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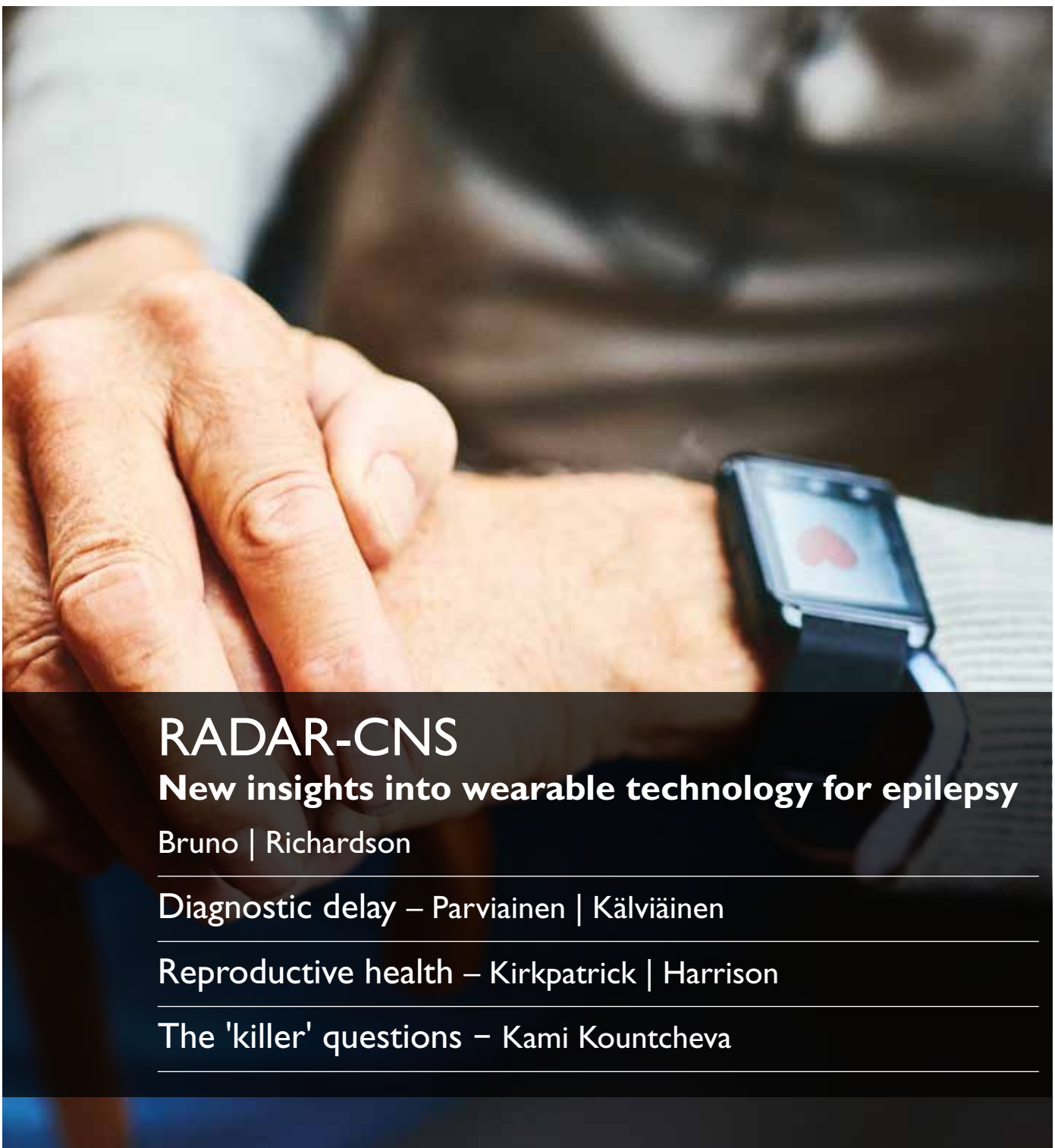

