epilepsy action

ISSN 2631-7400

Paediatric Epilepsy

Volume Nineteen | Number Four | December 2023

CURRENT AWARENESS SERVICE

Postcode prescription of anti-seizure medications: a worry

Socio-economic differences in healthcare and its impact on disease, including epilepsy, have existed for decades. These differences are inevitable between developed and developing countries and also in countries where there is a clear two-tier system – public and private healthcare. This encompasses services for people with epilepsy and the drugs they receive to manage their disorder, anti-seizure medications (ASMs). The 'exemplar' (if that is the most appropriate word) of this two-tier system is the USA. In 2019, the International League Against Epilepsy (ILAE) together with the International Bureau for Epilepsy (IBE) and World Health Organisation (WHO) raised this as a global public health priority called 'Epilepsy: A Public Health Imperative'.

I was wholly unaware of this document and, in my defence, probably because its principal objective was to examine the disparity of epilepsy care (in its broadest sense) between developed and developing countries. Living and working in the UK, this didn't seem entirely relevant to my practice. I never considered the child's (and family's) place of residence (and therefore postcode) at all relevant in how I cared for them. This could be seen as rather narrow-minded, even naïve, and I have learned much since reading the document in the preparation of this article. I would suggest that you all read or at least be aware of 'Epilepsy: A Public Health Imperative'. The preface of this document includes the following:

> "This report is the product of a long-standing collaboration between the WHO, the ILAE and the IBE. Together we have made substantial progress in encouraging countries to prioritise epilepsy in public health agendas. 'Epilepsy: a public health imperative', presents a comprehensive picture of the impact that the condition has on people with epilepsy, their families, communities and societies.
>
> Epilepsy has a high risk of disability, psychiatric comorbidity, social isolation and premature death. Across the world, people with epilepsy and their families suffer from stigma and discrimination. Many children with epilepsy do not go to school; adults are denied work, the right to drive or marriage. The human rights violations faced by people with epilepsy around the world are unacceptable. It is time to highlight epilepsy as a public health imperative, to strongly encourage investment in reducing its burden, and to advocate for actions to address gaps in epilepsy knowledge, care and research.
>
> The adoption of the World Health Assembly resolution on epilepsy by its member states drew attention to the need for coordinated action at country level. The resolution provides a powerful tool to engage governments and civil society in taking

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concrete action to promote access to care and to protect the rights of people with epilepsy."

The document was a call for sustained and coordinated action to ensure that every person with epilepsy has access to the care and treatment they need as well as the opportunity to live free from stigma and discrimination in all parts of the world.

Theoretically, there should be little difference in the outcomes, and therefore the quality of life, of patients (and particularly children, aged up to 16 years) with epilepsy of different socio-economic postcodes who live in countries where there is a total or nearly total national and state-funded healthcare system. As we have all learned and continue to learn, theory does not necessarily translate into real life.

Clearly, the concept of, and definition of 'quality of life' may well differ depending on the child and their family's circumstances, which is independent of epilepsy. In the UK for instance, the adverse impact of epilepsy on quality of life in a child that attends a state grammar or private public school and has a number of extra-curricular activities is likely to be greater than that of a child with a similar epilepsy and seizure control that attends a state school, is a home-bird video-game enthusiast and has a single parent. This does not necessarily suggest or mean that a 'financially privileged' child will actually suffer more from having epilepsy but it may simply reflect their perception that this is the case. This may indicate a degree of perceived stigmatisation. This has certainly been my experience over many years.

Regarding epilepsy itself, all children and teenagers should have the same access to healthcare professionals, necessary investigations, ASMs and epilepsy specialist nurse (ESN) support. One of the problems is that although all these resources are available for everyone, their uptake and compliance (concordance) may differ significantly. It is important to note that even within the constituent countries of the UK, there is a significant disparity in the number of ESNs (for children and adults). Northern Ireland has only 14 ESNs, which approximates to one ESN to every 2000 people with epilepsy; in Wales there are 23 ESNs which approximates to one ESN to every 1600 people with epilepsy (epilepsy.org.uk/epilepsy-specialist-shortage-a-crisis). We don't yet have similar data for the situation in England and Scotland, but Epilepsy Action is currently researching the figures. Children of a lower socio-economic status may access these resources less frequently and there is often lower and irregular concordance with clinic-attendance, ESN-engagement and use of ASMs. Consequently, their epilepsy may be poorly controlled and their quality of life may be described as being poor. It is important to recognise that there may be many justifiable reasons for poorer concordance with services by families from lower socio-economic areas. These include being allowed time off work to take their child to clinic and being able to pay for travel to attend the various clinics.

