epilepsy action

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CURRENT AWARENESS SERVICE

Pharma and epilepsy: the good, the bad and the ugly

Most patients with epilepsy will require at least one anti-seizure medication (ASM), and a significant minority will require two, to control their seizures. A much smaller number of patients will have to try multiple ASMs to optimise their seizure control, and, as we all know, not always successfully [Kwan and Brodie 2006; Kwan et al, 2010]. Such patients, with intractable epilepsy, are often recruited into randomised controlled trials (RCTs) of new ASMs, approximately 80% of which are designed, initiated and funded by the pharmaceutical industry (hereafter referred to as 'pharma') [The Times, 2022]. These studies are expensive, with an average RCT typically costing £8-12 million. It is important to understand that the primary objective of nearly all pharma-funded RCTs is to secure a licence for a drug, and specifically in adults because this is the largest prescribable population. Traditionally, studies of ASMs in children have been performed relatively late in the development of a drug and usually in Phase IV drug studies, after the pivotal Phase III studies and also after the ASM had been licenced and marketed. The aims of Phase IV studies are to obtain further information on the drug's effect in different populations (such as children or pregnant women) and also to identify any long-term side effects of the medication.

For decades, pharma was reluctant to undertake trials of ASMs in children. This was because any potential benefits of such a study would not justify their costs and also because of its perception that informed consent from families would be much more difficult and less successful. In fact, evidence suggests that parents are very willing to consent to their child with intractable epilepsy participating in an RCT, as evidenced by trials of cannabidiol (Epidyolex) and also fenfluramine (Zogenix) in children with Dravet and Lennox-Gastaut syndromes. In terms of pharma's financial concerns over undertaking RCTs in children, regulatory authorities now recognise the importance of such trials, and particularly early on in the development of an ASM. Many health bodies from different countries have emphasised that much more should be known about the effects of all new ASMs at the time of their approval. This includes the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) from the USA, the European Medicines Agency (EMA) in Europe and the Medicine and Healthcare products Regulatory Agency (MHRA) from the UK, as well as the International League Against Epilepsy (ILAE). It is no longer accepted that adult data can be simply and automatically extrapolated 'downwards' to children without paediatric data. To encourage pharma-sponsored trials in children, from 2006 the EU Regulation on

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Medicines for Paediatric Use made the testing of new products in children mandatory if regulatory approval is to be granted for the product to be used in adults [The European Parliament and the Council of the European Union, 2006]. A drug's process of development must now include a Paediatric Investigation Plan (PIP) that has to be agreed with the EMA. (***bit.ly/3Bafutz***)

A PIP should be submitted early during the development of an ASM, in time for studies to be conducted in children and specifically in Phase III trials, before marketing authorisation applications are submitted and licences granted.

The Association of the British Pharmaceutical Industry (ABPI) provides another regulatory eye on pharma. However, its executive comprises of representatives of pharma and consequently may have a different priority and agenda to that of the EMA and MHRA. The current president of the ABPI is Pinder Sahota who is also General Manager at a large pharma company, Novo Nordisk UK. The ABPI's Code of Practice includes the following statement regarding the interaction between pharma and doctors: "The pharmaceutical industry in the UK is committed to benefiting patients by operating in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high quality healthcare." The code covers the promotion of medicines for prescribing to both health professionals and other relevant decision makers and also includes requirements for interactions with health professionals. It also sets standards for information about prescription only medicines to the public and patients, including patient organisations. The code was most recently updated in July 2021.

Pharma is a huge business and clearly must be profitable to allow it to undertake the necessary but expensive Research and Development (R+D) of new ASMs. In 2020, it was estimated that the average R+D costs among 12 global biopharma companies to develop a new pharmaceutical compound from discovery to launch was $2.2 billion [The Times, 6 October 2022]. Importantly, their marketing budgets may be as high as their R+D budgets to maximise sales of their products.

The pharmaceutical industry plays a central role in the design and development of any new ASM and consequently in Public Health and the management of people with epilepsy. This necessitates a close working partnership with regulators and the NHS, which, at times, can be difficult. In part, this difficulty reflects the fact that the NHS is a Government-funded service, free at the point of use, which must try and minimise all of its costs, including drug costs. This is in contrast to pharma, which is a huge business with a global income in the many billions and a need to be profitable and satisfy their share-holders. Inevitably, this sets up a potentially fragile and often tense relationship between pharma and the NHS. Ultimately, it may lead to a conflict of interest between a private, profit-lead industry and public health and patient need [Brezis, 2008]. Overall, pharma, and particularly 'Big Pharma', could be regarded as showing the 'good, the bad and the ugly' aspects of their business, although not usually in equal measure. I will try and clarify…

The Good

In the early 1990s, Marion Merrell Dow, later Hoechst Marion Roussel (HMR), licensed a new and the first 'designer' ASM, vigabatrin (Sabril). As experience with, and the prescribing of, the medication rapidly grew the company introduced an educational initiative called the rather appropriate, 'Education in Epilepsy Group (EEG)'. This aimed to improve the knowledge and understanding of epilepsy in both primary and secondary care. It comprised of experts in adult and paediatric epilepsy, clinical pharmacology and neuropsychology. The format comprised lectures and seminars, one-day courses and regular newsletters, all of which were free to clinicians that had an interest in epilepsy. It ran for approximately five years before then being discontinued. In part this was because of another new ASM, gabapentin, manufactured by Parke-Davis, a subsidiary of Johnson and Johnson.

