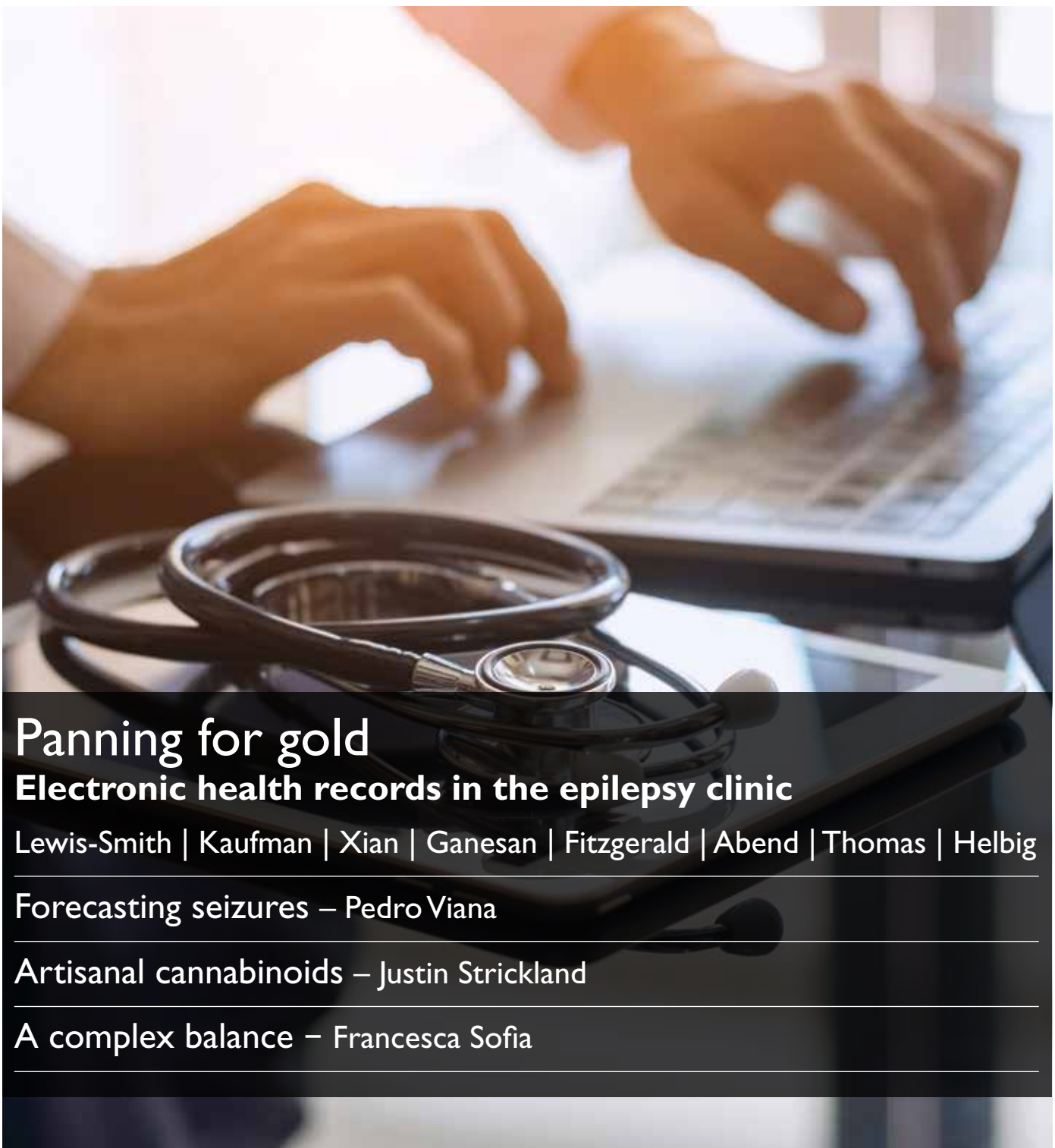
epilepsy action

issue sixty four / Spring 2022 £3.50
(Free to Epilepsy Action professional members)

epilepsy professional



Panning for gold

Electronic health records in the epilepsy clinic

Lewis-Smith | Kaufman | Xian | Ganesan | Fitzgerald | Abend | Thomas | Helbig

Forecasting seizures – Pedro Viana

Artisanal cannabinoids – Justin Strickland

A complex balance – Francesca Sofia

GIVE THEIR brain ITS BEST chance

Time is of the essence for every child with drug-resistant epilepsy.

Every minute that passes brings their next seizure closer.
Every seizure means a bigger impact on their lives.
The earlier we act for children with drug-resistant epilepsy, the more chances there are for a brighter future.

Giving their brain its best chance means considering VNS Therapy sooner rather than later.

LIVANOVA UK LTD
1370 Montpellier Court,
Gloucester Business Park,
Gloucester, GL3 4AH
T: 01452 638500

LIVANOVA BELGIUM NV
Ikaroslaan 83, 1930 Zaventem
Belgium
www.vnstherapy.co.uk

INTENDED USE / INDICATIONS:

Epilepsy (Non-US)—The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to seizure medications. AspireSR® and SenTiva™ feature an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

Incidence of adverse events following stimulation (>5%) included dysphonia, convulsion,headache, oropharyngeal pain, depression, dysphagia, dyspnea, dyspnea exertional, stress, and vomiting.

Visit http://en.eu.livanova.cyberonics.com/safety-information to view important safety information.

VNS Therapy®
by LivaNova

Soleman et al Epilepsy & Behavior 88 (2018) 139–145

CTBOVAd20E1

Welcome to the first edition of *Epilepsy Professional* of 2022.

As spring approaches and the days get longer, the world feels more optimistic about living with COVID-19 and returning to improving the day-to-day lives of our patients with epilepsy. This edition has several excellent articles.

Big data interpretation is already starting to pay off in research in the epilepsies. Dr David Lewis-Smith and colleagues describe how 'panning for gold' in electronic health records (EHR) can lead to advances in medical knowledge and, potentially, better care for our patients. They describe how using standard data sets at each clinical encounter, not only helps with individual patient care, but also allows us to get the most out of the EHR.

The interpretation of big data of another kind is discussed in Pedro Viana's article describing the use of subcutaneous EEG to try and forecast seizures. While still predominantly a research tool, they are gaining valuable insights into the seizure patterns already from several very prolonged recordings.

The importance of using real world data and encouraging patient health literacy and engagement in health policy are discussed by Francesca Sofia, the new president of the International Bureau for Epilepsy (IBE), in her interview with Kami Kountcheva. Francesca's insights as both a scientific manager and researcher, and now the mother to a child with epilepsy, are fascinating.

Pharmaceutical-grade cannabidiol is now available and licenced for the treatment of epilepsy in Dravet and Lennox-Gastaut syndromes, but not for other forms of epilepsy, due to limited current evidence for its use. However, patients can self-medicate with artisanal cannabinoid products available directly to consumers as nutritional or food supplements. Justin Strickland guides us through the composition of these and the available evidence for their use.

I hope you enjoy this edition of *Epilepsy Professional*.

Seán Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

22
artisanal cannabinoids

Justin Strickland

Dr Strickland describes the emergence of artisanal CBD and other cannabinoid products in epilepsy care and how to advance the science behind their use

I don't know what it is, but I love data. I love when seemingly random bits of information start to form a pattern. I love when answers start to appear where there were only questions. I love the reliability and clear-cut nature of data (even if their interpretation is not always so clear cut).

In this issue, data are the belles of the ball. Dr Pedro Viana updates us on the use of subcutaneous EEG to collect long-term continuous data (page 8). If this method is successful, the potential for these kind of data could be life-changing for patients. Seizures could become much more predictable, and treatment could become much more personalised. On a similar note, Dr David Lewis-Smith and colleagues discuss the data potential that electronic health records (EHRs) hold (page 12). These can be treasure troves of untapped data and information, and the authors discuss ways to make EHR data as standardised and machine interpretable as possible.

On page 28, the new president of the International Bureau for Epilepsy shares her hopes and plans for her term in this role. Among other things, she champions more patient engagement, as patients are an underused source of information. And finally on page 22, Dr Justin Strickland discusses artisanal cannabinoids. With cannabis-based medicines gaining more and more traction and publicity, it's important to be aware that some patients may be using products like these, and what this means for us in the clinic.

Ultimately, knowledge is power, and we're working hard to extract and fully utilise all the untapped information from sources we already have.

I hope you enjoy this issue!

Kami Kountcheva
Editor
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 (External affairs department)

Advertising: Kami Kountcheva (kkountcheva@epilepsy.org.uk)

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**

Whole-plant medical cannabis "effective and well-tolerated"

Reports from 10 children with refractory epilepsy show effectiveness of whole-plant cannabis medicines. This is according to a new paper published in the *British Medical Journal (BMJ) Paediatrics Open*.

The *BMJ* study, by authors Rayyan Zafar and colleagues, presents the cases of 10 children with refractory epilepsy and the effect that taking a whole-plant cannabis medicine has had on them.

The children had all tried other anti-seizure medications (ASMs) before, and some had tried Epidyolex (cannabidiol).

In the study, the whole-plant cannabis medicines and doses were different for each child, depending on each case, and were prescribed by each child's epilepsy specialist.

The research concluded that seizure frequency in the children reduced by 86% with no significant side-effects. The researchers found that the number of other ASMs the children were taking could be reduced from an average of seven to one after being treated with their cannabis-based medicine.

The study also acknowledged the cost of sourcing these medicines outside of the NHS, saying that it was, on average, £874 a month.

The researchers acknowledged the limitations of their study, including a small number of participants and not being a rigorous clinical trial. However, with a lack of research in the area of whole-plant cannabis medicine in epilepsy, the National Institute or Health and Care Excellence (NICE) has recently increased the use of different types of data in the development and evaluation of their guidance, including real world data.

The study authors also said that despite the limitations, this study shows that whole-plant medical cannabis could be well tolerated and effective for reducing seizure frequency in children with refractory epilepsies. They added that this research shows the value in further studies looking at whole-plant cannabis-based medicines.

You can read the study at: *bit.ly/3Metal5*.

Wales management pathway launched

The 'All Wales Adult First Seizure and Epilepsy Management Pathway' was launched by MS Jack Sargent at the Senedd in Cardiff on 8 December 2021.

The clinical pathway was developed by the Epilepsy Task and Finish Group and the Neurological Conditions Implementation Group in September 2020 to help structure and navigate care for people with epilepsy.

The groups comprise clinicians and charity representatives, including from Epilepsy Action.

Among its objectives, the pathway aims to improve access to epilepsy services in Wales, reduce variation of services across the country, and increase public awareness of epilepsy. More information about the pathway is available at: *bit.ly/3sxrL7B*.

COVID-19 antivirals trial open to adults with epilepsy

A "world-first" study on antiviral treatments for COVID-19 is inviting people over the age of 50 and adults with an underlying health condition, who test positive for COVID-19, to sign up. This includes people with epilepsy.

The UK-wide study, run by the University of Oxford, is investigating "cutting-edge" antiviral treatment, known as molnupiravir. It is aiming to understand more about how to use this treatment in the NHS more widely, which is expected to happen later in the year, as well as who would benefit most.

Molnupiravir has shown to reduce the risk of hospitalisation or mortality in people with mild or moderate COVID-19 by 30%, which could save thousands of lives once it's available on the NHS.

Molnupiravir was approved for use by the Medicines and Healthcare Regulatory Authority (MHRA) in November 2021. So far, no unexpected safety findings have been reported in clinical trials, according to the government. The manufacturer of molnupiravir has said no drug interactions have been identified, but that data are limited and there have been no specific studies on clinical interactions.

The study is open to people experiencing COVID-19 symptoms who have had a positive PCR or lateral flow test, regardless of whether they've had COVID-19 vaccines or not. People can sign up for this study at: *www.panoramictrial.org*.

Trend towards use of safer epilepsy medicines in pregnancy, studies show

Over the last 20 years, there has been an increase in the use of anti-seizure medicines (ASMs) known to be safer in pregnancy among pregnant women. This is according to a new study from the Netherlands, published in the journal *Epilepsy & Behavior*.

Sodium valproate is one ASM known to have teratogenic effects. In January 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) also reviewed the safety data of 10 of the most commonly prescribed ASMs.

The review found that four other ASMs (carbamazepine, phenobarbital, phenytoin and topiramate) also could have a teratogenic effect. Lamotrigine and levetiracetam were found to be safer than other ASMs, but the MHRA could not make any conclusions about a further 11 ASMs due to lack of data.

In the Netherlands research, study authors Eline Houben and her colleagues used population-based data to assess trends in use of ASMs in pregnant women in the country between 1999 and 2019. They also cross-referenced the information with the safety profile of the ASMs.

During the study period, the researchers found 2,405 pregnancies exposed to an ASM. They found that there was a significant increase in the use of ASMs known to be safer in pregnancy. However, there was also increased use of newer ASMs with uncertain risk in pregnancy. They found the use of ASMs with higher risk in pregnancy had decreased, except for topiramate. They also found that switching to safer ASMs before or during pregnancy was uncommon.

