epilepsy action

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epilepsy professional

A genomics revolution

Epilepsy genetics and precision medicine

Deb Pal | Stephanie Oates

Language of epilepsy – Richard Appleton

A history of stress – Christophe Bernard

Ultra long-term EEG – Duun-Henriksen | Richardson

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1. Eggleston KS, et al. Seizure 2014;23(7):496-505. 2. E-36/E-37 Integrated Clinical Study Report. Data on file, Cyberonics Inc Houston, TX

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LivaNova
Health innovation that matters

Welcome to the 2019 summer edition of *Epilepsy Professional*. I hope these longer days are inspiring and offer opportunity for outdoor activities, be it walking, cycling, summer fayres, or days at the beach. They may even provide an occasion or two to lose yourself in some summer reading of *Epilepsy Professional*.

This edition offers a feast of choice. I'll start by drawing your attention to, and asking for your reflection on, a very thoughtful tribute to Professor Graham Harding. This is a personal and professional piece by Professor Stefano Seri, acknowledging Prof Harding's great commitment and contribution to science and neurophysiology, and how he inspired friends and colleagues. It is clear he is and will be greatly missed.

Following this tribute, we have a selection of articles on genomics, stress and vulnerability to comorbidities, the use of ultra long-term EEG recording and the language of epilepsy.

Professor Deb Pal and epilepsy genetic counsellor Stephanie Oats provide a timely overview of the revolution in epilepsy genetics concentrating on single gene mutations. They demonstrate how these discoveries may provide some potential future treatment strategies for epilepsy.

Dr Jonas Duun-Henriksen and Professor Mark Richardson take a deeper look at diagnostics. They take us further by exploring the utility of ultra long-term EEG recording systems in the form of a sub-scalp EEG. This is designed to record seizure activity over a 12-month period. This is something that we often crave in the out-patient clinic. It's a tool that could give us reliable information on numbers of seizures at home, at work and, for those who live or sleep alone, during sleep. The theory seems reasonable, and might have some use in refractory patients, or those whose seizure diaries are unreliable. I'm sure no-one doubts the need for improved diagnostic accuracy, but can our systems handle the increased data burden?

Dr Christophe Bernard explores the interesting relationship between epilepsy and stress, and in turn vulnerability to comorbidities. Sometimes in the epilepsy clinic, seizures represent the tip of the iceberg. Often it is the associated psychiatric and neurological comorbidities which adversely affect a patient's quality of life as much as, if not more than, seizures. Dr Bernard outlines a conceptual framework of a vulnerability (stress) model. Using brain derived neurotrophic factor (BDNF), he sets out the basis for his multi-centre clinical trial, assessing BDNF as a predictive biomarker of vulnerability to depression in patients with epilepsy. Might this be progress in identifying individuals at risk and a step towards preventative treatments aimed at vulnerable individuals?

And finally, I absolutely love the article (I hope I am allowed to say this) by Professor Richard Appleton. I urge you to please read, enjoy, and see if you identify yourself within Prof Appleton's feature on the use of language in epilepsy. I'm sorry to say I feature more than once!

Ann Johnston
Consultant neurologist
Executive medical adviser
Epilepsy Professional

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a history of stress

Christophe Bernard

Dr Bernard looks at the way a history of stress may cause a vulnerability to epilepsy and comorbidities in some individuals, and suggests what future treatments there may be

In art, a little ambiguity can go a long way. Art is often 'open to interpretation' and an opportunity to share different perspectives. In science – and more specifically, medicine – ambiguity isn't so welcome. An ambiguous symptom, or test result, or diagnosis could be a big problem for doctor and patient alike.

One place where we can control ambiguity – but seemingly, sometimes don't – is in our literature and language. On page 16, Prof Appleton discusses some questionable terms we use in epilepsy which leave the door open for misunderstandings. He suggests ways in which we can avoid these and be a lot clearer when we discuss epilepsy.

And where an effort towards improved clarity is concerned, our other articles this issue follow suit. On page 10, Prof Pal and Stephanie Oates discuss how developments in genomics technology mean that we know a lot more about epilepsy causes than we did in the past. Dr Bernard's article on page 22 offers more clarity on why stress may be a catalyst for seizures, epileptogenesis and comorbidities in some – but not all – individuals. And on page 26, Dr Duun-Henriksen and Prof Richardson describe how ultra long-term EEG monitoring may be able to offer a more accurate picture of seizure frequency than seizure diaries.

Finally this issue, on page 31, Prof Seri pays a warm tribute to his friend and colleague, Prof Graham Harding, who died in 2018. If one thing *is* clear, it's that Prof Harding was very well loved and respected by everyone who knew him.

We hope you enjoy this issue.

Kami Kountcheva
Editor
Epilepsy Professional
If you no longer wish to receive Epilepsy Professional *magazine, email us at editor@epilepsy.org.uk or call us on 0113 210 8800*

Editor/desktop publishing: Kami Kountcheva (kkountcheva@epilepsy.org.uk)

Design: Suzanne Horvath (shorvath@epilepsy.org.uk)

Publishers: Epilepsy Action (Communications department)

Advertising: contact communications manager, Sue Mitchell – 0113 210 8865 smitchell@epilepsy.org.uk

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New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
tel: 0113 210 8800 | **fax:** 0113 391 0300 | **Epilepsy Action Helpline freephone:** 0808 800 5050
email: epilepsy@epilepsy.org.uk **epilepsy.org.uk**

Practical guidance for prescribing sodium valproate launched

Experts from 13 national organisations have launched new practical guidance for healthcare professionals prescribing sodium valproate to girls and women in the UK.

The guidance, published on 29 March, includes the 2018 regulations from the Medicines and Healthcare products Regulatory Agency (MHRA), but also addresses other challenges and issues prescribers might face.

Healthcare professionals can face complicated situations when prescribing sodium valproate. They include teenagers moving from children's to adult services, questions around consent, and issues with privacy.

The practical guidance offers prescribers data and best practice information, as well as directing them to other useful resources. The guidance is available online at: *bit.ly/2JOlDDI*

Seven of the UK's Royal Colleges were part of the organisations putting the guidance together. The clinical lead for the Royal College of Paediatrics and Child Health, Dr Daniel Hawcutt, said: "The dangers of valproate to the unborn child are now well recognised, so prescribing in women is now limited. However, it can be an effective medicine to treat seizures, especially in children."

He said that the guidance will help healthcare professionals apply the MHRA's guidance effectively across age groups. He added that it will help make treatment decisions in complicated circumstances, such as around puberty in girls and in people with learning disabilities.

Professor Helen Stokes-Lampard, chair of the Royal College of General Practitioners, said: "The care of women with epilepsy can span GP and specialist care, and I do hope this guidance will provide much-needed support to doctors across all medical specialties."

Epilepsy Action has welcomed the guidance providing best practice and addressing some of the challenges in carrying out the pregnancy prevention programme.

Chief executive, Philip Lee, said: "It is vital for the success of the programme to have consensus and consistency among healthcare professionals on how valproate should be used in women and girls of childbearing age. The advice on transition services is rather limited, considering the guidance acknowledges that this is where girls can fall between the gaps.

"It is crucial that this guidance is effectively publicised and disseminated, so that all relevant clinicians are aware of it. It is vitally important that healthcare professionals ensure that all women with epilepsy taking sodium valproate are reviewed in line with all recent guidance and regulations."

The National Institute for Health and Care Excellence (NICE) also recently published a summary of its recommendations around sodium valproate for healthcare professionals. NICE said it brings together information on safe prescribing from other sources, including the MHRA, and offers easy-to-access and practical information. This summary is available at: *bit.ly/2DKkM1q*

Some epilepsy medicines "cannot be stockpiled"

On 3 April, BBC Newsnight reported that some medicines, including some for epilepsy, bipolar disorder and neuropathic pain, cannot be stockpiled. This comes after the Health Secretary Matthew Hancock said in parliament that medical suppliers had been asked to stockpile an extra six-weeks' worth of medicines to ensure medicine supply continues in all Brexit scenarios.

Newsnight revealed that the NHS shared a list of the medicines that cannot be stockpiled with just a handful of senior clinicians who had been asked to keep quiet. Consultant neurologist David Nicholl, one of the recipients, shared the information with Newsnight, saying it is a "public interest issue". He told Newsnight the problems could have been solved more easily months ago if the documents had been more widely shared.

The list of specific medicines has not been made public. Reasons for not being able to stockpile them include capacity problems and "disruption in production".

Epilepsy Action's chief executive Philip Lee and the chair of the All Party Parliamentary Group (APPG) on epilepsy, Paula Sherriff have written to the health secretary. They have urged the government to share details of the report and set out what is being done to protect people who would be affected. Epilepsy Action has asked people to get in touch with their local MPs and asking them to raise their concerns with the health secretary. The full report is available at: *bbc.in/2YVj4D4*

UK government brings in serious shortage protocols in case of medicine shortages

The UK government's serious shortage protocol (SSP), giving pharmacists extra power to amend prescriptions when there is a medicine shortage, became law in February.

Epilepsy medicines can be subject to an SSP, but additional protections are in place because of regulations around medicine switching. The SSP is designed to reduce the impact of medicine shortages on people and is a change to the Human Medicines Regulations 2012.

An SSP can be issued if there is a serious shortage to a particular medicine. If one is issued, it would specify in what way pharmacists would be able to amend prescriptions.

Pharmacists may be advised to give a different dose, such as two 5mg tablets instead of one 10mg. Alternatively, they may need to supply a reduced quantity, for example changing a six-week supply to a four-week supply. They may be asked to give a different medicine that has the same effect as the one originally prescribed, or a generic form of the original medicine.

While it was previously reported that epilepsy medicines would not be part of the government shortage plans, pharmacists will be able to give a different dose or reduced quantity. But protections are in place, saying that "protocols for therapeutic or generic equivalents will not be suitable for all medicines and patients". In these cases, patients would be referred back to their prescribing doctor.

Epilepsy Action explains that SSPs are necessary as medicine shortages have become more common since 2017. The organisation said more clarity is needed around how a 'serious shortage' would be measured and when an SSP would be used. It added that no SSPs have yet been issued.

Teva oxcarbazepine tablets discontinued in the UK

Pharmaceutical company Teva is discontinuing its version of oxcarbazepine tablets.

It has already discontinued the 600mg and 300mg tablets, and will discontinue the 150mg tablets later this year when current stock runs out.

Other manufacturers' versions of oxcarbazepine are still available.

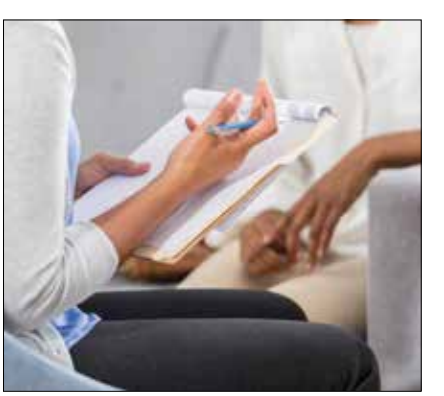
High premature mortality rates in epilepsy and schizophrenia

A new study in the journal *Epilepsia* has found that people with both epilepsy and schizophrenia have a very high premature mortality rate.

The research by Andersen and colleagues looked at people born in Denmark from 1960-87 and living in Denmark at age 25. People were followed-up until the end of 2012. The team identified people with epilepsy, schizophrenia, both conditions and neither condition. They aimed to find out the overall mortality rates.

The results found that the estimated mortality at the age of 50 years was 10.7% for people with epilepsy, 17.4% for people with schizophrenia and 27.2% for people with both conditions. This compared with a 3.1% mortality rate in people with neither condition.

The researchers concluded that the mortality rate in people with both epilepsy and schizophrenia between the ages of 25 and 50 was very high. They said this indicates that "these patients need special clinical attention".



Sodium valproate discussed at House of Lords debate

The UK's House of Lords held a debate on the safety of medicines and medical devices on 28 February, discussing issues around sodium valproate.

The debate follows the government's Independent Medicines and Medical Devices review into three 'public health scandals', which was launched on 22 February 2018. Baroness Cumberlege is chairing the review, which is looking into three separate scandals surrounding medicines and medical devices. These are sodium valproate, the pregnancy test drug Primodos, and the vaginal mesh implant. The findings of the review are expected to be reported later this year, alongside recommendations for improvements. Several organisations and patient groups, including Epilepsy Action, have submitted evidence for the review.