Parke-Davis was taken over by Warner Lambert and subsequently, Pfizer. Predictably, Parke-Davis introduced their own educational initiative, called 'Epilepsy Agenda'. Its composition also included epilepsy specialist nurses and the format was almost identical to that used by HMR in the 'EEG'. 'Epilepsy Agenda' also ceased to function after a few years, again in part because of the next newly-licensed and launched ASM, lamotrigine (Lamictal), manufactured by Glaxo Wellcome that subsequently became GlaxoSmithKline. Glaxo Wellcome also introduced its own programme, including an 'advisory board' but without a catchy name such as 'EEG' or 'Epilepsy Agenda'.

In the mid-to-late 1990s, soon after the licensing and launch of its novel ASM, topiramate (Topamax), Janssen Cilag set up an educational grant to produce a number of videotapes on the differential diagnosis of epilepsy and non-epileptic paroxysmal events in children and adults. The videos included voiceovers and brief interviews with paediatric and adult epileptologists and accompanying text to explain and discuss the different events.

In 2001, UCB Pharma introduced a similar educational programme with the launch of its novel ASM, levetiracetam (Keppra). The programme format was in a series of one or two-day adult and paediatric epilepsy courses which ran for a number of years and was called the 'Epilepsy Masterclass'. It subsequently introduced an 'investigator-led study' programme to help doctors design and operate studies that obviously included Keppra. These studies were mainly funded by the company and were very limited in number, primarily because of their cost.

There is no doubt that the above initiatives funded by pharma were popular and extremely useful in increasing the knowledge and understanding of the epilepsies from the mid-1990s onwards. The videos were particularly helpful in the diagnosis of epilepsy, largely because it was the first time that specialists, but particularly non-specialists (i.e. paediatricians, physicians and general practitioners), were able to actually see the different types of epileptic seizures and non-epileptic events that they had only previously heard or read about. Although there are no data to support this, it is very likely that such initiatives contributed to an improved diagnosis and management of the epilepsies from the early 2000s onwards. Clearly, these initiatives came at a time when there was a relative explosion of new ASMs on the market. The respective pharmaceutical companies hoped and expected that these educational programmes would also lead to increased prescribing of their ASMs. In my opinion, this was of mutual benefit for pharma and patients with epilepsy and as such, reflected the 'good' side of pharma.

The Bad

I have already explained that, prior to 2006 a paediatric indication or licence was only obtained after the drug had been launched and following 'post-marketing' paediatric-specific phase IV trials. An example of this was the gabapentin trial. This trial also highlighted another common and recurring problem with industry-funded RCTs. This is that they are undertaken in a selected population, using quite rapidly-escalating drug doses, with the double-blind comparator typically being a placebo and not an active drug and for a relatively short period, typically 12 or 16 weeks. This population cannot be regarded as being representative of the vast majority of people with epilepsy. In addition, the doses used in this RCT [Appleton et al, 1999] and possibly in the earlier adult equivalent RCT [Anhut et al, 1994] were inappropriately low, which clearly influenced the results and therefore the conclusions of the trial(s). It also influenced the conclusions from later meta-analyses, Cochrane Reviews and NICE recommendations of the RCTs of all ASMs, including gabapentin in treating focal seizures. However, it is of interest that longer-term open studies which used much higher doses of gabapentin did not show a significantly increased efficacy in preventing focal seizures [Appleton et al, 2001; Marson et al, 2007].

In July 2022, the Competition and Market Authority (CMA) published its report on an extended investigation of two pharmaceutical companies that manufactured phenytoin (Epanutin). The press release headlined the report as: "£70 million in fines for pharma firms that overcharged NHS'. The CMA had found that Pfizer and Flynn had abused their dominant positions to overcharge the NHS for a "life-saving epilepsy drug". Pfizer and Flynn had de-branded the drug (Epanutin) which meant that it was no longer subject to price regulation and the firms could set their own prices. As Pfizer and Flynn were the dominant suppliers of the drug in the UK at the time, the NHS had no choice but to pay the inflated prices. Over the following four years, Pfizer charged prices between 780% and 1,600% higher than previously. The company supplied the drug to Flynn, which then sold the capsules on to wholesalers and pharmacies at a price between 2,300% and 2,600% higher than the prices previously charged by Pfizer. This illegal behaviour led to NHS annual costs for phenytoin capsules increasing from £2 million in 2012 to approximately £50 million the following year.

The CMA first issued a record fine of £90m to the companies in 2016. Pfizer and Flynn challenged the fine and subsequently took their case to the Competition Appeal Tribunal. The tribunal set aside conclusions about whether the companies' price hikes were an unlawful abuse of dominance. The CMA and Flynn then appealed to the Court of Appeal. In March 2020, the court dismissed Flynn's appeal in its entirety and upheld aspects of the CMA's appeal relating to the application of the legal test for unfair pricing.

The CMA decided to reinvestigate and gather more evidence, which led to it reissuing the fine, this time for £70m, having found that the companies did charge unfairly high prices for over four years.

Finally, there is the important issue of publication bias, where pharma will only want to publish their trial data that show their new product (including an ASM) was effective and safe and they will not publish any negative trial data. This will lead to a publication bias in favour of the drug, which will subsequently be reflected in meta-analyses, Cochrane reviews and ultimately, NICE recommendations. Publication bias should be avoided in non-pharma funded studies such as SANAD I [Marson et al, 2007] and SANAD II [Marson et al, 2021]. However, this is still conditional on editors of scientific journals agreeing to publish papers that report negative trials which, in the past, they were reluctant to do. The above illustrates what many would regard as the 'bad' side of pharma.