RADAR-CNS
New insights into wearable technology for epilepsy

Bruno | Richardson

Diagnostic delay – Parviainen | Kälviäinen

Reproductive health – Kirkpatrick | Harrison

The 'killer' questions – Kami Kountcheva

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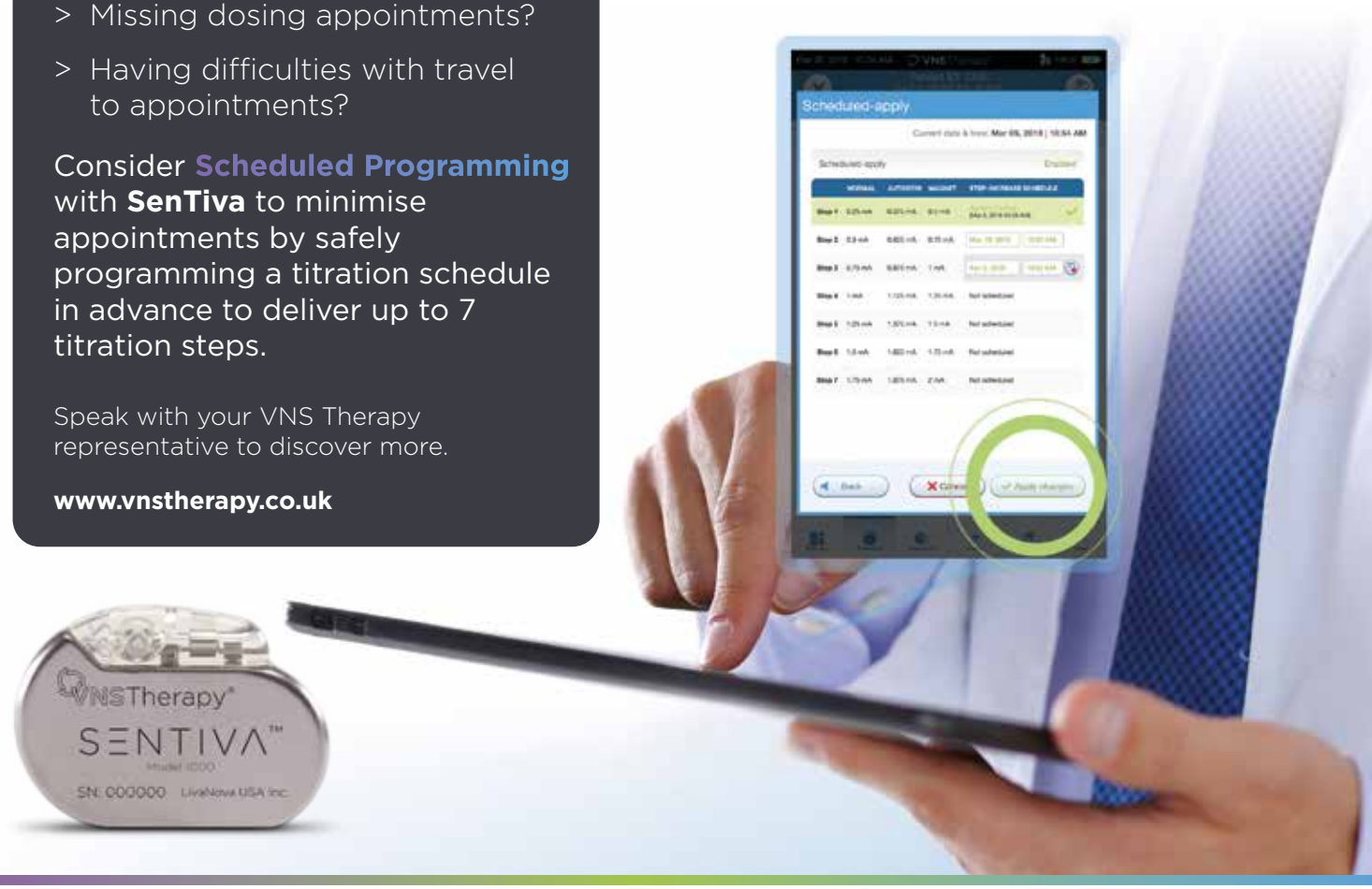

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LivaNova
Health innovation that matters

Welcome to the summer 2022 edition of Epilepsy Professional. We have a selection of articles showcasing the forefront of epilepsy research and patient care.

Our very own editor Kami Kountcheva reviews the Epilepsy Research UK (ERUK) Share Network Conference that took place in May this year. She focuses on answers from an expert panel to the "killer" questions from the audience at what sounds to have been a fantastic meeting.

Despite efforts over many decades, in most cases, the diagnosis of epilepsy is clinical. Dr Laura Parviainen and Prof Reetta Kälviäinen discuss their research into diagnostic delay, the impact this has on patients and what we may be able to do to improve this.

The RADAR-CNS study into the utility and benefits of wearable technology in epilepsy is discussed by Dr Elisa Bruno and Prof Mark Richardson. They describe a patient-focused approach to researching wearables to ensure patients get the most out of them in terms of acceptance and safety benefit.

Dr Laura Kirkpatrick and Dr Elizabeth Harrison discuss recommendations and best practice around providing reproductive health counselling to people with epilepsy and intellectual disability and their families. They remind us of the importance of these discussions in this population and have top tips to help us do this well.