The debate was secured and opened by Lord O'Shaughnessey. He quoted figures from the Independent Fetal Anti Convulsant Trust (In-FACT), suggesting that prescription numbers of sodium valproate for women remain similar to those in 2015. He acknowledged that change is happening in this area, but called its pace "glacial".

Baroness Blackwood from the Department of Health and Social Care said that the government's aim is to "reduce and eliminate pregnancies being exposed to valproate". She said that healthcare professionals are responsible for making women aware of the risks of this medicine and ensuring they are on the pregnancy prevention programme.

Baroness Walmsley added that Philip Lee, chief executive of Epilepsy Action, had stressed the importance of a mandatory discussion of the risks led by a healthcare professional for all women with epilepsy on sodium valproate. This is to help women make an informed choice before conceiving. Mr Lee's comment had followed two surveys in 2016 and 2017 showing that around one-fifth of women were not aware of the risks of this medicine in pregnancy.

She also suggested that community pharmacies have a role to play in ensuring the safe and cost-effective use of medicines and seeking feedback from patients. The debate also saw calls made for compensation to be provided to people who have suffered from unsafe medicines or devices.

Epilepsy Action has said it is pleased that the issues with sodium valproate have been raised in the House of Lords. The organisation has said it will continue to campaign to ensure every woman prescribed sodium valproate is aware of the risks.

Epilepsy-related deaths project

Project leaders of Epilepsy Action's 'Epilepsy-related deaths' project are looking for feedback from healthcare professionals and patients.

The project will focus on measures to reduce the causes of epilepsy-related deaths over the next 12 months. Neurologist and epilepsy specialist Dr Heather Angus-Leppan is leading the project.

Dr Angus-Leppan said: "It is estimated that more than 1,000 people die a year in the UK of epilepsy-related deaths. At least half of these are potentially avoidable, even without the much-needed further innovations in epilepsy treatment.

"We are looking at existing barriers to reducing these deaths. There are important themes emerging in this project, alongside the work of other organisations and researchers. These include education of patients, family and professionals; medication availability; resources for assessment and follow-up; mental health conditions; and social support.

"We are now surveying patients, carers and healthcare professionals to look at what resources are already available. We want to know what progress has already been made and what further needs to be done. We will be carrying out scoping meetings and reporting on areas of development."

The survey is available at *epilepsy.org.uk/erdsurvey*. Dr Angus-Leppan said she is also welcoming ideas, comments and questions from healthcare professionals and patients. She can be contacted at *heather.angus-leppan@epilepsy.org.uk* or *healther.angus-leppan@nhs.net*.

Changes to prescribing rules around pregabalin and gabapentin following reclassification

Epilepsy medicines pregabalin and gabapentin were reclassified as controlled medicines under the Misuse of Drugs Act 1971 from 1 April 2019. This aims to prevent misuse, harm or the medicines being sourced illegally.

NHS England explained that this has resulted in changes to prescription rules for pregabalin (brand names Axalid, Lecaent and Lyrica) and gabapentin (brand name Neurotin).

Only a 30 days' supply is allowed on one prescription. People will need to request repeat prescriptions from their GP each month and pick up their medicines within 28 days of the date on the prescription.

GP practices that don't use the electronic prescription service for controlled drugs may not be able to send electronic prescriptions for these medicines to the pharmacy. People will need to go to the GP to collect their prescription in person. If they can't, a representative can also be set up through their GP practice, who can do this in their place.

The person picking up the prescription will need to show proof

of ID and sign for their medicines at the pharmacy. NHS England advises that if people run out or need an emergency supply of pregabalin or gabapentin, they will need to contact their GP's out-of-hours service.

The government announced its plans to make the change to the classification of pregabalin and gabapentin in October 2018. The decision followed concerns raised by the Advisory Council on the Misuse of Drugs over the potential for misuse of or addiction to these medicines.

They will now be a Class C controlled substance. Other controlled medicines used for epilepsy include the emergency medicines midazolam and diazepam.

Pfizer's Epanutin 50mg Infatabs out of stock until November

Epanutin (phenytoin) 50mg Infatabs are out of stock until November 2019, manufacturer Pfizer has said.

While Epanutin Infatabs are out of stock, Pfizer will be importing a Canadian version of chewable phenytoin tablets, Dilantin Infatabs. The active ingredient is the same, but there may be differences between Epanutin and Dilantin that for some people could affect seizure control or side-effects.

Cannabis oil prescription given for nine-year-old

A nine-year-old girl, whose cannabis oil had been confiscated at the airport on Saturday, has been given a prescription from a UK specialist. The medicine had been taken after the girl's mother Emma Appleby brought the three-month supply into the UK illegally from the Netherlands on 6 April.

Teagan, from Aylesham, has a rare disorder and Lennox-Gastaut syndrome, and she can have up to 300 seizures a day.

The medicine had originally been prescribed by a paediatric neurologist in Rotterdam and had cost the family over £4,500.

The confiscation left Ms Appleby in tears. She said she had been "passed from pillar to post" trying to access the medicine in the UK and that she was at her "wits' end". She had reportedly been refused an import licence on compassionate grounds.

The law in the UK changed in November 2018 to allow specialist clinicians to prescribe cannabis-based medicines. However, since then the guidance produced for prescribers has been criticised for being too restrictive.

Health Secretary Matt Hancock said that without clinical authorisation, it is not possible to bring controlled substances into the country. However, the government had given the family the opportunity for a second clinical opinion.

The health secretary also said he is interested in hearing about specific cases to ensure that appropriate clinical decisions can be made.

A genomics revolution

Epilepsy genetics and precision medicine

Prof Deb Pal and epilepsy genetics counsellor Stephanie Oates describe the way genomics has enriched our epilepsy understanding. They look at possible future treatments for genetic epilepsy and discuss the importance of careful counselling for patients and families

In the year that Nelson Mandela was released from Robben Island and before the world-wide web had even launched, the international Human Genome Project was announced. Its intention was to sequence the entire human genetic code. Not since the NASA mission to the moon had there been a project of such unparalleled ambition, and to date, it remains the world's largest collaborative biological project.

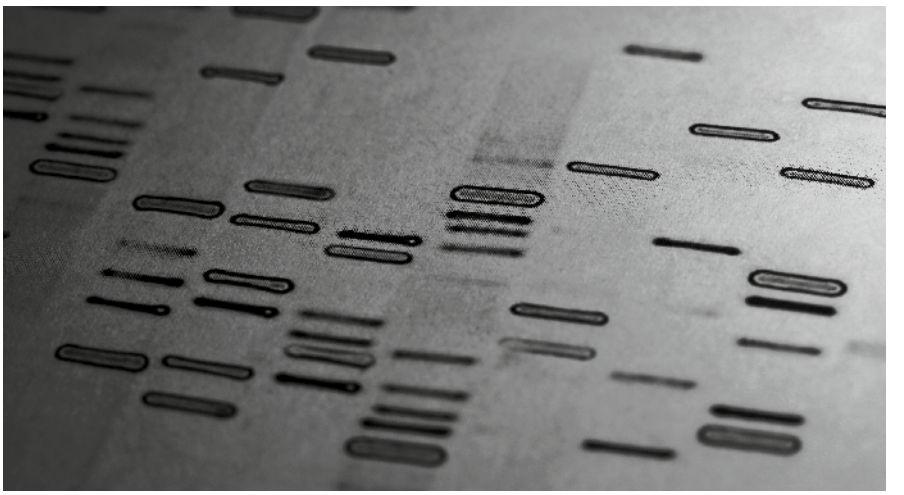
The impact of genomics on our knowledge of the underlying causes of epilepsy has been revolutionary and will continue to grow over the decades to come. Thirty years ago, epilepsy classification was crude. Almost all infantile onset epilepsies were lumped together while the vast majority of common epilepsies were labelled as 'idiopathic', which at that time meant 'unknown, presumed genetic'. Now, thanks to technology and international research collaboration, we recognise almost 200 separate genetic causes of rare and severe epilepsies caused by single genes. Progress is also being made in working out the more complex genetics of the common epilepsies too.

Fortunately, most professionals working with epilepsy won't need to remember all 200 genetic epilepsies. Around a dozen genes account for about 70% of genetic epilepsies: SCN1A, SCN2A, SCN8A, KCNQ2, KCNT1, SYNGAP1, STX1B, PCDH19, CHRNA4/B2, SLC6A1, SLC2A1. Nevertheless, every epilepsy professional should improve their genomic knowledge in order to keep up to date with evolving practice.

Health Education England is offering flexible and subsidised training [Genomics Education Training, 2019]. Comprehensive and up-to-date, expert-compiled information on many genetic epilepsies is also freely available at the National Center for Biotechnology Information (NCBI) Gene Reviews [Adam, 2019].

The most prominent impact has been on the diagnosis of infants with severe and rare types of epilepsy. The role and nature of genetic testing has rapidly transformed, and next-generation sequencing, either by targeted panel or whole exome sequencing (WES), is now considered a first-line investigation here. The diagnostic yield has correspondingly shot up to around 30-40% in this group. A genetic diagnosis can provide great comfort to many parents. It can allow them to better understand why their child has developed epilepsy and to know that there was nothing they did or didn't do that could have caused it. However, for others it may intensify feelings of anxiety, guilt, frustration and isolation. Skilful genetic counselling is essential prior to initiating genetic testing. It allows us to talk through the process, potential outcomes and benefits and limitations of genetic testing, and to support families through this part of their diagnostic odyssey. Through this process, you can find out what the patient and family know, what they want to know, manage expectations around genetic testing and identify those who might need extra support at this time. Counselling also allows a basis for calculating recurrence risks and discussing reproductive options in future pregnancies or among relatives, once the parental genetic status is known.

The consequences of a genetic diagnosis on treatment can be significant and will continue as a major area of growth and development over the next two decades. At present, a precise genetic diagnosis can suggest particular classes of treatment and in some cases, experimental therapies. The oldest examples include Glut-1 deficiency syndrome (SLC2A1 loss-of-function mutations) indicating ketogenic diet, and SCN1A loss of function in Dravet syndrome suggesting avoidance of sodium channel blocking agents. A pilot trial of transdermal nicotine patch is currently underway for sleep-related hypermotor epilepsy (SHE) [Epilepsy Research UK].



Thanks to technology and international research collaboration, we recognise almost 200 separate genetic causes of rare and severe epilepsies caused by single genes

As we learn more, we may be able to make reliable genotype-phenotype correlations, providing parents and health professionals alike with more certainty regarding prognosis and tailored treatment. But, at the moment, the correlation between specific genetic variants and particular clinical features and prognosis is variable and a matter for expert interpretation.

There are currently no published national practice guidelines on genetic testing for epilepsy. However, we suggest that, particularly for neonatal and infantile onset epilepsy or brain malformations, targeted panels or WES should be part of their first-line investigations [Sánchez Fernández *et al*, 2019]. Chromosome microarray yield is low and more relevant for patients with intellectual disability, autism spectrum disorder (ASD), dysmorphism or other neurological comorbidities. Single gene tests are best avoided due to extensive phenotypic and genetic heterogeneity, unless there is a strong clinical indication such as Dravet syndrome. But even in Dravet syndrome, several genes may mimic SCN1A while co-occurring sodium channel variants may modify the phenotype [Steel *et al*, 2017]. Whole genome sequencing (WGS) is not commonly used yet, but will likely be the next step in epilepsy genetic testing, in line with the new NHS Genomic Medicine Service [NHS.england.uk, 2019].

Aside from diagnostic purposes, genetic testing can also inform who not to give certain medications to. This is the field of pharmacogenetics. For example, HLA-B*15:02 testing should be carried out prior to commencing carbamazepine therapy for patients from high-risk populations (South and South-East Asia) to minimise the risk of adverse reaction [Amstutz *et al*, 2014]. In 2019, genetic testing is as quick and cheap as it has ever been, with some laboratories able to turnaround a WGS within one week. The technology only continues to improve. Unfortunately, our ability to interpret the results produced is still lagging somewhat behind, something that data gleaned from the 100,000 Genomes Project may help to improve in the future. Nevertheless, currently available genetic testing, appropriately selected after thorough patient phenotyping, has great potential. It can save time, money and reduce the number of other tests necessary to make a diagnosis [Oates *et al*, 2018]. This is a win for the health service and the family.

The Epilepsy Genetics Service, based at Kings Health Partners, has been running since 2015. It has two components: a specialist outpatient clinic and a molecular diagnostic service. The service is run by Deb Pal and Stephanie Oates. Deb Pal is a professor of Paediatric Epilepsy at Kings College London and an honorary consultant paediatric neurologist at Kings College Hospital and Evelina London Children's Hospital. Stephanie Oates is the first specialist genetic counsellor for epilepsy in England.

