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CURRENT AWARENESS SERVICE

Striking a balance: ASMs and teratogenicity

Anti-seizure medications (ASMs) have an incredibly important job in reducing or stopping seizures in children and adults with epilepsy. We know that this is vital in the management of epilepsy for many reasons, not least among them to reduce the risk of sudden unexpected death in epilepsy (SUDEP) [Hesdorffer *et al*, 2011; Sveinsson *et al*, 2019] and accidental death and injuries [Salas-Puig *et al*, 2019]. Seizures can also be debilitating and limit quality of life for people, affecting things like relationships, school and work [Lystad *et al*, 2022; Nishida *et al*, 2020]. In a significant minority of cases, frequent seizures may also contribute to the progression or worsening of some types of epilepsy, such as the developmental and epileptic encephalopathies and mesial temporal lobe epilepsy [Avanzini *et al*, 2013]. Additionally, Dr Laura Parvainen *et al* found that a higher number of seizures before diagnosis was linked to a greater risk of resistance to treatment [Parviainen *et al*, 2020].

ASMs are a crucial part of epilepsy care but their optimal use also involves balancing side effects with seizure management. Evidence shows that for some people, the side effects have a higher impact on quality of life than their seizures themselves [Modi *et al*, 2011; Mroueh *et al*, 2020]. Side effects span a wide range of problems, but will often resolve if the ASM is either reduced or stopped. However, one side effect which can have a particularly damaging and long-lasting impact is teratogenicity.

For many years phenytoin was considered to be associated with the greatest risk and incidence of teratogenicity. Phenytoin is now used only rarely as a maintenance ASM because of its significant short and long-term adverse safety profile. Sodium valproate (VPA) has now become the ASM that is most likely to be associated with teratogenic effects. In many people, it may be the most effective ASM for their seizures. This is particularly in those with an idiopathic or genetic generalised epilepsy and specifically, childhood and absence epilepsy, juvenile myoclonic epilepsy and myoclonic-atonic epilepsy (also known as Doose syndrome). However, there is a one in 10 risk of physical abnormalities and a four in 10 risk of developmental and learning problems in babies born to mothers who took VPA during pregnancy and specifically the first three to four months of pregnancy. VPA has been used since the 1970s and these effects have been known for almost as long [Robert and Guibaud, 1982; Kao *et al*, 1981]. However, it took many years for the cognitive and behavioural effects of the drug to be fully appreciated

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and even then communication over these effects was very poor. Understandably, this led to a public outcry and resulted in what could reasonably be called a scandal. An urgent safety review by the UK government followed, launched in 2018 [First Do No Harm, 2020]. Consequently, also in 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) changed its prescription guidance for valproate, banning its use in women and girls of childbearing potential without appropriate contraception being put in place [MHRA, 2018]. There is more detail on this in the introductory article in volume 15, issue 2 of PECAS [Kountcheva, 2021].

Since 2018, there has been a significant reduction in the number of prescriptions of VPA. NHS Digital published findings from the Medicines and Pregnancy Registry in March 2022 [NHS Digital, 2022] which showed that the number of women prescribed VPA in a month fell by over 7,000 between April 2018 (27,448 prescriptions) and September 2021 (20,192 prescriptions). In total, over the three year period, 49,599 females aged 0-54 years old were prescribed VPA on one or more occasions. Of the 20,192 prescriptions made in September 2021, 8.6% (1,738) were in girls aged 0-11 years, 2.6% (530) in girls aged 12-15, 40.1% (8,107) in females aged 16-44 years old and 48.6% (9,817) in women aged 45-54 years.

Of all the women prescribed valproate during the review period, 832 women had 938 conceptions. Of these, 247 were prescribed VPA in a month in which they were pregnant. It's important to note that the registry summary doesn't capture the circumstances around these prescriptions. They may have been made with the informed consent of the patients themselves and their families. However, equally, some or all of these prescriptions may not have taken into consideration the patients' wishes.

In January 2021, the MHRA published a new review, based on the available safety data of most of the ASMs, and not just VPA [Gov.uk, 2021]. Of the 10 most commonly prescribed ASMs, four were found to cause an increased risk of physical abnormalities at birth compared to the general population. These were carbamazepine (Tegretol), phenobarbital, phenytoin (Epanutin) and topiramate (Topamax). Compared to 2-3% in the general population, carbamazepine and topiramate increased the risk of birth abnormalities to 4-5%, phenobarbital to 6-7%, phenytoin to 6%. Clobazam (Frisium), gabapentin (Neurontin) and pregabalin (Lyrica) may also slightly increase the risk of birth abnormalities, but the review did not have enough data to form a proper conclusion on this. However, in a 2022 drug safety update for pregabalin, the MHRA stated that a study of more than 2,700 pregnancies showed that there may be a slightly increased risk of birth abnormalities with this drug, and effective contraception should be used. The 2021 review also found here were also too few data to comment on the teratogenic risk for zonisamide (Zonegran).