The document 'Epilepsy: A Public Health Imperative' comprised seven chapters; chapter 4 was entitled, 'Access to anti-seizure medications'. It is of interest, and also a concern, that a couple of studies undertaken in unequivocally 'developed' countries in which healthcare and the prescription of medications (including ASMs) is heavily subsidised, have shown that there is a socio-economic difference in prescribing patterns of ASMs to children with epilepsy.

A Swedish study, conducted in 2006 (but published many years later in 2012) found that levetiracetam (then a 'new' ASM) was more likely to be prescribed for children from families with higher incomes [Mattsson *et al*, 2012]. This is despite the fact that medication costs were heavily subsidised.

The same study also showed that children living in rural and lower socio-economic areas were less likely to be seen by a paediatric neurologist (known as a 'neuro-paediatrician' in Sweden). The authors made the following insightful comment: "Nevertheless, the results of this study are important because they show that universal coverage to medical care does not eliminate inequalities of access to healthcare services." The authors concluded that there were two main effects of giving care according to sociodemographic status and not to a child's needs. These were: "First, there is an ethical dimension. Second, treatment given according to sociodemographic belonging rather than needs may be suboptimal and can result in unfavourable health outcomes." This is a justifiable and somewhat chilling conclusion.

A very recent study from New Zealand showed similar findings [Ali *et al*, 2023]. It reported that 2,594 children with epilepsy (median age 12 years) were prescribed 357 ASMs; in 76%, this was for a seizure disorder. Despite no difference in the cost of any ASM to families, children from the lowest socio-economic group were more likely to be prescribed an 'old' rather than a 'new' ASM compared to children from the higher socio-economic group. It is interesting that the authors defined an 'old' ASM as ones available before 1993 and 'new' as those available after 1993. In view of this, we must be cautious in drawing any conclusions from the New Zealand study given how 'old' its ASM data were.

Both the Swedish and New Zealand studies ascribed the differences in ASM prescribing in rural and socio-economically deprived areas as reflecting an "inadequate access to paediatric neurologists". Although this is possible, I am not convinced that this is the most appropriate explanation. For instance, paediatricians will always be able to find other ways of communicating with a paediatric

neurologist (or neuro-paediatrician) than face-to-face. These obviously include telephone and e-mail discussions and, even pre-Covid, virtual clinics by Zoom or Teams. This has been the strength and the value of the peripatetic outreach service, which has been provided by paediatric neurologists in the UK for many decades and in most areas of the UK since the early 1980s. This type of service allows a much more equitable care of epilepsy in children who live in rural as well as socio-economically deprived places, such as inner city areas. This service has also facilitated a more cross-sectional and representative population of children to be recruited into research studies, including those involving the efficacy and safety of new ASMs. A reduction or withdrawal of such a peripatetic paediatric neurology service will have a detrimental effect on equitable epilepsy care between the tertiary centre and the rural and inner city communities. A potential, if not likely consequence will be a two-tier system of epilepsy care in the NHS (the UK) that may begin to mirror the situation in Sweden and New Zealand.

The Epilepsy Guidelines published by the National Institute for Health and Care Excellence (NICE) in both 2012 and most recently in 2022 gave specific recommendations on which children should be referred to or discussed with a paediatric neurologist who specialises in epilepsy and is based in a tertiary centre. This also includes how quickly they should be seen following this referral (four weeks): www.nice.org.uk/guidance/ng217/chapter/3-Referral-to-tertiary-specialist-services (sections: 3.1.1 to 3.1.4).