The researchers explained that the overall trends were very similar to those observed in other countries. A UK report by Michael Kinney and colleagues, published in the *Journal of Neurology, Neurosurgery & Psychiatry* in 2018, also looked at shifting trends in ASM prescriptions in women with epilepsy. The data came from the UK and Ireland Epilepsy and Pregnancy Register between 1996 and 2016. Of 9,247 pregnancies, the team saw a significant increase in the use of lamotrigine and levetiracetam in the pregnant women, and a reduction in valproate and carbamazepine.

However, the UK researchers also found the rate of birth abnormalities did not significantly reduce in the 20-year time period. They said their research needs to be replicated on a larger scale in order to better understand these trends.

The Netherlands study authors also concluded by calling for more research on an international scale to increase understanding around the risks of ASMs in pregnancy and improve care for women.

The Netherlands study is available at: *bit.ly/35flPGx*.

Lower heart rate variability could be risk factor for SUDEP

Heart rate variability (HRV) could help assess risk of sudden unexpected death in epilepsy (SUDEP) in people with epilepsy, according to a new Portuguese study in *Epilepsy Research*.

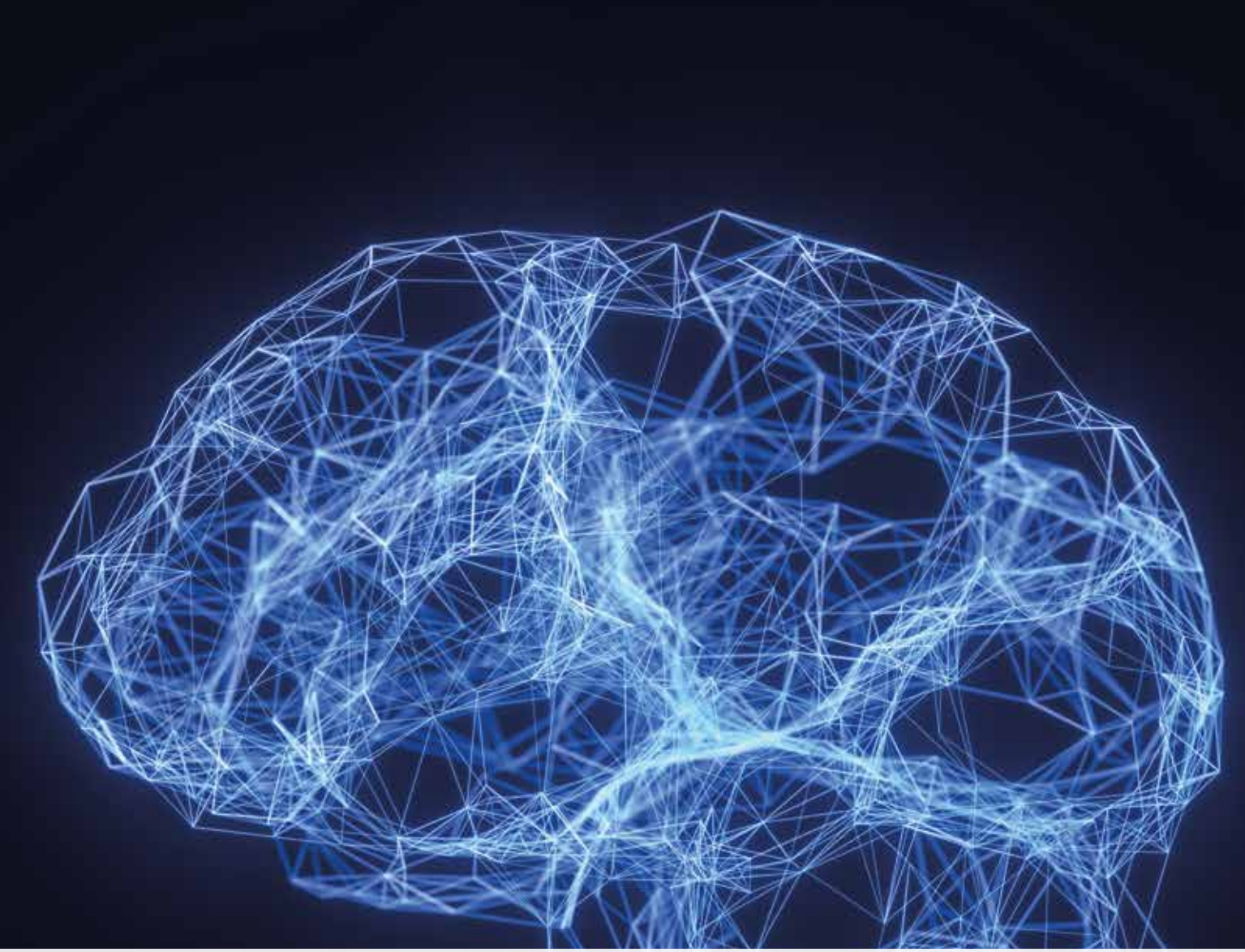
Researchers Maria Teresa Faria and colleagues explained that people with epilepsy, especially refractory epilepsy, have lower HRV. They said this reduced variability is a risk factor for sudden death in other diseases.

The researchers included 23 people, aged between 16 and 55 years, who have generalised tonic-clonic seizures in the research, as these types of seizure are known to be a risk factor for SUDEP. They measured HRV every five minutes, and looked at results during daytime, during night time and before and after a tonic-clonic seizure. The data were compared with values from people without epilepsy.

Of the participants, 30% had heart disease risk factors, such as smoking and high blood pressure, but none had had heart disease previously. The team found that HRV was significantly lower in the period after a seizure had occurred. They also found that HRV was generally lower in people with epilepsy than those without.

The team concluded that there may be a heart-related risk factor in people with refractory epilepsy, and this may play a part in some SUDEP cases. The full study is available online at: *bit.ly/3Kb29TQ*.

Pedro Viana



Forecasting seizures

Using subcutaneous EEG to develop personalised seizure prediction

Dr Pedro Viana provides an update on the Richardson Lab team's research on the use of subcutaneous EEG for collecting long-term and continuous EEG data discretely and in a real-life setting, and its potential applications

What is subcutaneous EEG?
Subcutaneous EEG, as its name implies, corresponds to recording brainwaves (electroencephalography, EEG) from electrodes placed under the skin. This technology belongs to a new generation of minimally-invasive brain monitoring systems, and there are several devices in the research pipeline. So far, one has been approved as a medical device for long-term continuous monitoring – the 24/7 EEG SubQ by UNEEG Medical. This is the system we are using in our research. Essentially, the system consists of an implantable part and an external (data logger) part. The implant - a 10cm wire with three electrodes, attached to a round ceramic housing that contains the electronics - is inserted under the skin with a brief procedure under local anaesthesia. The data logger is a credit-card-sized device that can easily be fixed to patients' clothing. Through a cable that attaches to the skin in the area overlying the implant, the logger wirelessly powers the implant, acquires and stores the EEG data. EEG data can be collected discretely, at home or in the community, and continuously over long periods of time.

What are the benefits of this device over standard EEG?
Standard scalp EEG electrodes are usually attached to the skin with collodium and must be held fixed for the signal to be stable. This requires regular attention by clinical physiologists. Moreover, visible electrode wires are obtrusive and not feasible for everyday life. This is why scalp EEG monitoring is limited to 20-30 minute-recordings, or to a few weeks at most, usually in the hospital setting.

With subcutaneous EEG, the signal is highly stable, enabling unobtrusive and very long-term recordings, all in a person's natural environment

EEG electrodes can also be placed inside the skull, directly on or inside the brain. These intracranial EEG systems allow very high-quality data to be recorded, and some have been designed for chronic use (NeuroVista, RNS Neuropace, Medtronic RC+S). However, they are considered too invasive and of potential risk for many patients.
With subcutaneous EEG, the signal is of similar quality to scalp EEG, but is highly stable enabling unobtrusive and very long-term recordings, all in a person's natural environment. The electrodes are placed quickly and outside the skull, with much lower risk for patients.

Can you tell us a bit about your study?
Our ongoing study is part of the My Seizure Gauge Initiative, an international consortium that includes centres in the US (Mayo Clinic), Germany (Freiburg University) and Australia (Seer Medical, University of Melbourne) and is funded by the Epilepsy Foundation of America.

In our study, we are monitoring a selected group of patients with drug-resistant epilepsy, with at-home subcutaneous EEG, an electronic seizure diary and a fitness tracker that records heart rate, sleep quality and general activity level.

The overall objective is to assess the feasibility of forecasting seizures with minimally-invasive (subcutaneous EEG) and non-invasive (diary and

wearable) data. We aim to use artificial intelligence methods to combine these data to better understand seizure risk factors and develop a personalised seizure predictor. At the same time, we are exploring the feasibility to objectively record and monitor epileptic seizures and how these can compare to subjective seizure diaries, which we know are often unreliable.

What findings can you share at this stage?
So far, we have found that the device is easy to use and is well tolerated for long-term recordings. We have so far monitored nine patients; most are now completing one year of monitoring and we have accumulated more than 25,000 hours of EEG in total.

We have looked at the signal quality and stability of this system, and have shown that it provides a very robust signal over several months. The recordings are very similar to scalp EEG, with typical findings such as recording of wakefulness and different sleep stages, epileptiform activity and seizures.

In a recent case report of a patient monitored for 7.5 months, we objectively recorded several seizures that weren't reported by the patient and were able to detect a cycling pattern of seizures at both circadian (24h) and multi-day (5 days) timescales.

How does subcutaneous EEG help to understand seizure cycles?
It has been known for a long time that despite their apparent unpredictability, seizures do not occur purely randomly but tend to cluster around certain periods of time. Only recently, however, thanks to better quantitative methods and the availability of long-term recordings, these high-risk periods are being better characterised. Recent studies analysing long-term seizure diaries, intracranial EEG and, more recently, subcutaneous EEG, have shown that these cycles occur in a high proportion of patients; they occur at different timescales and are quite unique to each patient.

Circadian cycles are usually the most obvious for patients to notice. For example, some patients only suffer from seizures at night, early morning and some only at particular times of day. Multi-day cycles are less obvious to detect, also due to the unreliability of seizure diaries, and this is what we showed in our study. That is, using subcutaneous EEG, we were able to detect a five-day seizure cycle, but this was not possible with diary data alone.

Seizure cycles are still a poorly understood phenomenon, but they are a potentially very powerful feature for seizure forecasting.

How does long-term monitoring compare with self-reported seizures?
Studies mostly done in the epilepsy monitoring unit have shown that patients are unaware and fail to report a large proportion of their seizures. In standard clinical practice, seizure diaries are the only available information on seizure occurrence. With subcutaneous EEG, we have been able to document patients' seizures more objectively, and we believe this may make a difference towards better-informed treatment decisions.

With subcutaneous EEG, we have been able to document patients' seizures more objectively and we believe this may make a difference towards better-informed treatment decisions

Importantly, this technology might be useful to classify some types of seizures. For example, a patient in our study reported a possible tonic-clonic seizure overnight; this was a particular worry due to the association with a higher risk of sudden unexpected death in epilepsy (SUDEP). However, upon reviewing the EEG data, the seizure we recorded was found not to be tonic-clonic. This was a good example of how objective seizure documentation may help patients to better understand their epilepsy and feel more in control of their condition. There are still limitations to address,

though. Some seizures do not show clear EEG changes at or near the scalp, including many focal aware seizures (auras) that patients often report, and the device might not capture seizures from brain areas distant from the electrodes. Hence, at the moment, patients need to be carefully selected and the location of the implant needs to be well planned, taking into consideration the results of previous investigations (neuroimaging, routine EEGs or video-EEG studies). In the future, with potentially larger electrode coverage and better knowledge about the electrographic seizure patterns detected by this device, a wider patient population could benefit from this type of monitoring.

With recordings of up to 7.5 months per patient, are we equipped to manage and utilise large datasets like this in epilepsy at the moment?

For big data, we need big data solutions. It is not feasible, at least in daily clinical practice, to manually review months of EEG data. Together with UNEEG Medical and within the consortium, we are working on solutions to automate the review process of these massive datasets. These include artificial-intelligence-based algorithms for automatic seizure detection, inspired by those developed for standard scalp EEG. This is a challenging process, given the current spatial limitation of the electrode, and the fact that we are looking at daily life EEG with frequent artefacts that do not occur as often when patients are collecting data in hospital. In our case study, for example, although we managed to reduce the amount of data to review to 15%, we had to review close to 5,000 events to only confirm 32 seizures. We are now working to improve the performance of these algorithms.

Is there scope to use this technology in children in the future?

Subcutaneous EEG is only being trialled in adults at the moment. However, there is no reasonable objection to start trialling in children, although one may need to take into account the rapid growth of the head and scalp in younger children.

What doors do your findings open in terms of using this subcutaneous EEG in clinical work and research?

This device has been medically approved for prolonged EEG monitoring in adults. So far, our research has shown that this system is very well suited for at-home, ultra long-term monitoring, with reliable and stable signal quality. This technology is able to detect and more accurately document epileptic seizures and their cycling pattern.