Phenobarbital and phenytoin were found to increase the risk of learning and developmental problems although the exact risk couldn't be determined. The data suggested that carbamazepine, lamotrigine and levetiracetam did not increase this risk, but it's important to note that the data for the latter two were very limited. Clearly, more data are needed to fully understand their effects and any other contributory factors, such as the total daily dose, blood levels and age of the female prescribed the ASM. There was also a lack of data for gabapentin, oxcarbazepine, pregabalin, topiramate and zonisamide. Consequently, there is no information on the potential adverse effects on the learning and behaviour on infants and young children of these ASMs.

The government assessment of ASMs also looked at the intra-uterine growth of babies. Data showed that phenobarbital, topiramate and zonisamide were linked to babies being born smaller than in the general population. Data suggested that lamotrigine and levetiracetam did not increase this risk. Data were limited or inconsistent for carbamazepine, gabapentin, oxcarbazepine, phenytoin and pregabalin and so it is not known whether these ASMs may also affect fetal growth,

For the ten most commonly used ASMs, some information could be gleaned about their safety in pregnancy. Lamotrigine and levetiracetam were found to be the safer options for use in pregnancy. However, for a large number of ASMs – brivaracetam (Briviact), clonazepam, eslicarbazepine (Zebinix), ethosuximide, lacosamide (Vimpat), rufinamide (Inovelon), perampanel (Fycompa), primidone, tiagabine (Gabitril) and vigabatrin (Sabril) – there were inadequate data to draw any conclusions about their safety. Although these ASMs may not be prescribed frequently, the impact on a child and a family could be huge if they also carry similar risks on foetal growth and infantile development and behaviour.

The lack of data is arguably more of a concern than the known effects, making it difficult to know how to treat and advise patients taking these ASMs. It is clearly very important to try and prevent another situation around the use of ASMs in pregnancy such as that with VPA, and further prospective research is required to clarify the effects of all ASMs in pregnancy.

To that end, the MHRA is continuing to closely monitor the prescription of all ASMs during pregnancy. They launched a new safety review into topiramate on 21 July 2022. This was based on a new JAMA Neurology study, published earlier that month, on the risks of autism and intellectual disability (ID) in babies exposed to intra-uterine ASMs. Bjørk *et al* [2022] looked at mono- and

duotherapy with ASMs, using health-register and social-register data from Denmark, Finland, Iceland, Norway and Sweden between 1996 and 2017. The study included 4,494,926 participants and excluded children born following multiple pregnancies and children with chromosomal disorders or uncertain or unknown durations of pregnancy. The children were followed up to a median age of eight years.

The study found that, at follow-up, of the 21,634 children born to mothers with epilepsy, who were not exposed to intra-uterine ASMs, 1.5% had a diagnosis of autism spectrum disorder (ASD) and 0.8% had a diagnosis of ID. Compared with this, of children of similar ages exposed to topiramate, 4.3% had a diagnosis of ASD and 3.1% of ID. With VPA, the figures were 2.7% for ASD and 2.4% for ID.

The risk of neurodevelopmental disorders was also higher with use of some duotherapies. These were levetiracetam in combination with carbamazepine (8-year cumulative incidence of 5.7%) and lamotrigine in combination with topiramate (8-year cumulative incidence of 7.5%).

The study found that levetiracetam with lamotrigine did not increase the risk of neurodevelopmental disorders beyond the average for the background general population. The authors also found "no consistently increased risks" from intra-uterine exposure to monotherapy with lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gabapentin, pregabalin, clonazepam or phenobarbital.

Recommendations from the safety review of topiramate to the Commission on Human Medicines (CHM) are expected in October this year.

As we continue to carry out research and gain more data and information into the teratogenicity and adverse effects on cognition and behaviour of ASMs prescribed during pregnancy, we should hopefully achieve greater clarity on the optimal management of epilepsy in girls and women of child-bearing age. It is particularly important for VPA because this is currently the most effective ASM in the treatment of the genetic generalised epilepsies as demonstrated in an old [Marson *et al*, 2007] and more recently-published studies [Silvennoinen *et al*, 2019; Marson *et al*, 2021]. Not only that, but it's important to be mindful of the risks of uncontrolled seizures in pregnancy. Depending on the types of seizure the woman has, it could lead to issues like preterm delivery, low birth weight, asphyxia in the foetus [Tomson *et al*, 2019]. Uncontrolled seizures during pregnancy can also result in a higher risk of maternal mortality.

There is obviously a delicate and complicated balance to be struck between maximising seizure management and preventing or minimising side effects. However, it is crucial that girls, young women and their families are made fully aware of any risks linked with any ASM that they may be prescribed and, crucially, they must be actively involved in decisions around their care.

