particularly in adults, despite the lack of good efficacy and safety data.[45]

A systematic review and meta-analysis by Abdelgadir et al in 2020[46] and also by Feng et al in 2021[47] both concluded that levetiracetam is comparable to phenytoin (or fosphenytoin) but has the advantage of being superior in safety outcomes. Abdelgadir et al[46] included only RCTs, which comprised of 10 studies involving 1907 children. Seven of the 10 studies compared levetiracetam to phenytoin (1640 children) and three compared levetiracetam to fosphenytoin or sodium valproate. They reported no statistically significant difference between levetiracetam and phenytoin in seizure cessation in the seven studies. However, in the levetiracetam versus fosphenytoin comparison, fewer children in the levetiracetam-treated group required RSI. There was no statistically significant difference in the rate of RSI between the levetiracetam and sodium valproate comparison. The study team found no statistically significant differences in adverse events or ICU admission in either the combined studies comparing levetiracetam to phenytoin, levetiracetam to fosphenytoin, or levetiracetam to sodium valproate. Feng et al[47] found similar results in their meta-analysis. They included 11 RCTs involving 2140 patients with an average age of 15 years and compared levetiracetam with fosphenytoin or phenytoin. Their pooled data also showed that there was no statistically significant difference in seizure termination rates or time to seizure termination in the two groups. A sub-analysis mirrored the earlier, 2020 meta-analysis[46] in that statistically more patients treated with fosphenytoin compared to levetiracetam experienced adverse drug events, respiratory depression and acute hypotension and also required more assisted respiratory support ($p = 0.002$). These differences were not seen in the levetiracetam and phenytoin comparison ($p = 0.06$).

Lacosamide

Lacosamide (LAC) is licensed as monotherapy for focal seizures with or without secondary generalisation and as an adjunctive treatment for partial-onset (focal) seizures with or without secondary generalisation in patients aged four years and above. It can be given IV or orally. A small open-label efficacy and safety study of its use in nine children with CSE showed it to be effective in 77.8% of patients but only 44% became seizure free.[48] The mean loading dose was 8.7mg/kg (range: 3.3 to 10mg/kg) the majority of patients received a dose of 10mg/kg. No significant adverse drug reactions were reported. The authors concluded that it was an appropriate adjunctive treatment option which may be more effective when given earlier and at an adequate dose although this conclusion was based on very limited data. They suggested

a safe loading dose of 10mg/kg in the emergency setting.[48] A systematic review of the use of lacosamide in SE which evaluated a total of 522 non-convulsive SE and CSE episodes in 486 adults and 36 children and adolescents demonstrated an overall efficacy of 57%.[49] Efficacy was comparable between its use in non-convulsive SE (57%) and CSE (61%). However, these findings must be regarded with caution because of methodological concerns with the studies included in the review, including the definition of CSE.[49] Another systematic review assessed a total of 115 patients treated with lacosamide and 166 treated with phenytoin from five studies.[50] Most patients were adults, and baseline characteristics were reported to be comparable between both groups. Seizure control was achieved in 57.3% of the lacosamide and 45.7% of the phenytoin-treated group. This included sub-group analysis for CSE and non-convulsive SE. Treatment-emergent adverse events were similar in both groups (17.6% in the lacosamide and 12.2% in the phenytoin group) but serious adverse events were higher in the phenytoin group (5.1% vs 0.8%).[50]

Finally, a position statement from the Canadian Pediatric Society published in 2021 reported that whilst lacosamide has the potential as a second-line treatment for CSE, there are insufficient data to recommend its use at the current time.[18]

Summary of Second-Line ASM-Treatment

Although the results of these three large RCTs[42–44] did not show levetiracetam to be superior (or non-inferior) to, or safer than either phenytoin (or fosphenytoin), additional numerous pooled efficacy and safety data, ease of use and shorter infusion times has led it to being widely considered as the "default", that is, first-choice, second-line ASM in the management of CSE in both children and adults.[51] This seems to apply throughout most of Europe and the US. This is certainly reflected in the recently published UK's Resuscitation Council UK guideline[14] and in the soon-to-be-published seventh edition of the APLS CSE guideline. Finally, it is important to acknowledge that, for many years prior to the publication of "EcLiPSE", "ConSEPT" and "ESETT", levetiracetam was being increasingly used in emergency departments and pediatric and adult intensive care units in the perception that it was as effective but easier and safer to administer than phenytoin. The results of "EcLiPSE", "ConSEPT" and "ESETT" showed that levetiracetam was non-inferior to phenytoin subsequently "convinced" many clinicians that their perception was correct.[51]