I hope you enjoy this edition.

Seán Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

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Not to kick off this issue by breaking the fourth wall, but for me, front and centre when I do my job is always you, the reader. I do my best to make sure what I put together here is interesting to you. And I think, you may well know the feeling, as front and centre for you must be the patient.

Not unlike many of our other issues, this one is very patient-focused to remind us of the huge benefit in involving patients in their own healthcare.

On page 10, you'll find some results from the RADAR-CNS epilepsy study from Dr Bruno and Prof Richardson, looking at the effectiveness and usability of wearable technologies for seizure detection. This is key, because even the most cutting-edge, next-generation technology is only as good as people's willingness to use it. On page 16, Dr Parviainen and Prof Kälviäinen discuss their research looking at reasons why diagnostic delay might occur, and the impact this could have on patients who have a lot of seizures before getting their epilepsy diagnosis. On page 20, Dr Kirkpatrick and Dr Harrison share some recommendations and best practice from the US on providing reproductive health counselling to women and girls with epilepsy and intellectual disability, a group that may sometimes be overlooked in this capacity.

Finally for this issue, you can read my report from the Epilepsy Research UK Share Network Conference in London in May. The conference brought together people with a connection to epilepsy, and researchers and clinicians, allowing for frank conversations and for people to share their questions on the latest research practices and techniques in epilepsy.

I hope this issue brings you food for thought and new ideas. Enjoy!

Kami Kountcheva
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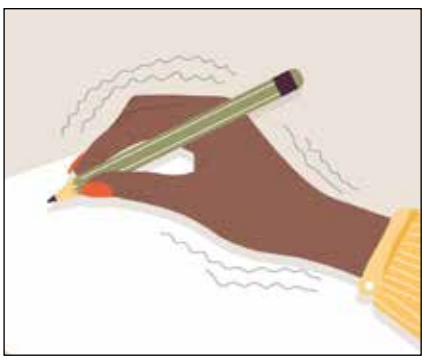
Epilepsy could be risk factor for Parkinson's disease, study suggests



Epilepsy and hearing loss are among some of the risk factors for developing Parkinson's disease later in life, according to a new study in *JAMA Neurology*.

Dr Christina Simonet and colleagues aimed to investigate common risk factors for Parkinson's disease and how early these can occur before a Parkinson's disease diagnosis is made. The research wanted to focus on an ethnically diverse group of people from less affluent backgrounds.

The study used the electronic health records from GP practices in East London of over a million people between 1990 and 2018. They compared people with Parkinson's disease stated in their medical record to those without. People with neurological diseases that get worse with time, such as dementia and multiple sclerosis (MS), were not included in the study.

The researchers found that people with Parkinson's disease tended to be older and more often male, compared to the group without. Loss of hearing and epilepsy were found to be risk factors for Parkinson's disease, which haven't been well reported before.

According to the NHS website, Parkinson's disease is thought to affect around one in every 500 people. The researchers found that people with epilepsy are 2.5 times more likely to be diagnosed with Parkinson's disease than the general population. This means for every 500 people with epilepsy, two or three people will go on to have a diagnosis of Parkinson's disease.

Consultant neurologist at the Royal Victoria Infirmary in Newcastle, Dr Rhys Thomas, said: "This is not the first time that epilepsy has been suggested to be a risk factor for Parkinson's disease, but the size of the study makes this finding potentially important.

"There could be a few different reasons for this increased risk of being diagnosed with Parkinson's disease in people with epilepsy. If you are already seeing a neurologist for something else, and you do have early signs of Parkinson's disease, you are more likely to have it diagnosed correctly. Also, some epilepsy medicines can cause a tremor, which could be misdiagnosed as Parkinson's disease (what is called parkinsonism) or it could prompt a doctor to investigate for Parkinson's disease.

"Epilepsy is a term for a number of diseases, and some of them may be more likely to increase the risk of Parkinson's disease than others, specifically vascular disease."

Other risk factors included tremors, seen up to 10 years before the diagnosis of Parkinson's disease, and memory problems, present up to five years before. Links were also found with high blood pressure, low blood pressure, constipation, depression and type 2 diabetes.

There is more information at *bit.ly/3PUhGLN*.

Valproate prescriptions drop between 2018-2021

New figures show that the number of women prescribed sodium valproate in a month fell by over 7,000 between April 2018 and September 2021. This is according to findings published by NHS Digital in March 2022.

The published figures showed that the number of women prescribed valproate fell from 27,448 in April 2018 to 20,192 in September 2021.

