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Learnings from the COVID-19 pandemic from the ILAE

Welcome to the latest issue of PECAS. It feels a little premature, but as it is the last issue of 2020, it seems fitting to bid this year farewell. Needless to say, 2020 did not go how any of us expected. The spread of coronavirus, the global pandemic and lockdown restrictions knocked us all for six. To a great many people everywhere, it felt like we spent half a year in a weird, and, at times fearful, daze – at home and at a distance.

But for healthcare systems and health professionals, the same period was more of a frenzy. Systems reconfigured staffing to meet the demand presented by COVID-19, and new and innovative ways of delivering care were implemented. Masks, personal protective equipment (PPE), and hand sanitiser became essential items in every clinic, ward and consultation room.

This year may be winding down, but COVID-19 and its legacy are here to stay. In light of this, the International League Against Epilepsy (ILAE) held a virtual epilepsy symposium entitled 'Learnings from the COVID Pandemic: The New Normal'.

The symposium was moderated by Julie Hall and chaired by Prof Helen Cross, Honorary Consultant in Paediatric Neurology and The Prince of Wales' Chair of Childhood Epilepsy. They were joined by Prof Samuel Wiebe, Prof Emilio Perucca and Prof Ingmar Blümcke. Prof Wiebe is a professor at the Department of Clinical Neurosciences, Associate Dean for Clinical Research and Director of the Comprehensive Epilepsy Program at the University of Calgary (Canada). Prof Perucca is a professor at the University of Pavia and Director of the Clinical Trial Center of the C. Mondino National Neurological Institute in Pavia (Italy). Prof Blümcke is Director of the Neuropathology Department at the University Hospital Erlangen and professor at Friedrich-Alexander University School of Medicine (Germany). The symposium focused on neurological implications of COVID-19, effects on anti-seizure medications, the pathology of COVID-19, attempts to optimise patient care during a pandemic and potential lessons from COVID-19 for the future.

COVID-19 and epilepsy risks

Prof Cross stated that having epilepsy does not seem to be a risk factor for getting COVID-19 or having more severe symptoms of the disease. She added that,

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generally, evidence suggests that COVID-19 seems less severe in children. However, some comorbidities of epilepsy could result in more severe COVID-19 symptoms, such as existing respiratory problems.

Prof Wiebe pointed out that people in more deprived socio-economic areas seem to be at higher risk of more severe COVID-19 symptoms and mortality. This is something that has been reflected in the media for many months.

The panel agreed that coronavirus does not appear to exacerbate seizures any more than other common respiratory viruses. However, they said people have reported an increase in seizure frequency during the pandemic.

Prof Wiebe highlighted that the disruption to people's lives by the pandemic could be a cause for an increase in seizures. A disruption in circadian hygiene in terms of sleep, eating patterns and exercise, among other things, could be contributing to the problem. He said that the pandemic has certainly uncovered pre-existing mental health problems in some patients with epilepsy. This will be incredibly important to address and manage both now and in the future.

Mental health is equally important in children and young people with epilepsy. A complete lack of routine, being out of school and constantly in the family environment is likely to affect many children. Prof Cross cited a survey carried out by 'Young Epilepsy' that reported an increase in seizures. She explained that possible factors for this increase could include difficulty accessing AEDs, a reluctance to go to hospital for fear of catching coronavirus and an inability to see their neurologist. She said behavioural changes, anxiety, depression and sleep disturbance were reported in the survey. The mental health of parents and carers has also been affected through economic, family dynamic, financial and employment problems, a lack of routine and stress. However, Prof Cross did highlight that there have been some positive experiences including more family time together and, in some cases, a healthier lifestyle.

Clinical practice

The COVID-19 pandemic has had a profound and lasting effect on epilepsy services. Prof Cross explained that throughout the pandemic, services have had to try to carry on. Service providers have had to ensure families have a continuous point of contact to seek advice, while keeping children out of hospital as much as possible. She added that very clear advice has had to be given about when to attend hospital and when not. Healthcare providers have also had to ensure a sustained supply of AEDs for patients through longer prescriptions. Prof Cross added that it

is particularly important to ensure patients with epilepsy know where to go for advice and support for mental health problems.