One issue that is rarely discussed in the second-line treatment of established CSE is the continuation of an IV-administered second-line ASM (ie lacosamide, levetiracetam, phenobarbital, phenytoin or sodium valproate) as an oral, maintenance ASM in those patients in whom this is considered necessary. Of these, levetiracetam and sodium valproate have the broadest spectrum of action against different types of seizures across all ages as well as the cleanest safety profiles. However, sodium valproate is now rarely used in females of child-bearing age because of concerns about its detrimental neuro-developmental effects on the fetus. Phenytoin and phenobarbital are only very rarely used as oral maintenance ASMs, particularly in children because of their adverse safety profiles. In the UK, lacosamide has yet to establish a clear role as an oral, maintenance ASM in children, other than as the fifth monotherapy choice in the treatment of focal seizures with or without evolution to bilateral tonic-clonic seizures.[52] This is in contrast to at least one center in the US[53] and Japan.[54] One observational study of CSE in adults showed that 8% of patients treated with IV fosphenytoin were subsequently commenced on oral phenytoin, in contrast to 78% treated with IV levetiracetam that were subsequently commenced on oral levetiracetam.[55]

A recently published meta-analysis compared the cost-effectiveness of five, non-benzodiazepine (ie second-line) ASMs in the treatment of benzodiazepine-resistant CSE.[56] Twenty-four studies were included with 1185 SE episodes. The most effective second-line ASM was phenobarbital with a probability of seizure-cessation of 0.8 (95% confidence interval [CI]: 0.69–0.88), followed by valproate (0.71 [95% CI: 0.61–0.79]), lacosamide (0.66 [95% CI: 0.51–0.79]), levetiracetam (0.62 [95% CI: 0.5–0.73]) and phenytoin/fosphenytoin (0.53 [95% CI: 0.39–0.67]). In pairwise comparisons, phenobarbital was more effective than phenytoin or fosphenytoin ($p = 0.002$), sodium valproate more effective than phenytoin ($p = 0.043$) and phenobarbital more effective than levetiracetam ($p = 0.018$). The most cost-effective non-BZD ASM was levetiracetam, followed by sodium valproate and lastly, phenobarbital. Phenytoin or fosphenytoin and lacosamide were not cost-effective compared to the other options. Sensitivity analyses showed a marked overlap in cost-effectiveness, but phenytoin or fosphenytoin were consistently less cost-effective than levetiracetam, sodium valproate and phenobarbital.[56]

Outstanding Issues

Pre-Hospital Use of Benzodiazepines

Debate continues on whether the out-of-hospital (pre-hospital) use of benzodiazepines (given by families, carers, paramedics, school nurses, etc.) should or should not be counted when an individual, and particularly a child, with CSE receives treatment in the AED or ER. One of the problems is the frequent under-dosing of both pre-hospital and also AED/ER-administered doses of benzodiazepines,[57–59] which is likely to make them less effective. A number of guidelines (including in the UK and Canada) state that if the child has already received two doses of a benzodiazepine, then no further doses should be given in the AED or ER, even if the previous doses were not given intravenously, and they should immediately receive a second-line ASM. This is to avoid causing respiratory suppression or arrest. However, the evidence to support this concern is limited and is beset by methodological difficulties;[30,60] respiratory depression was not reported to be a problem in more recent and much more scientifically undertaken studies.[42–44] Other guidelines (including those used in the US, Denmark and the Netherlands) recommend that if the child is still seizing in the AED/ER, then a further (third) dose of benzodiazepine could and even should, be given intravenously before then progressing to a second-line ASM. Their rationale is that giving a third dose is unlikely to cause a respiratory arrest, but if it does, then the patient is in a safe and monitored environment. Giving a third dose also provides a further opportunity to stop the seizure whilst the second-line ASM is being prepared and administered.