However, they also showed that 247 women were prescribed valproate while they were pregnant between April 2018 and September 2021 and 25 of the these were in the six months from April 2021 to September 2021.

Daniel Jennings, senior policy and campaigns officer at Epilepsy Action said: "We are pleased to see that the number of prescriptions for valproate have decreased, however it remains the case that for many people with epilepsy it is the only medication that controls their seizures. It is vitally important that women are made aware of the risks of taking this medication, and other AEDs, during pregnancy so they can make an informed decision about their treatment."

Discussions about the teratogenic effects of sodium valproate may not always be happening. A survey done by Epilepsy Action, Epilepsy Society and Young Epilepsy in 2020 found that two-fifths (44%) of women hadn't discussed the risks of valproate with their consultants in the last 12 months.

Mr Jennings added more research is needed into the teratogenicity of other AEDs.

Concentrations of some ASMs lower during pregnancy

The concentrations of some anti-seizure medications (ASMs) in the blood drops in women during pregnancy, according to a new study in *JAMA Neurology*.

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study, by Page Pennell and colleagues, investigated the pregnancy-associated changes in several ASMs. These were lamotrigine, levetiracetam, lacosamide, oxcarbazepine, zonisamide, carbamazepine and topiramate.

The research included 430 participants – 326 pregnant women with epilepsy (the study group) and 104 women with epilepsy who were not pregnant as controls – aged 14-45 years. The pregnant women were at less than 20 weeks of pregnancy when the study started. The study group was monitored for nine months after giving birth, with a similar timeframe used for the control group.

In the study group, blood tests were done four times during pregnancy and three times after the women had given birth. Seven blood tests were also done in the control group over 18 months.

Concentrations of ASMs in the blood were compared during and after pregnancy in the study group, and between the study and control groups.

When comparing the blood levels during and after pregnancy in the pregnant women group, levels of many of the ASMs were significantly reduced during pregnancy. Lamotrigine levels decreased by 56.1% and levetiracetam by 36.8%. Oxcarbazepine reduced by 32.6%, zonisamide by 29.8%, and lacosamide by 39.9%. The authors say that monitoring of ASM levels in the blood should start early in pregnancy, and that increasing the doses of some epilepsy medicines may be needed throughout pregnancy.

The full study is available at *bit.ly/3wTnoES*.

Cenobamate safe and effective in children

The new epilepsy medicine, cenobamate, has been found to be safe and effective in children with hard-to-treat focal-onset epilepsy, in line with study findings in adults with epilepsy. This is according to US research by Dr Robin Varughese and colleagues, published in *Epilepsy & Behavior*.

The team set out to assess how safe and effective cenobamate is as an add-on treatment in children with drug-resistant focal-onset seizures. They said this medicine is useful in adults but this has not yet been confirmed for children.

The study included 21 children with an average age of 16. Cenobamate was introduced and the dose slowly increased as needed or up to a maximum of 400mg a day. On average, children weighing over 50kg needed around 200mg a day. In children weighing under 50kg, the average dose was 4mg a day for each kilo they weighed. The average reduction in seizure frequency was over half. Around three in five children (62.5%) had their seizures reduce by at least half. In over half of the children, seizures reduced by three-quarters, similar to the seizure reduction in adults. Just under one in five children (19%) became seizure free.

Of the 21 children, nine (42.8%) had side effects from cenobamate, which were typically ataxia in 23.8% or sedation in 9.5%. Three children dropped out of the study because of the side effects.

The researchers concluded that cenobamate is effective, safe and well-tolerated in children, but larger studies are needed. The paper is available at: *bit.ly/3x3T4sD*.

Epilepsy Action urges Health Secretary to rethink sodium valproate redress scheme position

Epilepsy Action has written to Health Secretary Sajid Javid, urging the government to implement the recommendations of the 2018 patient safety review into the drug sodium valproate.

NHS Digital recently reported that valproate prescriptions for women fell by over 7,000 from April 2018 to September 2021.

While Epilepsy Action welcomed this development, the organisation is still concerned about the lack of progress on other recommendations around the sodium valproate scandal made by the Independent Medicines and Medical Devices Safety Review. These include appointing a Patient Safety Commissioner and creating a network of specialist centres to support people with epilepsy during pregnancy.

The organisation is also calling on the government to reconsider its decision not to provide a redress scheme for the families affected by the scandal.

Sodium valproate was launched in the 1970s, and there have been concerns about teratogenic effects on patient information leaflets as early as 1974.

Epilepsy Action believes women should be given an informed choice about using this medicine. However, the patient safety review, carried out by Baroness Julia Cumberlege, found that women had not been made aware of the risks of this medicine for many years.