These are all essential requirements to address some of the most pressing issues facing patients with epilepsy today – the unpredictability of seizures and epilepsy's hidden burden. We hope that this kind of technology will ultimately help patients be better informed about their condition and feel more in control of their lives.

Where can people read more about your study?

People can find regular updates of our study and our Lab's activity on our website (***epilepsy-london.org***), Twitter (***twitter.com/epilepsy_london***) and ResearchGate (***bit.ly/3uzFgoW***).

Dr Pedro Viana
Neurologist
King's College London

Panning for gold

Electronic health records in the epilepsy clinic

Dr David Lewis-Smith and colleagues discuss the huge potential of electronic health records, a largely untapped data treasure trove, and describe their work in making the information standardised and machine interpretable

Introduction

The enthusiasm that people now have for exploiting electronic healthcare records (EHR) can be described as a gold rush. Undoubtedly, there are data of great value stored within clinical record systems, but how does one go about finding what is valuable, or panning for gold, if you like? And how does one maximise their chances of finding these flecks, identifying the rare nuggets, while simultaneously avoiding being taken in by EHR-pyrite (or fool's gold, to me and you)?

Primary care has over a decade of experience with EHR, but for many of us in secondary care, they have only become the norm more recently. The switch to EHR might have imposed a learning curve on healthcare professionals more accustomed to thumbing through volumes of papers and finessing shorthand clinic notes than they are to clicking through digital forms and commanding voice-recognition dictation software. Additionally, using the EHR can feel restrictive, sometimes pushing clinicians to pigeon-hole our patients' unique features into categories from drop-down menus and tick boxes. However, we are starting to see that the benefits of recording clinical information in EHR formats extend beyond simple data storage and sharing between healthcare providers.

As busy clinicians seeking to help the patients in front of us, we appraise their current health status in the context of several factors. These are their history, the applicability of the results of clinical research to their particulars and the context in which we manage their epilepsy. We also reflect upon our experiences with similar patients that we have encountered previously. However, how can we maximise the amount of relevant information available to improve care and minimise recall bias, in which our most recent or memorable clinical experiences overly shape our clinical practice? We all know colleagues who perform excessive investigations, such as repeat bloods or imaging, because they got 'burned' once. Using paper notes or an unstructured EHR, it could take months or years to collate all the relevant information available within our service or our healthcare system. This makes it very difficult to evaluate the real-world efficacy and tolerability of a particular antiseizure medication (ASM), or to determine whether we assess SUDEP risk as often as we

should. Or it might be a challenge to measure how much variation exists in our standard of care, or track how the seizure frequency and quality of life evolves in people with juvenile myoclonic epilepsy under our management. While the desired information is typically collected by clinicians during routine care and represented in the clinical notes, our challenge is to extract and interpret those data at scale in a timely manner. We are beginning to optimise and exploit EHR to analyse clinical data computationally at a scale and speed that would not be possible by manual review. Thereby, we are facilitating learning healthcare systems in which we continuously learn from routine clinical data. With these we can monitor how our practice compares to expected standards and detect new patterns that, with further analysis, can lead to clinically relevant discovery. We are learning to mine and to bring gold nuggets to market.

Machine-readable clinical data

Most fundamentally, recording clinical information in digital rather than paper form makes data immediately available for computational analysis, minimising the distance between the bedside and data store. Without this, paper documents must be scanned and processed with tools such as optical character recognition software to convert images of the original documents into digital text. Alternatively, the relevant information would have to be extracted and coded manually in an often slow and resource intense manner. These avoidable steps reduce data acquisition efficiency and may even lead to information loss or introduction of errors with downstream consequences.

Once that clinical information is stored digitally, the next stage is to convert this into a format that can be searched and analysed efficiently (e.g. "Which female patients between the ages of 12 and 60 years are prescribed sodium valproate?"). This would allow us to find hidden patterns in complex data that we might interpret as clinically significant (e.g. "At what ages is the risk of status epilepticus greatest in people with variants in the *SCN1A* gene, the causative gene for Dravet syndrome?"). This is where the great value of *digital* data lies. Once data are machine-readable, we can develop computational tools to automate simpler tasks that we wish to repeat many times in a consistent and timely fashion; this is what computers are good at.

Recording clinical information in digital rather than paper for makes data immediately available for computational analysis, minimising the distance between the bedside and data store

However, computers are not epileptologists and do not possess the knowledge to interpret clinical data as a clinician might. A clinician may document that "Mr Bloggs has had four secondarily generalised convulsions in the past month". Alternatively, they may note: "Recent seizure pattern: one FBTC (focal to bilateral tonic-clonic) per week", or even "Mrs Bloggs reports that her husband's fits have recurred on a weekly basis since we last met". A computer would struggle to interpret these entries as being synonymous. In its naïve state, a computer does not know specialist terminology or how to harmonise information from multiple formal classifications and additional specialist and lay vocabulary. Even among healthcare professionals, the precise meaning of common terms such as "generalised tonic-clonic seizure" may depend on the expertise and preferences of the source or the norms at the time of documentation. The harmonisation of data containing such nuances, ambiguities and arbitrary distinctions poses a major challenge to the meaningful automatic interpretation of EHR, even with advances in natural language processing of free text.

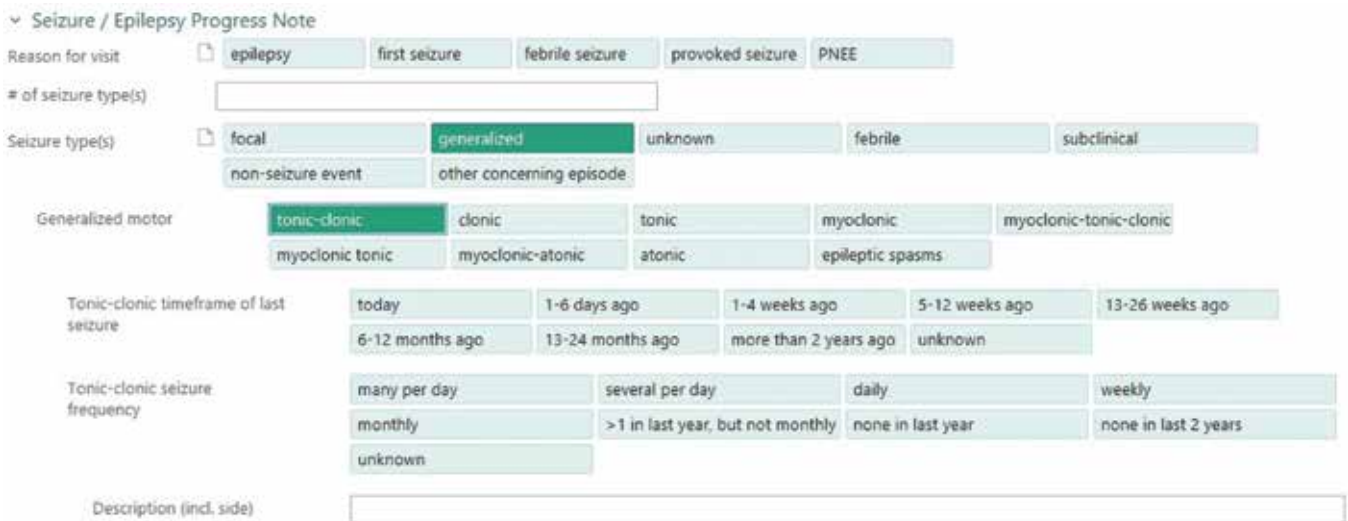
In the remainder of this article, we discuss how implementing and harnessing standardised EHR data can help us to improve the care of patients.

Standardising how we record information

Typically, a clinician can extract more information from their own records than their colleagues can infer from the same record. For example, they are likely to use jargon and expressions consistently. Also, they may know that if neither medication side-effects nor emergency hospital attendances are mentioned in their clinic letter then neither had occurred, because they always review these items and document their presence. Even the patient's name alone can carry a lot of contextual information if they know the patient well, such that extensive data may not need recording to jog their memory. In a busy healthcare system, it is common for follow-up consultations to generate short letters, so Dr Jones may write the following to the GP:

"Dear Dr Ahmad,
Andrew has had a few more seizures since we last met. I suggest that his dose of carbamazepine be titrated up to 600 mg twice daily over the next

Figure 1. The Epilepsy History Form. An example of how details of a patient's seizures can be entered into the EHR as structure data in a consistent format to aid manual and computational accessibility.



four weeks. We will review his progress in six months.
Yours sincerely,
Dr Jones"

This may be sufficient for Dr Jones to know what Andrew's seizure frequency and emergency care needs were come the next follow up, and for Dr Ahmad, the GP, to understand the plan. In fact, the short approach may avoid hiding the key information within an extensive array of details. However, this note may be of little help when Dr Jackson who covers her clinic six months later, after Dr Jones is knocked off her bicycle commuting to work that morning. Similarly, such documentation makes it difficult to include Andrew's information when auditing whether, for example, SUDEP risk is being reviewed sufficiently, or when tracking how often patients have needed emergency care. It may also not be usable in research, such as investigating which ASMs have been most effective for frontal lobe epilepsy in children without developmental delay. What type of epilepsy does Andrew have? Does he have developmental delay? Was he taking any other ASM? How many seizures occurred, and over what period, and of what type? Has he required emergency department care or rescue medications since his last appointment? Was SUDEP risk considered?

Common Data Elements – standardising data at source

The challenges above can be overcome if clinicians agree to what information should be documented in every clinic consultation. This information should be relevant, defined and limited, to minimise the burden on busy clinicians, and computational and data resources, and to adhere to data protection principles. For example, a department might decide on which data are required to meet minimal standards of care, facilitate efficient and optimal follow-up, enable meaningful clinical audit, drive quality improvement projects, ensure accurate clinical coding and facilitate research. At a simple level

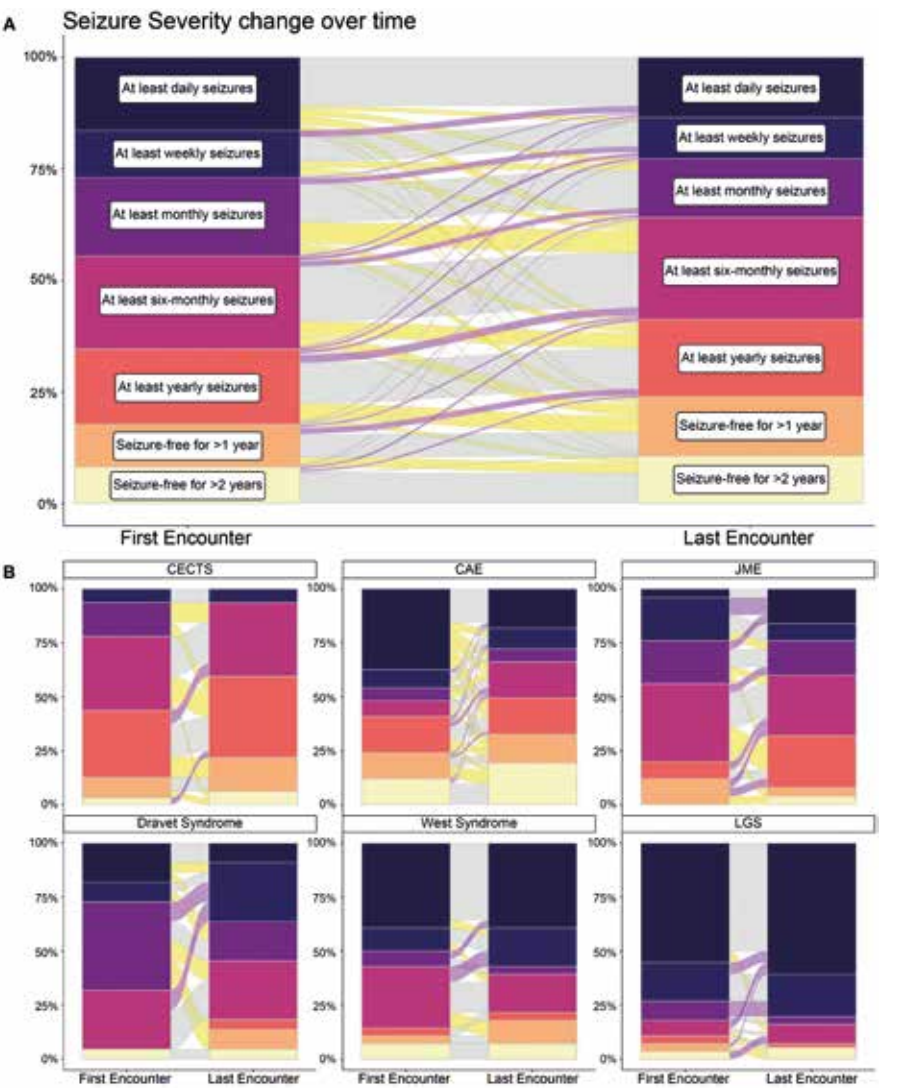
this might include tick boxes confirming a standard of care being met (for example, 'Epilepsy remains active', 'Free from treatment side-effects', 'SUDEP risk evaluated, discussed, and questions answered'). More complex approaches might gather more variables and more granular data.