There have been attempts to see if a delay in the use of, or an under dose of, benzodiazepines used in the community and prior to attendance in the AED/ER may have an impact on the outcome. A recent study published by the US pediatric status epilepticus research group (pSERG) investigated whether the publication of evidence on delays in time to treatment had shortened the time to treatment in pediatric refractory convulsive status epilepticus (RCSE). The group compared the time to treatment before (2011–2014) and after (2015–2019) publication of evidence of delays in the treatment of RCSE within the pSERG centers. They showed that publication of evidence on delays in time to treatment was not associated with improvements in time to treatment of RSE. However, the study did show an increase in the proportion of patients who received at least one dose of benzodiazepine before arrival in the ER. The analysis was assessed using patient interviews and a review of medical records, a methodology which may be compounded by significant reporting and selection bias.[61]

A very recent and small study from Seattle in the US evaluated the role of a specific tool to improve the management of children with a convulsion by the emergency medical services (EMS) and prior to attendance in the ER.[62] The aim was to determine if the tool improved the rate of the correct dosing of a benzodiazepine and also the outcome of pediatric SE. Forty-four children before and 33 children after implementation of the EMS tool were evaluated. The demography of the two groups was very similar. The percentage of children that received an under dose of a benzodiazepine fell from 52% to 6% after implementation of the tool ($p < 0.001$). However, the interval to treatment with a second-line ASM remained prolonged and there was no significant reduction in the requirement for intubation or ICU admission.[62]

A study undertaken between 2013 and 2018 in 2494 adults with SE showed that 1537 (62%) received midazolam at any dose but that none of these patients were given a dose and/or route of administration that was consistent with national guidelines. Rescue therapy with a second midazolam dose was required in 282 (18%) patients. Higher midazolam doses were associated with lower odds of additional rescue therapy and were not associated with increased respiratory support.[62]

Sequential Use of a Second-Line ASM in Established CSE

The authors of "ConSEPT"[43] suggested that two second-line drugs, phenytoin and levetiracetam, can be given sequentially if the seizure continues after infusion of the first drug and before progressing to RSI and intubation; by definition, the child is then in refractory CSE. Their argument is that both drugs are more effective than one drug alone and this will reduce the need to progress to RSI and intubation with their associated risks. However, the administration of two second-line drugs will inevitably prolong the episode of established and then refractory CSE and substantially delay the use of RSI. Assuming that phenytoin was the first second-line drug given, then the next would be levetiracetam, and in practice, the preparation and administration of this drug is likely to take 10–15 minutes. If levetiracetam was the first second-line

drug given, then the next would be phenytoin, and in practice, the preparation and administration of this drug is likely to take 20–25 minutes because of its pharmacokinetics. This would significantly add to the overall duration of CSE and increase the risk of neurological sequelae. However, it is acknowledged that the use of two second-line drugs might be relevant and important if emergency anaesthetic resources (and specifically early RSI and intubation), are limited or difficult to access. As yet there seems to be only minimal published support for this sequential two-drug approach amongst adult neurologists.[63] Zaccara et al concluded: "In patients with a benzodiazepine-resistant status epilepticus, we suggest the intravenous administration of levetiracetam as soon as possible. If levetiracetam is ineffective, a further antiepileptic drug among those currently available for intravenous use (valproate, lacosamide, or phenytoin) can be given before starting third line treatment".[63] It is important to note that these authors did not recommend giving phenytoin first and then followed by levetiracetam, sodium valproate or lacosamide.

Future Research

Most published RCTs and other ASM-related research in the management of CSE will usually include a comment that further studies are required to confirm or refute their findings, or to identify a new and more effective ASM. This is predictable because as yet there is no single drug or combination of drugs that will terminate either impending or established CSE in all patients. The three large RCTs that assessed the use of levetiracetam, phenytoin/fosphenytoin and sodium valproate in the second (established) stage of CSE demonstrated a success rate of only 50–70%, irrespective of the trial drug. This low success rate clearly raises a number of questions:

- Did it reflect a delay in starting first-line treatment, which then had a "knock-on" effect with passing on the delay to the second-line stage and consequently making it more difficult to terminate the episode of CSE? A study of 1049 adults with 1179 episodes of SE, of whom 457 had CSE, showed a significant delay in the administration of the first dose of benzodiazepine. Less than 50% received a first dose within 30 minutes of the onset of CSE, and in this group, there was a statistically significantly longer time to the end of CSE. The overall mortality was 9.4% (43), of whom 93% (40) had termination of SE within 60 min of treatment initiation ($p = <0.001$).[64]
- Did it reflect an under-dosing of benzodiazepines used prior to arrival in hospital or in the AED/ER, or both? Under-dosing of benzodiazepines as a first-line treatment has been reported in several publications. Some of these have described a poor response to subsequent management,[57,58,64–67] although this was not seen in the recent "ESETT" study.[44,59]
- Did it reflect a delay in starting the second-line treatment?
- Was it the underlying cause?
- Was it some other factor?
- Was it a combination of two or more of the above factors?