As we learn more, we may be able to make reliable genotype-phenotype correlations, providing parents and health professionals alike with more certainty regarding prognosis and tailored treatment

The service accepts referrals from local and regional paediatric neurologists and paediatricians specialising in epilepsy. It sees patients and families diagnosed with complex, early-onset, intractable epilepsy, with

or without a family history. The service will also soon accept referrals for adults with a history of drug resistant or comorbid epilepsy since childhood. As well as evaluating children and families for genetic testing, the service offers pre and post-test counselling in accordance with American College of Medical Genetics and Genomics (ACMG) guidelines.

The majority of patients who have genetic variants in one or more of the 500 plus epilepsy and neurodevelopmental genes we know about are the only ones in their family to be affected

For clinicians more experienced in offering their patients genetic testing, it also offers assistance post-test with interpretation and advice for the clinician. Post-test counselling for the patients and families is also available on request. The molecular diagnostic service is currently provided in collaboration with Amplexa Genetics, an ISO certified clinical laboratory in Odense, Denmark. However, it will likely move over to the NHS Genomic Medicine Service, in line with the rest of the country, when it officially opens.

Genetic counselling is defined as a communication process which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions [National Society of Genetic Counselors' Definition Task Force, 2006]. The process includes, but is not limited to:

- Interpretation of family and medical histories
- Discussion and education to fill in any gaps in patient knowledge about their epilepsy
- Counselling to promote informed choices regarding testing, treatment, and reproductive options, with respect to the patient and family's goals, ethical and religious values
- Support to encourage the best possible future adjustment to the condition

Epilepsy genetics is somewhat different to many other genetic conditions commonly seen by genetic health professionals. The majority of patients who have variants in one or more of the 500 plus epilepsy and neurodevelopmental genes we know about are the only ones in their family to be affected (the variant(s) are *de novo*). The incidence of germline and somatic mosaicism is now understood to be more common than previously thought. However, generally, the option of testing is mainly focused on the benefit of the affected child, not cascade testing for the rest of the family. But in cases where mosaicism is suspected or proven, careful genetic counselling can be extremely valuable for parents thinking of extending their family, particularly if they wish to consider prenatal diagnosis.

As technology improves and the available testing options become more wide-ranging, obtaining fully informed consent is only becoming more challenging. While we still don't know what we don't know, patients need to have some understanding that we might find things that none of us were bargaining on. This is most relevant when considering WES or WGS. The ACMG has provided some guidance around this [Kalia *et al*, 2016] but genomics is an ever evolving field so it

would be important to remain informed and cautious and to 'watch this space'.

In the same way that sequencing each human chromosome was internationally distributed across research labs, so too are the efforts to build translational models for different genetic epilepsies. As well as the traditional rodent models, there now exist zebrafish and fruit fly models of genetic epilepsy that offer advantages of higher speed and throughput and lower cost than conventional rodent models. These new models allow scientists to examine individual genomic variants to determine pathogenicity and functional consequence. From there, researchers can try and target the underlying mechanism of these epilepsies, whether that be using already known or repurposed drugs, or developing new agents. In this era of personalised medicine, the focus of research interest is shifting along from gene discovery to the development of gene- or mechanism-specific treatments. Three examples give an idea of what future treatments of genetic epilepsies might look like.

In order to rescue a 'faulty' gene, one can try to replace the gene with a normally functioning one. Or, in the case of a dominant disorder (where only one faulty gene copy or allele is sufficient to cause disease), the expression of product from the normal allele could be increased. In a dominant disorder, we could also try to compensate by increasing the expression of other genes that reduce brain excitability. The first gene therapy trials are already underway for Rett syndrome [Clarke and Abdala Sheikh, 2018] and Duchenne muscular dystrophy [Duchenne UK, 2019]. Meanwhile, preclinical trials have shown that an engineered potassium channel KCNA1 can be replaced in epileptic mouse brains by smuggling the gene through the blood-brain barrier inside a lentivirus vector [Snowball *et al*, 2019]. Other groups are on the verge of introducing anti-seizure agents into the human brain through adeno-associated virus 9 (AAV9) vectors [Noe *et al*, 2012].

The ability to help patients and families to have realistic expectations of new technology, and to cope with uncertainty, is becoming even more important

Genes also have multiple intrinsic regulation systems, one of which involves tiny fragments of RNA known as microRNAs (miRNAs). These bind to the tail ends of genes to increase or decrease expression. A second strategy is to use miRNAs and their antagonists ('antagomirs') experimentally to stop status epilepticus in mice. But the major challenge remains around how to deliver these miRNAs to the brain [Henshall *et al*, 2016]. While there is

plenty of excitement in experimental cellular and molecular approaches, there are still a few practical clinical questions to address. Which part of the brain to treat, when and how often?

Advocacy and support organisations provide patients and families with the opportunity to connect, advocate and collaborate with researchers

Will irreversible treatments be safe in the long term? If they are invasive (such as involving brain injection), will the benefits outweigh the risks?

A third and quite left-field approach is to exploit the diversity of excitatory and inhibitory neuronal populations and redress the balance in over-excitable brain regions. Researchers at University of California San Francisco are perfecting the science of transplanting early stage inhibitory neurons into epileptic brains of mice [Grone and Baraban, 2015]. They will shortly be upscaling the technique in the naturally occurring epileptic sea lion native to the California coast!

How do patients access these new experimental therapies once they have a genetic diagnosis? The first step is to register with research databases and patient registries to contribute as much information as possible about these rare epilepsies [for example with the Epi25 collaborative]. Many advocacy and support organisations have formed to try and push development in treatments farther and faster. These organisations provide patients and families with the opportunity to connect, advocate and collaborate with researchers. This will be an invaluable resource when the time comes for clinical trials of new therapies.

Professor Pal is a scientific advisor to Amplexa Genetics. He is also clinical advisor to CombiGene AB.

Prof Deb Pal
Paediatric neuroscience consultant
King's College Hospital NHS Trust

Stephanie Oates
Epilepsy genetics counsellor
King's College Hospital NHS Trust

Further reading

Adam, MP. (2019) GeneReviews. University of Washington, Seattle. Seattle. [online] Available at: https://www.ncbi.nlm.nih.gov/books/NBK1116/ [Accessed 1 May 2019]

Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, Connolly MB, Ito S, Carleton BC and CPNDS clinical recommendation group. (2014) Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 55(4):496-506.

Clarke AJ and Abdala Sheikh AP. (2018) A perspective on "cure" for Rett syndrome. Orphanet J Rare Dis. 13(1):44.

Duchenne UK. (2019). Gene Therapy Overview. [online] Available at: https://www.duchenneuk.org/gene-therapy-overview [Accessed 1 May 2019].

England.nhs.uk. (2019). NHS England » NHS Genomic Medicine Service. [online] Available at: https://www.england.nhs.uk/genomics/nhs-genomic-med-service/ [Accessed 1 May 2019].

Epi25 collaborative. (n.d.). Global Genetic Epilepsy Registry — Epi25 collaborative. [online] Available at: http://epi-25.org/info [Accessed 1 May 2019].

Epilepsy Research UK. Nicotine patch treatment for Sleep-related Hypermotor Epilepsy (SHE). [online] Available at: https://www.epilepsyresearch.org.uk/research_portfolio/nicotine-patch-treatment-for-sleep-related-hypermotor-epilepsy/ [Accessed 1 May 2019]

Genomics Education Programme. (2019). Master's in Genomic Medicine | Genomics Education Programme. [online] Available at: https://www.genomicseducation.hee.nhs.uk/taught-courses/courses/masters-in-genomic-medicine/ [Accessed 1 May 2019].

Grone BP and Baraban SC. (2015) Animal models in epilepsy research: legacies and new directions. Nat Neurosci. 18(3):339-43.

Henshall DC, Hamer HM, Pasterkamp RJ, Goldstein DB, Kjems J, Prehn JHM, Schorge S, Lamottke K and Rosenow F. (2016) MicroRNAs in epilepsy: pathophysiology and clinical utility. Lancet Neurol. 15(13):1368-76.

Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond, KE, Richards CS, Vlangos CN, Watson M, Martin CL and Miller DT. (2016) Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine* 19:249-255. [online] Available at: https://www.nature.com/articles/gim2016190 [Accessed 7 June 2019].

National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN and Williams JL. (2006) A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns. 15(2):77-83.

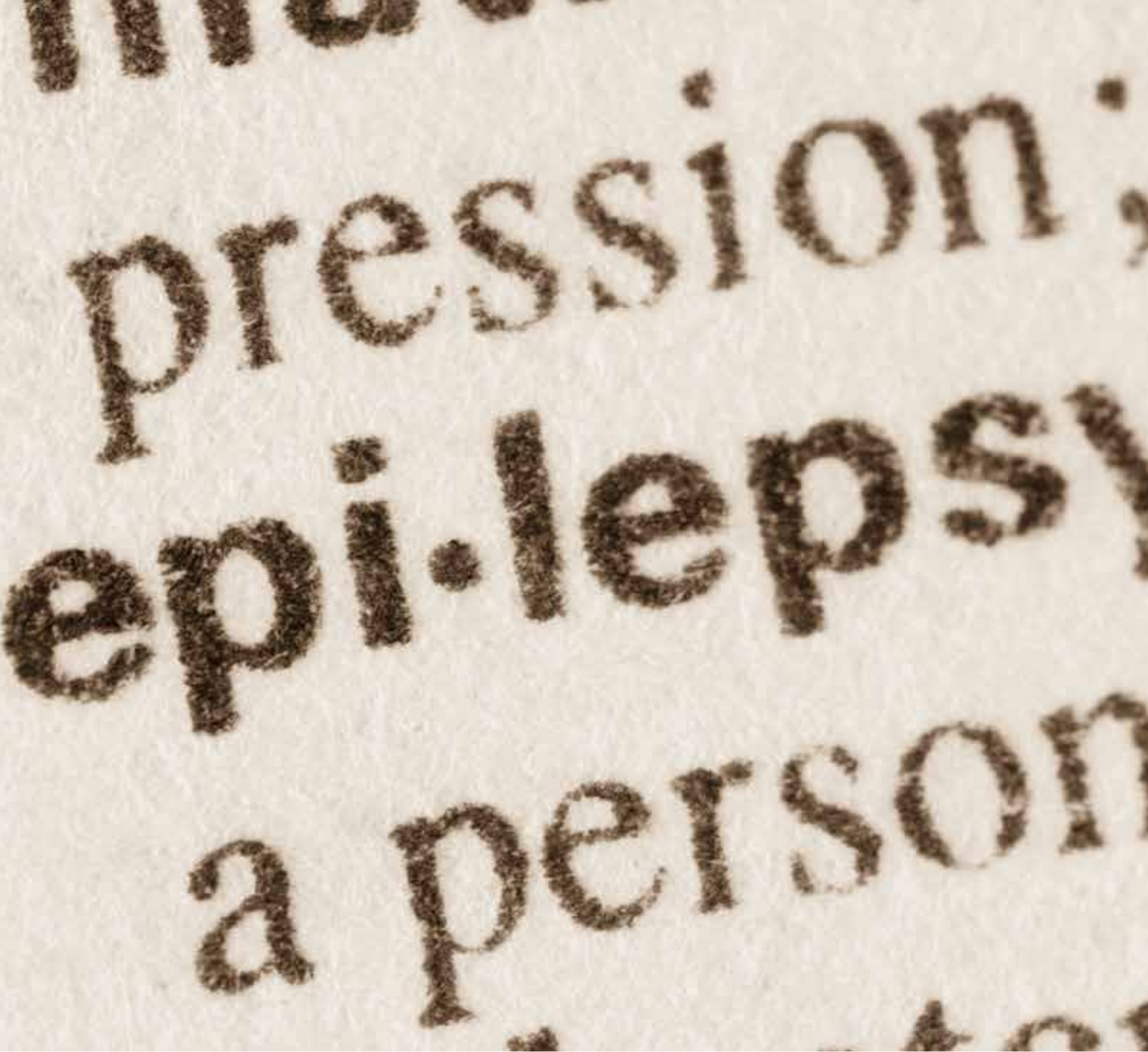
Noe FM, Sørensen AT, Kokaia M and Vezzani A. (2012) Gene therapy of focal onset epilepsy using adeno-associated virus vector-mediated overexpression of neuropeptide Y. In: Noebels JL, Avoli M, et al., eds. Jasper's Basic Mechanisms of the Epilepsies. Bethesda (MD).