In the review's report, "First Do No Harm", Baroness Cumberlege acknowledged the "intensity of suffering" families have experienced because of this, and the fact that it was due to "failings in the health system".

Epilepsy Action told the Health Secretary that the organisation remains "disappointed that the government has rejected the recommendation to establish a redress scheme. This is essential for families who have experienced avoidable harm associated with sodium valproate and pregnancy, and to meet the cost of providing additional care and support."

You can find out more about the issue, and read the letter sent to the Health Secretary, and download a letter to send to your own local MP at *bit.ly/3t7B4uU*

Post-traumatic epilepsy linked to poorer QoL

Post-traumatic epilepsy, occurring after brain injury, is linked to a lower quality of life than non-traumatic epilepsies, according to a US study in the journal *Neurology*.

Dr Gugger and his colleagues carried out a survey of 529 people who went through the events of 9/11, many of whom had experienced traumatic brain injury. The respondents were split into four groups: epilepsy controlled with anti-seizure medications (ASMs) (249), drug-resistant epilepsy (DRE) (124), post-traumatic epilepsy (86) and drug-resistant post-traumatic epilepsy (70).

The study authors found that DRE was more common in people with post-traumatic epilepsy than with non-traumatic epilepsy. People with post-traumatic epilepsy and DR post-traumatic epilepsy had significantly more additional health conditions alongside their epilepsy than the groups with non-traumatic epilepsy. The poorest quality of life scores were reported by people with both DRE and post-traumatic epilepsy.

The researchers concluded that people with post-traumatic epilepsy are especially vulnerable to having other health conditions linked to their epilepsy and their traumatic brain injury. They said this "at-risk group" should be the focus of future studies looking into factors linked with poorer health and finding treatments that could stop epilepsy from developing, following a traumatic brain injury.

The study is available at *bit.ly/3GAm1zo*.

Annual reviews and ketogenic diet among changes to NICE guidelines

People with well controlled epilepsy may not be offered an annual review, according to the updated guidelines for epilepsy healthcare professionals from The National Institute for Health and Care Excellence (NICE).

NICE now recommends that regular reviews (at least once a year) a should be offered to certain groups of people with epilepsy, according to the new guidelines published on 27 April. These include, children and young people, those with drug-resistant epilepsy and those at a high risk of sudden unexpected death in epilepsy (SUDEP).

People with a learning disability or serious comorbidities, such as complex mental health problems, will also be offered annual reviews. Those taking anti-seizure medications (ASMs) with long-term side effects, such as bone health problems, and women of childbearing potential taking ASMs which may carry a risk of teratogenicity, should also be offered reviews.

The guidelines say people who continue to have seizures should be offered appointments with an epilepsy specialist nurse (ESN) at least twice a year and after any A&E visits.

Another change is that the ketogenic diet can be considered as a treatment option in adults as well as children, according to the updated guidelines. This is in people with certain epilepsy syndromes or in people with drug-resistant epilepsy where other treatments haven't worked or are not suitable. In the previous guideline, the ketogenic diet was only recommended for children and young people.

The guidelines also state that clinicians should urgently refer someone who has had a breakthrough seizure after a period of being seizure free. Urgent assessments should happen within two weeks.

Those who might be suitable for epilepsy surgery and have an epilepsy likely to be drug-resistant should also have an early referral for surgery assessment, according to NICE.

The full guidelines are available on the NICE website at *bit.ly/3IZ5bAJ*

Epilepsy Action NI secures £60k grant

Epilepsy Action Northern Ireland has secured funding of approximately £60,000 for a part time family support officer in Northern Ireland.

The funding from the Department of Health (DoH) will be for two years and will go towards the project aiming to support around 2,300 carers to people with epilepsy.

Epilepsy Action explains that there are a number of problems with provision of epilepsy care in Northern Ireland at the moment. They include the longest waiting times for services in the UK at the moment and a "severe lack" of neurologists and epilepsy specialist nurses (ESNs).

The new project will support carers through activities like information events, raising awareness, working with healthcare professionals and working to reduce social isolation.

Epilepsy Action NI gets £200k grant to expand counselling service

Epilepsy Action will expand its counselling service for people with epilepsy in Northern Ireland, after securing a £200,000 grant from the Department of Health Northern Ireland's Mental Health Support Fund. The fund was set up to help charities to provide mental health support in the communities.

Currently, the counselling service includes free online and telephone counselling for adults with epilepsy, or parents or carers to someone with the condition, who are based in NI. The counselling sessions are delivered by qualified volunteer counsellors.