Unfortunately, a number of paediatric neurologists in the UK now refuse to see children with epilepsy in outreach, peripatetic clinics in rural areas and special schools (the latter for children with learning and physical difficulties and epilepsy) and insist that these children and their families travel to see them in their tertiary centre. In part this reflects the policy of their employing trust management, but in many cases it reflects the personal view of many paediatric neurologists.

For a large number of families this may mean a round trip of more than three or four hours to the tertiary centre as well as time off work and some expense. It also deprives the local paediatricians in rural, non-rural areas, and community paediatricians in special schools, the opportunity to learn from the paediatric neurologists. Personal experience gained over a quarter of a century has also taught me that it is important that the child and their family can see the specialist, have their views heard and be reassured that their child's management is being shared between their child's local paediatrician and the 'expert'. Consequently, I do not believe that such an important outreach service to, and in support of, district and community paediatricians should be withdrawn or even reduced. It also disregards the past and updated NICE guidelines. Finally, it will continue the trend of a two-tier system within the NHS and will add impetus to the rise of private medicine and establish a socio-economic divide.

The somewhat surprising but clearly worrying results of the Swedish and New Zealand studies must be taken seriously if only to ensure that these do not reflect the situation in England and Wales. The majority of children and young people with epilepsy will not live within the postcode catchment area of a tertiary epilepsy centre and will not be managed by a paediatric neurologist with epilepsy expertise. Consequently, it is important that the general paediatricians who do manage these children endeavour to ensure that they are seen by a tertiary specialist in the local hospital to optimise their care. This may require involvement of and lobbying of patient-advocacy groups and charities including Epilepsy Action, Young Epilepsy and the Epilepsy Society.

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Richard Appleton
Co-editor

Forthcoming courses and conferences

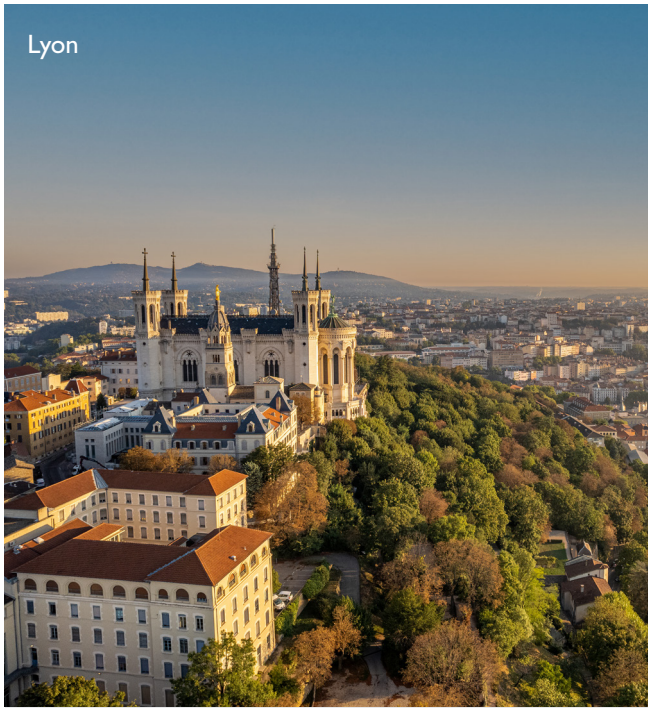
The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

January 2024
24-26
BPNA 2024 Annual Conference
Bristol, UK
bpna.org.uk/conference/2024

March 2024
3-8
4th International Training Course on Neuropsychology in Epilepsy
Lyon, France
bit.ly/3VvHu2Z

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


Helsinki


Lyon

June-July
29-2
10th Congress of the European Academy of Neurology
Helsinki, Finland
https://bit.ly/47LSi3L

September 2024
7-11
15th European Epilepsy Congress
Rome, Italy
ilae.org/congresses/15th-european-epilepsy-congress