Prof Wiebe said the young adult population has been affected slightly differently. Factors such as isolation, not being able to gather with others, and not being able to see friends face to face have played a part in their wellbeing and stress levels.

When these people are seen in clinic, most of the time is spent managing psychosocial problems. He said the requirements for effective communication have increased. In this group of patients, asking the right questions is important to uncover any mental health concerns, as they can go undetected. This is key, as mental health problems can then affect things like medicine adherence and sleep.

Drug therapy management

Prof Perucca spoke about the importance of maintaining a supply of medicines for patients at a time when supply could be affected. He acknowledged that it is difficult to give advice applicable across the world, as different places are at different stages with the pandemic. However, he said ensuring that patients don't run out of medicines is vital, possibly through prescriptions that allow medications to be supplied for many, rather than just one month. He also said the threshold for using rescue medicines should be reviewed and, in specific situations, lowered to prevent or avoid prolonged seizures and the need for hospital care. He added that changes to medicines that could compromise seizure control, such as withdrawing medicines in patients who are seizure free, should be postponed.

Regarding interactions with COVID-19 treatment, he highlighted that we do not yet have a drug to treat COVID. But he said the classes of drugs currently used are steroids. These may be significantly affected by enzyme inducing agents, so care should be taken with certain AEDs. Prof Perucca suggested that intravenous

rather than oral administration of COVID-19 medicine (such as steroids) could minimise any interactions. He also added that people being treated for COVID-19 will probably also be taking many other medicines, which might also interact with AEDs. He said that, wherever possible, AEDs with the lowest risk of interactions with other drugs should be prescribed.

Telemedicine

Telemedicine has also become a staple of healthcare services during the pandemic to help ensure that care is optimised during this time and disparity of care is avoided. It offers much in terms of being able to see the patient, as well as speak to them. It should be stressed that this is not ideal for everyone. Prof Cross said some patients may prefer a simple phone call. But in the absence of face-to-face consultations, it is an important tool. Prof Cross added that young people can often feel more comfortable with video calls, if only because they are much more used to this form of communication.

She added that there can be issues with video calls. People may not have access to the internet or have the bandwidth to do these types of calls. Telemedicine also requires good preparation in advance on the part of the clinician and the patient, which may be more so than would have been needed previously.

Prof Wiebe added that patients with cognitive impairment or who need somebody with them could struggle with video calls. As well as this, issues with language barriers may be more challenging to solve through video conferencing and can make communications difficult and confusing. Working out a secure and private way to share video footage of epilepsy events is also important. Clinicians must be readily available and sensitive in recognising which patients need urgent consultations and investigation. The panel agreed that in this day and age, internet access and good bandwidth is part of, and should become standard practice in, healthcare provision.

New normal

The panel were sure that the healthcare landscape looks and will continue to look very different to what it did before the pandemic. However, all were in agreement that there should be one clear, coherent and consistent message – that healthcare, research and learning must continue.

Prof Cross said that during the beginning and at the peak of the pandemic, hospitals stopped doing investigations. She argued that it is now safe to do EEGs, MRIs and video telemetry with appropriate precautions. These investigations must continue to maintain the best levels of patient management. Prof Wiebe added that recent events have highlighted the need to empower patients to take control of their own conditions when access to specialists is difficult (although it must be acknowledged that this is often easier said than done). This includes patients and their families understanding their epilepsy and things like what medicines they are taking and at what doses. He also stressed that mental health cannot be overemphasised or neglected.

Prof Blümcke explained that online teaching may become the new normal. He also believes that there may be a change in medical competencies in case professionals need to respond to a medical emergency like this again.

Prof Perucca said COVID has slowed research and he had three messages to share. Firstly, epilepsy research should not stop, as this is clearly important, particularly for those with intractable epilepsy. Secondly, he said that the pandemic has revealed extraordinary opportunities to use new technology which has been incredibly useful, and we should learn how to best integrate it into research. Lastly, we must establish contingency plans to try and ensure research can continue.

Prof Cross closed, saying that we can't stop treating patients with epilepsy when we have an illness like COVID-19. She said we should all strive to advocate continuing care and deliver the service our patients need.