The Ugly

In 1996, a previous employee of Parke-Davis filed a law suit in the US against the company for the off-label use of gabapentin (Neurontin) [Lenzer 2003]. Executives in Parke-Davis were worried about the future market for gabapentin, as its original patent was set to expire in December 1998 and particularly because it was approved for use only as adjunctive treatment in patients with focal seizures. Parke-Davis decided that it was not sufficiently profitable for them to obtain FDA approval for Neurontin's alternative uses. Although federal regulations, such as the FDA, would not allow Parke-Davis to promote gabapentin for un-approved uses, drug companies are allowed to distribute third party publications that promote an off-label use in response to unsolicited requests. The

employee stated that Parke-Davis had undertaken an "elaborate programme to exploit this narrow window of opportunity" to sell gabapentin. A thinly disguised incentive scheme to get doctors to prescribe the drug off label was to pay them as 'consultants' to attend all expenses paid trips to resorts where doctors were encouraged to prescribe the drug for disorders including migraine, bipolar (manic-depressive) disorder and attention deficit disorder. 'Studies' that were reported to support the use of the drug in these areas ranged from occasional case reports to fabricated and non-existent data. In bipolar disorder, no study ever showed that the drug had any benefit over placebo. The company also hired and paid non-medical technical ghost-writers to write 'scientific' articles. The articles were then filtered through 'medical education' companies, which in turn submitted them for publication. This practice could be reasonably labelled as representing both professional bribery and fraud and could be reasonably regarded as representing pharma's 'ugly' side.

There is no doubt that pharma hospitality was wide-spread in the 1990s and early 2000s to try and encourage doctors to prescribe their new drugs, including ASMs. The ABPI subsequently, and quite appropriately, placed significant and quite tight restrictions on the types and financial limits of 'hospitality' offered by pharma to doctors. From the early 2000s, most Hospital Trusts also introduced quite strict guidelines on how much hospitality doctors were allowed to receive from drug companies.

Conclusion

Pharma is a huge business that has to be profitable to survive. They rely on specialist doctors to advise them on trial design and to participate in large RCTs with the hope that they demonstrate their new ASM's efficacy and safety and consequently gain a licence to be marketed and sold. The NHS continues to face increasingly rising costs, including new medications that are often expensive, in order to maximise benefit and minimise harm to patients. This is irrespective of the 'branded versus generic' debate which is ongoing. The regulators, such as the ABPI, EMA and the MHRA have important roles in policing new medications and protecting the patient but they face sustained and often fierce lobbying from the pharmaceutical industry over their drugs. There has to be effective and transparent collaboration between all parties that allows each one to thrive but not at the expense of the others and particularly the patient. Although this has been a challenge in the past it will become even more so in the coming decades.

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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.

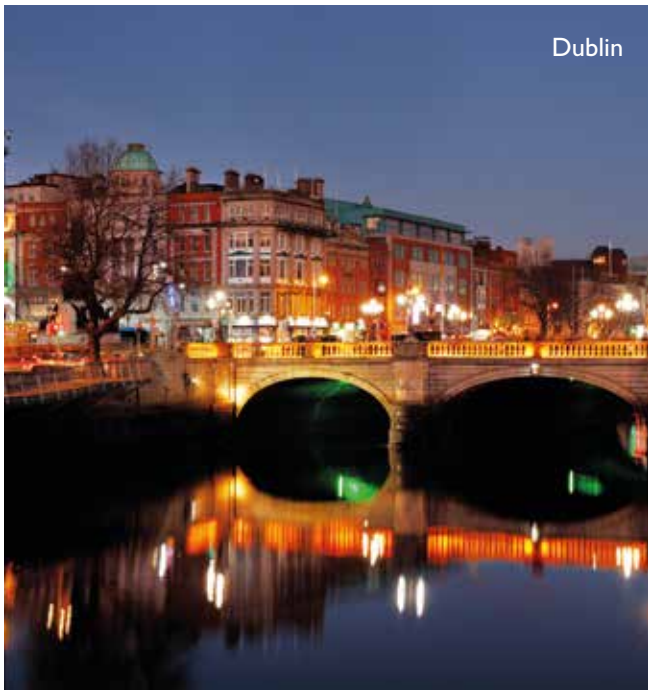
February 2023
8-11
14th International Newborn Brain Conference
Clarwater, Florida, USA
mcascientificevents.eu/inbc/

23 February - 25 June
IInternational Online Course on Pathogenesis of Epilepsy Online
4euepilepsy.lf2.cuni.cz

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


Lyon


Dublin

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

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

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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**

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Managing epilepsies in children and young people who also have learning disabilities

Dr Dan Hindley, consultant community paediatrician, Bolton NHS Foundation Trust

Introduction

The term 'learning disability' (LD) is often used in UK clinical settings as shorthand for disorders of intellectual development in the International Classification of Diseases (ICD-11) which has now (appropriately) replaced mental retardation (ICD-10). Core features of Disorders of Intellectual Development are:

1. Significant limitations in intellectual functioning
2. Significant limitations in adaptive behaviour functioning
3. Onset during the developmental period

There are four levels of severity: mild, moderate, severe and profound.

There is also a category of provisional disorder of intellectual development either where:

1. There is evidence of a Disorder of Intellectual Development but the child is under the age of four years making it difficult to know whether the observed impairments represent a transient delay.
2. There is evidence suggestive of a Disorder of Intellectual Development but it is not possible to conduct a valid assessment because of other impairments; eg. sensory, physical, communication, behaviour.