September 2024
23
ILAE British Branch Annual Scientific Meeting
Liverpool, UK
bit.ly/3Gjx8g0

epilepsy action

epilepsy.org.uk/yourchild

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

Free course

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**

Drug-resistance: definition and approach to management

Professor Richard Appleton, University of Liverpool

The resistance of seizures to anti-seizure medication (ASM) has been and will almost certainly remain a topic for discussion, debate and novel drug development for decades. For some pharmaceutical companies, drug resistance and the development of novel ASMs to address it, represents their main or, rarely, even their only business. Drug resistance will continue to drive research into why it occurs and, of course, how to best manage it. Despite a justified optimism that the future will lead to a better understanding about seizure-onset and seizure-propagation, including the importance of genetic factors, this must be grounded in realism and not fantasy. When I started my consultancy at Alder Hey Children's Hospital in 1989, the then cited proportion of drug-resistant patients was 30-35%. More than three decades later and, despite at least a trebling of available ASMs, the current cited prevalence remains at a stubborn 30-35%. However, this figure is derived from quite old data, specifically that of Kwan et al [Kwan *et al*, 2000].

Finally, long-term outcome studies in newly treated patients with epilepsy suggest that, after failure of two well-tolerated ASM regimens appropriately chosen for the seizure type(s), the chance of success with further drug changes becomes progressively less likely. However, this study was undertaken in an adult population in a single tertiary epilepsy centre and therefore did not take account of epilepsy syndromes of infancy and early childhood [Chen *et al*, 2018].

1. Definition

Drug or ASM resistance has always been and remains a problem in the management of epilepsy for children and adults. Drug resistance (DR) in adults more commonly occurs in the focal rather than generalised epilepsies. In children, DR is more complex and will vary considerably depending on the specific epilepsy syndrome. For example:

- The developmental and epileptic encephalopathies (DEE: the most common ones being, Ohtahara; Infantile epileptic spasms; Dravet and Lennox-Gastaut syndromes): these probably constitute 8-10% of all epilepsy in children. At least 90% will be drug resistant.

- Epilepsy with centro-temporal spikes (previously termed benign rolandic epilepsy): this constitutes 15-20% of all epilepsies. Only 3-5% with this syndrome will be drug resistant.

- The presumed genetic generalised epilepsies (previously termed idiopathic generalised epilepsies): this constitutes approximately 25% of all epilepsies. Only 10-15% will be drug resistant.

- Temporal lobe epilepsy with an identified lesion: this is estimated to comprise 4-5% of all epilepsies. Most (70-75%) will be treatable with surgical resection and therefore approximately 25% will be drug resistant.

- Non-syndromic and symptomatic focal epilepsy, excluding temporal lobe epilepsy (i.e a focal lesion identified in the frontal parietal or occipital lobe). It is very difficult to know the number of children with this epilepsy, but it is likely to be approximately 20-25% of all epilepsies. The literature suggests that 60-65% will be drug resistant although there is significant uncertainty over this figure.

It is estimated that up to 35-40% of all patients with epilepsy, irrespective of the syndrome, will be resistant to one ASM and the figure falls to only 30-35% on two ASMs [Kwan *et al,* 2000]. There are no useful and certainly no robust data to suggest that this figure falls any lower when taking three ASMs simultaneously. Clearly, these data are very crude and refer to all patients with epilepsy. Predictably, when considering individual epilepsy syndromes, there is a wide range of DR as outlined above.

There is another factor that may determine the rates of DR, and this is the origin of the study population and typically populations with focal epilepsy. In a recently published study, the prevalence of drug resistant epilepsy (DRE) was 13.7% in population or community-based populations, but 36.3% in clinic-based cohorts. Meta-regression confirmed that the prevalence of DRE was higher in clinic-based populations and in those with focal epilepsy [Sultana *et al*, 2021]. This is not surprising in view of the fact that patients who attend epilepsy or neurology clinics will be biased towards the more complex and difficult-to-treat epilepsies. Children with DEE form the bulk of most paediatric clinics and adults with focal epilepsy form the bulk of most adult clinics.