At one of our epilepsy services, we developed an epilepsy history form (EHF) to aid efforts to ensure a high minimum standard of care and facilitate quality improvement projects and research [Fitzgerald *et al*, 2021]. The EHF was developed by multiple epilepsy specialists (physicians and nurse practitioners) with varied areas of interest. It uses standardised terminology based on respected clinical guidelines, and has been tried on paper, modified over a series of group sessions over a year, and eventually built into the EHR. It consists of 26 major Common Data Elements (CDE) that can be completed at each encounter by clicking on a range of responses. Each of these has additional fields for completion, contingent on the main item. The EHF facilitates a comprehensive epilepsy history that is recorded in a standard structure. This facilitates efficient interpretation by clinicians, for use during follow-up visits or when providing cross-coverage, and by computers. It has been integrated into our EHR software for both new patients and follow ups at outpatient sites, and it generates a clinical note that is efficient to read once clinicians become accustomed to its template (*Figure 1*).

Measuring seizure severity and its trajectory

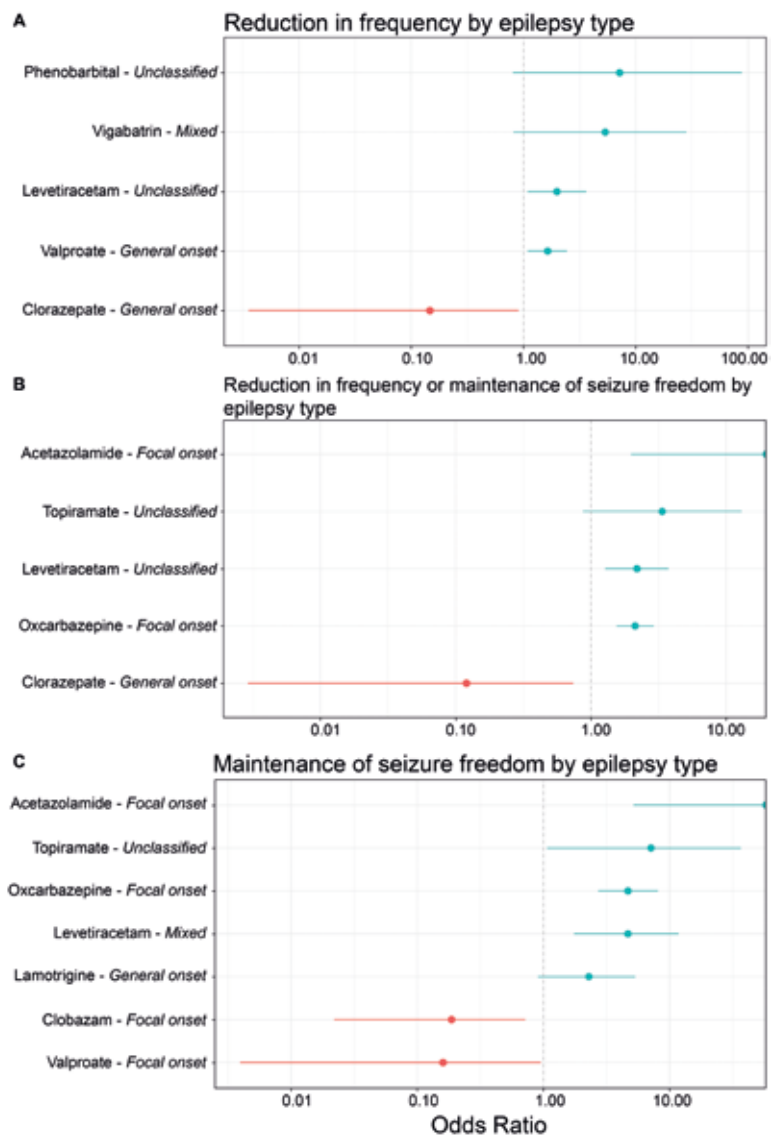
One example of how we have been able to exploit standardised data from the EHF has been for the quantitative analysis of clinical seizure burden at 1,696 clinical encounters — a challenge, given the broad range of seizure types and frequencies encountered in clinic.

Figure 2. Seizure severity changes from each patient's first encounter to their most recent encounter. Coloured paths between columns indicate the individuals who move from one seizure severity score to another, with grey indicating no change (A) 1,277 individuals with serial encounters, irrespective of syndrome (median age eight years, range one month – 33 years). (B) The subset of individuals with the six most common syndromes in our cohort (CECTS = childhood epilepsy with centrotemporal spikes, CAE = childhood absence epilepsy, JME = juvenile myoclonic epilepsy, LGS = Lennox-Gastaut syndrome).



We did this by summarising data as a seizure severity score (SS) [Fitzgerald *et al*, 2021]. Clinicians using the EHF can document the types of seizures that the patient is experiencing and their frequency over recent months. In this initial study, we analysed the overall seizure frequency over one year to assess healthcare utilisation and test the potential of this approach. We mapped the seizure frequencies recorded in the EHF to ordinal values 1-7, spanning 'seizure free > 2 years' (SS = 1) to '> 1 seizure per day' (SS = 7).

Figure 3. The odds ratios of anti-seizure medication (ASM) comparative effectiveness on three measures of treatment response over time by epilepsy type in a cohort of 237 children with epilepsy (median age = 9.5 years, range = 4 21 years). (A) Achieving a reduction in seizure frequency measured by seizure severity score. (B) Achieving a reduction in seizure frequency or maintenance of seizure freedom, and (C) maintenance of seizure freedom. Higher odds ratios (to the right on the x-axis) favour the medication in that epilepsy type.



We calculated seizure improvement scores (SI) as the difference between serial assessments for the same patient over time. For example, SI = +6 represented an improvement from '> 1 seizure per day' to 'seizure free > 2 years', and SI = -6 represented the reverse. This approach facilitated use of routinely collected real-world clinical data to compare the seizure frequencies of patients with different syndromes and to assess how individual patients' seizure frequency changed over repeated clinical encounters.

We found that the seizure frequency varied by epilepsy syndrome. Patients with Lennox-Gastaut syndrome had the highest seizure frequency (mean SS = 6.02), while patients with Childhood Epilepsy with Centrotemporal Spikes had the lowest seizure frequency (mean SS = 3.19). Children with Childhood Absence Epilepsy, Juvenile Absence Epilepsy or West syndrome had a broader range of seizure frequencies within the well-defined age ranges of these disorders. Additionally, serial entries allowed us to track individuals' longitudinal trajectories, and to compare their seizure frequency at the first entry to the last. Continued EHF use has yielded data from 1,277 patients (*Figure* 2). The general trend is for seizures to become less frequent, most notably for those with Childhood Epilepsy with Centrotemporal Spikes or Childhood Absence Epilepsy. Those people with developmental and epileptic encephalopathies characterised by high seizure frequency (West syndrome and Lennox-Gastaut syndrome) tend to continue having frequent seizures. A proportion of people with Juvenile Myoclonic Epilepsy and low seizure frequency at presentation appear to experience an increase in seizure frequency. This might be due to the emergence or greater recognition of myoclonic seizures after education at their first consultation.

These insights are generated easily if data are collected in a standardised format, greatly assisting with quality improvement and service evaluation. For example, in Fitzgerald *et al* [2021] we were able to assess the consequences of moving from a predominantly face-to-face consultation practice to telemedicine practice (when necessitated by the COVID-19 pandemic) on seizure frequency.

Furthermore, by combining these data with routine patient demographics, we were able to explore racial and socioeconomic health disparities. We found that Hispanic or Latino patients living at postal codes with lower median household incomes were less likely to use telemedicine and more likely to experience seizures. Moving forward, using patient-level serial EHR data, we can combine seizure frequency data with prescription records, providing a crude and pragmatic means to assess the comparative effectiveness of ASMs in various epilepsy types (*Figure 3*).

Given how readily CDE can enable clinical data analysis at an institutional scale, imagine the potential of bringing clinical epileptologists and people affected by epilepsy together. It creates the potential to develop a consensus set of important clinical data documented and monitored at a national level. The data could be combined efficiently for multicentre audit, quality improvement projects, and pragmatic research, as well as prompting clinicians to address important topics at each consultation. This is the aim of the Pediatric Epilepsy Learning Healthcare System (PELHS) developed through a mixed methods approach involving people and families affected by epilepsy, as well as clinicians across the USA and three major EHR vendors able to offer practical advice and implantation into their EHR platforms [Grinspan *et al*, 2021]. It is also the aim of the Epilepsy Learning Health System developed across multiple adult and paediatric centres across the USA [Donahue *et al*, 2021].

Representing the clinical diversity of epilepsy for computational analysis

The availability of clinical information for machine-interpretability depends on its standardised recording in the EHR by the clinician so that it requires minimal processing and harmonisation. The CDE approach is well suited to features that are sufficiently common to merit consideration at every consultation. However, the epilepsies are clinically diverse disorders, spanning not only different types of seizures but also various specific types of neurodevelopmental, affective, cognitive and other neurological disorders. In some cases, the epilepsy may only be part of a complex genetic syndrome with clinical manifestations that extend well beyond the nervous system. It would be impractical and arduous for clinicians to record the presence or absence of every possible clinical feature that could be encountered in the EHR at every consultation. So, how should we record rarer features?

International League Against Epilepsy (ILAE) task forces have provided definitions and classifications of epilepsies [Fisher *et al*, 2014; Scheffer *et al*, 2017], seizures [Fisher *et al*, 2017; Trinka *et al*, 2015; Pressler *et al*, 2021], pathology [Blümcke *et al*, 2011] and outcomes [Kwan *et al*, 2010] that can be used for precise and succinct documentation between professionals. In this way, the classifications represent controlled dictionaries: limited vocabularies reliably defining specific concepts into which nomenclature from alternative sources can be translated. For example, it can help communication with patients and carers to use and record the words that they use to describe their seizures. However, after confirming a diagnosis of epilepsy, the first step to reach a syndromic diagnosis that guides management is to interpret these descriptions in the

Figure 4. An ontology of seizure types can be used to represent the relationships between seizure types. Despite having no word in common in their raw seizure descriptions, mapping these to an ontology representing the concepts of the ILAE Classification of Seizures allows an algorithm to recognise that Andrew's and Barbara's seizures have more in common with each other (focal-onset seizures) than they do with Colin's. Each node (seizure type) in the graph has a human-readable label that can be amended with changes in nomenclature or translated into different languages, and a machine-readable identifier that consistently refers to the same concept across versions of the ontology (the prefix 'HP:' indicates that these terms are from the Human Phenotype Ontology – see text).