In practice working as a community paediatrician in secondary care in the UK, the diagnosis of learning disability/intellectual disability depends on information obtained by the education system usually after assessment by an educational psychologist. If the child's learning disability requires extra support and funding above and beyond the usual school budget, the child will receive an individual Education and Health Care Plan (EHCP). The extra support can be provided in a mainstream or special school. Most children in receipt of an EHCP for learning support will have moderate, severe or profound learning disability.

In general, people with learning difficulties are more likely than those without to have additional health needs. In one recent study [Tyrer et al, 2022], 46.4% of 7794 individuals with intellectual disabilities (compared with 9.7% of 176,807 in a comparison group) had more than one health need. This was indicated by the following: epilepsy, incontinence, severe visual loss or impairment, severe mobility difficulties, cerebral palsy and the need for per gastrostomy (PEG) feeding. Epilepsy was the most common health need (18.7% vs. 1.1%). Similarly, for children with a diagnosis of epilepsy made within the first 10 years of life, 17.4% (475/2728) had a diagnosis of cognitive impairment compared to 1.7% (2309/139835) in controls [Sorg et al, 2022]. The relative risk for cognitive impairment compared to age-matched controls was 10.5 (95% CI 9.6, 11.6) and was highest in those children whose seizure onset was within the first two years of life.

This article considers some aspects of the management of epilepsies in children and young people with learning disabilities, specifically issues with regard to accurate diagnosis, seizure management and service provision. When referring to LD, I will concentrate on those with moderate to severe LD, acknowledging that many of these children and young people will often have other, often complex, comorbid neuro-developmental and medical diagnoses, as well as epilepsy.

Diagnosis

Seizure diagnosis

Accurate identification of seizures remains a challenge both for people presenting for the first time, and for those with an established diagnosis of epilepsy, irrespective of if they have a learning disability. The misdiagnosis of epilepsy in children and young people is considered to be approximately 25-30%. One systematic review [Chapman et al, 2010] included and critically appraised six cohort studies and two case studies of individuals with intellectual disabilities and epilepsy, most of whom were children. Between 32% and 38% were considered to have been misdiagnosed with epilepsy. The main reason for misdiagnosis was the misinterpretation of behavioural, physiological, syndrome related, medication related or psychological events by parents, paid carers and health professionals. Examples of events that contributed to diagnostic confusion included:

- stereotyped repeated blinking or swallowing
- self-stimulatory tics or behaviours such as hand-flapping or hand-waving
- spontaneous smiling; grimacing; laughing episodes
- staring spells; inattention; unresponsiveness
- simulation of convulsions (psychogenic non-epileptic seizures)
- head and/or eye turning
- bucco-lingual movements
- hypnic jerks
- dystonic and tonic posturing; stiffening of limbs (particularly in children with four limb spastic or dyskinetic cerebral palsy).

DeToledo et al [2002] examined 63 requests for video EEG of 'new seizure types' in adults with learning disabilities which had been initially suspected by care staff. Epileptic seizures were confirmed in only four of the 63 (6.3%) patients. The list of non-epileptic causes was very similar to that described above.

Difficulties with investigations

The diagnosis of epilepsy in practice still depends on a full and accurate history, a witnessed account of a number of the typical episodes and, ideally, a video recording of the events. Other investigations can also contribute to the classification and specificity of diagnosis. Some of these investigations can be more difficult in a child and young person with LD. Paediatric EEG departments are skilled in achieving quality recordings in this group by using many of the techniques described by Paasch et al, including involvement of carers, patience, behavioural approaches, acclimatisation and good preparation [Paasch et al, 2012]. Home video-telemetry has been shown to be comparable, and in some ways better than inpatient video-telemetry in terms of ease and acceptance for people with severe disability, learning disability or challenging behaviour [Biswas et al, 2016]. However, the success of home video-telemetry relies on the parents or carers to successfully record the time of any events and to ensure the video is also recording the events. In addition, home video-telemetry is not yet widely available.

Magnetic resonance imaging (MRI) can also be a challenge because of the need to obtain high quality images and avoid movement artifacts. Children and young people with learning disabilities are often automatically assumed to need a general anaesthetic to achieve this, consequently increasing waiting times. However, Nordahl et al [2016] reported a group of children with autism spectrum disorder (ASD) and LD in whom acceptable scans were achieved in 100% for T1-weighted, and 94% for diffusion-weighted images. This was when they were prepared before the scan by behavioural analysts using mock scanners and behavioural strategies.

Finding a cause

The ILAE classification of epilepsies (2017) incorporates aetiology alongside the three levels of classification for epilepsies (seizure type, epilepsy type, epilepsy syndrome). Causes can be structural, genetic, infectious, metabolic, immune and unknown; some may have a combined cause, as in tuberous sclerosis complex (genetic and structural). Finding the cause is increasingly helpful when considering the best treatment of an epilepsy (see below) but is also very important for families. Knowing the cause improves understanding and often allows clinicians to provide a more accurate prognosis – for both seizure control and learning potential. There are other benefits, including improved estimates of recurrence risk and screening for associated medical conditions. Sometimes a cause can open the door to resources and family support. These benefits are equally important for families who have children with LD, and those who have children with both LD and epilepsy. Have a look at the Syndrome Without a Name (SWAN) website: ***undiagnosed.org.uk/support-information/what-does-getting-a-genetic-diagnosis-mean/***

A cause is often immediately obvious after clinical assessment and first line tests. However, even in 2022, every paediatrician will look after a number of children in whom no cause is found even after undergoing all the available tests specialist opinions (particularly genetics). This is understandably a source of great frustration for the family and the paediatrician. SWAN asserts that 'approximately 6,000 children are born in the UK every year with a genetic condition likely to remain undiagnosed'. For some, this will be because there is not yet a test for their condition, but for others, it will be because the right test is available but has not been done. It is important to review whether your patients with no identified cause for their epilepsy have undergone the latest genetic analyses, whether or not they also have LD. This is particularly important following the recent roll-out of whole genome sequencing availability across the NHS.