The obvious 'elephant-in-the-room' in the area of DR is how it is actually defined. Much has been debated and written about the definition of DR. For decades, one or more of these definitions have been used as a key inclusion criterion in trials of new ASMs. The most commonly used factors that have been used (and are still used) to define DR are the number of ASMs that have been tried, the duration of seizure freedom that is required and the frequency of seizures. However, the frequency of seizures was omitted from the definition a number of years ago. In 2010, an ad hoc committee of the International League Against Epilepsy (ILAE) published its consensus definition on DR:

'The failure of adequate trials of two tolerated and

> appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom' [ILAE 2010]

Unhelpfully, 'sustained' was not further defined. However, the committee attempted to define 'sustained' as freedom from seizures for a minimum of three times the longest pre-intervention, inter-seizure interval (determined from seizures occurring in the past 12 months) or 12 months, whichever was longer. This was shortened to mean 12 months and the revised pragmatic definition is now:

> 'The absence of complete seizure control for a period of at least 12 months following an adequate trial of two appropriate and tolerated ASMs' [Alexis Arzimanoglou, personal communication, December 2022]

The inclusion of seizure frequency as a criterion was dropped from the definition. Importantly, 'complete' seizure control included all seizure types, including focal sensory seizures with retained awareness, previously termed 'simple partial seizures' or 'auras'. In other words, within this definition, 'auras' are considered to be the same and have the same impact as seizures with focal motor and also generalised seizures, that is: tonic; atonic; clonic; tonic-clonic and myoclonic. Whether this is appropriate and too 'black and white' an approach to total seizure control is debatable. Finally, this definition should also apply to the Engel classification of seizure control following epilepsy surgery.

The period of 12 months was arbitrarily determined by the ILAE committee. However, it is entirely reasonable, because 12 months provides a critical milestone and watershed that was considered to be functionally important, such as allowing the patient to apply for a driving licence. The phrase 'appropriate' in the definition clearly mandates that the correct diagnosis has been made of both the type of epileptic seizure(s) and, usually, the epilepsy syndrome. It is well-recognised (and still occurs) that some seizure types and epilepsy syndromes are incorrectly classified. Typical examples are the 'atypical' and often prolonged absences that occur in juvenile absence and, less commonly, juvenile myoclonic epilepsy, which are occasionally misdiagnosed as focal seizures with impaired awareness and subsequently treated with carbamazepine or levetiracetam. This often results in poor (or worsening) seizure control and can lead to an (erroneous) diagnosis of DR.

Equally well recognised is the fact that, although the ASM may be appropriate for the seizure type, it might be prescribed or taken (or both) in too low a dose resulting in the patients having 'poor seizure control', or too high a dose resulting in adverse side effects and the patient labelled as 'not tolerating the ASM'. This will result in pseudo-drug resistance. A recently published study described the inter-rater reliability between neurologists (investigators) who had recruited 1,053 consecutive adults with focal epilepsy into trials of new ASMs and an independent expert panel of epileptologists. Both groups had used the ILAE definition of DR given above. Overall, 19% of patients (almost 1 in 5) classified as having DRE by the investigators were considered by the expert panel to have 'undefined responsiveness' and consequently probably did not meet the definition of DR [Zaccara *et al*, 2019]. Clearly, if a patient has been taking an inappropriate drug or dose (or both), then the clock stops in terms of defining DR and only starts again as soon as an appropriate ASM or its dose, or both, is taken.

Consequences of drug resistance

These are multiple consequences of DR that may adversely affect a child's (and particularly an adult's) quality of life. They can be broadly classified into physical, psychological and economic. The latter frequently translates into limited education and employment potential and therefore may restrict a person's contribution to society.

Physical

Children and young people (12-16 years of age) have a significant increase in the risk and incidence of physical injuries, convulsive status epilepticus and mortality – mortality may be secondary to convulsive status epilepticus (CSE) but also sudden unexpected death in epilepsy (SUDEP). A recent small study of 31 adults with DRE underwent subcutaneous cardiac monitoring for a median range of just over two years [Sivathamboo *et al*, 2022]. During this period, 28 patients (90%) had episodes of tachycardia lasting at least 30 seconds, eight (26%) had bradycardia and three (9.7%) had asystole. In total, three of the 31 patients (9.7%) had a serious cardiac arrhythmia that required additional cardiac intervention. There was no clear correlation between seizure occurrence and arrhythmia and whether the seizure was focal or generalised. This is not surprising, given the relatively small study group. There was also no control group comprising of patients with well-controlled epilepsy or without epilepsy at all. Nevertheless, these results should be taken seriously.