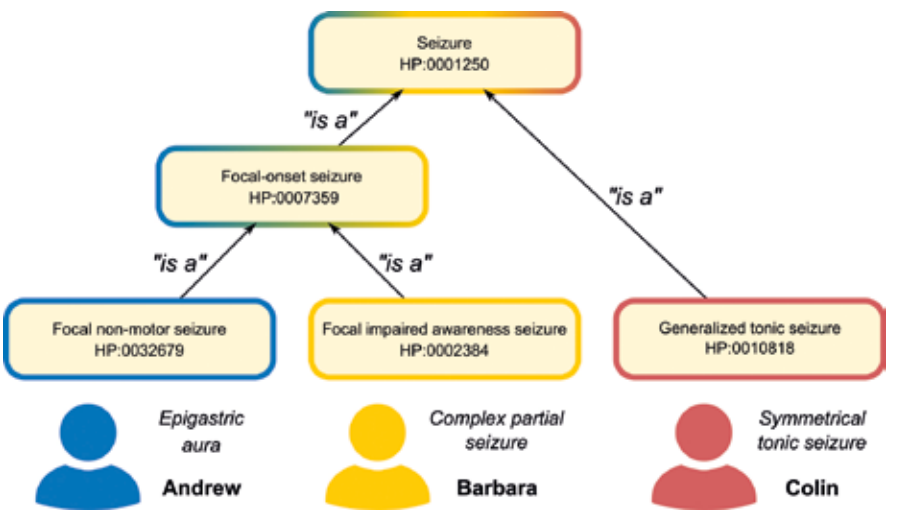
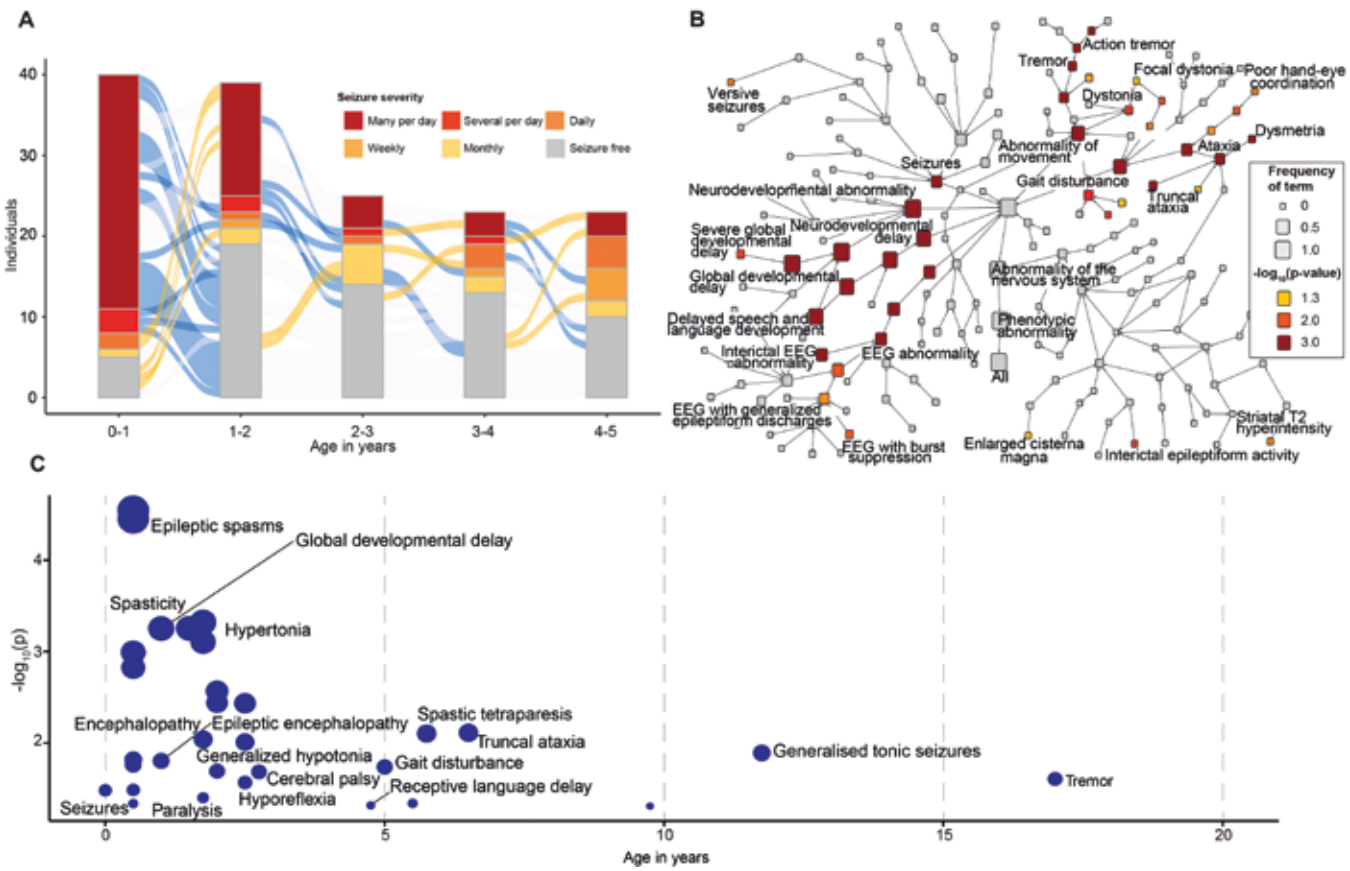


Figure 5. The clinical landscape of STXBP1 disorders. (A) Trajectory of seizure severity score of 40 children with STXBP1 disorders followed up at Children's Hospital of Philadelphia up to five years of age, with censoring of children who have not yet been followed up to the applicable age [Xian et al, 2021].26 (B) The clinical features that were annotated more commonly to 14 people with STXBP1 disorders than to the rest of a genetic epilepsy cohort of 846 people. Clinical features are shown as a simplified representation of the HPO with the relationship between clinical features (nodes) shown by lines (edges). (C) The clinical features enriched in the EHR of 22 people with STXBP1 disorders from a cohort of 658 at Children's Hospital of Philadelphia, according to age. Each feature is plotted at the age at which it is most confidently associated with STXBP1 with more confident association indicated by larger points lying further up the y-axis. The features shown in (B) and (C) all have association with odds ratio > 8 and p-values < 0.05, and these two panels were modified from Ganesan et al [2020] under CC-BY.



context of the past medical and developmental history, our examination findings, and investigation results. We classify their seizures, giving them a label that links the patient's experience to guidelines and bodies of evidence. By reducing redundant variability, recording or translation of clinical data into the lexicon of a controlled dictionary is a large step towards making it EHR machine-readable.

While controlled dictionaries are lists of standardised terminology with definitions and synonyms, ontologies are more comprehensive maps of knowledge. They are formal representations of the relationships concepts defined in the controlled dictionary [Haendel *et al*, 2018]. Ontologies can be used for automated reasoning in their domain, allowing algorithms to upscale interpretation of large complex bodies of data. For example, a clinical epileptologist possesses the expert knowledge to know that a 'focal impaired awareness seizure' and 'focal non-motor seizure' are forms of a 'focal-onset seizure' but not forms of a 'generalised-onset seizure'. They also understand that synonyms for the first term include 'complex partial seizure'. For a computer algorithm to replicate this reasoning, it needs a model representing this domain knowledge.

An ontology can represent these clinical concepts and their subclass relationships. With this model, a computer can recognise that one EHR documenting a 'complex partial seizure' and another documenting a 'focal impaired awareness seizure' are referring to the same clinical concept. It can also infer that an individual whose EHR includes either of these terms is likely to have seizures that are more similar to those of someone else whose EHR documents 'focal non-motor seizure' than they are to those of a third person with a 'generalised tonic seizure' (*Figure 4*). Consequently, a well-designed ontology can scale up the automated interpretation of clinical data, making this much faster than is possible manually. A challenge for ontology design in epilepsy is that consensus is incomplete, with professionals using different classifications or terminology according to their experience and expertise. It is common for non-specialists to continue using terms such as 'petit mal' (sometimes indiscriminately for any seizure except a generalised convulsion) or 'complex partial seizure'. Similarly, many experts (particularly in epilepsy surgery programmes) favour a non-ILAE, descriptive classification of the semiological components of a seizure [Lüders *et al*, 2019].

The Human Phenotype Ontology (HPO) is a model of over 16,000 concepts that can be used to describe the clinical features encountered in disease [Kohler *et al*, 2021]. It has become the lingua franca of clinical data in genetics and is used by diagnostic services such as the NHS England Genomic Medicine Service [NHS Health Education England, 2020]. It is also used in large research projects such as the Genomics England 100,000 Genome Project [Turro *et al*, 2020], and Deciphering Developmental Disorders [Akawi *et al*, 2015]. Over the past decade, as part of the Epilepsiome Task Force of the ILAE [2022], we have contributed to the representation of epileptological phenotypes in the HPO to optimise it for handling data from people with epilepsy [Kohler *et al*, 2021; Kohler *et al*, 2014]. In particular, we have helped revise the entire representation of seizure types to represent and harmonise concepts from multiple modern ILAE and the semiological seizure classifications [Lewis-Smith *et al*, 2021].

While controlled dictionaries are lists of standardised terminology with definitions and synonyms, ontologies are more comprehensive maps of knowledge and formal representations of the relationships concepts defined in the controlled dictionary

When entering clinical descriptors of a patient undergoing diagnostic genetic testing or when harmonising the clinical data of a research cohort, these data are typically translated into HPO format through manual review of clinical records. In research, tools used for data capture entry, such as REDCap [Harris *et al*, 2019], can be set up for efficient manual data entry into fields that map directly to concepts in the HPO. However, advances in natural language processing techniques tailored to medical vocabulary are improving automated annotation of raw medical text and may eventually reduce the burden of data capture.

Using the ontologies in epilepsy

The HPO was developed to facilitate the analysis of clinical features of people with rare genetic disorders. Over recent years, we have mapped clinical data to the HPO to find the clinical features that identify and predict a particular genetic epilepsy. We have confirmed the clinical impression that people with the same genetic form of developmental and epileptic encephalopathy are more similar clinically than expected by chance [Galer *et al*, 2020]. Using the same techniques, we discovered that de novo variants in *AP2M1* can cause an epilepsy with myoclonic-atonic seizures [Helbig *et al*, 2019]. More recently, we have developed these approaches to handle longitudinal data extracted from EHR, allowing us to compare the clinical trajectories of people with various genetic epilepsies in our specialist service [Ganesan *et al*, 2020; Lewis-Smith *et al*, 2021].

Harmonisation of clinical data is particularly important when these are collated from multiple centres or published case series. We have used the HPO to harmonise and document the published clinical landscape of two genes. *SCN2A* is a gene in which variants can cause self-limiting familial infantile seizures, developmental epileptic encephalopathy, and neurodevelopmental disorders including autism and intellectual disability. Analysis of HPO data from 413 individuals according to their *SCN2A* variant confirmed that general missense variants are more likely to cause seizures than protein truncating variants, which are more likely to cause autism spectrum disorders [Crawford *et al*, 2021]. However, if a person's missense variant is located near the pore of this ion channel, then they are more likely to have clinical features akin to people with protein truncating variants.

Another gene we have collated published clinical data for is *STXBP1*,

classically associated with Ohtahara syndrome and other developmental and epileptic encephalopathies, movement disorders, and neurodevelopmental disorders without seizures. Using 19,973 HPO annotations from 534 individuals, we found that 89% had seizures, with nearly all of these experiencing their first seizure in infancy and nearly half in the neonatal period [Xian *et al*, 2021]. Protein truncating variants were particularly likely to present as West syndrome with infantile spasms. Focussing on the longitudinal seizure profile of those with CDE showed that the frequency of seizures in each individual varies greatly throughout early childhood (*Figure 5*). The relationship between various

treatments and seizure responsiveness suggested particular benefit from adrenocorticotropic hormone and phenobarbital for infantile spasms and focal seizures. We also saw that patients on the ketogenic diet were more likely to remain in remission. While such observational evidence must be interpreted with caution, it is valuable to individual clinicians with limited experience of individually rare disorders to understand the disease presentation of complex conditions over time.

Ambitious projects are underway to improve the representation of clinical epilepsy concepts for harmonisation and computational analysis of routine clinical data. SNOMED-CT is becoming the international standard framework for routine clinical coding, and a task force of the ILAE Big Data Commission [2022] is aiming to bring its representation of seizures and epilepsies in line with modern concepts.

Conclusions

The greatest returns from using standardised data formats come with increasing scale — we benefit more as datasets get larger and a greater proportion of clinicians engage with these tools. To fall back on the gold rush metaphor from the start, this would be the industrialisation and mechanisation of mining. A significant hurdle to implementation of healthcare innovations, even in 2022, is generating sufficient confidence among clinicians that new approaches are sufficiently valuable to justify the burden of modifying their existing practice in an already busy clinical setting. Additionally, we need financial business models that recognise the value of investment in tools and clinician time to generate data in a tractable format that can be combined across entire healthcare systems to improve the care of people with epilepsy. As EHRs become ubiquitous, we hope that the studies we have highlighted above indicate the potential of ensuring that clinicians engage with EHR development to focus it on what matters and minimise unnecessary burden. Over the coming years, the availability of routine clinical

Further reading

Akawi N, McRae J, Ansari M, *et al*. Discovery of four recessive developmental disorders using probabilistic genotype and phenotype matching among 4,125 families. *Nat Genet*. 2015;47(11):1363–1369.

Blümcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia*. 2011;52(1):158-174.

Crawford K, Xian J, Helbig KL, *et al*. Computational analysis of 10,860 phenotypic annotations in individuals with SCN2A-related disorders. *Genet Med*. 2021;23:1263–1272.

Donahue MA, Herman ST, Dass D, *et al*. Establishing a learning healthcare system to improve health outcomes for people with epilepsy. *Epilepsy Behav*. 2021;117:107805.

Fisher RS, Acevedo C, Arzimanoglou A, *et al*. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.

Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530.

Fitzgerald MP, Kaufman MC, Massey SL, *et al*. Assessing seizure burden in pediatric epilepsy using an electronic medical record-based tool through a common data element approach. *Epilepsia*. 2021;62(7):1617-1628.

Galer PD, Ganesan S, Lewis-Smith D, *et al*. Semantic similarity analysis reveals robust gene-disease relationships in developmental and epileptic encephalopathies. *Am J Hum Genet*. 2020;107(4):683–697.

Ganesan S, Galer PD, Helbig KL, *et al*. A longitudinal footprint of genetic epilepsies using automated electronic medical record interpretation. *Genet Med*. 2020;22:2060–2070.

Grinspan ZM, Patel AD, Shellhaas RA, *et al*. Design and implementation of electronic health record common data elements for pediatric epilepsy: Foundations for a learning health care system. *Epilepsia*. 2021;62(1):198-216.

Haendel MA, Chute CG, Robinson PN. Classification, Ontology, and Precision Medicine. *N Engl J Med*. 2018;379(15):1452–1462

Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95:103208.

Helbig I, Lopez-Hernandez T, Shor O, *et al*. A recurrent missense variant in AP2M1 impairs clathrin-mediated endocytosis and causes

data in standardised digital form, collected as close to the clinical consultation as possible, will enable computational analysis. This can contribute to clinical research, and also help us to learn how to improve care more effectively by broadening our horizons from the individual clinician experience to that of entire learning healthcare systems.