Kami Kountcheva
Co-Editor

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Forthcoming courses and conferences

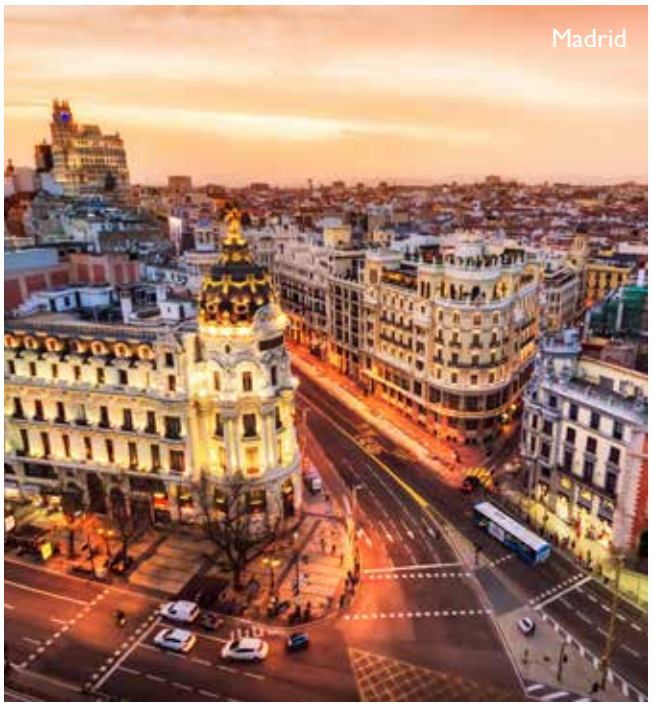
The following are details of forthcoming conferences and coourses in epilepsy and general paediatric neurology.

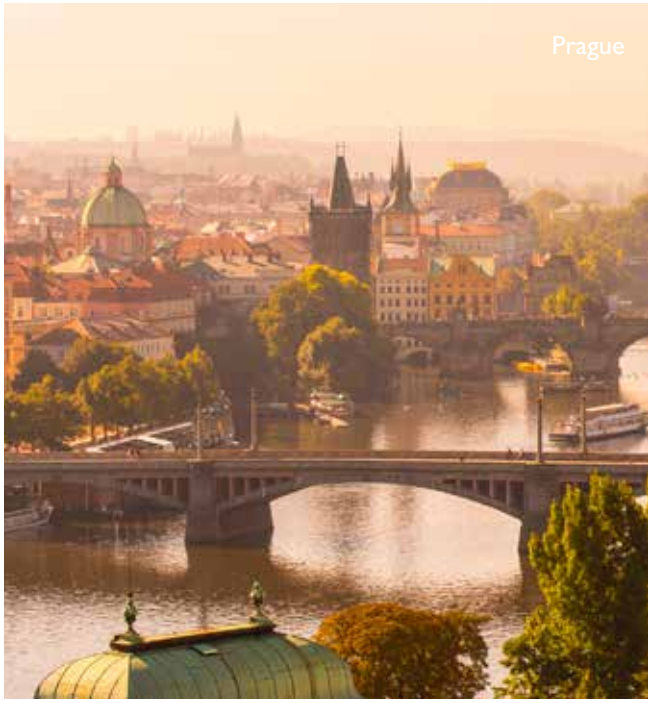
October 2022
1-13
4th Bologna EPIPED-EEG Course:EEG interpretation in pediatric epilepsies
Bologna, Italy
epiped-eeg-course.com

12-14
2022 ILAE British Branch Annual Scientific Meeting
Cardiff, UK
ilaebritishconference.org.uk

27-29
4th International Video-EEG Course in Paediatric Epilepsies: From seizures to syndromes
Madrid, Spain
2022.videoeeg.es

29-31
2022 Epilepsy Neuroimaging Course
Chalfont, UK and Online
bit.ly/3LBgZFt


Madrid


Prague

June 2023
20-24
15th European Paediatric Neurology Society Congress (EPNS)
Prague, Czech Republic
epns-congress.com

September 2023
2-6
35th International Epilepsy Congress
Dublin, Ireland
bit.ly/3S5ANDj

May 2024
5-8
Seventeenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3fdKAbT

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Your child and epilepsy

Grow your confidence managing epilepsy in your family

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.

This course is a helping hand to support families on their epilepsy journey. It's full of advice and stories from parents. It aims to give parents and carers the confidence, skills and knowledge to support their child to manage their epilepsy.

There are eight parts that cover:

- Understanding epilepsy
- Supporting your child with their epilepsy
- Keeping your child safe
- The impact of epilepsy on family life
- Your child's wellbeing
- Learning and behaviour
- Growing up and independence
- Sources of help and support

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The course is free and flexible. It can be accessed at any time on a computer, tablet or smartphone with internet access.