The symposium showed the importance of adapting services in order to continue to deliver the highest quality of care despite the crisis and chaos around us. The pandemic has also shown how common and under-managed mental health problems are in patients with epilepsy, and other chronic conditions. This must be addressed help reduce seizure frequency and optimise people's self-management of their epilepsy and overall quality of life. Clinical practice now relies more heavily than ever on very effective communication between healthcare professionals and patients, as well as on new technologies to help bridge the face-to-face gap left by COVID-19. The biggest take-home message the panel wanted to share was that patient management, teaching and research must continue even when there is a global medical emergency. The tools we have developed for patient care and teaching are here to stay and we should ensure they are improved and become an integrated part of patient care wherever possible.

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epilepsy action

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Your child and epilepsy is a new online course for parents and carers of children with epilepsy. It's been developed with parents, epilepsy nurses and psychologists.

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Convulsive status epilepticus in children: a new era

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Background

Status epilepticus (SE) underwent a review of its definition and classification by the International League Against Epilepsy (ILAE) in 2015. It included the following definition: '*SE is a condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point* $\mathbf{t_1}$*). It is a condition that can have long-term consequences (after time point* $\mathbf{t_2}$*), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.*' For convulsive (tonic-clonic) SE, the ILAE defined $\mathbf{t_1}$ as '*five minutes*' and $\mathbf{t_2}$ as '*30 minutes*' [Trinka *et al*, 2015]. Practically, this means that if a tonic-clonic seizure has lasted five minutes, treatment should be given to try and terminate it.

The ILAE also recommends that, wherever possible, every person in SE should be described using four domains or 'axes':

- Semiology (the clinical features of the status)
- Aetiology (its cause)
- Its EEG correlate (this aspect will not be addressed in this article, but includes non-convulsive status epilepticus)
- Age:
  - Neonatal (birth – 30 days)
  - Infancy (1 month – 2 years)
  - Childhood (>2 – 12 years)
  - Adolescence and adulthood (>12-59 years)
  - Elderly (>60 years)

The ILAE also classified convulsive status epilepticus (CSE) by duration or the response to anticonvulsant medication [Trinka and Kälviäinen, 2017]:

- **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 anticonvulsant (traditionally a benzodiazepine but it could be paraldehyde on the person's individualised rescue plan)
- **Refractory CSE** – the seizure has persisted after failure of a benzodiazepine followed by another class of anticonvulsant (in most situations this will be phenytoin, fosphenytoin or phenobarbital, but levetiracetam, sodium valproate and even lacosamide are becoming increasingly used – see later)
- **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

Further information on the detailed ILAE report of the classification of SE and on refractory CSE can be found in Trinka *et al* [2015] and Fernandez *et al* [2014] respectively. This article will address only convulsive or tonic-clonic SE (CSE) in children aged <18 years. This is in view of the acquisition of new and important scientific data on its second-line management and also the fact that, fortunately, only 20-25% of children will progress to refractory CSE.

Why is CSE important?

CSE is the most common and most serious, life-threatening neurological emergency in children. The estimated incidence is approximately 15-25 in 100,000 children a year [Chin *et al*, 2006; Novorol *et al*, 2006], with the highest incidence in children aged less than three years. Up to 3-4% of children that present with CSE will die. The figure increases dramatically if the CSE becomes refractory (15-20%) and can reach 32% [Sahin *et al*, 2001]. Mortality may exceed 60% in super-refractory CSE, although this figure is derived from predominantly adult data. There is also a risk of irreversible neurological morbidity following CSE, including a new and chronic epilepsy, neuro-disability and learning difficulties [Chin *et al*, 2006; Hussain *et al*, 2007; Novorol *et al,* 2006]. The most important factor that determines mortality and morbidity of CSE is its aetiology, followed by age, although this is closely linked to the aetiology. The duration of CSE is the next most important and for obvious reasons, its management is closely linked with the duration. Over 90% of all convulsive seizures end spontaneously within four minutes [Shinnar *et al*, 2001]. However, a paediatric study showed that, once a convulsive seizure has lasted >5 minutes, it is likely to last at least 30 minutes [Eriksson *et al*, 2005].

Mismanagement is more often an under-treatment (anticonvulsants given too late or in too low a dose), rather than an over-treatment (anticonvulsants given too rapidly, in too high a dose or continuously) [Chin *et al*, 2004].