Psychological and emotional

Clearly, DRE has many psychological and emotional consequences, independent of the underlying epilepsy syndrome or cause. The most common consequences include: limited or no employment; depression; para-suicide and suicide. This is reviewed in the article by Laxer *et al* [Laxer *et al*, 2014].

Economic

Although it might be considered that pseudo-drug resistance is predominantly an academic issue, it is not and may have its own significant clinical implications. These broadly fall into three areas:

- It might have denied the patient much better seizure control and an improved quality of life. The use of appropriate ASM(s) or dose(s) (or both) might then render the patient seizure free and negate the label of the patient being 'drug resistant'.

- It might have led to the patient undergoing an inappropriate (and usually expensive) comprehensive evaluation for a surgical treatment of their DRE. Although it could be argued that this might not necessarily be detrimental to the patient, it could be regarded as being wasteful of both resources and finances if such tests were unnecessary.

- The patient may be inappropriately enrolled into a trial of a new ASM for intractable seizures and DRE. Clearly, if there were many such patients in a trial, it could influence its results and, more importantly, its conclusions.

2. Approach to management

As you would predict, there are some important questions to address in this process.

- Is the patient really resistant to at least two appropriate ASMs (type and dose) and have they really not achieved a 12-month seizure-free period?

- Is there any underlying cause that might require a different approach and specifically epilepsy surgery or the ketogenic diet, rather than another ASM? An example is where a child has what seems to be childhood-onset absence epilepsy but has not responded to two first-line ASMs. In this situation, and particularly if there are any subtly atypical features in either the child's seizure semiology or inter-ictal and ictal EEG findings, then they should undergo an MRI brain scan.

In my 27 years at Alder Hey, I saw this in two children who presented with classical electro-clinical features of childhood-onset absence epilepsy. Neither child responded to two ASMs in appropriate and well-tolerated doses.

The first child (a girl) presented initially with infrequent absence seizures. When receiving two ASMs (valproate and lamotrigine), the absences increased in frequency to many times a day and a repeat and sleep-deprived EEG showed a subtle asymmetry. MRI revealed focal cortical dysplasia in the right frontal lobe. The second child (a boy), having received two ASMs (valproate and ethosuximide) with good seizure control for six months then developed a new and extremely subtle head and eye deviation to the right. In addition, the absences started to become more prolonged at more than 30 seconds. There was no improvement following increases in the dose of both ASMs. MRI revealed a large brain tumour (grade I glioma at biopsy) that occupied much of the left fronto-temporal region.

Both of these children met the ILAE definition for DR. It could have been assumed that they were in the unfortunate 5-7% of children with childhood absence epilepsy (CAE) in whom seizure freedom is never achieved. In addition, being a genetic generalised epilepsy syndrome, there would be no obvious indication for an MRI scan. If a patient's clinical course is unusual for a specific epilepsy syndrome despite good compliance with medication, and specifically where DR would not be expected, an underlying cause should be suspected and looked for.

As well as MRI, genetic and metabolic disorders may also be appropriate. An obvious example is GLUT-1 deficiency due to a mutation in the SCN2A gene in which children may present with what appears to CAE but develop resistance to all three of the recognised ASMs used to treat absences. The response to a ketogenic diet is often dramatic and results in rapid and complete seizure freedom and, if started early enough (probably <4 or 5 years of age), may prevent significant cognitive impairment although this remains unproven [Alter *et al*, 2015], [Di Giorgis *et al*, 2019].