Leaflets about the course to give to families can be requested by emailing **nurseorders@epilepsy.org.uk**

To view the course go to: **epilepsy.org.uk/yourchild**
Get in touch **learning@epilepsy.org.uk**

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The prevention of epilepsy: now, there's a thought...

Prof Richard Appleton, consultant and honorary professor in paediatric neurology, Alder Hey Children's Health Park, Liverpool and Suffolk

Epilepsy is a markedly heterogeneous group of disorders with multiple aetiologies. The aetiologies range from unknown, although clearly there must be a cause that has not (yet) been identified, to known. The ratio of known to unknown is gradually increasing through improved genetic and radiological technologies. The most common known causes are genetic (as in an identified mutation or chromosomal abnormality), following an acquired cerebral insult or due to a cerebral malformation, which itself may be genetically-determined. The cerebral insult may be traumatic, ischaemic, haemorrhagic, hypoxic, metabolic or toxic or a combination of one or more of these. It has been estimated that approximately 20% of all epilepsy is caused by an acute acquired cerebral insult such as traumatic brain injury (TBI), stroke or encephalitis [Klein and Tyrlikova, 2020]. Others have suggested the figure is higher, at closer to 40% [Schmidt and Sillanpää, 2016]. I suspect that the figure is probably nearer to 20-30%, at least in children. Many, if not all, of these insults involve the cerebral cortex and are therefore potentially epileptogenic and consequently are likely to cause epilepsy. Epileptogenesis describes the progressive pathological structural and functional brain changes that follow a brain injury or insult and result in the development of spontaneous recurrent seizures – or epilepsy.

It is interesting that not every individual, but only a significant minority, develop epilepsy following encephalitis, a traumatic brain injury, stroke or other acute cerebral insult. This would suggest that there must be other factors, possibly biochemical or genetically determined, that will determine whether or not epilepsy will subsequently develop in these individuals. This is also likely to apply to some individuals with a cerebral, and, specifically cortical, malformation. For some years, there have been reports of individuals (children and adults) with the apolipoprotein E epsilon4 genotype (ApoE epsilon4) being at an increased risk. This group is more likely to develop late, post-traumatic epilepsy and worse cognitive outcomes following a head injury than compared with those without it [Brichtová and Kozák, 2008]. It is yet to be confirmed if this is a definite association [Maiti *et al*, 2015]. However, the concept of the identification of a biomarker that shows a clear and consistent association with later epilepsy is obviously exciting. It would identify those at risk of developing epilepsy, although not necessarily how and with what to treat them, which is arguably the more clinically important issue.

There is typically a latent period between the cerebral insult and epilepsy onset that presents a potential 'window of opportunity' to intervene with preventive treatment. This may be unique in neurology. The duration of this latent period is unknown but varies from days to even years in different individuals and also depending on the type of insult. Some consider that during this latent period there is a process of 'epileptic maturation' rather than a prolonged period of epileptogenesis [Sloviter and Bumanglag, 2012]. This is a concept I find difficult to accept, in part because maturation is typically considered a positive and beneficial process, a term that would not intuitively be ascribed to epileptogenesis and the development of epilepsy.

It is still not entirely clear as to why a first seizure occurs (whatever the aetiology, including in the 'idiopathic', presumed genetic epilepsies) and consequently, why epilepsy starts. What is clear is that once epilepsy has started, it may never stop, and during the time that the epilepsy is 'active', seizures may not respond to anti-seizure medications (ASMs). The treatment with ASMs may also be associated with adverse side effects, some of which might have to be 'accepted' to allow some seizure control. It is also clear that patients with epilepsy, and particularly those with refractory epilepsy, generally have a poorer quality of life. And of course, there is still the persisting societal stigma of having epilepsy and particularly if it is chronic and difficult to control.

In addition, and in a very specific paediatric population, there is a clear and direct relationship between clinical seizures, persistently abnormal ('epileptic' or 'epileptiform') activity and developmental or cognitive function. This population comprises infants and children who have a developmental and epileptic encephalopathy (DEE), such as West, Dravet and Lennox-Gastaut syndromes. In these syndromes, it is generally believed that it is not only the control of clinical seizures that's needed. The 'normalisation' or near 'normalisation' of the EEG is also associated with a better developmental and cognitive, and therefore functional, outcome [Specchio and Curatolo, 2021].