Current management of CSE

The current UK-wide emergency or 'rescue' care pathway for the management of acute tonic-clonic seizures and CSE in children is the Advanced Paediatric Life Support (APLS) guideline [Advanced Life Support Group, 2011]. It

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is also the one cited in the National Institute for Health and Care Excellence (NICE) guidance on epilepsy [NICE, 2012]. This is a timed, step-by-step approach with recommended doses of anticonvulsants based on actual or estimated body weight.

First-line management (impending or premonitory CSE)

The initial, first-line step is a maximum of two doses of a rapid but short-acting benzodiazepine. This is either intravenous lorazepam (when intravenous access is available), or buccal midazolam (for use in the community or when intravenous access is unavailable) [McTague *et al*, 2018]. However, in the USA, rectal diazepam is preferred to buccal midazolam, but the reason for that is not entirely clear. When a benzodiazepine is contra-indicated because of lack of efficacy or previous acute respiratory suppression or arrest, the child will have their own specific, individualised emergency care plan. This could include rectal paraldehyde for both out-of-hospital use and use in emergency departments (EDs) prior to establishing intravenous access [Rowland *et al*, 2009].

Another option is intramuscular, rather than buccal, midazolam when intravenous access is not possible. Recently, a randomised controlled trial (RCT) of 150 children aged 4.5 months to 14 years, presenting with an acute seizure to the ED, was undertaken. It showed that seizure-cessation within five minutes of administration of the randomised medication occurred in 61% of the intramuscular and 46% of the buccal treatment groups – a statistically significant difference. Additional anti-seizure medications were required in 39% of the intra-muscular and 51% of the buccal group. One patient in the intramuscular group developed respiratory depression and hypotension; no patient in the buccal group had any adverse reactions [Alansari K *et al*, 2020]. Optimistic as the results of this single RCT may be, one must not forget that intramuscular injections may be painful, even after the child has recovered from the seizure or episode of CSE. The injection of a drug is also unlikely to become accepted as the preferred out-of-hospital and home- or school-administered route of administration of a benzodiazepine.

Second-line management (established CSE)

When CSE has persisted for 10 minutes following two doses of benzodiazepines, a second-line (and typically longer-acting) anticonvulsant is administered [Advanced Life Support Group, 2011]. Traditionally, this has been, and remains, phenytoin, introduced in the early 1950s. In the US, fosphenytoin replaced phenytoin over a decade ago. Phenobarbital is the alternative medication for children allergic to phenytoin or that have not responded to it previously. Those few children who take phenytoin as a maintenance anticonvulsant for their chronic epilepsy may or may not be given intravenous phenytoin. It is possible, if not likely, that a low level of the phenytoin drug will have been responsible for the episode of CSE. Nevertheless, some EDs would not give intravenous phenytoin in this situation because of concern over causing phenytoin-toxicity. Finally, it is important to understand that up until 2018, there had been no RCT data to justify phenytoin's position as the first choice, second-line drug treatment of CSE.

Levetiracetam was introduced in early 2000. Considerable anecdotal evidence over the following decade suggested that the drug was effective in the treatment of adults and children with CSE, non-convulsive status epilepticus, and those with acute repetitive seizures [Berning *et al*, 2009; Kirmani *et al*, 2009; Knake *et al*, 2008; McTague *et al*, 2012; Michaelides *et al*, 2008; Trinka *et al*, 2009]. Reported success rates in terminating the seizure ranged between 75% and 100%. In a single small RCT in adults, intravenous levetiracetam was as effective as intravenous lorazepam in terminating CSE in approximately 74% of patients [Misra *et al*, 2012]. Levetiracetam can be given over 5-10 minutes and this shorter infusion time would suggest, at least theoretically, that the seizure may terminate more rapidly than with phenytoin. There have been no reports of cardiac arrhythmias, hypotension, severe tissue extravasation reactions (including the 'purple glove' syndrome) or Stevens-Johnson syndrome with intravenous levetiracetam [Wright *et al*, 2013]. Mild and usually transient sedation and agitation have been reported infrequently, as has a mild and transient skin rash at the infusion site. For those patients that require oral maintenance treatment following an episode of CSE, it is much easier to continue with oral levetiracetam than with phenytoin [Nakamura *et al*, 2017]. Finally, there is no clinical need to measure blood levels of levetiracetam.