3. So, drug resistance is confirmed, now what?

First, a priority is to involve the parents (or carers) and the child, whenever this is appropriate, in a discussion, and specifically discuss that the seizures may now be difficult to fully control. This may simply reinforce what might have been said and discussed at the time of the initial diagnosis of epilepsy and the specific syndrome. This is because the epilepsy syndrome is likely to provide some useful prognostic information with regard to both the likelihood of seizure control as well as the eventual long-term remission of the epilepsy. Nevertheless, it is still important to have and repeat such a discussion. The approach should be one of hope but within the context of an honest and realistic optimism – it must not be overly optimistic or pessimistic. Any discussion should address the issue of other ASMs but also other treatments and specifically surgery, the ketogenic diet and vagus nerve stimulation (VNS). At this stage, it will not usually be necessary or appropriate to discuss the ketogenic diet and VNS in great detail. However, epilepsy surgery may need to be discussed in detail, particularly if the child has drug-resistant focal seizures or the child meets the criteria for a formal evaluation in a Children's Epilepsy Surgery Service (CESS) centre [Parida and Agrawal, 2021]. These criteria are broad and one could argue that any child with confirmed DR should be referred to a CESS centre.

I will not address the option of epilepsy surgery, including VNS (as this is a form of 'palliative' surgery), as this has been discussed in much detail in previous issues of PECAS [Parida and Agrawal, 2021]. I will also not discuss the ketogenic diet, as this will be the subject of a future leading article in PECAS in early 2024 by the team at Great Ormond Street Hospital.

Another ASM: Should all hope be abandoned in the use of yet another ASM in an individual with genuine DRE? The obvious answer is no, but this is a broad answer and, as always, will depend on the individual. If another ASM is used, it is important that the person and family should not be given advice and hope that is wholly unrealistic. A study reported in 2007 provides some support for some realistic optimism in the use of other ASMs in this group [Luciano and Shorvon, 2007]. 155 adults with DRE received a total of 265 new drug introductions (125 by addition and 140 by substitution) and were followed up for a mean of 18 (range,

6-60) months. Seizure freedom was defined as seizure freedom at the last follow-up for at least 12 months. Seizure freedom was seen in 16% of all introductions of one or more ASMs. More clinically useful findings were that 26 of the 155 patients (17%) became seizure free after the addition or substitution of only one previously untried ASM; 10 patients (14%) became seizure free after a second ASM was introduced and four patients (15%) became seizure free after the introduction of a third ASM. Consequently, at the end of the study, 43 of the 155 patients (28%) had become seizure free by the addition or substitution of a previously unused ASM. Predictably, those patients who had received less than five ASMs previously, those who had a duration of epilepsy of less than 10 years and those with an 'idiopathic' rather than 'symptomatic' or 'cryptogenic' epilepsy had a statistically higher chance of becoming seizure free. The study did not report on any adverse side effects that resulted from the introduction of these 265 "new drugs". It would be useful to repeat this sort of study in a paediatric population; clearly, this would have to take account of the many different epilepsy syndromes.

New therapies: The last few years have seen a number of completed RCTs that have shown significant improvements in seizure control in a couple of the developmental and epileptic encephalopathies, specifically Lennox-Gastaut syndrome (L-GS) and Dravet syndrome (DS). However, only patients with DS were shown to become seizure free and this was in a small minority of patients (between 5% and 10%). In addition, there are no data on whether any of these patients achieved a 12-month period of seizure freedom beyond the trials' designated 14-week treatment periods.

- Epidyolex, the only currently licensed cannabidiol, and in a dose of 20mg/kg/day, was associated with 5% of patients with DS becoming seizure free. No patient who received the placebo became seizure free [Devinsky *et al*, 2017].

- More recently, fenfluramine (Zogenix) was also shown to be efficacious in patients with DS. Seizure freedom during the 14-week treatment period was seen in three (8%) patients in the fenfluramine 0·7 mg/kg/day group and three (8%) patients in the 0.2 mg/kg/day group. No patient who received the placebo became seizure free [Lagae *et al*, 2020]. It will be important to see if this improvement, including seizure freedom, is maintained in the longer term.