Oates S, Tang S, Rosch R, Lear R, Hughes EF, Williams RE, Larsen LHG, Hao Q, Dahl HA, Møller RS and Pal DK. (2018) Incorporating epilepsy genetics into clinical practice: a 360 degrees evaluation. NPJ Genom Med. 3:13.

Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, Sheidley BR and Poduri A. (2019) Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study. Neurology. doi: 10.1212/WNL.0000000000006850 [published Online First: 2019/01/06]

Snowball A, Chabrol E, Wykes RC, Shekh-Ahmad T, Cornford JH, Lieb A, Hughes MP, Massaro G, Rahim AA, Hashemi KS, Kullmann DM, Walker MC and Schorge S. (2019) Epilepsy gene therapy using an engineered potassium channel. J Neurosci. 39 (16) 3159-3169.

Steel D, Symonds JD, Zuberi SM and Brunklaus A. (2017) Dravet syndrome and its mimics: Beyond SCN1A. Epilepsia 2017;58(11):1807-16.



Language of epilepsy

The importance of the words we use

Prof Richard Appleton considers some of the ambiguous and confusing terms used in epilepsy, their potential for misunderstanding and impact on patient care

"When I use a word", Humpty Dumpty said in a scornful tone, "it means just what I choose it to mean, neither more nor less".

"The question is," said Alice, "whether you can make words mean so many different things."

Through the Looking Glass by Lewis Carrol

An understanding of medicine, diseases and their symptoms is frequently complicated by the words and terminology used to describe them. This can often result in confusion for both healthcare professionals and the public. In part, this arises from a limited understanding of the derivation of many medical words because of differing levels of linguistic skills, including a relative unfamiliarity with Latin and Greek. This is particularly relevant for the younger generation of healthcare professionals in the 21st century, as the study of Latin and Greek in schools was, until recently, a near-historical phenomenon. (The famous poem reads, "Latin is a dead language, as dead as dead can be" – but in reality, the converse is true.) Semantic confusion, and the extent of this confusion, may also differ among medical specialities. Neurology, including epilepsy, is particularly vulnerable, being the least understood, and is therefore regarded as one of the most complex and challenging medical specialities.

Unfortunately, in medicine, and particularly in the field of epileptology, people don't always know what they mean when they use words. One explanation is the inaccurate use of English by clinicians in Europe and the US. Good, scientific research does not necessarily equate with good English, using the spoken or written word, and the opposite is also true. The challenges with this have been highlighted by the International League Against Epilepsy (ILAE) Commission for Classification and Terminology. It has provided various iterations of seizure, epilepsy syndrome and epilepsy classifications published over the past decade. However, the ILAE cannot be held responsible for all these language difficulties as many predate their publications.

Neurology, including epilepsy, is particularly vulnerable to semantic confusion, and is therefore regarded as one of the most complex and challenging medical specialties

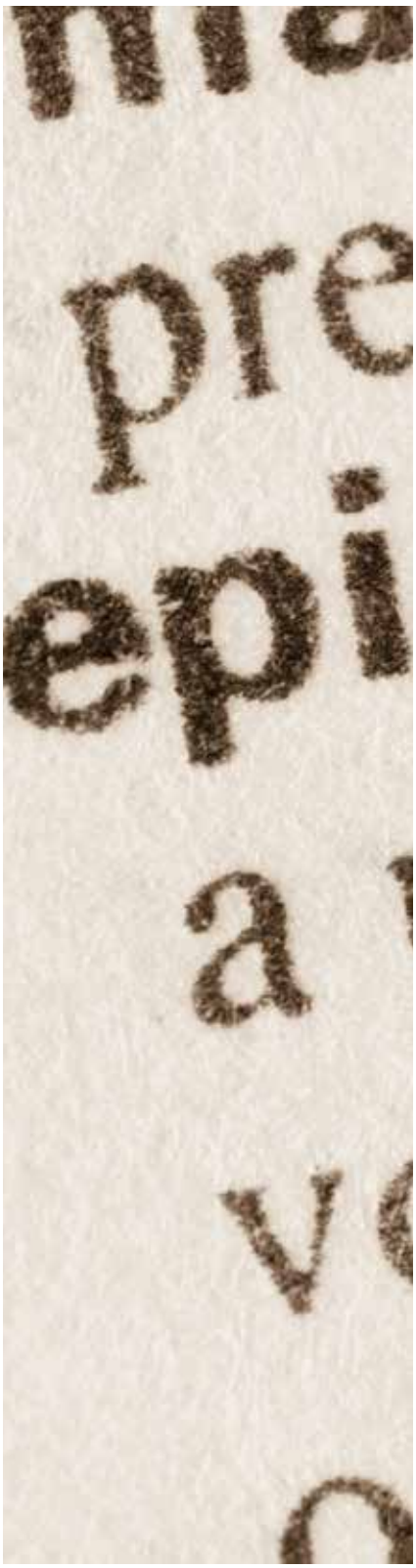
The terms listed below in alphabetical order are some examples showing the reasons for concern over the use of inaccurate terminology.

Drop attack

It is puzzling why the term, 'drop attack', and not 'drop seizure' was ever used within the broader definitions of seizures and epilepsy. Both are commonly-used terms among specialists and non-specialists in epilepsy, as well as the public. Some understand precisely what they mean when using this term, but many do not. Traditionally, 'drop seizures' refer collectively to those seizures in which the person 'drops' or falls down. Those of us entering antiquity can easily recall that epilepsy was often known somewhat colloquially as 'the falling sickness' [Temkin 1945]. Although a 'drop' seizure is usually interpreted as meaning an atonic seizure, other seizure types may also fit this description.

Theoretically, therefore, 'drop seizures' could include all those seizures in which the person may 'drop' – atonic, astatic, focal (specifically arising from the frontal lobes), myoclonic, myoclonic-astatic and tonic seizures. Tonic-clonic seizures have never been included as a type of 'drop seizure' but the initial tonic phase nearly always involves a drop or fall. The testimony of all patients (and parents or carers) also supports this.

Many drug studies report outcome and 'responder rates' on the basis of the percentage reduction in 'drop seizures'. However, they often don't define a 'drop seizure' or fail to separate out the different 'drop' seizure types. Both rufinamide and, more recently in the US (and hopefully in mid-2019 in the UK), Epidiolex were granted licences to be used in



the management of patients with Lennox-Gastaut syndrome. This was on the basis of a greater than 50% reduction in the frequency of 'drop seizures' in significantly more children taking those medicines than those in placebo groups. The reason for not specifically classifying the type of the drop seizure may reflect uncertainty as to what the seizure was. However, this is not a cogent argument for those clinicians that specialise in epilepsy, particularly when video-footage of seizures is so readily available with the ubiquity of mobile phones, not to mention the use of inpatient and home telemetry. The identification of the correct seizure type fulfils more than one's linguistic lust; it may have diagnostic, investigative and therapeutic implications. Fortunately, 'drop seizure' as a seizure type does not appear in the new classification of epileptic seizures and epilepsy or its supporting glossary of descriptive terminology (for seizures) published by the ILAE [Fisher *et al*, 2017]. Hopefully, this will mean the term ceases to appear in future drug-trials.

Epilepsy

In 2005 the conceptual definition of a seizure as described by the ILAE was "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain". Epilepsy was defined as "a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure." In 2014, the ILAE Taskforce proposed the following operational (practical) definition of epilepsy [Fisher *et al*, 2014]:

"Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring more than 24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome"

This publication included eight very brief case vignettes to help the reader navigate this new operational definition of epilepsy. The authors added a footnote in which they cited support for this definition which they had obtained during the 2013 ILAE Congress Presidential symposium [Fisher *et al*, 2014]. This definition continues to generate debate with many considering the second definition far too liberal. This is particularly relevant for children for a couple of reasons. First, it is highly unlikely any paediatrician (or paediatric neurologist) would consider a single seizure as representing an onset of an epilepsy, even if the probability of a recurrence was at least 60%. Second, many paediatricians,

The identification of the correct seizure type fulfils more than one's linguistic lust; it may have diagnostic, investigative and therapeutic implications

and even some paediatric neurologists, may not know which children are at risk of this 60% probability of a

recurrence. This is because of the different epilepsy syndromes that occur in children, which are associated with a wide range of seizure recurrences. In addition, there may be a difference of opinion as to whether 60% constitutes a high or low risk. For adults, and their treating doctors, 60% is likely to be considered high and lead to a diagnosis of epilepsy and the introduction of an antiepileptic drug. This is largely because of the employment, social and driving implications of a second seizure.

As is common in EEG reporting, terminology such as 'epileptiform activity' is open to misinterpretation and this may adversely affect patient management

In the new definition, epilepsy is now called a disease, rather than a disorder or condition. This was a decision of the Executive Committees of the ILAE and the International Bureau for Epilepsy. They argue the word 'disease' better relays the seriousness of epilepsy to the public. This revision also remains fiercely debated, particularly by those with epilepsy. My preference is disorder because there are many different diseases of which epilepsy may simply be one manifestation.

Epileptiform

The term, 'epileptiform activity' is typically used to describe changes seen on an EEG. It has also been used interchangeably with 'epileptic activity'. Depending on the technologist that has undertaken the EEG, or the doctor that has interpreted the results, or both, it is used to describe a number of different phenomena. These generally include sharp waves or spikes, with or without slow wave activity; however, polyspikes may or may not be included in this term.

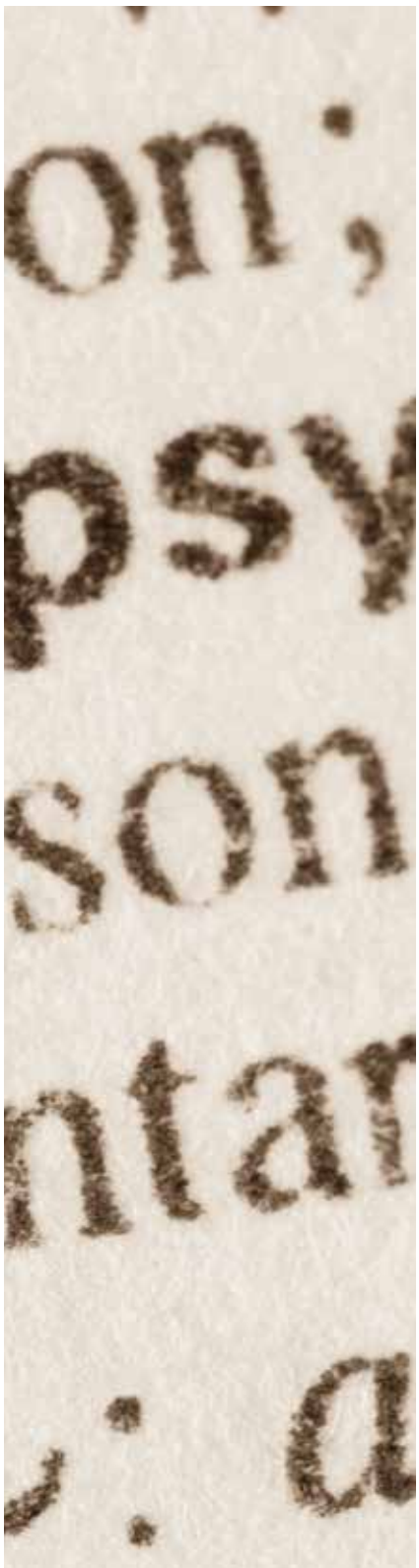
'Epileptiform activity' in isolation cannot make a diagnosis of epilepsy. As is common in EEG-reporting, such terminology is open to misinterpretation and this may adversely affect patient management. It would be simpler and clearer to avoid the term altogether and to simply describe the activity as 'sharp waves, spikes or polyspikes' with the reporter then attempting to correlate its significance within the context of the clinical history. This is often appropriately termed, the 'electro-clinical report'. This clearly emphasises the importance of an accurate description of any paroxysmal events, including epileptic seizures.

Minor and major

These words are still occasionally used to qualify motor seizures, including in status epilepticus, as 'minor motor status'. The terms are inappropriate and meaningless, largely because the interpretation of what constitutes minor and major is not defined. These terms have no place in the language of the epilepsies and should not be used. Fortunately, they do not appear in the 2017 'operational classification of seizure types' [Fisher *et al*, 2017].