This has led many to believe that levetiracetam is more effective, safer and easier to use in CSE than phenytoin. Predictably, its use has been expanding in many paediatric and adult EDs. However, this risks repeating the phenytoin story, namely using an anticonvulsant in a medical emergency with no good scientific data, a practice with which many clinicians feel uncomfortable and consider inappropriate. However, the accumulating evidence clearly indicated levetiracetam should be evaluated as a replacement for phenytoin as the first-choice, second-line anticonvulsant [Trinka and Dobesberger 2009; Hirsch *et al*, 2008; Zelano and Kumlien 2012]. Ideally, these evaluations should be conducted using the gold standard RCT. Research in the management of CSE was cited as one of five priority areas in the epilepsy guideline published by NICE [NICE, 2012]. This was one of the factors that led to the conception of the UK study, Emergency treatment with levetiracetam or phenytoin in status epilepticus in children – the EcLiPSE study. This national study was funded by the National Institute for Health Research's Health Technology Assessment (NIHR HTA) programme.

And now, at last …

Suddenly, from there being no robust RCT, including in adults, over the last 18 months, three large RCTs have now reported on the second-line drug treatment of CSE. The first two, published in early 2019, compared the efficacy and safety of phenytoin and levetiracetam in open and pragmatic trials. The third, published in late 2019 and early 2020, compared the efficacy of fosphenytoin (a pro-drug of phenytoin), levetiracetam and sodium valproate in a double-blind RCT. Collectively, these three trials studied almost 750 children aged between two months and 18 years.

The first published study was undertaken in the UK (the 'EcLiPSE' study) and involved 286 children aged six months to 18 years. Of these 286, 152 were allocated levetiracetam (receiving a dose of 40mg/kg infused over five minutes), and 134 phenytoin (receiving a dose of 20mg/kg infused over a minimum period of 20 minutes) [Lyttle *et al*, 2019]. The primary efficacy outcome was time from randomisation of the trial drug to seizure cessation. The presenting episode of CSE was terminated in 106 (70%) children allocated levetiracetam and 86 (64%) allocated phenytoin. The median time from randomisation to CSE-cessation was 35 minutes in the levetiracetam and 45 minutes in the phenytoin-treated group, but this was not statistically significant. Secondary analysis showed that the median time from the start of the infusion of the randomised medication to cessation of CSE was 17.5 and 24.5 minutes for levetiracetam and phenytoin respectively. No participant died as a direct result of either of the trial medications and only one participant (who received phenytoin) experienced a serious adverse reaction.

The second study was undertaken in New Zealand and Australia (the 'ConSEPT' study). It involved 233 children aged two months to 16 years using a similar protocol, including identical doses and rates of administration of the two drugs to EcLiPSE (Dalziel *et al*, 2019). The primary efficacy outcome was clinical cessation of seizure activity five minutes after completion of infusion of the study drug. This was achieved in 68 (60%) patients in the phenytoin group and 60 (50%) patients in the levetiracetam group – also not statistically significant. The median time from the start of the infusion of the randomised medication to cessation of CSE was 17 and 22 minutes for levetiracetam and phenytoin respectively. No participant died as a direct result of either of the trial medications and no participant was reported to have experienced any serious adverse reaction or event.

The third and most recent study was undertaken in the US (the 'ESETT' study). It involved 225 children aged 2-17 years and 237 adults (186 aged 18 to 65 and 51 aged >65 years) [Kapur *et al*, 2019; Chamberlain *et al*, 2020]. The primary efficacy outcome in ESETT was the absence of clinically apparent seizures with improving responsiveness at 60 minutes without additional anti-epileptic medication. The dose of levetiracetam was 60mg/kg. The primary outcome was achieved in 52% of levetiracetam, 49% of fosphenytoin and 52% of valproate-treated children – clearly, not statistically significant. The proportions of those achieving seizure cessation were similar across the three age groups, although the number in the >65 group (51) was very small. No statistical difference was seen between the treatment groups for the age groups <18 and >18 years. The primary safety outcome (life-threatening hypotension or life-threatening cardiac arrhythmia) was rare and did not differ by treatment group in any age. Significantly more children treated with fosphenytoin required intubation and respiratory support.