Dual pathology

It is worth keeping an open mind about cause and not necessarily attributing everything to the one condition when there may be two. It is easy to rest on your laurels once an answer is found but that might not be the whole answer. This is illustrated in the following case:

I had been looking for a child with pyridoxine responsive seizures for a long time. This boy was born at term and had severe unexpected hypoxic ischaemic encephalopathy with multi-organ failure. He suffered intractable seizures resistant to multiple anti-seizure medications (ASMs). By seven months of age, he had global developmental delay, four-limb spasticity and up to forty seizures a day, despite treatment with sodium valproate. He was given a trial of pyridoxine and never had a further seizure. A diagnosis of pyridoxine-dependent epilepsy was subsequently confirmed. He continued to have complex medical problems which were spastic quadraparesis, severe learning disability, gastro-oesophageal reflux and feeding problems, recurrent tonsillitis, chest infections and failure to thrive (weight on 91st centile at birth and on the 0.4th centile at two years of age).

His brother was born when he was almost two years old. The brother had a cough and frequent loose stools from birth and his weight fell from the 91st centile at birth to the 0.4th centile at five months. His sweat test was diagnostic of cystic fibrosis. The older brother was also tested and his sweat test confirmed that he also had cystic fibrosis. Both boys were homozygous for the mutation delta F508. Both boys subsequently made good weight gain on appropriate treatment.

There is no known link between pyridoxine-dependent epilepsy and cystic fibrosis. I had been pleased with the

first boy's remarkable response to pyridoxine and had ascribed his failure to thrive and respiratory symptoms to aspiration and gastro-oesophageal reflux disease (GORD), as is often seen in children with severe cerebral palsy. He taught me to keep thinking about other possibilities even in children where the diagnosis seems secure, that Occam's razor does not always apply and that in medicine as in rugby, 'The moment you think you've cracked it, you're going to come second' (Clive Woodward, Nov 2003).

Seizure management

'Difficult to treat' epilepsies

In general, the more severe the learning difficulty is, the more severe is the epilepsy. Most of my patients with difficult epilepsies have severe learning difficulties and attend special schools. If a child develops epilepsy having had normal development and cognition up until that point, then very often a learning difficulty will subsequently develop if they have frequent seizures. We try to achieve control as quickly as possible but everything seems so slow and particularly for families. The introduction and upward titration of most ASMs have to be gradual. If changes are made too quickly, an ASM that might otherwise have been efficacious can be lost to a preventable or avoidable side effect. The increments of ASMs tend to have to be gradual and small, whether increasing or decreasing the dose. Usually, a new drug is added in and then once the expected therapeutic level the drug it replaces is weaned off. However, if the young person is already on a number of ASMs, a see-saw switch (increasing a new medication at the same time as decreasing another in increments) can work, although this breaks the rule of not making more than one change at once. It can be tempting to leave a drug in rather than weaning it off, even when it manifestly has not made much difference, which leads to needless and unwanted polypharmacy with potential adverse side effects.

With time, technology may allow us to analyse a sample of saliva from all patients with newly-diagnosed epilepsy to predict which ASM (or ASMs) is most likely to be efficacious and the least likely to cause serious adverse side effects. Until then, we must continue to treat patients as best as we can, using current knowledge and experience. At times, this will feel like an empirical process. For those with chronic active epilepsy who have tried many different medications, failed on the ketogenic diet and are not surgical candidates, it is important to keep trying and not fall into therapeutic nihilism. There are always new innovations (eg. cannabidiol (Epidyolex) and fenfluramine), old drugs not tried for years and maybe even drugs which you think you might have considered in the past but in fact were never used. For example, a teenager with severe LD and apparently uncontrolled myoclonic seizures as well as other seizure types, responds to carbamazepine, introduced by a brave paediatric neurologist. Another child with post-herpes encephalitis brain injury, LD, and autism had tried 'everything' – except that he had never received lamotrigine, to which he subsequently had a 'golden' response. In one study, 16% of all new drug changes resulted in seizure freedom (defined as having no seizures for 12 months or longer at the last follow-up) in a group with epilepsy that had remained active for at least five years after initiation of therapy [Luciano and Shorvon, 2007]. The study also demonstrated that another 21% of patients showed a 50-99% seizure reduction. Of 155 patients, 28% were rendered seizure free following the introduction of a different ASM. Clinical factors associated with a better effect were: fewer previously used ASMs, shorter duration epilepsy and an idiopathic epilepsy.

Cause influencing treatment choices

The choice of ASM has traditionally been based on seizure type and epilepsy syndrome but is now being increasingly influenced by the underlying cause and particularly if it is genetic. Sometimes it is the genetic cause of the epilepsy, eg. an SCN1A mutation for Dravet syndrome, that is most important. Sometimes it is the genetic cause of the overall clinical phenotype of which epilepsy is only a component, eg. maternal loss of UBE3A function in Angelman syndrome. The three ASM combination of stiripentol, valproate and clobazam is particularly efficacious in Dravet syndrome whilst sodium channel blockers (such as carbamazepine and phenytoin) are not. Valproate and levetiracetam work well in Angelman syndrome but not carbamazepine. There are many examples now of this so called 'precision treatment' of the epilepsies, helping clinicians to choose the best drug(s) to give control early on, and avoiding those that are likely to make the epilepsy worse. Sometimes the cause is found quickly using microarray tests and sometimes the new technology, such as whole genome sequencing, will take much longer to give a result.