Myoclonic jerks

This is a good example of tautology – we're essentially saying 'myoclonic myoclonus' or 'jerk jerks'. In addition, 'myoclonic jerk' gives no indication as to its cause, as this could be epileptic or non-epileptic. The correct terms should be 'myoclonic seizure', 'jerk seizure', or simply 'myoclonus', as the myoclonus may be non-epileptic, as in benign, neonatal sleep myoclonus or



sleep-related (hypnopomic) myoclonus. 'Negative myoclonus' is a rare and very specific seizure type that requires confirmatory EEG and electromyography (EMG) evidence. Although there are no specific management consequences of the term, it is important the correct terminology is used. Unfortunately, the term 'myoclonic jerk' has been and remains ubiquitous in the epilepsy literature and appears in the ILAE Seizure Classification in the description of a myoclonic-atonic seizure [Fisher *et al*, 2017]. Sadly, I think it will prove difficult to delete this term unless deemed appropriate by the ILAE Commission for Terminology and Classification in its future deliberations.

Petit mals or petit mal seizures

Incredulously, this remains a commonly used term, predominantly among older generation clinicians and the public. It is often used to describe all seizures that are not tonic-clonic (formerly called 'grand mal') in type, including typical and atypical absence, focal and even myoclonic seizures. Both 'grand mal' and 'petit mal' reflect the very limited knowledge and understanding of the types of seizure in the late 19th and early 20th centuries. Clearly, we now know far more about seizure types and these terms should be obsolete. Unfortunately, however, a minority of general practitioners, general paediatricians and adult physicians continue to use these terms in the belief this very simple classification will improve their patients' understanding of epilepsy. This is no longer acceptable. I would also argue this again emphasises the need for people with epilepsy to be seen and managed by a doctor with expertise in epilepsy, and this includes general practitioners. This is the model used and widely accepted, and expected, in the care of patients with diabetes mellitus and asthma. It must become the model for the epilepsies.

Sub-clinical seizure and sub-clinical status epilepticus

A seizure is a clinical event with clinical manifestations that may be obvious or subtle, as defined by the ILAE in 2017. It either is, or is not a seizure. It cannot be something in between or 'beneath' or 'under' a seizure, which is implied by the term 'sub-clinical'. The term is most commonly used to try to ascribe some significance to an EEG finding of frequent, if not persistent, or contunous, 'epileptiform' (itself an ambiguous term, as described above) activity. The implication is that this abnormal activity must be having some clinical effect but because no seizure can actually be seen, heard or felt, it is termed 'sub-clinical'. I would argue that this is nonsense and dangerous. Some epileptologists have suggested the term, 'transient cognitive impairment (TCI)' as again, an assumed, clinical manifestation of frequent epileptiform activity. This can only be accepted if the EEG activity can be shown to definitively impair a patient's cognitive (including attention and short-term memory) performance during formal psychometry as the EEG is being recorded.

Both 'grand mal' and 'petit mal' reflect a very limited knowledge and understanding of the types of seizure in the late 19th and early 20th centuries

This also applies to 'sub-clinical status epilepticus' and to the syndrome of electrical status epilepticus during slow-wave sleep (ESESS) also known as continuous spike and wave activity in slow sleep (CSWSS). CSWSS is often used to describe the electrical (EEG) feature of the syndrome and ESESS as the clinical feature. Unfortunately, this again makes no sense unless the syndrome is associated with obvious clinical symptoms or signs. Finally, 'non-convulsive' status epilepticus should only be used if the patient has some clinical manifestation during the continuous spike and wave activity, even if this manifestation is subtle. The potential danger is that the EEG, and not the patient, becomes the focus of management with a consequent risk of over-treatment and iatrogenic consequences.

Ambiguity and lack of clarity could impact directly on patient care

'Predisposition, susceptibility, tendency or vulnerability to epilepsy'

This is one of many examples of the type of misleading and potentially dangerous terms used in EEG-reporting. The vast majority of reporting is the responsibility of doctors, specifically neurophysiologists and neurologists, although this also included some psychiatrists and general practitioners in the mid to late 1900s. The use of these terms may reflect reporters' uncertainty about whether an EEG is normal or abnormal, and a consequent reluctance in making a definite decision. It might also reflect uncertainty about the clinical significance of equivocal findings, including 'epileptiform activity'. Consequently, it is likely the general paediatrician, adult physician or, rarely, general practitioner who receives such a report will interpret the patient's episodes or 'funny turns' as being epileptic in nature. This is particularly likely when the description of the episodes is incomplete or inaccurate. This type of EEG report, in conjunction with an incomplete or inaccurate history, is the most common reason for a misdiagnosis of epilepsy [Jeavons, 1975, Gibbs and Appleton, 1992]. It is highly likely this is happening somewhere in the UK as you read this article.

There seems to be no consistency of language, in both scientific and grammatical structure, used by the clinicians that write the interpretation or conclusion on the EEG report. This is in contrast to the more structured and standardised format by the physiologists that perform the EEG and write its technical report. Many paediatricians have told me they frequently find the technical report more intelligible than the clinical interpretation. Unfortunately however, this does not necessarily help in the management of their patients.

Final thoughts

The above examples represent more than academic word-play or scientific semantics. Ambiguity and lack of clarity could impact directly on patient care. The investigation and management of the epilepsies depends to a large extent on the identification of the correct seizure type(s) and the correct interpretation of the EEG. These are key criteria in the identification of the epilepsy syndromes and subsequent choice of anti-epileptic drug. This was identified by the ILAE when publishing its glossary of terms in both 2014 and 2017. Inaccurate and incorrect terminology perpetuates the misunderstanding among often cynical healthcare professionals and a suspicious public, that epilepsy is poorly understood and poorly managed.

It is a priority and a challenge of any language to facilitate communication. For the epilepsies, good communication will help improve understanding by all involved in the care and education of patients with epilepsy and their families. To manage individuals with an epilepsy effectively and continue to deconstruct the stigma associated with the condition, we need to know, understand and use language appropriately and consistently.

Richard Appleton
Consultant and honorary professor in Paediatric Neurology
Alder Hey Children's Health Park, Liverpool and Holton St Mary, Suffolk

Further reading

Berg AT *et al.* (2010) Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 51: 676-85
Fisher RS *et al.* (2014) A practical clinical definition of epilepsy. *Epilepsia*. 55: 475-82
Fisher RS *et al.* (2017) Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 58: 522-30
Gibbs J and Appleton RE. (1992) False diagnosis of epilepsy in children. *Seizure*. 1: 15-18
Jeavons PM. (1975) The practical management of epilepsy. *Update*. 1: 11-15
Scheffer IE *et al.* (2017) ILAE classifications of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 58: 512-21
Temkin O. (1945) *The falling sickness. A history of epilepsy from the Greeks to the beginning of the modern neurology*. Baltimore: The Johns Hopkins Press

A history of stress

Development of epilepsy, depression and cognitive deficits

Dr Christophe Bernard looks at the way a history of stress may cause a vulnerability to epilepsy and comorbidities in some individuals and suggests what future treatments there may be

Epilepsies are often associated with comorbidities, including depression and cognitive deficits [Hesdorffer, 2016; Kanner, 2016; Kanner and Hesdorffer, 2012]. Comorbidities are often reported by patients as more detrimental to their quality of life than seizures themselves. Not all patients with epilepsy develop comorbidities. Comorbidities are a major health issue and determining which patients are likely to develop them is an important scientific challenge. Many factors could play a role, including the genetic background, the environment (all life experiences), epilepsy itself and the epilepsy treatment. Several anti-epileptic drugs (AEDs) can have strong side-effects in some patients.

Epilepsy is usually associated with large alterations of neuronal networks (for example neuronal death, inflammation etc). If such modifications alter the circuits involved in depression and memory, their dysfunction may lead to the emergence of comorbidities. Patients can feel stigmatised, a highly stressful situation that can lead to depression and cognitive deficits [Mula, 2017]. Although we have scant data on the role of the genetic background in patients, intuitively, it is a major contributing factor.

The problem of the development of comorbidities in epilepsy is thus as difficult to address as it is multifactorial. Ideally, we would need predictive biomarkers to identify at-risk patients (such as a gene mutation, some molecules present in the blood etc) in order to treat them in a preventive manner.

Ideally, we would need predictive biomarkers to identify patients at risk of comorbidities in order to treat them in a preventative manner

Experimental models of epilepsy can provide some insight. Indeed, the development of co-morbidities is strain- and epilepsy model-dependent [Chauviere *et al*, 2009; Inostroza *et al*, 2011; Inostroza *et al*, 2012; Sankar R and Mazarati A, 2012]. In addition, not all animals (including animals from the same litter) develop comorbidities in experimental epilepsy [Becker *et al*, 2015; Pineda *et al*, 2014]. This demonstrates that genetics and life experiences are key determinants for the expression of comorbidities. Importantly, experimental studies have also demonstrated the existence of predictive biomarkers for the development of comorbidities in rats with epilepsy [Becker *et al*, 2015; Medel-Matus *et al*, 2017].

There is strong bidirectional relationship between stress and epilepsy. In some people, stress can be a major seizure trigger. The unpredictable nature of seizures is a stressful situation for patients, which could also contribute to worsening the phenotype [Hoppe and Elger, 2011]. Some patients report that they

have experienced highly stressful situations in their past (eg death of relative, divorce, unemployment) before having spontaneous seizures. This led us to test the hypothesis that intense stress could sensitise certain individuals to the development of epilepsy and comorbidities. The diathesis (ie vulnerability) stress model provides a conceptual framework to understand why some patients may develop comorbidities and not others [Hoppe and Elger, 2011].

The main idea is that there is a threshold (specific to each individual) that needs to be crossed for the expression of a phenotype. The accumulation of stressful events can generate a state of vulnerability in some individuals as they get closer and closer to the threshold [McEwen, 2013; McEwen *et al*, 2015]. Then, a subsequent hit or insult will make them cross the threshold [de Kloet *et al*, 2005]. If unresolved, such intense stress may have left a biological imprint in some individuals, driving them closer to the threshold of depression, cognitive deficits and so on. Epileptogenesis or seizures could then act as secondary hits to make them cross the threshold. Non-vulnerable individuals remain far from the threshold.

We managed to reproduce this situation experimentally. Rats were exposed to an intense stressful situation (social defeat when exposed to a dominant alpha male). Ten days later, half of the animals become vulnerable to depression (at that time they did not display any phenotype). When exposed to a second hit (mild stress) one month later, only the vulnerable animals developed a depression-like profile and cognitive deficits. The non-vulnerable animals did not develop a phenotype although they had been exposed to the same experimental procedure [Blugeot *et al*, 2011; Bouvier *et al*, 2016]. At present, we can only conjecture about the reasons for such splitting into two populations. It could be due to differences in genetic background or the way the pups were taken care of, among other possibilities. Importantly, we identified serum BDNF (Brain Derived Neurotrophic Factor) levels as a predictive biomarker for vulnerability to depression [Blugeot *et al* 2011; Bouvier *et al*, 2016].

Going a step further we demonstrated that the state of vulnerability could be reversed before and after the second hit with analogs of BDNF and antioxidants, respectively [Blugeot *et al*, 2011; Bouvier *et al*, 2016]. Once the vulnerability model was validated, we applied it to epilepsy. We replaced the second hit with status epilepticus, which triggered epileptogenesis in the animals. We found that vulnerable animals (sensitised by the intense stress provoked by social defeat) developed a severe form of epilepsy as well as depression and cognitive deficits. In contrast, non-vulnerable animals developed a less severe form of epilepsy and no comorbidities [Becker *et al*, 2015; Becker *et al*, 2019]. We also demonstrated that the vulnerability could be reversed before and after the induction of epilepsy, in particular with antioxidants [Becker *et al*, 2015; Becker *et al*, 2019].

We are now entering the age of personalised medicine – if groups of patients with epilepsy can be stratified and be identified, this would be really valuable

Based on these results obtained in animal models, we have started a multi-centre clinical trial in patients. We want to determine whether serum BDNF can be used as a predictive biomarker of vulnerability to depression in patients with epilepsy. This will be the first step toward preventive treatments of vulnerable individuals.

These results validate the hypothesis that past stressful events may render some individuals vulnerable to epilepsy and comorbidities. These events brought them close to the threshold, and the processes responsible for epileptogenesis (eg brain trauma) made them cross the threshold. Of course, this scheme may apply to a subset of patients (hopefully identifiable with a biomarker). It does not mean that all patients developing comorbidities fit in this scheme. Many mechanisms can account for the expression of comorbidities. A past stressful event is one of them. We are now entering the age of personalised medicine. If groups of patients with epilepsy can be stratified (here rendered vulnerable after a non-resolved intense stress) and be identified, this would be really valuable. Being able to treat them – if only for their comorbidities – would constitute a major advance.