It is relevant to compare and contrast two earlier paediatric RCTs that were published in 2018. Both investigated a small number of children. In addition, the methodology, including statistical analysis, was unclear. These issues clearly raise some potential concerns about the study's findings. The first evaluated 100 children (50 receiving phenytoin [dose of 20mg/kg] and 50 levetiracetam [dose of 30mg/kg]) aged 3-12 years with acute seizures. Unfortunately, there were many important exclusion criteria. These included: children with epilepsy and already on antiepileptic medication, clinical evidence of meningitis and sepsis, acute head trauma, febrile seizures, congenital anomalies and developmental delay. The authors' reasoning was that the "underlying aetiology made them more resistant to anticonvulsant response". In addition, the primary outcome ('Absence of seizure activity within the first 24 hours after admission') is not a usual and meaningful clinical outcome for acute seizures. The results were also presented in a confusing manner. Eighteen (36%) children had seizure activity at a presentation in levetiracetam and 12 (24%) children in phenytoin group. All received diazepam before a loading dose of phenytoin or levetiracetam. The seizure stopped in all children and the time taken for the seizure to stop was 30 ± 19 (range, 10-60) seconds in the levetiracetam-treated group and 28 ± 11 (range, 15-60) seconds in the phenytoin-treated group – not statistically significant. This speed of seizure cessation is barely credible. Based on their primary outcome, two children in the phenytoin and three in the levetiracetam-treated group experienced a seizure in the 24 hours after admission. Consequently, the overall efficacy was 96% in the phenytoin and 94% in the levetiracetam group; again, these results are again barely credible and must be open to question [Singh *et al*, 2018].

The second paediatric RCT published in 2018 was smaller. It comprised only 50 children aged three months to 12 years admitted with CSE and in whom the seizure failed to terminate with two doses of benzodiazepine. Twenty-five children received 20mg of fosphenytoin (phenytoin equivalent (PE)/kg) and 25 received 30mg/kg of levetiracetam. The primary outcome was clinical cessation of seizures five minutes following the completion of the infusion of the study medication. A secondary outcome

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was the number of seizures within 24 hours following admission. Fosphenytoin terminated seizures in 84% of the children compared with 92% in the levetiracetam group, which was not a statistically significant difference. The time taken to terminate the seizure was 2.5 ± 1.4 minutes in the fosphenytoin and 3.3 ± 1.16 minutes in the levetiracetam-treated group, which was statistically significant. These times are extremely, if not amazingly short. A seizure recurrence occurred in 24 hours in 9.5% of the fosphenytoin and 17.5% of the levetiracetam-treated group, which was not statistically significant [Senthilkumar *et al*, 2018].

There has been a cascade of further studies published around the time of EcLiPSE and ConSEPT, three of which will now be summarised.

A study from Pakistan over four and a half years evaluated 600 children. Seventy-nine percent were aged less than five years and were openly-randomised to receive levetiracetam (40m/kg) or phenytoin (20mg/kg) [Noureen *et al*, 2019]. The reported success rates for both drugs were very high. In the levetiracetam group, 278 of 300 (92.7%) achieved seizure cessation at 30 minutes after drug administration was completed, which was the primary outcome. In the phenytoin group, the figure was 259 of 300 (83.3%). Levetiracetam was found to be significantly more effective than phenytoin. Adverse events were seen in eight children in the phenytoin-treated group.

Another open randomised study undertaken in India described 104 children aged one month to 12 years, whose episode of status had not responded to a single dose of intravenous midazolam [Wani *et al*, 2019]. The methodology of this study was also confusing. Fifty-two children received levetiracetam (40mg/kg) and 52 received phenytoin (20mg/kg). The seizures were controlled in all 104 patients within 40 minutes. However, to achieve this 100% success rate, 13 of the 52 (25%) levetiracetam and seven of the 52 (17.5%) phenytoin-treated patients required an additional 'mini-bolus' of each drug, an extra 10mg/kg of each drug if the presenting seizure had not stopped. The authors did not specify when precisely the 'mini-bolus' was given after the initial loading dose. The mean time to control seizures in the two groups was six minutes with levetiracetam and 5.7 minutes with phenytoin, again not a statistically significant difference. This response was again very rapid. There was no significant adverse effect in both the groups.