Rare conditions causing epilepsy and LD are seldom seen by the same clinician and so it can be difficult to collect information about their clinical characteristics from an adequate sample. Specialist genetic and MDT clinics, e.g. for tuberous sclerosis, Angelman syndrome, Rett syndrome etc, can collect information about specific rare diagnoses. Another good way to find out the best and worst drug to use for a given cause of LD and epilepsy is to ask a group of families who all have a child with the same cause, about their experience with different medications. A good way to find a group of families who all have a child with the same (often rare or recently discovered) cause is to collaborate with the relevant parent support group, or charity, eg. Unique rarechromo.org/. By these means, the epilepsy phenotype for an increasing number of genetic conditions has been characterised.

Early assessment for non-drug treatments

There are established criteria for referral to Children's Epilepsy Surgical Service (CESS). A number of these are likely to apply especially to those with LD and epilepsy:

- Children with catastrophic early onset epilepsy with evidence of lateralisation of seizure onset.
- All children under 24 months of age with evidence of focality to seizure onset, with or without an identified MRI lesion.
- Children of any age with evident focal epilepsy, or lateralised seizures associated with congenital hemiplegia, resistant to two appropriate ASMs.
- Children with epilepsy associated with Sturge Weber syndrome, benign tumours with developmental issues 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.

In the most recent data released from the Epilepsy12 national audit, only 36% (49/135) of patients who met the criteria for a referral to a children's surgical service had been referred. This would merit an audit of your current practice to ensure that all children that meet the above criteria are discussed with or referred to a CESS centre.

The same principle applies for the use of a ketogenic diet where it should no longer be considered as a treatment of 'last resort'. There are some specific epilepsy syndromes where it should be considered much earlier and possibly after the failure of two appropriate and tolerated ASMs (e.g. myoclonic-atonic epilepsy and Dravet syndrome) [Kossoff et al, 2018].

Triggers and seizure detection

Given that those with significant learning disabilities will often have difficult-to-treat epilepsies, it is important to emphasise that the identification and avoidance of triggers for seizures may significantly help to improve seizure control. Seizure exacerbation associated with menstrual periods, constipation, dental/hip pain and impaired sleep can all be addressed by appropriate care. Sleep disorders and anti-seizure medications can cause sleep fragmentation and worsen seizures [Gibbon et al, 2019]. Sleep apnoea can be an important treatable cause of drug resistant nocturnal seizures [Youssef et al, 2022]. Treatment of other comorbidities, such as ADHD and mood disturbance, are said to have a bidirectional association with epilepsy, with the comorbidity increasing the risk for seizures and seizures increasing the severity of the comorbidity. There had been the perception that some of the treatments for these comorbidities might exacerbate seizures, but more recent evidence indicates that these treatments are safe and do not lower seizure threshold [Holmes, 2021].

I have often seen that reducing the child's levels of stress and arousal by changing the child's environment can also be helpful in seizure management for those with epilepsy and learning difficulties. This is especially true for those with autistic features. On starting a new educational placement specialising in the management of children with these difficulties, there will often be an initial increase in baseline seizure frequency as the child becomes accustomed to the new environment. This is subsequently followed by a fall in seizure frequency, even to below pre-admission levels, once the child becomes used to their new environment, positive life style changes, experienced behaviour management and a safe, calm atmosphere.

Seizure detection, especially at night, is important for carers and families who have children with LD and epilepsy. Reliable alerts for generalised tonic-clonic seizures can allow rescue treatment and prevent prolonged and potentially damaging seizures. This topic was discussed in more detail in PECAS recently [Hindley, 2021].

Getting the medications in reliably

Encouraging any child to take regular medications for prolonged periods can be a challenge. Adolescents with learning disabilities have worse medication adherence than those without [Dharmapuri et al, 2015]. For a child or young person with epilepsy and significant LD, good adherence requires information to be given to the family about the pros and cons of medication, and long-term motivation by the carers to administer the medication as prescribed. It also requires organisation and routine. Clinicians can make administration of medications easier for families/carers by prescribing the most tolerable preparation for an individual taking into account frequency of administration, taste, physical form (liquid, granule or tablet) and dose. Giving 5mls of sodium valproate (Epilim) twice a day is considerably easier than giving 4.85mls as following a strict interpretation of the British National Formulary (BNF) would suggest (rounding up or down).

People with LD can become averse to regular medication and often require pragmatic, creative strategies to mask the flavour or texture of what is administered (what is often termed 'covert administration'). There is sometimes an anxiety about mixing medications with foodstuffs or drinks but unless a pharmacist says otherwise it might be the only way of achieving successful and sustained administration of the ASM. Examples of foods used this way include yoghurt, chocolate mousse, gravy and cheese on toast! Gastrostomy is also sometimes required as a last resort. Howard et al [2019] reported 10 children in whom a PEG was inserted for administration of medication rather than for nutritional reasons. Families reported easier administration of medications and improvements in quality of life. Other benefits were a reduction in seizure frequency and a decrease in the number or dose of drugs administered. There were seven reported PEG complications, which did not require removal of the PEG. I have cared for three such patients over a number of years,

all of whom had severe, life-threatening epilepsies and who regularly required persistent restraint for medication administration until they had a PEG inserted.