This research was funded in whole, or in part, by the Wellcome Trust [203914/Z/16/Z] supporting D.L.S. I.H. was supported by The Hartwell Foundation (Individual Biomedical Research Award), the National Institute for Neurological Disorders and Stroke (K02 NS112600), and by Children's Hospital of Philadelphia through the Epilepsy NeuroGenetics Initiative (ENGIN). N.S.A is supported by the Wolfson Foundation. I.H. serves on the Scientific Advisory Board of Biogen. The other authors declare no conflict of interest. R.H.T. has received honoraria and meeting support from Arvelle, Bial, Eisai, GW Pharma, LivaNova, Novartis, Sanofi, UCB Pharma, UNEEG and Zogenix. N.S.A is a consultant for the Epilepsy Foundation, received royalties from Demos, and has received research funding from NIH, AHRQ, UCB Pharma, and PCORI. The other authors report no competing interests.

Dr David Lewis-Smith
Neurologist
Newcastle University
Royal Victoria Infirmary, Newcastle
Children's Hospital of Philadelphia

Michael Kaufman
Data scientist
Children's Hospital of Philadelphia

Julie Xian
Student in Neuroscience
Children's Hospital of Philadelphia

Shiva Ganesan
Bioinformatician
Children's Hospital of Philadelphia

Dr Mark Fitzgerald
Paediatric neurologist
Children's Hospital of Philadelphia
University of Pennsylvania

Dr Nicholas Abend
Paediatric neurologist
Children's Hospital of Philadelphia
University of Pennsylvania

Dr Rhys Thomas
Consultant neurologist
Newcastle University
Royal Victoria Infirmary, Newcastle

Dr Ingo Helbig
Paediatric neurologist
Children's Hospital of Philadelphia
University of Pennsylvania
Contact author
helbigi@email.chop.edu
+1 215-590-1719

developmental and epileptic encephalopathy. *Am J Hum Genet*. 2019;104(6):1060–1072.
International League Against Epilepsy. Epilepsiome Task Force. [online] Available at: *https://www.ilae.org/about-ilae/committees-task-forces-and-advisory-commissions/epilepsiome/amp;/amp%3B*. Published 2022. Accessed Feb 2022.
International League Against Epilepsy. SNOMED Task Force. [online] Available at: *https://www.ilae.org/about-ilae/committees-task-forces-and-advisory-commissions/snomed*. Published 2022. Accessed 2022-01-20.
Kohler S, Doelken SC, Mungall CJ, *et al*. The Human Phenotype Ontology project: linking molecular biology and disease through phenotype data. *Nucleic Acids Res*. 2014;42(Database issue):D966–974.
Kohler S, Gargano M, Matentzoglu N, *et al*. The Human Phenotype Ontology in 2021. *Nucleic Acids Res*. 2021;49(D1):D1207–D1217.
Kwan P, Arzimanoglou A, Berg AT, *et al*. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069-1077.
Lewis-Smith D, Galer PD, Balagura G, *et al*. Modeling seizures in the Human Phenotype Ontology according to contemporary ILAE concepts makes big phenotypic data tractable. *Epilepsia*. 2021;62(6):1293–1305.
Lewis-Smith D, Ganesan S, Galer PD, *et al*. Phenotypic homogeneity in childhood epilepsies evolves in gene-specific patterns across 3251 patient-years of clinical data. *Eur J Hum Genet*. 2021;29:1690–1700
Lüders H, Vaca GFB, Akamatsu N, *et al*. Classification of paroxysmal events and the four-dimensional epilepsy classification system. *Epileptic Disord*. 2019;21(1):1–29.
NHS Health Education England. Requesting whole genome sequencing: information for clinicians. [online] Available at: *https://www.genomicseducation.hee.nhs.uk/supporting-the-nhs-genomic-medicine-service/requesting-whole-genome-sequencing-information-for-clinicians/*. Published 2020. Accessed Dec 2020.
Pressler RM, Cilio MR, Mizrahi EM, *et al*. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia*. 2021.
Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.
Turro E, Astle WJ, Megy K, *et al*. Whole-genome sequencing of patients with rare diseases in a national health system. *Nature*. 2020;583(7814):96–102.
Xian J, Parthasarathy S, McKeown S, *et al*. Assessing the landscape of STXBP1-related disorders in 534 individuals. *Brain*. 2021.

Justin Strickland

Artisanal cannabinoids

The promises and frustrations of novel cannabinoids in epilepsy care

Dr Justin Strickland describes the emergence of artisanal CBD and other cannabinoid products in epilepsy care and how to advance the science behind their use.

Accounts of the therapeutic utility of the cannabis plant date back centuries. However, the past decade has seen a resurgent interest in the use of cannabinoid compounds in the treatment of epilepsy, as well as in co-occurring psychological and physical health domains. This renewed attention is owing to factors including shifting regulatory landscapes surrounding cannabis legality and decreasing stigma associated with cannabis use. For many of the approximately one-third of patients that experience epilepsy symptoms refractory to treatment, cannabinoid products can be a promising outlet for symptom relief and reduction. However, not all cannabinoids are created equal, resulting in equal parts confusion and frustration alongside this promise for those patients and clinicians navigating this new frontier of care.

The cannabis plant contains dozens of cannabinoid constituents. Two of the most prominent and abundant of these constituents are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a partial agonist at the cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors. It is the substance that induces most of the hallmark and overt acute effects attributed to cannabis use (such as, subjective high,

increased appetite, mood alteration and memory impairment). CBD has a complex pharmacology and the direct mechanisms for its anti-convulsant effects are still being characterised. Currently, these mechanisms appear to be independent of CB1 receptor activity. They may relate to effects on intracellular calcium signalling via the orphan G protein-coupled receptor-55 (GPR55), transient receptor potential vanilloid-1 (TRPV1), or through modulation of adenosine-mediated signalling.

Not all cannabibnoids are created equal, resulting in equal parts confusion and frustration alongside this promise for those patients and clinicians navigating this new frontier of care

Highly purified, pharmaceutical CBD products have received the most attention when it comes to the treatment of epilepsy within both the scientific literature and popular press. This interest partly stems from the successful demonstrations of the safety and efficacy of these products in highly controlled, randomised clinical trials. For instance, one landmark trial found that purified CBD as an add-on treatment for patients with Lennox-Gastaut syndrome resulted in a reduction in monthly drop seizure frequency of 43.9% compared to a reduction of 21.8% in the placebo control group [Thiele *et al*, 2018]. Data from various trials motivated the recent approvals in the European Union, Australia, and the United States of CBD in this highly purified, pharmaceutical form to treat specific epilepsy subtypes (such as, Lennox-Gastaut syndrome, Dravet syndrome).

At the same time, recent legislation has led to a growing market of alternative cannabis products that are available directly to consumers through commercial pathways outside of traditional and highly regulated medical ones. For example, the 2018 United States Farm Bill allowed for the commercial sale of hemp and hemp-derived products by removing these products from the definition of "marijuana" as a controlled substance. Hemp is legally defined as any cannabis product containing less than 0.3% THC on a dry weight basis. Similar laws and guidance passed in the UK allow for commercial sale of CBD as a nutritional or food supplement. However, more recent legislation has added the requirement that producers obtain a novel food authorisation prior to sale.

These laws have opened a floodgate of new products on the commercial marketplace that are broadly categorised and considered artisanal products. Artisanal CBD products in the US and elsewhere are commonly sold as dietary supplements by commercial vendors under these hemp or hemp-derived sale exemptions. Although published prevalence estimates are limited, a 2017 study in Australia found that 14% of people with epilepsy had a history of trying medicinal cannabis and these artisanal products to treat their seizures [Suraev *et al*, 2017]. However, it should be noted that at the time of that report, only artisanal cannabis products were available in Australia.

Artisanal CBD products are often less refined than pharmaceutical products and thus contain other terpenoids and phytocannabinoids found in the cannabis plant. This complex pharmacology, rather than being considered an 'impurity' of production, is marketed as a strength with advertisements selling these product's as 'full-spectrum' or 'broad-spectrum'. Such marketing claims emphasise how the very low amounts of THC, minor cannabinoids, and terpenoids present in the CBD extract exploit a supposed 'entourage effect'. This is the suggestion that cannabis chemical constituents act synergistically to modulate and enhance the desired effects of the cannabis plant [Ferber *et al*, 2020]. Motives for the use of artisanal products parallel these claims with anecdotal, consumer testimonials highlighting perceptions of greater effectiveness or tolerability compared to alternative anticonvulsants [Thomas & Cunningham, 2018]. Greater accessibility is also noted, compared to pharmaceutical counterparts. This is because pharmaceutical CBD products are restricted prescription medications in most jurisdictions with insurance coverage mostly limited to those patients with the specific approved indications [Porcari *et al*, 2018].

Greater accessibility to artisanal products is also noted as a motivation for their use, compared to pharmaceutical counterparts

It is important to note that while the entourage effect is a popular hypothesis presented in the cannabis literature, it is one that is yet to be rigorously tested in human laboratory or clinical trials (although such studies are ongoing; NCT04130633). This gap emphasises a broader problem regarding artisanal CBD products.

Despite their widespread availability and variety, controlled studies evaluating safety and efficacy are rare. This makes conclusions about utility difficult to determine for both patients navigating product selection and healthcare providers wanting to offer clinical guidance.

Those data that exist do offer some promising findings for the clinical benefit of artisanal products, particularly in those domains for which pharmaceutical products have been successful. One recent observational study evaluated cross-sectional and longitudinal comparisons of patients with epilepsy. One group had initiated artisanal CBD use (active group) and the other was contemplating their use, but had not yet initiated (control group) [Strickland *et al*, 2021]. Patients using artisanal CBD products had higher quality of life and lower psychological distress. For instance, 67% of control patients reported clinically relevant anxiety symptoms compared to 50% of patients using artisanal CBD products. Nearly half of these patients (45%) reported using an artisanal CBD product as an adjunctive medication while another quarter reported using these products as a last resort (after all other options failed; 29%). Notably, tolerability of typical anticonvulsant side-effects was higher among those patients using artisanal CBD products, with 36% reporting clinically relevant side-effects compared to 54% in the control group. A notable feature of this study was the prospective follow-up of participants in a longitudinal phase of the research. Those in the control group who initiated artisanal CBD use showed increases in quality of life, and physical and psychological health, while those who did not initiate failed to see this similar improvement.

Research nonetheless remains scarce regarding artisanal products and key clinical and policy directives are needed to inform the patient navigation process and clinical care. First, accurate labelling and product supply is a critical concern when it comes to artisanal formulations. One study in 2017 found that of a sampled 84 CBD products purchased online, only 31% were accurately labelled with respect to CBD concentration [Bonn-Miller *et al*, 2017]. The remaining products were either under-labelled (43%), containing more CBD than advertised, or over-labelled (26%), containing less CBD than advertised. Unlabelled THC was also detected in 21% of samples. Other reports have described how cannabis-derived products, when poorly regulated, can also contain harmful contaminants such as microbes, pesticides, heavy metals and other toxins [Montoya *et al*, 2020].

To date, no randomised clinical trial has directly compared artisanal and pharmaceutical products to determine superiority, equivalence or inferiority

These data on poor labelling and quality control emphasise the need for a better regulated marketplace surrounding CBD (and other cannabinoid products) as opposed to an intrinsic harm inherent to these products. The artisanal market disproportionally suffers from these concerns, given that manufacturing and testing standards are inconsistent or absent, compared to the tight controls over pharmaceutical products. An

unintended consequence is that irregularities or inconsistencies across product batches due to horticultural or manufacturing factors can occur even when the same product is obtained from the same producer. Steps at a policy level are needed to ensure consistent product standards, such as those made by the UK in its recent focus on requiring and enforcing novel food authorisation for CBD products. At a clinical level, healthcare providers should be prepared to inform patients about the potential dangers of mislabelled products and encourage careful research of the supplier's quality control and product testing.

Clinical research is also needed to inform unanswered questions about the unique benefits and harms of artisanal products. To date, no randomised clinical trial has directly compared artisanal and pharmaceutical products to determine superiority, equivalence or inferiority. Most studies have also relied on observational, retrospective recall or chart records of seizure outcomes, limiting the body of evidence on how artisanal products directly impact seizure control and related outcomes. Rigorous, controlled research informed by the positive observational data is needed to inform these clinical outcomes.

Finally, stigma remains an important barrier when it comes to artisanal product use, just as it does for medical cannabis more generally. Despite changing cultural norms surrounding both the recreational and medical use of cannabis, many patients remain reluctant, and some report experienced or perceived stigma as a direct barrier [Martin *et al*, 2021]. Perceptions of stigma from medical providers can also serve to reduce patient-provider communication about ongoing cannabis use. These barriers to communication can subsequently increase potential risks to patients who are interested in or intending on initiating artisanal product use. For instance, non-disclosure of ongoing CBD use may increase harm due to potential drug-drug interactions. Similarly, patients worried about sharing their intentions to initiate product use may undertake a self-guided rather than patient-provider monitored taper of traditional anticonvulsant use. Ultimately, clinicians are encouraged to engage in open, honest dialogue within clinical care to ensure benefits are maximised and harms are reduced as patients navigate the ever-growing world of novel cannabinoid products.