With the grant, Epilepsy Action Northern Ireland will be able to expand its counselling services. It will also offer online therapy groups covering issues like new diagnosis, independence and change to relationships, as well as resilience sessions teaching self-help techniques. The funding will also help the organisation develop training materials and resources for counsellors.

RADAR-CNS

New insights into wearable technology for epilepsy

Dr Elisa Bruno and Prof Mark Richardson describe the findings of the Remote Assessment of Disease and Relapse in Central Nervous System disorders (RADAR-CNS) epilepsy study looking at usability and effectiveness of wearable technologies for seizure detection and reducing seizure-related risk

The last decade has seen an explosion in the capability of monitoring different health conditions via wearable devices, offering the advantage of an easy and continuous non-invasive recording of different physiological parameters [Naslund *et al*, 2015].

Wearable technologies appear particularly interesting for those chronic disorders, such as epilepsy, in which clinical manifestations (seizures) are characterised by significant alterations in multiple physiological parameters, including movements, heart rate and electrical skin conductivity.

Despite the rapid advancement of the technology and the availability of new medical devices to detect seizures, the integration of wearables into daily clinical epilepsy care remains rare. It is limited by the lack of studies demonstrating the validity and utility of data collected with wearables, as well as patients' acceptability [Bruno *et al*, 2021a].

RADAR-epilepsy is a six-year project that has been designed to provide a complete insight into the role of wearable non-EEG devices in the field of seizure detection.

RADAR-CNS and RADAR-epilepsy

RADAR-epilepsy is part of the Remote Assessment of Disease and Relapse in Central Nervous System Disorders (RADAR-CNS) study, a major international research project [RADAR-CNS]. RADAR-CNS' main aim is to develop new ways of measuring major depressive disorder, epilepsy and multiple sclerosis using wearable devices and smartphone technology. The project was officially launched in March 2016, and it has come to an end in March 2022.

RADAR-epilepsy is an observational prospective cohort study including people with epilepsy from two participating sites, King's College London and the University of Freiburg.

Our research demonstrated that wearable technology is very welcomed by the larger epilepsy community

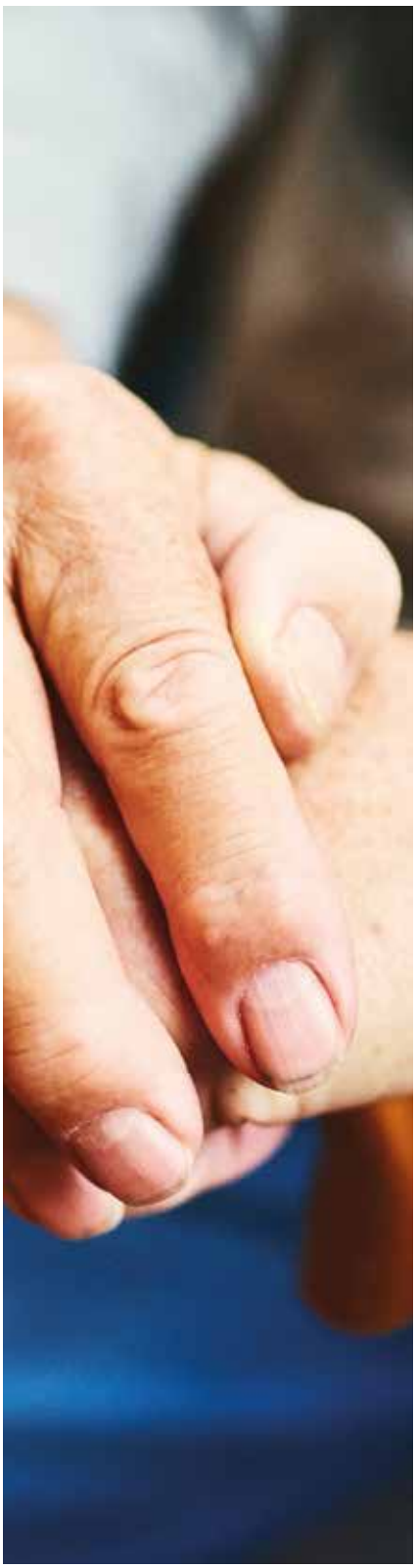
The study was designed to answer three main research questions:

1. Are non-EEG wearable devices acceptable for long-term use?
2. Are non-EEG wearable devices accurate for seizure detection?
3. Can non-EEG wearable devices help at reducing seizure-related risk?