A double-blind RCT was undertaken in 102 children aged three months to 12 years in CSE that was unresponsive to a single dose of intravenous lorazepam. Thirty-two children were randomised to receive levetiracetam (20mg/kg), 35 phenytoin (20mg/kg) and 35 sodium valproate (20mg/kg) [Vignesh *et al*, 2020]. The primary outcome was the proportion of patients that achieved control of convulsive status epilepticus 15 minutes after completion of study drug infusion. The study was stopped after the planned mid-interim analysis for futility. Statistical analysis was on an intention-to-treat basis. Very high success rates were again found: 30 of 32 (94%) in the levetiracetam, 31 of 35 (89%) in the phenytoin and 29 of 35 (83%) in the sodium valproate-treated group achieved the primary outcome. This was also not a statistically significant difference. There were no differences between the groups for secondary outcomes. One patient in the phenytoin group experienced fluid-responsive shock and one patient in the valproate group died due to encephalopathy and refractory shock. The mean times to terminate the CSE after administration of the randomised medication were almost identical (levetiracetam 3.1 minutes; phenytoin three minutes; sodium valproate 3.2 minutes). They were extremely rapid, particularly in view of the fact that each of the three randomised medications was given over 20 minutes. These response times were almost identical to those reported by Senthilkumar *et al* [2018].

The findings of the above five studies [Noureen *et al*, 2019; Senthilkumar *et al*, 2018; Singh *et al*, 2018; Vignesh *et al*, 2020; Wani *et al*, 2019) are difficult to understand. This is particularly in view of their somewhat limited, unclear and, at times, confusing methodologies and statistical analyses. The doses of levetiracetam ranged from 20 to 40mg/kg, compared to 40mg/kg in EcLiPSE and ConSEPT and 60mg/kg in ESETT. The findings of these five studies and specifically their very high rates of success in achieving their primary outcomes (which included stopping CSE), are in sharp contrast to the results of three much larger RCTs. The latter showed a much lower success rate of 50-70%. Consequently, the findings of these five studies must be open to question. Finally, it is uncertain, if not unlikely, that their results can be generalisable to other, and specifically UK and European paediatric populations. In part, this reflects the studies' extensive exclusion criteria and therefore selective nature of their recruited patients.

The ESETT team concluded that levetiracetam, fosphenytoin or sodium valproate could be used as the first-choice second-line treatment [Kapur *et al*, 2019]. Clearly, this mirrored the conclusions of the authors of the earlier EcLiPSE and ConSEPT studies for levetiracetam and phenytoin.

The ConSEPT team took a further leap of faith and largely into the unknown. They suggested that clinicians should consider the sequential use of levetiracetam and phenytoin (in any order) before progressing to third-line management of rapid sequence induction with anaesthesia [Dalziel *et al*, 2019]. The inclusion of sodium valproate in a three-drug sequence will inevitably prolong status, risk irreversible neurological sequelae and would be untenable

and clinically indefensible. The conclusion of the ConSEPT team was based exclusively on their own findings. Their protocol included the option to give the other trial medication if the initial (randomised) medication did not terminate the presenting CSE. Further assessment of seizure activity could be performed five minutes after the infusion of the second trial drug was completed. Consequently, 42 participants received phenytoin (the initial randomised medication) followed by levetiracetam and 48 received levetiracetam (the initial randomised medication) followed by phenytoin. Clinical cessation of seizure activity at two hours following the administration of only the randomised medication was seen in 62 patients (54%) in the phenytoin group and 61 (51%) in the levetiracetam group. However, seizure cessation at two hours, having received one or both study drugs, increased to 89 participants (78%) in the phenytoin group, and 86 (72%) in the levetiracetam group. The authors concluded that although both drugs failed to terminate CSE in a significant number of patients when given alone, treatment with one drug and then followed by the other reduced the failure rate by more than 50%. This was at the expense of only an additional 10 minutes (compared with giving phenytoin alone). They argued that clinicians should therefore consider the sequential use of either medication first, before progressing to RSI and intubation. Their logic is that clinicians might (understandably) consider the risks of RSI and intubation to be greater than the risks of administration and assessment of an additional second-line treatment. However, the administration of two second-line treatments might substantially delay the use of RSI. The ConSEPT team suggest that any delay would be less than 10 minutes. In my opinion, this is highly optimistic. In practice, the preparation and administration of either of the second-choice, second-line drugs after the first has been given and failed to terminate the CSE, is likely to take longer than 10 minutes. It could be closer to 15 minutes for levetiracetam or 20-25 minutes for phenytoin because of its more complicated preparation and longer duration of infusion. Such a delay would significantly add to the overall period of CSE since its onset and would significantly increase the risk of neurological and cognitive impairment. A factor in their argument is the geography of New Zealand and Australia. The use of two second-line drugs might be important if emergency anaesthetic resources (early RSI and intubation) are limited or difficult. As yet there seems to be only limited support for the ConSEPT approach amongst adult neurologists, at least in Italy. Zaccara *et al*, [2018] 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". Third-line treatment is traditionally an anaesthetic, such as thiopentone or propofol, or a continuous infusion of midazolam. Ketamine is a potential alternative that merits further research.