- Other treatments, some as recognised ASMs, others as drugs with as yet unknown mechanisms of action in epilepsy, have emerged and are being increasingly targeted at epilepsies caused by specific genetic mutations, the so-called 'individual-specific treatments'. One of these epilepsies is CDKL5 deficiency disorder (CDD). This is a rare, X-linked, developmental and epileptic encephalopathy that was at one time considered to be a severe type of Rett syndrome. It is characterised by severe or profound global developmental impairment and frequent seizures that can begin in the first few months after birth and are often drug resistant. Ganaxolone is an investigational neuroactive steroid that has been reported to be beneficial in the management of a few epilepsies, including infantile spasms [Kerrigan *et al*, 2000], children and young people with refractory epilepsy [Pieribone *et al*, 2007] and more recently in adults with drug-resistant focal epilepsy [Sperling *et al*, 2017]. Although ganaxolone was associated with a 31% median reduction in major motor seizure frequency at 28 days in 50 patients with a CDKL5 mutation, no patient became seizure free.

Novel and more targeted surgical procedures are likely to be developed that can better access areas of cortical dysplasia or tumours (such as hypothalamic hamartomas) with less risk of damaging eloquent cerebral cortex or other brainstem structures. An emerging therapy is Laser interstitial thermotherapy (LiTT), including in children [Hoppe and Helmstaedter, 2020]. The reality is that even if this technique becomes an established surgical procedure, it is likely to benefit only a small proportion of patients (including children) with medically refractory (drug-resistant) epilepsy. Another promising therapy is neuromodulation. This can be invasive, such as VNS, deep brain stimulation (DBS), or responsive neurostimulation (RNS); or non-invasive, specifically transcutaneous auricular VNS or transcranial direct current stimulation. This was discussed in much more comprehensive detail by Dr Anand Iyer in his recent article in PECAS [September 2023].

Conclusion

Resistance to ASMs remains a significant clinical problem and is still reported to affect approximately 30% of all patients, across all ages and epilepsies. The range varies widely in children under 16 because of the many different epilepsy syndromes. It is unlikely to fall below 25% in the next few decades.

The key approaches to its management in a child or young person are:

- Establish the correct diagnosis of the seizure(s), epilepsy and syndrome.

- Use the most appropriate ASM and in an appropriate dose.

- Give time for any change in ASM (including its dose) to have an effect (i.e. don't rush to exclude a particular ASM too soon). This may take a number of weeks depending on the seizure frequency.

- Always consider an underlying and a treatable cause and particularly a structural or metabolic cause.

- Ensure the child has met the defining criteria of DR before making this diagnosis an discuss or refer the child who appears to be drug resistant with a paediatric neurologist who has a specific expertise in epilepsy.

- Finally, although the goal in any child is to obtain seizure freedom, this must not be at the expense of the child's ability to develop and function – including within their family and school.

Appendix

Referral criteria to a CESS centre

- Children with catastrophic early onset epilepsy with evidence of lateralisation to the seizure onset.
- All children under 24 months old with evidence of focality to seizure onset, with or without an MRI-evident lesion.
- Children of any age with evident focal epilepsy or lateralised seizures associated with congenital hemiplegia, resistant to two appropriate ASMs.
- Children who have epilepsy associated with a lateralised abnormality seen on a brain scan.
- Children with epilepsy associated with Sturge Weber syndrome, benign tumours with developmental issues and/or ongoing seizures, or Rasmussen's syndrome.
- Children of any age with epilepsy associated with tuberous sclerosis resistant to two ASMs where seizures may arise from a single focus (probably from a single tuber).
- Children who have 'drop attacks' as part of a more complex epilepsy.
- Children with epilepsy associated with hypothalamic hamartoma.

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epilepsyspace.org.uk

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:

- Manage their epilepsy
- 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

Epilepsy Action
Information you can trust

Find out more
epilepsy.org.uk/trust

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 more than 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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Paediatric Epilepsy Current Awareness Service is published by: Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
Date of preparation: September 2023
Epilepsy Action is a working name of British Epilepsy Association. British Epilepsy Association is a Registered Charity in England and Wales (No. 234343) and a Company Limited by Guarantee (No. 797997).
 ISSN 2631-7400
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