To answer to these questions, an in-hospital and a community-based study were conducted and a total of 243 inpatients and 27 outpatients with a diagnosis of pharmaco-resistant epilepsy were recruited. Seven wearable devices, including commercially available devices and research prototypes, were tested (E4, Faros, Biovotion, IMEC, Epilog, Byteflies, NightWatch).

The value of patient experience

Patients' involvement has been an integral part of RADAR-CNS from the outset. Alongside clinical experts, the RADAR-CNS consortium has a team dedicated to ensuring patient and public involvement at every stage of development. Several people with epilepsy, in collaboration with Epilepsy Action, were appointed to join a patient advisory board to help steer the project. People with epilepsy also took part in focus groups so we could gather their views on the outcomes of importance to patients and potential barriers and facilitators to engagement with technology [Simblett *et al*, 2019]. Our research demonstrated that wearable technology is very welcomed by the larger epilepsy community, including patients, carers, and healthcare professionals. It has also highlighted how potential barriers to the use of new technologies may be mitigated by adopting multimodal (multiple sensors on a single device), small and familiar products. This may



also help with preventing stigma and anxiety related to the technology adoption [Bruno *et al*, 2018].

Are non-EEG wearable devices acceptable for long-term use?
Users' long-term engagement is key to the successful adoption of wearable technology, and it is essential to guarantee optimal data collection and a continuous monitoring throughout day and night. In our hospital cohort, different wearables were considered convenient and practical to use and wear, also during sleep [Simblett *et al*, 2020]. Devices were also stable during seizures. However, wearables requiring additional wires and electrodes not only were less preferable but also had a lower degree of stability to the body, especially at night [Bruno *et al*, 2020a]. This is a very important factor to consider, as reduced stability to the body may reduce a device's performance in a potentially critical situation, such as during nocturnal, unsupervised seizures which notoriously cause a higher risk of sudden unexpected death in epilepsy (SUDEP).

When using a wearable device, users are also going to be entrusted with the responsibility to operate the system to facilitate data collection. Users' independence in the use of a wrist-worn device was explored, and, specifically, users' ability to wear the device correctly, switching it on and off, connecting it to a smartphone and charging it when needed. Despite overall good skills, half of our patients needed assistance and technical support from the team in one or more tasks during the study, highlighting how technical support and supervision should be easily available [Bruno *et al* 2020b].

Are non-EEG wearable devices accurate for seizure detection?
Using a wrist-worn device, our team developed a model to detect tonic-clonic seizures (both generalised and focal to bilateral tonic-clonic seizures) and focal motor seizures. For tonic-clonic seizures, a sensitivity of 91% and a false alarm rate of 0.19/day were achieved [Böttcher *et al*, 2021]. This performance is comparable with the best models reported in the literature for medical devices approved for seizure detection.

One of the major difficulties in detecting focal seizures is related to their clinical complexity and variability across subjects

While many studies on wearable devices have focused on tonic-clonic seizure detection, focal seizures have received less attention. Focal seizures are the most common seizure type and are associated with poorer control as compared to other seizure types [Christensen *et al*, 2012]. One of the major difficulties in detecting focal seizures is related to their clinical complexity and variability across subjects [Bruno *et al*, 2021b]. Individualised models, accounting for patient-specific clinical manifestations, should be developed for accurate detection of these seizures, to improve detection sensitivity and reduce false alarm rates. For focal motor seizures, our research team performed the first ever study analysing specifically focal motor seizures with multimodal data. An individualised model was developed, and it demonstrated a sensitivity of up

Table 1. Wearable devices use-cases and applications

Use-cases	Patient and caregiver level	Clinician and service level
Automatic seizure detection and counting	• Communication and memory aid: facilitate communication with healthcare providers; • Self-management and independence: planning activities, rest, treatment; • Reduce strain and workload for caregiver: automatic identification of seizures, alleviate the anxiety related to the responsibility of constantly monitoring PWE.	• Support during daily clinical practice: longitudinal insights of the patient seizure activity and objective measure of seizure occurrence, frequency and distribution guiding management and treatment optimization decisions; • Identification of treatment failure and life-style restrictions (e.g. driving); • Identification of seizure freedom and benefit on driving/sports/personal life/employment.
Seizure alerting and seizure-related-risk prevention	• Improve safety, increase independence and reduce limitations, fear and uncertainty (psychosocial burden); • Provide reassurance and reduction of anxiety and burden for caregivers. • Continuous monitoring including night and sleep: SUDEP prevention.	• Activate a protective device, or therapy, as in closed-loop systems; • Prevent seizure-related accidents and disability: reduced access to A&E and emergency services for injuries related to seizures. • Triage level of urgency to see patients in a follow-up clinic. • Prevent seizure-related death and SUDEP.

to 100% and a false alarm rate of 0.85/day [Böttcher *et al*, 2022], a very promising performance for future clinical applications.