For almost a century, the focus of management of the epilepsies has been to stop or reduce seizure frequency. An important study, published almost 20 years ago, demonstrated that ASMs do reduce the risk of experiencing seizures but they do not reduce the risk of developing epilepsy [Marson *et al*, 2005]. Up until very recently, ASMs were (and still are largely) only prescribed once epilepsy has already developed. Typically, they are then continued long-term to prevent a recurrence of

seizures and enable individuals to have as good a quality of life as possible. Importantly, in most epilepsies, ASMs do not affect the natural history of the epilepsy or epilepsy syndrome. However, even with the latest generation of ASMs, variants of the ketogenic diet and improved and sophisticated surgical procedures, epilepsy remains a refractory and life-long disorder for at least 1 in 4 (25%) people with epilepsy. Consequently, if 25% of individuals with epilepsy can never be satisfactorily treated, an alternative approach would be to try and stop epilepsy happening in the first place. This leads to the obvious question: "Can epilepsy be prevented?"

Approximately 30 years ago I took part in a small UK two-day workshop that was keen to address this theme of the 'prevention of epilepsy'. Predictably, it was a largely philosophical and speculative attempt to determine if it was even possible. At that time, in the mid-1990s, there were minimal data to suggest it might be preventable. Expectedly, we discussed the obvious factors. They included the reduction of the incidence of traumatic and hypoxic cerebral insults, the early diagnosis of sepsis, meningitis and encephalitis, and the improvement of resuscitation following a cerebral insult. Improved resuscitative times and techniques had then and have continued to reduce the mortality rate following many acute cerebral injuries. However, this has been at the expense of an increase in neurologically-impaired survivors across all age groups many of whom developed epilepsy. A relatively recent study from Finland showed that, over a period of 40 years, the prevalence of epilepsy in people below 65 years had not fallen and there had been a "massive increase of epilepsy in the elderly" (i.e. >65 years of age) [Sillanpää *et al*, 2016]. This was primarily explained by the increased life-expectancy of individuals (with its associated age-related morbidity including strokes) but also the increased survival rate following stroke and other acute cerebral insults. The workshop also briefly discussed the onset of epilepsy following convulsive status epilepticus (CSE). This is important because de novo epilepsy may subsequently develop in 10-60% of cases of established, and certainly refractory, CSE. A recently-published paediatric study investigated 101 de novo cases (aged 0-18 years) of status epilepticus (SE), most with CSE and a minority with non-convulsive SE (NCSE). Of these, 51 (50.1%) subsequently developed epilepsy for the first time. Importantly, after a median follow-up of almost five years, the epilepsy had become drug-resistant in 32 of the 51 individuals (62.7%) [Specchio *et al*, 2019]. Although this figure largely reflects the cause of the SE, the age at which it occurred and its duration and management are relevant. It is very unlikely that all of these (and other) cases of a new-onset epilepsy following SE could have been prevented. However, it remains important to treat CSE as quickly as possible to at least try and minimise the risks of developing late epilepsy.

In the 1990s and early 2000s, the only real focus on the prevention of seizures (and epilepsy) was following traumatic head (and brain) injuries and craniotomies, the latter as part of an elective or emergency neurosurgical procedure. A number of studies showed that prophylactic carbamazepine, phenobarbital and phenytoin, given within 24-72 hours following a head injury, were effective in reducing the incidence of seizures over the subsequent few weeks. However, these ASMs did not reduce the risk and incidence of seizure recurrence and the development of late epilepsy [Schierhout and Roberts, 1998; Formisano *et al*, 2007]. There was the added problem of common adverse side effects on the long-term use of these ASMs, and particularly with phenytoin and phenobarbital. It is generally considered (although unproven) that the newer ASMs, such as levetiracetam, brivaracetam or perampanel would be unlikely to be more successful in the prevention of late epilepsy in these scenarios. Finally, a review published very recently concluded that there was no scientific evidence to support the use of prophylactic ASMs in adults that had experienced an intracranial haemorrhage [Derex *et al*, 2021].

In 2011, a small study looked at the 'pre-emptive versus reactive' use of phenobarbital in 37 infants with Sturge-Weber syndrome (in which epilepsy develops in at least 60% of cases) [Ville *et al*, 2011]. The study showed that in 16 infants treated with prophylactic phenobarbital before the onset of any clinical seizures, reduction was seen in epilepsy ($p < 0.01$) and 'mental retardation' ($p < 0.05$). This was in comparison with the other 21 children, who were treated with phenobarbital after the onset of clinical seizures. There was no difference in the incidence of motor deficit. Eighty five percent of the 37 infants developed epilepsy. In those who had been commenced on prophylactic treatment, the epilepsy started "significantly later" than those who did not. In the prophylactic group, there was also a trend towards less severe epilepsy with less prolonged seizures. Clearly, this was a very small and observational study and with a very wide range of follow-up, from two years and nine months to 28 years [Vile *et al*, 2011]. Despite this (and other methodological limitations), the study's findings are of interest.