Service provision

Continuity of care

The majority of the children with difficult to treat epilepsies will also have significant learning disabilities, and many will attend special schools. These are the most complex of our patients with numerous comorbidities and often significant social challenges. We will manage and care for these children and their families for many years. Continuity of care has been shown to be associated with a variety of positive outcomes in the management of chronic disease including patient satisfaction [Hjortdahl et al, 1992], adherence with medication regimens [Becker et al, 1974] and health service use [Raddish et al, 1999]. One explanation for this is that continuity leads to better communication [Love et al, 2000] and to increased knowledge and trust between the patient and the doctor [Starfield, 1992]. This makes it easier for the doctor to understand the patient's and family's attitudes and to individualise management decisions. It is helpful to try to maximise continuity of care in the epilepsy clinic by having a low turnover of staff and to endeavour that the child and their family are seen by the same clinician each time. In practice, this means having the long-term children seen by permanent (and senior) staff rather than by a junior doctor that may change every six months.

Epilepsy Specialist Nurses

The pivotal role of epilepsy specialist nurses (ESNs) in the support and management of children with epilepsy and their families is increasingly recognised. Much of their time is spent helping those with the most resistant epilepsies and usually in association with challenging learning and behaviour problems. A recent study [Beesley et al, 2022] undertaken in the North West of England, gave semi-structured interviews to carers from service areas with an ESN and compared these to interviews from areas without an ESN. Four themes relating to different aspects of carers' needs were identified. These were: needs for understanding the condition, ongoing support for management of the condition, educational liaison support, and emotional support. The ESNs were able to meet these diverse support needs of families proactively and sensitively, whereas in services without ESNs, carers were left to attempt to fulfil needs across different contexts in an ad hoc and often ineffective manner. The study concluded that paediatric ESNs provide an essential resource for children, carers and other professionals that help to mitigate carer burden.

Special school clinics

It can be very helpful to hold epilepsy clinics in special schools. The paediatrician and the ESN go to the school rather than the children travelling in to a hospital based general paediatric or paediatric epilepsy clinic. This is beneficial as the children with LD (and other comorbidities such as behaviour problems and ASD) are seen in a familiar environment and families avoid the stress of having to travel to clinic. Useful background information is often given by special school nurses and teaching staff and the clinic provides excellent opportunities to build links and offer support in a wider setting. In the ideal situation, it would be very useful to have regular educational psychology input to a clinic. This would help regularly assess the degree and changing course of learning disabilities, as well as providing advice about seizure recognition, behaviour and recommendations for school staff. This is unlikely to occur in the near future because of the scarcity of educational psychologists.

Transition

Much has been said and written about easing the transition of young people from paediatric to adult care. Some describe this as though the young person is 'out of the pond and into the sea'. There are regular talks at meetings, guidance and structured methods of achieving effective transition. Everyone (including the National Institute for Health and Care Excellence (NICE, 2016) agrees it is a good idea and evidence suggests it brings significant benefits. The Care Quality Commission (2014) has recommended the following key components for a transition service for young people:

- A key accountable individual responsible for supporting their move to adult health services.
- A documented transition plan that includes their health needs.
- A communication or 'health passport' to ensure relevant professionals have access to essential information about the young person.
- Health services are provided in an appropriate environment that takes account of their needs without gaps in provision between children's and adult services.
- Training and advice to prepare them and their parents for the transition to adult care including consent and advocacy.
- Respite and short break facilities available to meet their needs and those of their families.
- Children's services provided until adult services take over.
- An effectively completed assessment of their carers' needs.
- Adequate access to independent advocates for young people.

So we know what 'good' transition looks like for young people both with and without a learning disability. For those with epilepsy much of the focus has been on those without learning disability introducing transition clinics and using 'Ready, Steady, Go' [Nagra et al, 2015] etc. There appears to have been less emphasis on how to achieve good transition in those with a learning disability who often have complex health needs, and chronically difficult epilepsy. The young person will usually not have capacity to understand information given or complete questionnaires. If this is the case, the transition process should be more aimed at the family and carers. A recent NICE evidence