Christophe Bernard
Research director
Aix-Marseille Université

Further reading

Becker C, Bouvier E, Ghestem A, Siyoucef S, Claverie D, Camus F, Bartolomei F, Benoliel JJ, *et al.* (2015), Predicting and treating stress-induced vulnerability to epilepsy and depression. Ann Neurol 78:128-136.
Becker C, Mancic A, Ghestem A, Poillerat V, Claverie D, Bartolomei F, Brouillard F, Benoliel JJ, *et al.* (2019), Antioxidant treatment after epileptogenesis onset prevents comorbidities in rats sensitized by a past stressful event. Epilepsia 60:648-655.
Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel JJ, *et al.* (2011), Vulnerability to depression: from brain neuroplasticity to identification of biomarkers. J Neurosci 31:12889-12899.
Bouvier E, Brouillard F, Molet J, Claverie D, Cabungcal JH, Cresto N, Doligez N, Rivat C, *et al.* (2016), Nrf2-dependent persistent oxidative stress results in stress-induced vulnerability to depression. Mol Psychiatry.
Chauviere L, Rafrafi N, Thinus-Blanc C, Bartolomei F, Esclapez M, Bernard C (2009), Early deficits in spatial memory and theta rhythm in experimental temporal lobe epilepsy. JNeurosci 29:5402-5410.
de Kloet ER, Joels M, Holsboer F (2005), Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6:463-475.
Hesdorffer DC (2016), Comorbidity between neurological illness and psychiatric disorders. CNS Spectr 21:230-238.
Hoppe C, Elger CE (2011), Depression in epilepsy: a critical review from a clinical perspective. Nat Rev Neurol 7:462-472.
Inostroza M, Cid E, Brotons-Mas J, Gal B, Aivar P, Uzcategui YG, Sandi C, Menendez de la PL (2011), Hippocampal-dependent spatial memory in the water maze is preserved in an experimental model of temporal lobe epilepsy in rats. PLoSONE 6:e22372.
Inostroza M, Cid E, Menendez de la PL, Sandi C (2012), Different emotional disturbances in two experimental models of temporal lobe epilepsy in rats. PLoSONE 7:e38959.
Kanner AM (2016), Management of psychiatric and neurological comorbidities in epilepsy. Nat Rev Neurol 12:106-116.
Kanner AM, Hesdorffer DC (2012), Neuropsychiatric complications of epilepsy. Handb Clin Neurol 107:461-482.
McEwen BS (2013), The Brain on Stress: Toward an Integrative Approach to Brain, Body, and Behavior. Perspect Psychol Sci 8:673-675.
McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C (2015), Mechanisms of stress in the brain. Nat Neurosci 18:1353-1363.
Medel-Matus JS, Shin D, Sankar R, Mazarati A (2017), Inherent vulnerabilities in monoaminergic pathways predict the emergence of depressive impairments in an animal model of chronic epilepsy. Epilepsia 58:e116-e121.
Mula M (2017), Depression in epilepsy. Curr Opin Neurol 30:180-186.
Pineda E, Jentsch JD, Shin D, Griesbach G, Sankar R, Mazarati A (2014), Behavioral impairments in rats with chronic epilepsy suggest comorbidity between epilepsy and attention deficit/hyperactivity disorder. Epilepsy Behav 31:267-275.
Sankar R, Mazarati A (2012) Neurobiology of Depression as a Comorbidity of Epilepsy. In: Jasper's Basic Mechanisms of the Epilepsies, vol. (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds). Bethesda (MD).

Ultra long-term EEG

Illuminating a blind spot in epilepsy care

Dr Duun-Henriksen and Prof Richardson look at a new device for ultra long-term EEG recording. They discuss the practicalities, possible value and potential issues and implications of using such a device to more accurately establish seizure frequency and activity

When optimising treatment for people with epilepsy, doctors are faced with two key blind spots. One is the exact number of seizures the patient is having and the other is how well the patient adheres to taking their medication. With the arrival of an entirely new medical device for continuous EEG monitoring in everyday life, it might be possible to shine a light on the first blind spot. We discuss this new device, its advantages and caveats, potential other ways to obtain the same kind of data and how it will impact clinical practice today and in the future.

Current tools for seizure detection

Seizure detection and monitoring has been an important area of research for many years. For example, sleep seizures are shown to be a risk factor for sudden unexpected death in epilepsy (SUDEP) [Nobili *et al*, 2011; Lamberts *et al*, 2012]. Effective monitoring of these and intervention from carers or family members can help reduce this risk. We also know that reducing the number of generalised tonic-clonic seizures (GTCS) is one of the biggest elements in reducing SUDEP risk [Hesdorffer *et al*, 2011]. Accurate detection and monitoring of seizures is

therefore an essential part of managing these. Monitoring devices can offer promise with data collection, future possible seizure prediction and better epilepsy treatment.

Different monitoring devices have been developed and studied, and while some have seen successes, they are not without their problems. For more than 25 years, patients have used a motion detector under the bed mattress for sleep seizure monitoring. However, a lot of patients and their caregivers complain that they are not sufficiently reliable [Bruno *et al*, 2018]. Recently, different wearable sensors have become available, but only a few are classified as medical devices for detecting seizures. One medical grade solution is the Empatica Embrace wristband. While it relies on measures such as movement, electrical skin conductivity and temperature of the skin, it is approved exclusively for GTCS. Another solution is the NightWatch from Livassured which bases its recordings on heart rate and movement. By focusing on sleep seizures, they have managed to get few false alarms. The device is approved for convulsive seizures and only during sleep.

Many patients are unaware of their actual seizure frequency – studies have shown that self-reported sensitivity is as low as 30% in focal epilepsy and even lower for sleep seizures

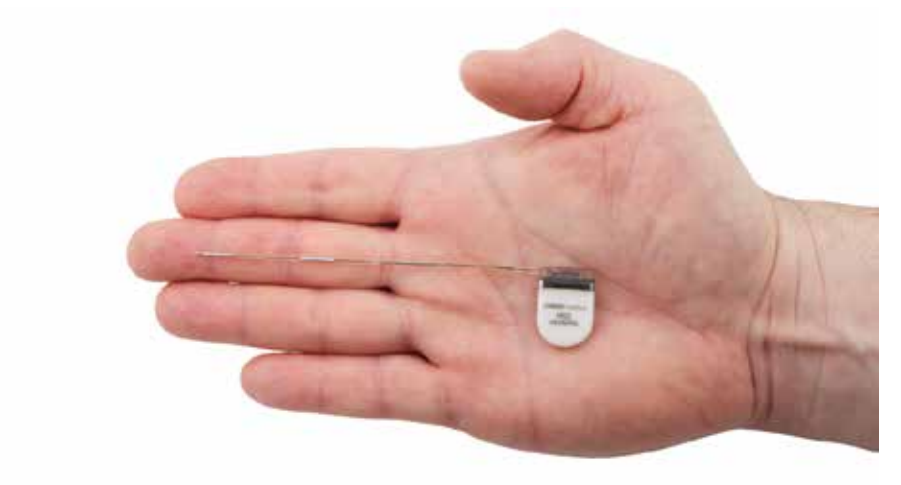
Many patients are unaware of their actual seizure frequency. Studies have shown that self-reported sensitivity is as low as 30% in focal epilepsy and even lower for sleep seizures [Hoppe *et al*, 2007]. But even with the tools that are currently available, achieving an objective measure of the individual patient's seizure burden to guide treatment remains a challenge.

A more accurate seizure detection could be achieved with EEG. Current EEG monitoring is limited to five to 10 days, either as an in-hospital stay or an ambulatory home monitoring. While these methods yield a high sensitivity in epilepsy diagnosis, their value in treatment optimisation is limited as they are costly and can be a burden. Patients might have seizures too infrequently to be measured during a conventional EEG-recording.

A new EEG monitoring device

The 24/7 EEG SubQ device from UNEEG medical was just recently CE-marked. It was developed to get an objective measure of seizure burden in people with epilepsy by continuously recording in their everyday life in an unobtrusive and discreet way. A 10cm lead with electrodes to measure two-channel EEG as seen in *Figure 1* is implanted in the sub-scalp layer during a 20-minute procedure under local anaesthesia. The device was developed using standards from cochlear implants, so after implantation, it can stay implanted for up to 12 months. There is no battery in the implant, so an external device smaller than a £1 coin needs to be placed on the outside of the skin to transfer power wirelessly and receive the recorded data. This data is transferred by a small wire to a data recorder the size of a match box which can be worn underneath the patient's clothing. *Figure 2* gives an overview of how it is worn. This

Figure 1: The 24/7 EEG SubQ implant, which gets placed in the sub-scalp layer under local anaesthesia



Current EEG monitoring is limited to five to 10 days, either as an in-hospital stay or an ambulatory home monitoring

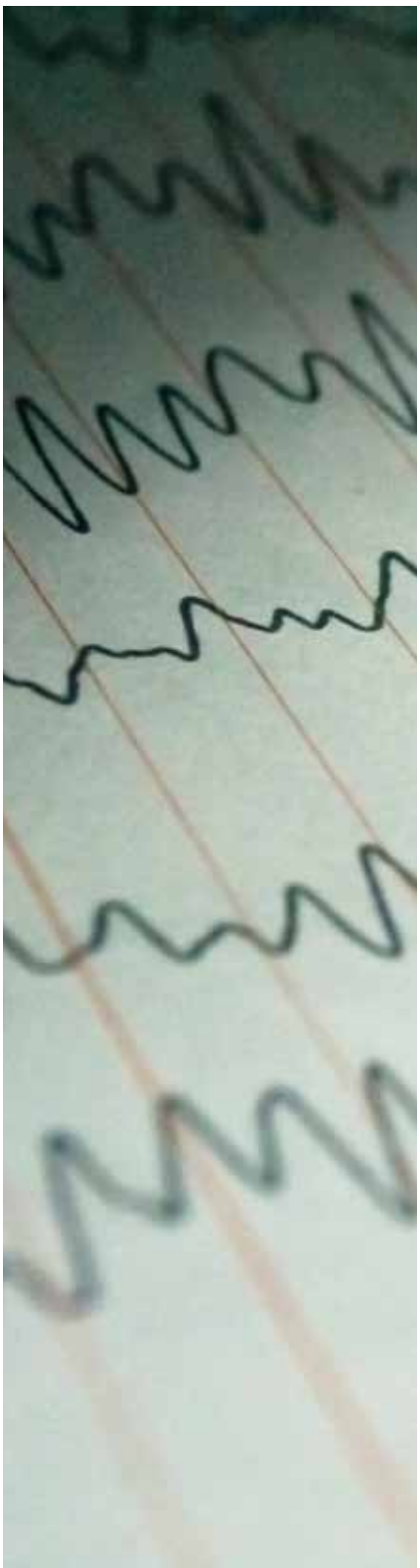


Figure 2: The UNEEG 24/7 as worn in everyday life. A disc smaller than a £1 coin is attached to the skin behind the ear by double adhesive tape while the storing- and battery-unit is worn underneath the clothes. Only a magnet to attach the logger and a small wire from the disc to the logger are visible

technology means the patient can be sent home with a discreet device which records brain activity day and night for as long as required.

All evidence of the performance of the device comes from studies in Denmark so far. A study at King's College London has just commenced, but no results are yet available. Thirty-five subjects, of whom nine have epilepsy [Weisdorf *et al*, 2018], have been using the device for between four and 13 weeks. A total of more than 1,500 days of continuous EEG have been collected without any device-related serious adverse events. Some patients reported headache as a result of surgery. One also had a minor rash due to continuous use of the double adhesive pad to attach the external device. However, all events were transient. One patient withdrew prematurely because the device was felt to be annoying.