Our horizon is now beginning to widen but, at the same time, become slightly more focused. One of the earliest diseases in which the prevention of clinical seizures and, more importantly, the suppression of 'epileptiform activity' (i.e. sharp wave, spike and wave or polyspike activity) were seriously considered was tuberous sclerosis complex (TSC) [Józwiak and Kotulska, 2014]. In 2017, a European panel of specialists in TSC reviewed the management of epilepsy associated with TSC and published updated clinical recommendations [Curatolo *et al*, 2017]. These included (my words are in italics):

- "The need for early diagnosis of TSC-associated seizures is well established, electroencephalographic monitoring has good predictive value for epilepsy before seizure onset in TSC, and, until conclusive data from the EPISTOP* trial are available, administration of vigabatrin may be considered in children with subclinical

epileptiform EEG discharges. Evidence suggests that its early use may prevent the onset of both focal seizures as well as focal seizures evolving into infantile spasms." (*i.e. Infants and children with TSC should undergo regular EEG investigations and, as soon as it shows any epileptiform activity, vigabatrin (VGB) should be commenced. For those supervising specialist TSC clinics, 'regular' implies at least every month*).

- "The early use of adjunctive everolimus for TSC-associated drug-refractory seizures and ideally if seizures remain inadequately-controlled after the use of two appropriate anti-seizure medications." (*Everolimus is a mammalian Target Of Rapamycin (mTOR) inhibitor that acts on cell growth and reduces the growth and size of the renal angiomyolipomata AMLs) and sub-ependymal giant cell astrocytomas (SEGAs), lesions that frequently occur in TSC. However, everolimus has no known anti-seizure or anti-epileptogenic properties*).

The results of the EPISTOP* trial were published in 2021 [Kotulska *et al*, 2021]. This was a multi-centre study of 94 infants with TSC, none of whom had any clinical seizures. They were reviewed monthly with video electroencephalography (EEG) to detect any epileptiform activity. They received VGB either as conventional anti-epileptic treatment started after the first electrographic or clinical seizure, or preventatively when epileptiform EEG activity was first seen and before any witnessed clinical seizures had occurred. The doses of VGB were similar in the two groups. At six sites, patients were randomly allocated to treatment in a 1:1 ratio in a randomised controlled trial (RCT). At four sites, treatment allocation was fixed and was denoted as an open-label trial (OLT). All patients were followed-up until two years of age. The primary endpoint was the time to first clinical seizure. Of the 95 infants enrolled, full results were only available in 54 infants (40 were excluded for a variety of reasons) in whom epileptiform EEG abnormalities were seen before any clinical seizures. Twenty-seven were included in the RCT and 27 in the OLT. The time to the first clinical seizure was significantly longer in the group that had received preventative than conventional treatment (RCT, 364 days vs 124 days; OCT, 426 days vs 106 days). At 24 months, pooled analysis showed that preventative treatment reduced the risk of clinical seizures (odds ratio [OR] = 0.21, $p = 0.032$), drug-resistant epilepsy (OR = 0.23, $p = 0.022$), and infantile spasms (OR = 0, $p < 0.001$). The study reported no adverse events related to the use of preventative treatment. The authors' interpretation of these results was predictably upbeat: "Preventative treatment with vigabatrin was safe and modified the natural history of seizures in TSC, reducing the risk and severity of epilepsy" [Kotulska *et al*, 2021]. Clearly, a number of important issues need to be addressed. First, this was a small study with full data on only 54 infants and children. Second, will the reported benefit persist after three, five or more years of follow-up? Third, will developmental progress and cognitive function show any significant difference between the conventionally and prophylactically-treated groups? And fourth, will the frequency (and severity) of visual field deficits, and other potential adverse side effects associated with the long-term use of VGB, be significantly different between the two groups?

In the management of epilepsy in TSC, VGB is clearly a well-established ASM, particularly in the treatment of infantile spasms in this disorder. Therefore, its effect in the EPISTOP trial might have been expected. In contrast, everolimus has no known inherent ASM or anti-epileptogenic (AEE) properties and represents an entirely new approach to the management of seizures and epilepsy in TSC. Thus far, it is has only been used (and has a license) as an adjunctive drug to be used in combination with conventional ASMs in the management of refractory epilepsy in people aged two and over with TSC [French *et al*, 2016]. It is not known whether everolimus used prophylactically might be effective in the prevention of a first seizure and the subsequent development of epilepsy in this population. Limited animal (rodent) data suggest that mTOR inhibition may reduce or even prevent early-onset seizures and autistic-like behaviour in later life following an acute neonatal brain hypoxic insult [Talos *et al*, 2012]. Clearly, much more work must be undertaken to confirm these early animal data and then, of course, considering and assessing its possible clinical effect in human neonates. In addition, there are potential concerns with the use of everolimus. First is the drug's long-term adverse effect on the immune system and whether this may have any significant clinical consequences, particularly in the developing infant. Second is that there is some evidence that AMLs and SEGAs can show a sudden increase in growth and therefore in their size if the drug is discontinued. It is unknown whether there might be a sudden deterioration in seizure control if the drug is discontinued in patients in whom it is being used to control their epilepsy.