Dr Justin Strickland
Assistant professor
Behavioural pharmacologist
Johns Hopkins University School of Medicine

Further reading

Bonn-Miller MO, Loflin MJ, Thomas BF, Marcu JP, Hyke T and Vandrey R. 2017. Labeling accuracy of cannabidiol extracts sold online. *JAMA*, 318(17), pp.1708-1709.
Ferber SG, Namdar D, Hen-Shoval D, Eger G, Koltai H, Shoval G, Shbiro L and Weller A. 2020. The "entourage effect": terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. *Current neuropharmacology*, 18(2), pp.87-96.
Martin EL, Strickland JC, Schlienz NJ, Munson J, Jackson H, Bonn-Miller MO and Vandrey R. 2021. Antidepressant and Anxiolytic Effects of Medicinal Cannabis Use in an Observational Trial. *Frontiers in Psychiatry*, p.1554.
Montoya Z, Conroy M, Vanden Heuvel BD, Pauli CS and Park SH. 2020. Cannabis contaminants limit pharmacological use of cannabidiol. *Frontiers in Pharmacology*, 11, p.1439.
Porcari, GS, Fu C, Doll ED, Carter EG and Carson RP. 2018. Efficacy of artisanal preparations of cannabidiol for the treatment of epilepsy: Practical experiences in a tertiary medical center. *Epilepsy & Behavior*, 80, pp.240-246.
Strickland JC, Jackson H, Schlienz NJ, Salpekar JA, Martin EL, Munson J, Bonn-Miller MO and Vandrey R. 2021. Cross-sectional and longitudinal evaluation of cannabidiol (CBD) product use and health among people with epilepsy. *Epilepsy & Behavior*, 122, p.108205.
Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K and Gunning B. 2018. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*, 391(10125), pp.1085-1096.
Thomas RH and Cunningham MO. 2018. Cannabis and epilepsy. *Practical Neurology*, 18(6), pp.465-471.

Markus Reuber

Highlights

Top picks from *Seizure*

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

It should be clear to all involved in the care and treatment of epilepsy that this disease is much more than the total sum of seizures. There is a complex interaction between aetiological and risk factors, seizures with their physiological, psychological and social manifestations and consequences, and comorbidities, as well as beneficial and iatrogenic treatment effects. How this interaction plays out depends on who is affected (including how vulnerable individuals are from a psychosocial and financial point of view) and from what age. This interaction is even more complicated in children, where epilepsy may affect education, and psychological and social maturation, and thereby have consequences which can outlast the seizure disorder itself for several decades [Chin *et al*, 2011; Geerts *et al*, 2011].

Given the importance of education for longer term social, psychological and medical outcomes, it is of great importance how well children and adolescents with epilepsy get on at school. My editor's choice from issue 93 of *Seizure*, an original research paper by Colin Reilly *et al* [2021], makes an important contribution to this topic. It uses a combination of quantitative as well as qualitative analyses of a survey of children with epilepsy and their parents and teachers, and raises some important issues. The biggest concern is that 63% of the children reported that they have been bullied – although many did not think that reasons for the bullying were directly related to their epilepsy. A similar number reported that they were restricted in their activities because of their epileptic seizures. As worrying as these facts are, the findings that teachers did not seem to perceive the reported bullying or restrictions as often as the children or their parents did were at least as troubling, if not more so.

Some restrictions of the education and social life of children may well be unavoidable because of seizures, their consequences or because of other manifestations of the underlying condition or associated disorders. However, the fact that teachers may often fail to notice that restrictions exist and that children with epilepsy in their care are often the victim of bullying is a call for urgent educational measures. That is, educational measures for teaching staff, who need to learn to be more sensitive to the needs of children with epilepsy.

Predicting risk with statistical model

The recent ILAE decision that clinicians should diagnose epilepsy after a single seizure in the presence of a 60% risk of seizure recurrence has not really helped with decisions about starting anti-seizure treatment. It has only brought the need to make a decision into starker relief. It has also introduced a numeric threshold (without taking account of the size of the risk per year) although the precise lifetime seizure recurrence risk is impossible to calculate accurately for an individual patient.

One important step to reducing the gap between diverse bits of evidence and individual treatment decisions involves statistical modelling. This approach can deliver numeric risk values and take account of a range of potentially relevant clinical characteristics of the patient in the room. My editor's choice from issue 94 of *Seizure* is an article by Laura Jayne Bonnett which validates one such model [Bonnett *et al*, 2022]. This paper follows the 'gold standard' modelling approach of externally validating a model developed on the basis of data from one dataset (the large MESS study) [Marson *et al*, 2005] by testing the model on other, independently collected datasets (in this case from the equally impressive NGPSE, Western Australia and FIRST studies) [Hart *et al*, 1990; Lawn *et al*, 2015; Musicco *et al*, 1993]. My editor's choice paper demonstrates that, in patients with a single or small number of seizures first seeking neurological advice, the model is capable of correctly predicting the likelihood of seizure occurrence by one or three years. The estimated mean risks of seizure recurrence were 35.1% and 46.2% at these time points. However, the model will demonstrate its real clinical utility when the patient's particular personal risk factor profile is used to generate an individualised risk estimation.

Admittedly, there is more work to do (for instance in terms of finding out

what sense patients make of a given percentage of seizure recurrence risk). However, providing patients with their individual risk of having another seizure within one or three years should certainly help to close the gap between knowledge from research studies and personal decisions about starting ASMs.

Seizure phobia

Health-related quality of life (HRQoL) is often regarded as a 'soft' outcome. However, HRQoL measures how independently and well people are able to lead their lives, and, in the context of epilepsy, many studies have shown that 'comorbid' symptoms, such as those of anxiety and depression, are much more closely related to patients' quality of life than more directly seizure-related variables such as seizure frequency or severity [Rawlings *et al*, 2017].

My editor's choice from issue 95 of *Seizure* explores one particular comorbidity exclusively found in people with seizure disorders. This original research by Aviva Weiss *et al*. [2022] focuses on seizure phobia. One of the earliest descriptions of this condition may have been delivered by Tim Betts, who reported that some people with epilepsy may develop a "true phobic anxiety state" relating to their seizures, causing them to become "panic-stricken at the thought of going out in a public place lest they should have an attack". However, he felt that this was much less common than more generalised anxiety [Betts, 1981]. A phobia would be distinguished from less focused anxieties by involving excessive fear triggered by a specific object or situation capable of provoking an immediate anxiety response in case of (real or imagined) exposure. Seizure phobia has been distinguished from other interictal anxiety disorders associated with epilepsy: anticipatory anxiety of epileptic seizures, epileptic social phobia, and epileptic panic disorder [Hingray *et al*, 2019]. All of these potentially disabling problems may be missed by clinicians, not least because patients typically realise that their fears are irrational and may therefore be ashamed of discussing them with a physician.

The first key finding of the study by Weiss *et al*. is that seizure phobia does not seem to be as rare as initially reported. Phobic responses to seizure-related situations or triggers were reported by over one quarter of the 69 individuals with epilepsy who were questioned in detail about anxieties in the context of this study. However, the phobic responses often occurred in the context of more generalised anxiety disorders. People were at greater risk of having seizure phobia if they were female, had more anxiety symptoms in general, a history of major depressive episode or post-traumatic stress disorder. Over one third of the patients with epilepsy and seizure phobia also had psychogenic non-epileptic seizures – in some cases perhaps as a dissociative response provoked by seizure phobia. Seizure phobia was unrelated to epilepsy-related variables. This supports the idea that the patients described as having seizure phobia were not exhibiting adaptive anxiety symptoms as an appropriate response to particularly dangerous or troublesome seizure disorders.

This study reminds clinicians to be more aware of this treatable problem, which may well be overlooked if no questions about patients' fears in relation to their seizures are asked, especially about fears that seem 'crazy'.

Further reading

Betts, T.A. Epilepsy and the mental hospital. In: *Epilepsy and Psychiatry* (Eds E.H. Reynolds and M.R. Trimble). Edinburgh, Churchill-Livingstone, 1981.

Bonnett LJ, Kim L, Johnson A, Sander L, Lawn N, Beghi E, Leone M, Marson A. Risk of seizure recurrence in people with single seizures and early epilepsy – model development and external validation. *Seizure* 2022; 94: 26-32

Chin RF, Cumberland PM, Pujar SS, Peckham C, Ross EM, Scott RC. Outcomes of childhood epilepsy at age 33 years: a population-based birth cohort study. *Epilepsia* 2011; 528: 1513-1521.

Geerts A, Brouwer O, van Donselaar C, Stroink H, Peters B, Peeters E, Arts, WF. Health perception and socioeconomic status following childhood onset epilepsy: The Dutch study of epilepsy in childhood. *Epilepsia* 2011; 52: 2192-2202.

Hart, Y.M., *et al*., National General-Practice Study of Epilepsy - Recurrence After a First Seizure. *Lancet*, 1990. 336(8726): p. 1271-1274.

Hingray C, McGonigal A, Kotwas I, Micoulaud-Franchi JA. The Relationship Between Epilepsy and Anxiety Disorders. *Curr Psychiatry Rep* 2019; 29:40, doi: 10.1007/s11920-019-1029-9

Lawn, N., *et al*., Is the first seizure epilepsy—and when? *Epilepsia* 2015;56: 1425-1431.

Marson, A., *et al*., Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005; 365(9476): 2007-2013.

Musicco, M., *et al*., Randomized Clinical-Trial on the Efficacy of Antiepileptic Drugs in Reducing the Risk of Relapse after a 1st Unprovoked Tonic-Clonic Seizure. *Neurology* 1993;43:478-483.

Rawlings GH, Brown I, Reuber M. Predictors of health-related quality of life in patients with epilepsy and psychogenic nonepileptic seizures. *Epilepsy Behav*. 2017;68,153-58.

Reilly C, Johnson E, Muggeridge A, Atkinson P and Cross H. Inclusion and participation of children with epilepsy in schools: Views of young people, school staff and parents. *Seizure* 2021; 93: 34-43

Weiss A, Canetti L, David SD, Reuveni E, Ekstein D., Seizure phobia: a distinct psychiatric disorder among people with epilepsy. *Seizure* 2022; 95: 26-32.

A complex balance

IBE president shares her unique perspective

Francesca Sofia became the new president of the International Bureau for Epilepsy (IBE) in 2021. She tells Kami Kountcheva about her plans to help increase patient engagement in epilepsy healthcare, the challenge of differing needs of professionals and patients, and the value in improving health literacy.

Kami Kountcheva: Congratulations on being appointed president of the International Bureau for Epilepsy (IBE)! How does it feel to take up this role?

Francesca Sofia: Well, the feeling is that of something big in terms of the responsibility involved, but also in the underlying potential. There is no doubt that the IBE is big, with a membership that includes more than half the countries on Earth. In its 60-year history, the IBE has contributed to countless initiatives around the world to change social attitudes towards epilepsy. Before the IBE, people with epilepsy had no voice in the global arena and in all contexts where public policy, health policy, culture and society are shaped. The very concept of epilepsy was distorted, due to medical misconceptions and lack of knowledge. However, we still have a long way to go to bring epilepsy to the level of recognition, inclusion and care that would be needed to speak to real social change. Therefore, 'big' is also a word that applies to future challenges. The COVID-19 pandemic has just shown us how precarious our very existence is and has profoundly changed social dynamics. Meanwhile, health systems are facing dwindling resources, rising costs and the impact of chronic diseases. And all this while huge inequalities in access to care, discrimination and human rights violations still plague vast regions of the planet. It is a worrying landscape, but amid the difficulties, there are opportunities. And I see my work over the next four years to be in the field of opportunities.

KK: What are your aims and objectives for your term?

FS: The overall goal of my term is to enable transformational social change for people living with epilepsy worldwide by fostering patient engagement. I know that may sound overly ambitious, so, put it this way: I would like to be able to trigger a long-term process that will ultimately lead there.

Health systems are facing dwindling resources, rising costs and the impact of chronic diseases

In several medical fields, the concept of 'patient engagement' is shifting systems and processes from a traditional provider-focused stance to healthcare that involves patients and integrates their experiences and preferences. This transformation is having a profound and positive impact on people's quality of life, as well as on the health and social systems. At the individual level, engagement impacts health and clinical outcomes, promoting improved disease management, effective use of health services, improved health status, and adherence to therapy. At the community level, patient engagement in research promotes better targeting

President of the IBE Francesca Sofia

of what matters most to patients. At a more global level, coordinated and effective advocacy by empowered patient communities is driving momentous changes in several fields related to cancer, rare diseases, multiple sclerosis, Alzheimer's disease and many others.

If we want this to happen in the field of epilepsy, too, we will have to invest in education and empowerment of people with epilepsy, to foster their participation in health care advancement.