Without wishing to sound nihilistic, realistically it is very unlikely that any new ASM will ever be discovered, designed or developed that will terminate all episodes of impending or established CSE in all patients. This is due to the marked heterogeneity of the epilepsies and their many different etiologies.

However, there are potential areas of further research. One would be to consider an entirely new, and potentially non-ASM approach to the management of impending CSE in the AED/ER. Another would be to compare CSE-termination rates, rates of RSI and intubation and admissions to intensive care units between centres that use a second-line sequential, two-drug policy and those that use only a single second-line drug for established CSE. The design of such a study would need to be meticulous and robust to minimise the effect of other confounding factors which beset many published studies of the management of CSE. Finally, intravenous levetiracetam has been shown to be as effective (76%) as intravenous lorazepam (a first-line ASM) in terminating CSE in a small pilot study of 79 patients, most of whom were adults.[65,68] The 24-hour seizure freedom rate was also comparable in the two groups (79.3% in the levetiracetam and 67.7% in the lorazepam-treated group). Lorazepam was associated with a significantly higher rate of hypotension and assisted ventilation.[65,68] These very preliminary results probably justify further research.

Conclusions

Evidence from a number of good RCTs over the past 10 to 15 years has shown that benzodiazepines are effective in stopping an episode of impending CSE in approximately 60–90% of cases. When intravenous access is not immediately available, meta-analyses of these RCTs have not demonstrated that midazolam (buccal or intra-nasal) is statistically more effective or safer than rectal diazepam. Current evidence has shown no difference in efficacy between the buccal and intranasal routes of administration of midazolam. Despite there being less robust evidence of midazolam's perceived superior efficacy, together with a much preferred use of its buccal or intra-nasal administration, rather than diazepam administered rectally, midazolam has become the benzodiazepine of first choice in the treatment of the first or impending stage of CSE when intravenous access is not immediately available. Intra-muscular midazolam offers a third option when intravenous access is not possible. When intravenous access is immediately available, evidence suggests that there is no significant difference in efficacy and respiratory depression between intravenous lorazepam and intravenous diazepam. However, pooled efficacy and safety data from RCTs and open studies would suggest that intravenous lorazepam is preferred to intravenous diazepam.

Until recently, there was limited evidence for the justification of phenytoin, fosphenytoin or phenobarbital to treat the second or established stage of CSE. The recent publication of three large RCTs (comprising almost 750 children and adults), together with some earlier but smaller trials, has provided much-needed RCT evidence for the management of this stage of CSE. However, this new evidence has shown no significant difference in the use of levetiracetam (in doses of 40 or 60mg/kg), phenytoin (or fosphenytoin) or sodium valproate in the treatment of established CSE in children. Specifically, there was no statistically significant difference between these drugs in stopping the presenting seizure, time to seizure cessation, seizure-recurrence within 24 hours, the need for RSI, adverse events or mortality. Consequently, levetiracetam, phenytoin (or fosphenytoin) or sodium valproate could be considered as the first choice, second-line ASM in the management of CSE. Despite this lack of superiority or non-inferiority between these three ASMs, it is clear that levetiracetam is becoming, or has already become in many centres (and in many countries) the ASM of first-choice in the second-line management of benzodiazepine-resistant (established) CSE primarily because of its ease of administration and perceived better safety profile.

Finally, it is clear from the literature that there continues to be a delay in the management of convulsive seizures and the appropriate dosing of rescue ASMs and specifically benzodiazepines. Although this primarily involves the community or out-of-hospital situation, it also involves the AED and ER. Further training and guidance is certainly required to prevent or at least minimise these delays and to ensure an appropriate timing and dosing of ASMs in the management of CSE.

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Author Contributions

All authors made a significant contribution to the work reported, including in the study conception, design and execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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