As mentioned earlier, the DEE is a group of syndromes and diseases in which epileptiform activity itself is of significance. It is considered to be as important as the clinical seizures in the cause of severe cognitive and behavioural impairments above and beyond what might be expected from the underlying pathology alone. In addition, these impairments may be progressive. This is well recognised in some well-known genetically-determined metabolic disorders such as pyridoxine, biotinidase and GLUT-1 deficiency (glucose transport type 1 deficiency). Clearly, it would be extremely useful for these DEEs to be diagnosed before the onset of seizures to prevent not just the often intractable epilepsy that usually develops, but the associated cognitive impairment. For obvious reasons, this is currently unrealistic and therefore unlikely to be achieved. However, it does emphasise the importance of diagnosing these groups of conditions as early as possible

to allow treatment to be started and to potentially minimise or prevent the establishment of chronic epilepsy and other impairments.

The identification of a drug that has specific AEEs and that can prevent the development of epilepsy is clearly an exciting prospect. To be considered a viable AEE drug, it must show the following features:

- It must prevent epilepsy, even if it is initiated after the epileptogenic brain insult has already occurred (for example, following a stroke, traumatic or hypoxic brain injury, or encephalitis)
- Its anti-epileptogenic effect must continue even after the treatment has been stopped
- It must have no serious short or long-term adverse side effects

Numerous compounds have been considered that might have an AEE, including rapamycin and curcumin. Rapamycin has been discussed earlier. Curcumin is the main component of the natural spice turmeric, which has anti-inflammatory and anti-oxidant properties [Drion *et al*, 2018]. However, the group that appears to be showing the greatest promise is the statins. This is probably for the following reasons:

1. Statins are readily and cheaply available throughout the world.
2. Statins are safe and well-tolerated, and widely accepted by prescribers and patients. In 2020, atorvastatin (brand name Lipitor) and simvastatin (brand name Zocor) were the two most commonly prescribed statins in the UK.
3. Statins are reported to be anti-epileptogenic in more published studies than any other individual or class of compounds. However, this does not necessarily mean that statins have the highest anti-epileptogenic efficacy. The larger number of studies reporting the AEE of statins compared to other compounds might simply be because, to date, they are the most commonly used drug for this specific research. This is due to their longstanding and widespread clinical use.
4. Statins are reported to be anti-epileptogenic in a wider range of brain insults (clinical and experimental) than any other individual or class of compounds
5. Statins are the only compounds with pre-clinical and clinical evidence of potential AEE.
6. Statins are the only compounds with retrospective and prospective clinical evidence of potential AEE.
7. Finally, significant members of the populations, who are at relatively higher risk of developing epilepsy (for example, older people and people with diabetes), can potentially gain cardio- and cerebro-vascular benefits from statins' lipid lowering effect.

In addition, statins only have to be taken once a day when used to prevent cardiovascular or cerebrovascular disease and it is possible if not likely that this will be also the regimen when using it as an AEE drug.

It is important to acknowledge that nearly all of the data on statins have been derived from adult studies. This is also predominantly in older adults who have had a stroke (ischaemic or haemorrhagic) or some other significant medical disorder. In addition, these data are also based only on observational data.

The predominant clinical use of statins is to reduce hyper-cholesterolaemia, which they do very well. The primary molecular mechanism of most statins is the competitive inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase (HMGR), an enzyme involved in the rate-limiting step in cholesterol biosynthesis in the liver. Statins are recognised to also have an anti-inflammatory effect and one hypothesis is that their AEE might be mediated through this anti-inflammatory action [Oliveira *et al*, 2018]. I consider that this hypothesis is somewhat simplistic. However, there is, as yet, no other convincing cogent hypothesis for the reported AEE of statins.

Well-designed preclinical studies show that statins are anti-epileptogenic in animal (predominantly rat) models. Statins have been shown to reduce seizure severity and related hippocampal cell death in rodents; this may be important in CSE and particularly refractory CSE. To date, there are very limited data on the effect of statins in CSE in patients. One study described 413 consecutive adult patients with CSE treated over a six-year period in a single epilepsy centre in Switzerland [Sierra-Marcos *et al*, 2015]. The outcome of SE at hospital discharge was broadly classified into 'return to baseline', 'new disability' and 'mortality'. The role of potential predictors of outcome, including statin treatment prior to admission, was evaluated using a multinomial logistic regression model. The mean age was 60.9 (±17.8) years. Two hundred and eleven patients (51%) had a potentially fatal SE aetiology and 170 (46%) had generalised CSE. Statins (atorvastatin, simvastatin or pravastatin) had been prescribed prior to admission in 76 (18%) patients, mostly in the elderly. At discharge, 208 (50.4%) had 'returned to baseline' but 58 (14%) died. After adjustment for established SE, outcome predictors (age, aetiology, SE severity score), the use of statins correlated significantly with lower mortality (relative risk ratio 0.38, p = 0.046). There was no correlation with the use of statins and a 'new disability'. Clearly, although this is a single observational study and any conclusions must be treated with caution, the potential effect of statins in modulating the mortality outcome of SE, including CSE, merits further thought and possible investigation.