KK: Can you tell me a little bit about your connection to epilepsy?

FS: In the beginning of my professional path, I wanted to become a scientist. I started out as a PhD student in neuroscience, tackling the functions of the Emx1 gene in brain development. We found a mutation of this gene in two families which had members with what was, at that time, called idiopathic generalised epilepsy.

After my PhD, I became interested in the economics and management of the biomedical research sector, and obtained a master's degree in International Healthcare Economics, Policy and Management. This eventually led to a visiting scholarship at the Georgetown University Kennedy Institute of Ethics in Washington DC, USA. There, I studied and researched bioethics and science policy.

It was through these studies that I decided that science management could be a good fit for me. The opportunity came soon after, when I was recruited by the Telethon Foundation in Italy, whose mission is to advance research towards cures of rare genetic diseases. As a manager there for 10 years, I gained long-standing experience in matters pertaining to science evaluation and management of a research portfolio contributing to the mandate of a stakeholder's community. Another important part of my position regarded the management of the Patient Support Office that gathered all outreach activities with the stakeholders – mainly patients and their representatives.

If I connect the dots, I would say that I was preparing for the big transition that happened later with my daughter's epilepsy diagnosis. Epilepsy has crossed my life twice, and the second time it was to stay there forever. Eventually, I embraced a new personal and professional path when I became involved with the Italian Epilepsy Federation, which led me to start collaborating with the IBE. I served IBE as a member of the European Regional Executive Committee (EREC) for four years and gradually became passionate about this work. I began to see the opportunity for long-overdue social change in the epilepsy community.

If I connect the dots, I would say that I was preparing for the big transition that happened later with my daughter's epilepsy diagnosis

KK: What has your personal experience with epilepsy brought to your work?

FS: I believe that my experience as a health and science manager and as a parent of a child with epilepsy puts me in the quite unique position of knowing both sides of the advocacy dialogue. As a professional, I know that progress in health and social care requires time and is subject to

complex economic, political and social logics in order for the whole system to keep in balance. As a patient representative, I see (and face myself) the urgency for better care expressed by the patient community. How do these different needs come together? I don't have a definitive answer, but, based on my dual role, I tend to believe that multi-stakeholder commitment and synergy are key. This is especially so today, when global public policies are increasingly moving towards cross-cutting solutions to benefit many communities and groups of stakeholders. So, ultimately, I believe I bring to my role as president of the IBE the ability to bring together different perspectives. And I can do it with the drive and humanity that come with living with the condition.

The progress we're seeing in many fields with patient engagement is not happening for epilepsy, at least not at the same pace. The majority of people with epilepsy are not adequately informed about their condition and are not able to solicit interventions or investigations based on their real-life experiences with the condition. So far, there has been much less public awareness and discussion about epilepsy compared to other conditions. Despite its high frequency in the population, public and private investments in epilepsy research and healthcare are lagging behind other neurological disorders. This stagnation is mirrored by the lack of new and effective disease-modifying treatments, including developments in technology and digital health solutions.

The progress we're seeing in many fields with patient engagement is not happening for epilepsy, at least not at the same pace

Among the barriers preventing empowerment of people with epilepsy, social stigma is the biggest one. In spite of significant social progress, epilepsy remains a largely hidden condition. The stigma surrounding epilepsy takes many forms and infects every aspect of the lives of people with epilepsy from school to the workplace, and virtually every social setting. As a result, people with epilepsy tend to hide their condition and do not engage in advocacy.

We need to change this. The epilepsy community could be more proactive and effective if people can overcome their low level of empowerment.

KK: You advocate for more use of real-world evidence in research and patient care. How can this kind of data play a part?

FS: Real-world evidence is a term that has been introduced to describe information and data derived from multiple sources outside of typical clinical research settings. This includes things such as electronic health records, claims and billing data, product and disease registries, and data collected through personal devices and health apps. It is now well established that real world evidence can inform therapeutic development, research outcomes, patient care, safety surveillance, and effectiveness. And, it can be used in a broad spectrum of research, ranging from observational studies to studies incorporating interventions.

Real-world evidence is an important concept and 'tool' to incorporate patient needs and experiences into research and care, complementing medical knowledge gained through

traditional tools. If we think of epilepsy, the main measures of therapeutic outcome are the number of seizures, their duration and their frequency. It is on these data that a treatment's ability to reduce or suppress the symptoms of the condition is established. But we, patients and caregivers, know that there is so much more to it than that.

So far, efforts to incorporate real-world evidence in epilepsy care and research have been limited. By researching the scientific literature, it is evident that we need to find a consensus on how to collect data and analyse and interpret them. Just think; despite the increasing availability of new digital health technologies, epilepsy management has not widely embraced the use of innovative devices and apps that could be valuable sources of real-world evidence.

I know that there are many issues that still need to be addressed about the application of real-world evidence, as well as digital technologies in epilepsy management practices. But, I would not want concerns to hinder progress. If these tools are not being used because they are not reliable enough, on the flip side, they may never become more reliable because they are not used in a research or clinical context. If this is so, we must break this vicious cycle!

KK: You also champion health literacy to help improve patient healthcare – can you tell us more about this?

FS: Health literacy is defined as the personal skills and environmental conditions that enable individuals to obtain, process, understand and use health information. Health literacy is considered an important determinant of health. Research conducted in the past two-to-three decades showed that poor literacy predicts poorer health outcomes and quality of life, and is linked to more hospitalisations, less preventive healthcare, poorer medical adherence, and unfeasible self-management. Also, unequal levels of health literacy contribute to disparities by denying health benefits to portions of the population. There are huge differences between countries, and huge differences within the populations of individual countries, with some groups more disadvantaged and vulnerable than others, for example the elderly. Finally, low health literacy is cause of inefficient healthcare spending.

I have come to understand that our lives are played out on a complex balance between seizures, comorbidities, the consequences of treatments and also what we face at a more social level. Health professionals can be our best allies in driving us towards finding this balance

KK: In what ways can the healthcare professional community help to foster and encourage better health literacy in patients with epilepsy?

FS: Being in close contact with patients, health professionals are a fundamental part of the environment that influences and determines patients' ability to understand and use health information. Therefore, they should play a crucial role in promoting health literacy. However, they are not always aware of – and often, not trained for – this.

Although still few in number, there are studies [Bautista *et al*, 2019; Scrivner *et al*, 2019] that show that

health literacy may function as a tool through which participation of people with epilepsy in healthcare can be enhanced. They suggest this could lead to better self-management capacity and less perceived stigma. Unfortunately, the whole system seems not to be ready if, in 2020, the readability of health-related information on internet was found to be suboptimal, if not poor [Correa *et al*, 2020]. It comes as no surprise that, in 2017, parents of children with epilepsy were found to have a poor understanding of the term epilepsy itself [Nagan *et al*, 2017].

There is definitely a need to invest in the development of effective health literacy promotion interventions by working in two directions: towards the community of people with epilepsy to equip them with knowledge and tools, and towards health professionals to involve them and enable them to transfer information in ways that will increase overall health literacy.

KK: Being able to see epilepsy care from both the side of the care provider and from the family living with epilepsy, what do you think we need to be doing to better support people with epilepsy?

FS: In my 10 years as a caregiver, I have come to understand that our lives are played out on a complex balance. This is between seizures, comorbidities, the consequences of treatments and, also, what we face at a more social level outside the home and the hospital. Health professionals can be our best allies in driving us towards finding this balance. For this to happen, it all starts with their willingness to recognise the work we do in self-care, and to use our observations and experiences to improve and expand their own understanding of the condition.

Willingness cannot be taught but, hopefully, can be persuaded by showing the impact that such practices can have on health (and social) outcomes.

Francesca Sofia
President
International Bureau for Epilepsy

Further reading

Bautista RE, Glen ET, Shetty NK, Wludyka P. The association between health literacy and outcomes of care among epilepsy patients. *Seizure*. 2009 Jul;18(6):400-4. doi: 10.1016/j.seizure.2009.02.004.

Correa DJ, Milano L, Kwon CS, Jetté N, Dlugos D, Harte-Hargrove L, Pugh MJ, Smith JK, Moshé SL. Quantitative readability analysis of websites providing information on traumatic brain injury and epilepsy: A need for clear communication. *Epilepsia*. 2020 Mar;61(3):528-538. doi: 10.1111/epi.16446.

Nagan M, Caffarelli M, Donatelli S, Rosman NP. Epilepsy or a Seizure Disorder? Parental Knowledge and Misconceptions About Terminology. *J Pediatr*. 2017 Dec;191:197-203.e5. doi: 10.1016/j.jpeds.2017.08.068.

Scrivner B, Szaflarski M, Baker EH, Szaflarski JP. Health literacy and quality of life in patients with treatment-resistant epilepsy. *Epilepsy Behav*. 2019 Oct;99:106480. doi: 10.1016/j.yebeh.2019.106480.

Self-care and managing risk in new parents

I thought in this edition's opinion piece we could consider the delicate balance of promoting independence and instilling confidence in people with epilepsy, and yet at the same time, being vigilant to situations of risk. No more so is this apparent than in the work that our epilepsy nurses do in antenatal care.

Part of living with a chronic condition like epilepsy is the concept of self-care. We encourage people to take ownership and personal responsibility for their own condition. This is, of course, challenged in new parenthood. With this increased, individual, new parental responsibility, there may also be added risk from epilepsy and its associated comorbidities.

Living with a chronic unpredictable condition like epilepsy no doubt amplifies the emotions of joy, anticipation, fear and excitement of becoming a new parent. Our epilepsy nurses play a pivotal role in building confidence in new mums and dads who have epilepsy.

Most of the work our nurses do in these scenarios is to provide reassurance and build confidence. Consultations will, of course, involve discussions on minimising seizure risk and altering medications. But, foremost, they will reinforce general advice on how new parents with epilepsy can continue to look after themselves and their condition, as this will have an impact on the care of their new baby. Even for parents who are seizure free, advice around sleep deprivation and avoiding complacency is still paramount. Dialogue will also explore some of the practical issues, such as managing sleep deprivation and advice on how to feed, carry and bathe the newborn baby, to name but a few. I'm not ashamed to say that when I'm asked questions from my patients on becoming a new parent, I know can confidently refer them to one of our specialist nurses. I am sure I, like others, have learned much about these practicalities from our nursing teams.

Most people with epilepsy are generally fairly risk adverse, and so becoming new parents, although another challenge, can be done safely with a bit of support and guidance. This is the take-home message our nurses aim to reinforce. What we need to provide is gentle encouragement, good dialogue, and a point of contact within the NHS system.

Ultimately in order to provide support to a parent, we also must be able to identify risk to a child or parent. As clinicians, we are always navigating risk, and sadly, there are a few scenarios for individuals with epilepsy in which having a baby may carry undue risk of harm to themselves or the baby. It is important that we try to identify these situations in order to protect the parents and the child. Thankfully these are not common, but areas worth of mention might include non-engagement in antenatal care, single parents with unstable epilepsy, individuals with seizures causing significant injury, complete lack of social support, and significant mental health concerns. Having these frank and open discussions requires trust on behalf of the new parents, and although it risks harming the clinician-patient relationship, we cannot shy away from them. It's vital that information is shared across the epilepsy and specialist antenatal teams, as well as social services and safeguarding if needed.

Dates for the diary

Dates and events may be subject to change – please check on the relevant websites.

2022

24-27 March
16th World Congress on Controversies in Neurology
London, UK
cony.comtecmed.com

10-13 April
EEG in the First Year of Life
Cambridge, UK and online
bit.ly/3oSA234

28 April - 2 May
14th European Paediatric Neurology Society Congress (EPNS)
Glasgow, UK
epns-congress.com/

14-15 May
ILAE British Branch 18th Specialist Registrar Epilepsy Teaching Weekend
Birmingham, UK
epilepsyteachingweekend.com

22-25 May
16th EILAT Conference on New Antiepileptic Drugs and Devices
Madrid, Spain
eilatxvi.com

25-28 June
8th Congress of the European Academy of Neurology (EAN)
Vienna, Austria and online
ean.org/congress2022

8-9 July
Epilepsy Surgery Techniques Meeting
Geneva, Switzerland
estmnet.com

9-13 July
14th European Epilepsy Congress
Geneva, Switzerland
epilepsycongress.org/eec

2023

2-6 September
35th International Epilepsy Congress
Dublin, Ireland
bit.ly/30Spwk8

Next issues:

Elisa Bruno

Dr Bruno and Prof Richardson describe the Remote Assessment of Disease and Relapse in Epilepsy (RADAR) study and discuss findings

Laura Kirkpatrick

Dr Kirkpatrick discusses information delivery around sexual health and reproduction to teen and young adult women with epilepsy and intellectual disability

If you are interested in submitting a research paper for inclusion in *Epilepsy Professional,* please contact the Editor:

kkountcheva@epilepsy.org.uk

Epilepsy Professional's advisory panel

optima

XLTEK

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

To find out more call 020 3058 0850

www.optimamedical.com