The subcutaneous EEG device has the potential to provide crucial data when routine or video-EEG and patient seizure diaries are inadequate. However, the extensive amount of data the new device provides can pose a problem in clinical care. No epilepsy clinic will have resources to review months or years of data from a single patient. The solution thus comes with a specialised tool for visualisation of the two channels of EEG with machine learning capabilities to automatically detect EEG recorded seizures. An expert still needs to review all automated annotations, but instead of looking through huge amounts of continuous data, only epochs of interest need to be considered. EEG experts will need to widen their skills as they would no longer have the conventional full electrode array of the international 10-20 system. This is the case even though the signal is very similar to usual scalp recordings [Duun-Henriksen *et al*, 2015]

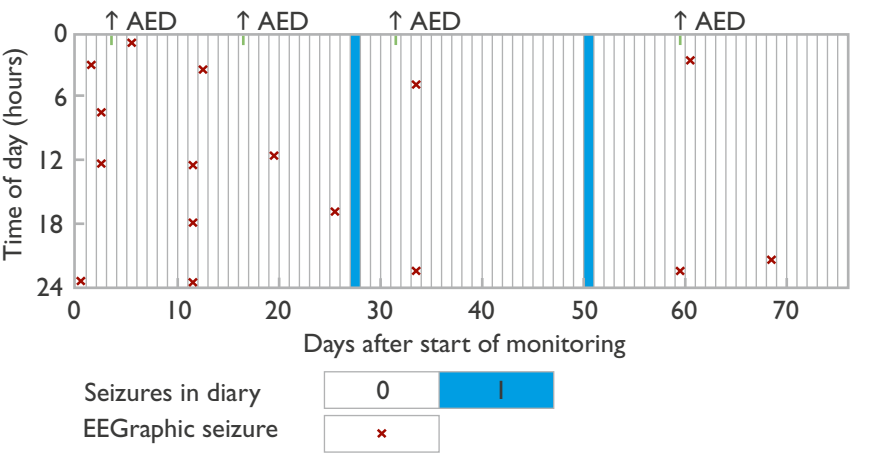
First results from subcutaneous recordings

When investigating the Danish epilepsy recordings, a lot of new information is apparent. A journal article of all the results was recently submitted by Prof Kjaer and colleagues [Weisdorf et al, submitted for publication], but here we bring a case-study regarding a 44-year-old female diagnosed with epilepsy in childhood. Her seizures started again in 2016 after 15 years of seizure freedom. At this point, her medical history raised suspicion of temporal lobe epilepsy. This was confirmed by video-EEG with a left temporal onset of both focal to bilateral tonic-clonic seizures, as well as focal onset seizures with impaired awareness. MRI and CSF were normal. In her diary, she reported

one to three seizures a month, but there was a strong suspicion of many more unrecognised seizures.

In *Figure 3* we see how 16 unreported seizures were identified in the 76 days of sub-scalp EEG recordings (red crosses), while only two were reported in the diary (blue lines). As sometimes seen, there is no correlation between the EEG recorded seizures and those reported in the patient's diary [Cook *et al*, 2013]. This is probably due to low seizure awareness, as she reported that seizures are usually noted by her boyfriend. At the top of *Figure 3* we see that her anti-epileptic drug (AED) dose was increased four times during the study. We can see that she had fewer EEG recorded seizures after the dose increases, but the same conclusion could not have been reached using the diary. We believe that more and longer studies are needed to confirm this observation. Recent reports have shown that multi-day rhythms of seizures are evident in both males and females [Karoly *et al*, 2018]. Understanding the occurrence of seizures in such patterns may be key for both patients and doctors.

Figure 3: EEG recorded seizures and diary seizures for one patient. ↑AED shows where the patient had an increase in anti-epileptic drug dose [based on Weisdorf et al, submitted for publication]

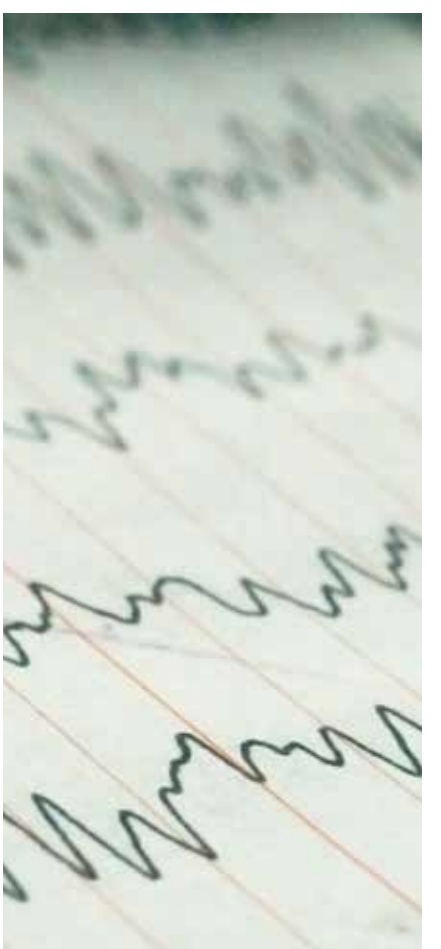


We can see that the patient had fewer EEG recorded seizures after the AED dose increases, but the same conclusion could not have been reached using the diary

Impact on clinical practice

In a survey of 21 neurologists [Casson *et al*, 2010], 16 agreed that current ambulatory recordings are diagnostically useful over traditional inpatient recordings. Eighteen agreed that there is a need for wearable EEG devices. The questionnaire addresses standard ambulatory EEG. However, it does give a good indication that there is an unmet need that exceeds the 30-minute routine EEG and few days epilepsy monitoring unit stay. When asking people with epilepsy whether they would agree to wear a device on a daily basis, the participants saw the possible benefits for improved treatment. They said they valued this benefit more than they were put off by the possible inconvenience of wearing a sensor [Ozanne *et al*, 2017].

We suggest that the new ultra long-term EEG recordings can be useful for managing refractory epilepsy for patients. This is particularly where there is a suspicion of low reliability of their seizure diary or for patients with infrequent seizures where the doctor would like to see the morphology of the EEG. However, sufficient evidence of seizure onset is critical in order to position the two-channel recorder optimally for the EEG recording. Seizure occurrence cannot be ruled



out based on the lack of EEG recorded seizure activity, as it might not be apparent in the area of the brain covered by the device.

Finally, these new recordings might expose a fundamental issue that needs to be addressed – how should clinicians generally handle the possibility that seizure diaries are not reliable? Most management of epilepsy relies on the diary. If we are not able to rely on them, what can we then trust without implanting devices underneath the scalp in all patients? This will be left as an open question until more patients have been studied.

Future perspective

There seems to be a lot of future potential applications for this new ultra long-term EEG recording device which has just entered the market. For patients, reliable seizure alarms notifying family or caregivers when a seizure is occurring are likely to be desirable and should thus be prioritised for development. This would be especially valuable for children, although, currently the device is only approved for adults. Furthermore, as the recordings are based on EEG, one could speculate that the device could be used for recording sleep quality reliably. This could be important for the patient in providing information about recent seizures and sleep patterns. Whether seizures can be predicted, and patients thus warned before they happen, is still to be demonstrated. But some evidence shows that it might be possible [Cook *et al*, 2013], and something that would provide the largest improvement in quality of life for many patients. However, before ultra long-term EEG recordings are viable for widely distributed use, more evidence of clinical impact is needed from clinical trials, and a reimbursement code needs to be obtained.

Jonas Duun-Henriksen is a visiting researcher at King's College London on a secondment from the company manufacturing the device described in this article. Mark Richardson is on the advisory board for the company but has no other affiliation to UNEEG medical.

Jonas Duun-Henriksen
Head of epilepsy research
UNEEG medical

Mark Richardson
Vice Dean of the Division of Neuroscience at the Institute of Psychiatry, Psychology and Neuroscience
King's College London

Further reading

Bruno E, Simblett S, Lang A, Biondi A, Odoi C, Schulze-Bonhage A, Wykes T, Richardson MP and RADAR-CNS Consortium. (2018) Wearable technology in epilepsy: The views of patients, caregivers, and healthcare professionals. *Epilepsy & Behavior*, 85, pp. 141–149. doi: 10.1016/j.yebeh.2018.05.044.

Casson A, Yates D, Smith S, Duncan J, Rodriguez-Villegas E. (2010) Wearable electroencephalography. What is it, why is it needed, and what does it entail? *IEEE Engineering in Medicine and Biology Magazine*. IEEE, 29(3), pp. 44–56. doi: 10.1109/MEMB.2010.936545.

Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, D'Souza W, Yerra R, Archer J, Litewka L, Hosking S, Lightfoot P, Ruedebusch V, Sheffield WD, Snyder D, Leyde K and Himes D. (2013) Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurology*, 12(6), pp. 563–71. doi: 10.1016/S1474-4422(13)70075-9.

Duun-Henriksen J, Kjaer TW, Looney D, Atkins MD, Sørensen JA, Rose M, Mandic DP, Madsen RE and Juhl CB. (2015) EEG Signal Quality of a Subcutaneous Recording System Compared to Standard Surface Electrodes. *Journal of Sensors*, 2015, pp. 1–9. doi: 10.1155/2015/341208.

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ and Hauser A for the ILAE Commission on Epidemiology; Subcommission on Mortality. (2011) Combined analysis of risk factors for SUDEP. *Epilepsia*, 52(6), pp. 1150-9. doi: 10.1111/j.1528-1167.2010.02952

Hoppe C, Poepel A and Elger CE. (2007) Epilepsy: accuracy of patient seizure counts. *Archives of Neurology*, 64(11), p. 1595. doi: 10.1001/archneur.64.11.1595.

Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH and Cook MJ. (2018) Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. *The Lancet Neurology*. Elsevier, 17(11), pp. 977–985. doi: 10.1016/S1474-4422(18)30274-6.

Lamberts RJ, Thijs RD, Laffan A, Langan Y and Sander JW. (2012) Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk. *Epilepsia*, 53(2), pp. 253-7. doi: 10.1111/j.1528-1167.2011.03360

Nobili L, Proserpio P, Rubboli G, Montano N, Didato G and Tassinari CA. (2011) Sudden unexpected death in epilepsy (SUDEP) and sleep. *Sleep Medicine Reviews*, 15(4), pp.237-246. doi: 10.1016/j.smrv.2010.07.006

Ozanne A, Johansson D, Hällgren Graneheim U, Malmgren K, Bergquist F and Alt Murphy M. (2017) Wearables in epilepsy and Parkinson's disease-A focus group study. *Acta Neurologica Scandinavica*. doi: 10.1111/ane.12798.

Regalia G, Onorati F, Lai M, Caborni C and Picard RW. (2019) Multimodal wrist-worn devices for seizure detection and advancing research: Focus on the Empatica wristbands. *Epilepsy Research*, 153, pp. 79–82. doi: 10.1016/j.eplepsyres.2019.02.007.

Weisdorf S, Gangstad SW, Duun-Henriksen J, Mosholt KSS and Kjær TW. (2018) High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. *Journal of neurophysiology*, 120(3), pp. 1451–1460. doi: 10.1152/jn.00320.2018.

Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW and Kjær TW. 11774 hours of EEG from nine patients - Ultra-long-term subcutaneous home monitoring of epilepsy. Submitted for publication

For more information about the UNEEG 24/7 see *www.uneeg.com*

Tribute to Prof Graham Harding

Professor Graham Frederick Anthony Harding died in October 2018. Professor Stefano Seri remembers his colleague and friend

It was with great sadness that on 20 October 2018 I received a message from Graham's son Anthony informing me of the passing of his father.

Graham was a friend, a colleague and a source of inspiration. I had the honour of being chosen to continue his work at Aston University as professor of Clinical Neurophysiology in the unit he created in 1963 and led until his retirement in 2002.

Graham graduated in psychology from University College London in 1961. He obtained a PhD in EEG and psychiatry from Birmingham University. Graham studied with Grey Walter at the Burden Neurological Institute. He also learned the secrets of EEG interpretation from Dr Giuseppe "Pep" Pampiglione at Hospital for Sick Children Great Ormond Street in London.

In 1998, Graham was awarded an Honorary Membership of the Royal College of Physicians for outstanding contributions to medicine. This was an accolade he was especially proud of. Graham was the first professor of Clinical Neurophysiology in the UK, president of the British Society for Clinical Neurophysiology and secretary of the International Federation of Clinical Neurophysiology.

His affiliation with the medical profession consolidated in Birmingham with his friendship and clinical partnership with the late paediatric neurologist Peter M. Jeavons. This collaboration led to ground-breaking discoveries in the field of photosensitivity and epilepsy. Together, they wrote the first monograph on photosensitivity in 1975 after meticulously studying the brain responses to flashing lights in 460 patients. This wealth of knowledge has inspired many clinicians for years to come. His scientific work was a fulgid example of how laboratory research can lead to societal impact through the development of UK broadcasting guidelines on flashing images. This paved the way for their adoption by many other countries worldwide.