Prospective and retrospective observational clinical cohort studies have suggested that the use of statins is associated with a reduced risk of developing epilepsy. Additional observational clinical studies undertaken in specific populations (including following ischaemic or haemorrhagic

stroke [Lin *et al*, 2018; Vitturi and Gagliardi, 2020; Acton *et al*, 2021]) have indicated that starting statins, even after the brain insult has already occurred, reduces the risk of subsequent epilepsy. It is more difficult to determine from all of these observational studies if the AEE and efficacy of statins persists after they have been discontinued. This is because statins are typically continued life-long in the patient populations, including in these cohort studies. However, some observations from both pre-clinical animal studies and clinical cohort studies support the possibility that the AEE of statins is sustained after the statins have been stopped. It must be acknowledged, however, that this is based on very limited data.

There is no clear evidence that any one statin is more efficacious than another in reducing the risk of post-stroke epilepsy. Lovastatin and pitavastatin have been shown to have no AEE. However, this might simply be explained by the fact that atorvastatin and simvastatin are the most commonly-prescribed, whilst lovastatin and pitavastatin are the least commonly prescribed statins. One study [Etminan *et al*, 2010] undertook a dose-response analysis for all individual statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin). It reported a dose-response relationship only with atorvastatin; this was a 5% reduction in the risk of epilepsy with every gram of atorvastatin used annually. Once again, it is possible that the other statins were used in insufficient numbers to detect a dose-response relationship. Numerous clinical studies have reported a dose-dependent relationship between statins and a reduced risk of developing epilepsy [Lin *et al*, 2018; Li *et al*, 2019; Vitturi and Gagliardi, 2020]. This suggests that the higher the statin dose, the greater the AEE, but again, these are based on observational and not RCT data.

Clearly, many questions remain to be answered as to whether the statins are feasible AEE drugs:

1. Can the findings of these observational clinical studies be duplicated in a gold standard, randomised controlled trial (RCT)?
2. Is there a window of opportunity after the cerebral insult for a statin to exert its effect? Importantly, what is their latest 'use-by date' following any insult?
3. What is the minimum duration of the use of a statin for its AEE to be seen – and also to be sustained after it has been withdrawn? As Her Majesty the Queen so insightfully said in a speech during the D-Day commemorations in June 2014: "The true measure of all our actions is how long the good in them lasts"… Will this apply to the effect of a statin after it has been discontinued?
4. Will the principle of the AEE of a statin apply to children as well as adults, and, if 'yes', how young a patient might this effect be seen in?
5. Although there are no recognised serious adverse side effects with the long-term use of statins in adults, there are no equivalent data on children as young as 10 or 12 years of age. Is there a need for concern in using statins in children as young as this, even if the statin is used for a short period?

Answers to these (and other questions) will only be answered by carefully designed and conducted RCTs. No pressure then…

In conclusion, there is no doubt that the prevention of epilepsy, and specifically epilepsy that has developed following an acute cerebral insult, is both an exciting but also challenging prospect. The epilepsy that develops in this population is often chronic and medically refractory. It typically has a significant detrimental effect on an individual's ability to fully participate in life, and, therefore, on their quality of life. At this stage, it is impossible to know, or even predict, what proportion of people with epilepsy might have it prevented by the use of a drug with AEE, including statins. However, it would be naïve to expect that any drug will be the 'magic bullet' that has been ascribed to novel ASMs for almost a century. As Hufthy and colleagues state in their recent paper, there are probably adequate pre-clinical and observational clinical data to indicate that the time is right for an RCT of statins in the potential prevention of epilepsy [Hufthy *et al*, 2022]. This novel approach in the management of epilepsy should serve as an interesting and exciting opportunity to grant-giving bodies, particularly in light of the medical mantra that 'prevention is better than cure'.

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The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

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- Feel less alone
- Increase their confidence
- Get the support they need

There's lots of epilepsy facts, tips and stories from young people sharing their experience.

The content is short and interactive. It's not all reading, there's video and young people can share their own quotes, stories and videos too.

It's been created with young people and reviewed by epilepsy nurses.

Take a look at:
epilepsyspace.org.uk

Leaflets about The Epilepsy Space to give to young people can be requested by emailing:
nurseorders@epilepsy.org.uk

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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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