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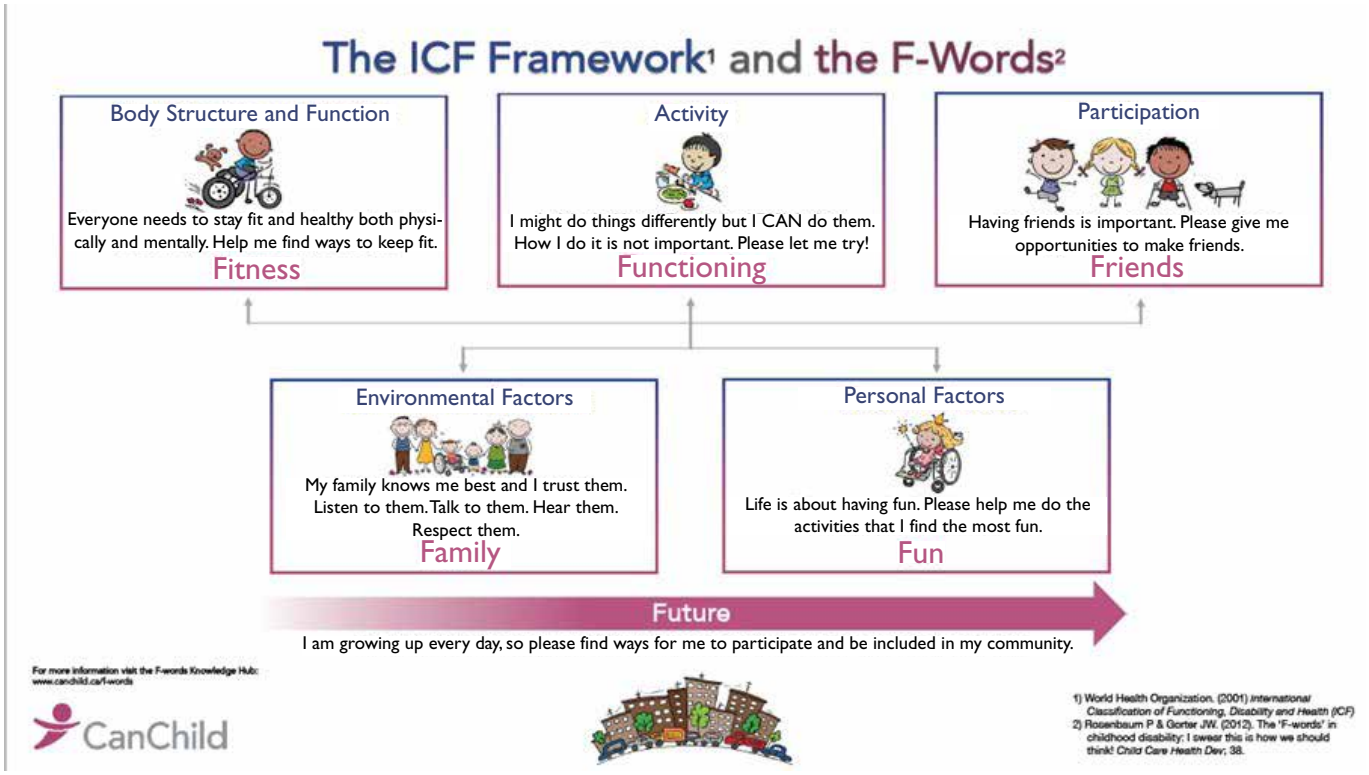

review [NICE, 2022] found familiar concerns expressed by families of young people with epilepsy and LD:

"The themes arising from the evidence on young people with learning disabilities were turmoil, parents as advocates, information, waiting, and transition as a result of a crisis. Parents of young people with learning disabilities expressed feelings of fear, rejection or uncertainty around their child's transition from paediatric to adult services. Parents assumed the role of protector and information gatherer and described difficulty in finding information and understanding the implications of the changes in service provision for their child.

"Parents observed discontinuity between agencies involved with transition of care, who often acted as a barrier to successful transfer due to lack of coordination between teams, leading to delays in moving plans forward. It was noted that transitioning was often not planned and would occur as a consequence of a crisis.

"People with learning disabilities may have very complex needs, and transition to adult services could require more planning, need longer appointments and involve many other specialities, including professionals from a learning disabilities MDT, CAMHS and special needs schools."

As with so much guidance it is usually much easier to describe the 'gold standard' but far less easy to implement it from within already hard pressed services. However, it is highly likely that we can (and should) work on information provision and self-management plans for parents and carers better than we do currently in the two to three years leading up to discharge from children's health services. One possible approach would be to hold specific hand-over transition clinics during the summer term in the secondary special schools. Parents, adult and paediatric ESNs, paediatric and adult learning disability services (if available) and learning disability social workers should be invited to prepare and write a mutually agreed healthcare plan. Families are often equally concerned about ongoing education placements and social care issues, which require their own transition planning using a range of other agencies.

Service ethos

It is worth taking stock to consider what our goals of management are for the children and young people with epilepsy and a LD we see in clinic, and their families. For most, the focus is likely to be on seizure control and medication, specifically to maximise adherence and minimise adverse side effects. Sometimes we will try to screen for and help with comorbidities. We try but often struggle to fix the wider issues outside the medical bubble such as education, housing, welfare benefits and respite. There are other ways of thinking about our goals in terms of what is most important for the young person, rather than ourselves, and then planning their current and future management in a more holistic way.

The International Classification of Functioning, Disability and Health (ICF) provides a model for describing health and disability [de Carmago et al, 2018]. The ICF framework shows how body structure and function, activity, participation, environmental factors and personal factors are interrelated and equally influence health and functioning. This framework has also been linked to 6 F-words [Rosembaum and Gorter, 2012] (*Figure 1*).

Examples of using the F-words to think about what working with young people with epilepsy and learning disability might involve include:

Functioning: refers to what people do - how things are done is not what is important. For example, let me go to school and don't send me home every time I have a seizure.

Family: represents the essential 'environment' of all children and youth. For example, listen to and respect my parents' views, they know me best.

Fitness: refers to physical and mental wellbeing. For example, don't let ignorance about epilepsy stop me boxing, playing football, swimming etc.

Fun: includes activities that people enjoy. For example, let me go dancing or work on that computer – I don't have photosensitive epilepsy.

Friends: refers to the friendships established with others. For example, tell me about local disability sports resources and social clubs for teenagers with disabilities.

Future: is what life is all about. For example, keep asking me about my aspirations and help me to achieve them as fully as possible.

Conclusion

This article has covered a number of important topics that need to be considered when working with children and young people with epilepsy and a learning disability. It has been a 'scatter gun' approach and there are many other associated topics which I have not covered, such as the association of epilepsies with specific learning difficulties, and the impact of seizures directly on attention, working memory and learning. Much of what I have covered has involved the management of medication resistant epilepsies, as this is often a major challenge in people with severe and profound learning disabilities.

Working with families who have children with severe learning disabilities and epilepsy is often frustrating because we do not have all the answers, including a 'cure' for their many comorbid problems. However, it is also a privilege to work, sometimes over many years, with this group and to make our best efforts to improve their health and quality of life. Even making a small difference may help the family in ways that we might not have anticipated.

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epilepsy action

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 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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