It was very clear in Graham's mind that clinical research had to be driven, in equal amount, by two important aspects. One is the desire to understand the intimate mechanisms of disease and the other is the ambition to translate discoveries into actions that improve the quality of life of patients. This led him to realise that a medication like vigabatrin, widely used in the 80s and 90s for focal epilepsies, was associated with changes in the way the retina responded to visual stimulation. It was only a few years later that clinicians started reporting loss in parts of the visual field in patients taking vigabatrin long-term. However, most of the patients taking vigabatrin were young and didn't tolerate the procedure necessary to measure the response of the retina. Convinced that the scientific method had to be used to improve the life of individuals, Graham developed a new test (the H-Stimulus) that children would tolerate and made it available to clinicians worldwide.

Graham was also a visionary scientist. He was probably the first to believe that a new methodology that was being developed in physics laboratory – Magnetoencephalography (MEG) – would revolutionise how we study brain function. Much to the dismay of his collaborators, he invested all the money his department had in acquiring the first MEG system in the UK. Decades later, Aston University became one of the few centres in Europe to have an established clinical activity. It serves patients with epilepsy who are referred to find out where within the brain their seizures are originating.

Graham was a strong supporter of UK charities, working to help and support patients diagnosed with epilepsy and their families. He had an unsurpassed ability to make complex scientific material understandable to the many. He helped to develop the Epilepsy Action information on photosensitive epilepsy and I had the pleasure to contribute to it.

Those of us who had the fortune to work with him will miss him dearly for his energy, inspiring vision and dedication to science and patient welfare.

Highlights

Top picks from *Seizure*

Editor of the journal *Seizure*, Markus Reuber highlights his key papers from the latest editions

For those experiencing recurrent unprovoked epileptic seizures, epilepsy is much more than the sum of ictal events. This has been underscored by the 2005 and 2014 International League Against Epilepsy (ILAE) definitions of epilepsy [Fisher *et al*, 2005; Fisher *et al*, 2014]. In fact, for many of those affected by epilepsy, the challenges of the interictal state are more distressing than those directly related to the seizures themselves. This means that a comprehensive understanding of the disability related to epilepsy must not only take account of seizure manifestations and injuries. It also needs to consider the physical and emotional consequences of seizures for the person with epilepsy. Epilepsy may not only be disabling because of perceptions of the condition held by individuals experiencing epileptic seizures, but also because of those around them and society at large.

My editor's choice from issue 65 of *Seizure* is by Holmes *et al* [2019]. It is an analysis of responses from 3,875 members of the UK public to a survey based on the Attitudes and Beliefs about Living with Epilepsy (ABLE) scale. It explores to what extent this interictal disability could be related to unhelpful societal perceptions of epilepsy rather than seizures themselves or any attributes of those affected by it. Although this study reflects attitudes in the UK, the findings include a number of lessons which are likely to be relevant in other countries.

The headline findings are encouraging. On the whole, the UK public has a relatively positive attitude towards epilepsy. Frankly negative views were only held by one in one hundred respondents. This might suggest that stigma is more often perceived by people with epilepsy than explained by the views of the public. However, there were also some more troubling findings. For instance, there was an inverse relationship between self-reported knowledge about epilepsy and evidence of such knowledge. This means that it might be difficult to reach those with the greatest need to learn more about epilepsy because they already feel well informed about this disease. Educational efforts are also complicated by the fact that higher levels of knowledge about epilepsy were associated with greater risk and safety concerns. These, in turn, were associated with the highest level of stigma. This suggests that educators have to be very circumspect about improving attitudes towards epilepsy without inadvertently increasing anxiety about seizure-related risks and increasing stigma overall.

Wearable devices versus patient reports

Adults with epilepsy undergoing video-EEG monitoring fail to report over 85% of seizures in sleep and up to 50% of those occurring in the waking state [Hoppe *et al*, 2007]. However, the development and licensing of anti-epileptic drugs (AEDs) and anti-seizure devices continues to rely on patients' self-reports of seizure number and frequency. This should be a matter of major concern.

The use of wearable devices capable of detecting seizures seems to be an obvious answer to the deficiencies of patients' self-reports. There has been impressive progress with the development of such devices over recent years, using a range of different measures to identify seizures.

My editor's choice from *Seizure* issue 66 is a review article by Kurada *et al* [2019]. It focuses on this idea and explores how close we have come to employing wearable automatic detection devices in AED development studies. This review is based on an analysis of 38 original research papers about commercial or non-commercial devices. These papers provide sufficient data to allow the calculation of an F1-score based on positive (correct), false positive and false negative detections.

The review identified a number of devices capable of outperforming patient report in relation to bilateral tonic seizure and focal seizures with impaired awareness. Devices were also capable of capturing potentially useful secondary outcome measures such as seizure duration and vital signs during the ictal period. However, so far no reviewed device has been shown to be capable of reliably detecting focal seizures with retained awareness, atonic or clonic seizures. What is more, many of the device validation studies had significant shortcomings. These include a small sample size, the inclusion of highly specific patient populations, short study duration and a lack of replication across multiple

patient cohorts. Another problem is that (for obvious methodological reasons) most validation studies were carried out in Epilepsy Monitoring Unit settings. This means that participants were restricted in the range of activities they could engage in during monitoring. The performance of different devices was difficult to compare because studies had employed a range of different validation measures. This means that, although devices hold much promise and are highly likely to complement or replace patient reported outcome measures in the future, there is more work to be done. Kurada *et al* propose a logical framework for this work involving sequential inpatient validation, outpatient validation, and experimental validation in clinical intervention trials.

Reducing the treatment gap

It is often highlighted that epilepsy can affect anyone around the world. However, it is not as often highlighted that it is not evenly distributed among the rich and the poor – neither globally nor in individual countries. Of the 60 million people with epilepsy worldwide, 80% live in lower or middle income countries (LMICs). Two-thirds of all presentations of epilepsy should be 'controllable' with optimal AEDs. But almost three-quarters of individuals living in rural regions of LMICs receive inadequate or no AED treatment at all [Espinosa-Jovel *et al*, 2018]. It's really important that we do not lose sight of problems like the massive epilepsy treatment gap, especially as means of tackling some of these problems are within our grasp.

My editor's choice from *Seizure* issue 67 is an article by Prajapati *et al* [2019] describing one low cost means of reducing the treatment gap. The authors describe the outcome of single therapeutic encounters between individuals with epilepsy living in rural districts of India and clinicians. The clinicians are making diagnoses and providing treatment advice in epilepsy outpatient clinics on the 'Lifeline Express' (LLE), a train service run by the Impact India Foundation. This is an Indian non-governmental organisation, which takes medical specialists to the most inaccessible Indian communities [Impact India Foundation]. This service does not just deal with epilepsy but with a wide range of medical disorders. One thing it cannot offer is regular follow-up. The vast majority of the patients seen will only receive treatment advice on one occasion. They will then have to find ways of following this advice without further support from the experts they have met on the LLE.

The study compared the LLE service with patients with epilepsy seen and followed up by some of the LLE doctors at AIIMS, a national specialist neurology centre in New Delhi. The study shows that outcome of those who received advice on the LLE was worse. At least two years after the initial contact, 72% of the LLE versus 87% of the AIIMS patients were still taking AEDs. Also, 22% (LLE) versus 6% (AIIMS) had discontinued medication against medical advice and 7.5% versus 2.8% had died. However, more importantly, the single contact with an expert on the LLE had reduced the epilepsy treatment gap from 49% at first contact to 22% at follow up. Of course, there is so much more to do – but facilitating a single contact with an epilepsy expert may be a good way to start!

Further reading

Espinosa-Jovel C, Toledano R, Aledo-Serrano Á, García-Morales I, Gil-Nagel A. (2018) Epidemiological profile of epilepsy in low income populations. *Seizure* 56:67–72.

Fisher RS, van Emde Boas W, Blume W, *et al*. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–472.

Fisher RS, Acevedo C, Arzimanoglou A, *et al*. A practical clinical definition of epilepsy. *Epilepsia* 2014; 55:475–482.

Holmes E, Bourke S, Plumpton C. Attitudes towards epilepsy in the UK population: results from a 2018 national survey. *Seizure* 2019; 65:12-19

Hoppe C, Poepel A, Elger CE. (2007) Epilepsy: accuracy of patient seizure counts. *Arch Neurol* 64(11):1595–9.

Impact India Foundation – NGO in India: An International Initiative Against Avoidable Disablement. Available from: *https://www.impactindia.org/lifelineexpress.php#content-start*

Kurada AV, Srinivasan T, Hammond S, Ulate-Campos A, Bidwell J. (2019) Detection Devices for use in Antiseizure Medication Clinical Trials: A Systematic Review. *Seizure* 66:61-69.

Prajapati C, Bhushan Singh M, Padma Srivastava MV, Sreenivas V, Goyal V, Shukla G, Vishnu VY, Gursahani R, Patterson V, Bajpai S, Jain P. (2019) Comparing long-term outcomes of epilepsy patients from a single-visit outreach clinic with a conventional epilepsy clinic: A cross-sectional observational study from India. Seizure 67:5-10

Should we keep banging on about safety?

Epilepsy is a dangerous and life changing diagnosis, especially for the 30% of patients who are refractory to medical treatment.

When I make a diagnosis, I talk to patients about safety. I tell them not to drive (which is a legal requirement), but also not to use heavy machinery or to go up ladders. I warn them about being safe at home, and especially not to have baths unsupervised. I talk about sudden unexpected death in epilepsy (SUDEP) and how to reduce the risk of this devastating consequence of poorly controlled epilepsy. But often, that's the last time I talk about safety. Following that first consultation, I know the points will be reiterated when they see one of my colleagues, the epilepsy specialist nurse. I know he or she will go over the same points in greater detail.

After that, I think we just discuss safety if we are directly asked. Clinic appointments are filled with talking about seizure frequencies, side-effects, fertility issues and pregnancy plans, as well as comorbidities such as anxiety and depression. There just often isn't time for anything else.

But do we need to keep banging on about safety? For all of us, memories fade over time. And this is often more pronounced in patients with epilepsy, where both the seizures and the treatments can compound memory difficulties.

I have become aware of patients who I know I have given safety advice to and who years later tell me about the problem they have while having a bath! 'Having a bath?' I ask them. 'But I told you that isn't safe!' I show them the letter and they tell me they don't remember. Fortunately, the few examples I have had like this have been near misses. But there are fatalities every year where patients with epilepsy die because they are not following advice given to them at diagnosis. Often, for those patients, their diagnosis was made years ago.

I don't know how often we need to reiterate our safety advice, but I think we do need to do so. Patients with epilepsy need reminding to help them to remember not to do things that can be life-threatening. I've started to wonder if reminding patients of this simple safety advice, might, for some, have a bigger impact than yet another change in medication.

Dates for the diary

June 2019

21
Genetic Generalised Epilepsies: From Basic Science to Clinical Practice
London, UK
bit.ly/2Lby1hV

22-26
33rd International Epilepsy Congress (IEC)
Bangkok, Thailand
internationalepilepsycongress.org

July 2019

7-18
2019 Advanced San Servolo Epilepsy Course
Venice, Italy
bit.ly/2H8NuK7

August 2019

25-28
5th SuSIE
Bochum, Germany
imaging-in-epilepsy.org/

September 2019

2-5
International Conference for Technology and Analysis of Seizures, 2019 (ICTALS2019)
Exeter, UK
exeter.ac.uk/livingsystems/newsandevents/events/ictals2019/

6-7
International Congress on Mobile Devices and Seizure Detection in Epilepsy
Lausanne, Switzerland
mhsdepilepsy2019.com/

6-7
4th International Epilepsy Symposium – epilepsy and psychology
Bilefeld, Germany
bit.ly/304InDx

14-15
ILAE British Branch 17th SpR Epilepsy Teaching Weekend
Oxford, UK
epilepsyteachingweekend.com

Dealing with burnout

Clinical psychologist Dr Judith Johnson discusses spotting and tackling burnout in ourselves and colleagues, and avoiding burnout going forward.

Neonatal seizures and treatments

Dr Ronit Pressler discusses the work of the ILAE's Neonatal Seizures Task Force on neonatal seizure guidelines for treating this group.

Epilepsy Professional's advisory panel

optima

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Diagnostic EEG

- Lightweight ambulatory EEG for comfortable at home recordings
- Continuous video and EEG monitoring for the I.C.U.
- Longterm video EEG including intracranial recording

natus neurology

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