In my opinion, a more rational first step would be a meta-analysis of these three and other relevant RCTs. It is very likely one will be published within the next 12 months. This will then help to inform a multi-specialist debate between general paediatricians and paediatric specialists in emergency medicine, neurology, anaesthetics and intensive care. It is important that the management of a medical emergency, as is paediatric CSE, is as evidence-based as possible.

Conclusion

The second-line management of CSE in children (and possibly young adults), led by the UK's EcLiPSE study, now has a robust and scientifically reliable evidence-base for its management. This new evidence suggests that levetiracetam, phenytoin or sodium valproate could be used as the first-choice second-line treatment of CSE. Fosphenytoin is unlikely to ever be used in the UK because of its relative high cost with no clear additional safety benefit over phenytoin.

However, there are two additional caveats with sodium valproate. The first is the potentially fatal hepatotoxicity (acute liver failure) that is recognised to occur particularly in children aged two and possibly up to three years of age. This is possibly because of an underlying and potentially undiagnosed metabolic (including a mitochondrial) disorder. Up to 50% of all cases of paediatric CSE occurs in children aged ≤3 years [Lyttle *et al*, 2019; Dalziel *et al*, 2019]. Therefore, sodium valproate is unlikely to be one of the first-choice second-line anticonvulsants in this age group. The second, but much less important issue, is the concern over the use of sodium valproate in girls of child-bearing potential (i.e. aged 12 years and above). This is only relevant, if after receiving intravenous valproate to treat an episode of CSE, they are then continued on this medication as oral maintenance. However, in reality, this is unlikely to be common practice because only ≤5% of all cases of paediatric CSE occur in children aged ≥12 years [Dalziel *et al*, 2019; Lyttle *et al*, 2019; McIntyre *et al*, 2005].

All recently-published RCT data must now be carefully interpreted by a multi-speciality national group and the application of this interpretation must be guided by the following:

- The two key principles of the Hippocratic oath: 'do the patient no harm' and then, 'do the patient good'
- The avoidance of subjective bias by one or two outspoken clinicians within any multi-speciality group when revising the APLS (and other) national guidance on the management of paediatric CSE.

Hopefully, NICE in its ongoing comprehensive review of its Epilepsy Guideline, will also undertake its usual stringent,

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RCT-based and cost-effective analysis when it publishes its revised recommendation on the treatment of paediatric CSE. stringent, RCT-based and cost-effective analyses

Finally, it is important to acknowledge that the termination of CSE in the three most robust RCTs undertaken in the UK, New Zealand/Australia and the USA was achieved in only 50-70% of patients, irrespective of the trial medication. This clearly raises a number of questions:

- Why was the response rate so low?
- Did this reflect a delay in starting the first-line treatment, which then had a 'knock-on' effect with passing on the delay to the second-line stage?
- Did this reflect a delay in starting the second-line treatment?
- Was it the underlying cause, or was it some other factor – or a combination of two or more of these factors?
- Should efforts be made to identify a different, including novel, second-line anticonvulsant that is more effective than, and at least as safe as, levetiracetam, phenytoin or sodium valproate?

And a final question:

- What should be the most appropriate timing of the different steps in the treatment algorithm of CSE? Particularly, how much time should be left between the administration of the last of the two possible doses of the first-line treatment and the administration of the second-line treatment? The UK and much of Europe use 10 minutes whilst New Zealand and Australia use five minutes whilst the timings in the USA seem much less precise.

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Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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