Can non-EEG wearable devices help at reducing seizure-related risk?

SUDEP represents the leading cause of mortality directly related to seizures and is also considered an unpredictable event [Tomson *et al*, 2008]. The pathophysiological mechanism underlying SUDEP remains elusive, and the identification of clinical markers has been the target of many studies aimed at identifying patients at risk in order to develop preventive measures.

SUDEP has been mainly reported following unsupervised nocturnal tonic-clonic seizures. It has been associated with a specific EEG pattern, called post-ictal generalised EEG suppression (PGES, a flattening of the EEG following a seizure) and with post-ictal immobility (PI). PI is characterised by a persistent immobility hampering body and head repositioning, which are necessary for an optimal airflow. This state of immobility has a role in the cascade of events leading to cardiorespiratory dysfunctions and death, characterising SUDEP [Bruno *et al*, 2020c].

Our research demonstrated that PI was accurately identified by the movement sensor (accelerometer) of two different wearable devices, and that it

Table 2. Uses of wearable devices and applications in clinical trials.

Pre-trial level	• Identification of a target population with a specific seizure frequency; • Identification of a target population with a specific seizure type.
Trial level	• Objective outcome measurements: seizure reduction; reduction of specific clinical manifestations (e.g. for the assessment of interventional trial aimed at reducing seizure-related risks); • Identification of sub-populations showing a different response to the trial medication (responsive/ unresponsive individuals); • Supplement the information acquired with subjective diaries. • Acquisition of longitudinal data over a longer period of time lasting beyond the current clinical trials duration; • Explore the benefit of closed-loop seizure detection/ drug delivery systems.
Post-trial level	• Prolonged monitoring of a specific outcome in the real-world environment; • Continuous monitoring of adverse effects.

correlated with PGES. This finding highlights the application of wearables in the identification of potentially life-threatening post-ictal states and in the identification of seizures causing a higher risk of mortality [Bruno *et al*, 2020d]. This opens the possibility of developing prompt interventions and of surveillance systems.

Clinical significance of RADAR-epilepsy findings

RADAR-epilepsy is a pioneering study in the world of seizure detection. It is one of a very few available studies prospectively collecting wearable data from patients and obtaining information related to compliance, technology acceptability and usability.

The implications of this work span the realms of healthcare and research, as illustrated in *Tables 1* and *2*.

The current work has produced evidence on the usefulness of wearables by highlighting patients' willingness to use wearable devices for seizure detection and the feasibility of using wearable devices over long periods. It has also shown the role of technology in the identification of specific seizure patterns and of potentially dangerous post-ictal states. This can impact clinical practice, both at the patient/caregiver level and at the clinician/service level, as reported in *Table 1*.

Moreover, the potential benefits of the employment of objective tools to measure seizure frequency in clinical trials could revolutionise the way in which the effectiveness of new medications is assessed, as reported in *Table 2*.

We anticipate that automatic seizure detection will open new

avenues to improve both the safety and the treatment of people with epilepsy.

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Diagnostic delay

Reasons and consequences of diagnostic delay in focal epilepsy

Dr Laura Parviainen and Prof Reetta Kälviäinen discuss their research into diagnostic delay and the role this plays in the overall prognosis of patients, as well as the reasons this may be happening

Up to 38–55% of patients report previous undiagnosed seizures before the index seizure that led them to seek medical advice [Firkin *et al*, 2015; Jallon *et al*, 2001; Hamiwka *et al*, 2007; Sander *et al*, 1990]. In previous studies, 14–50% of patients experienced years of delay before diagnosis [Firkin *et al*, 2015; Hauser *et al*, 1975; Gasparini *et al*, 2013]. Diagnostic delay refers to the time from the first seizure to diagnosis. Factors that cause diagnostic delay are:

1. No access to medical care
2. Patients not seeking medical care due to a failure to recognise the nature of their symptoms
3. Symptoms brought to medical attention but not diagnosed as seizures [Jallon *et al*, 2001; Gasparini *et al*, 2016].

Some seizures, such as tonic-clonic seizures, are clearly observable and quickly bring people to medical attention. They are also easier for healthcare professionals to recognise as epileptic. Diagnostic delay seems to be particularly common among patients with nonmotor seizures [Firkin *et al*, 2015]. In a recent study, delay was 10 times longer among patients with nonmotor seizures compared to those with motor involvement at epilepsy onset [Pellinen *et al*, 2020].

If we look at short-term effects, diagnostic delay of nonmotor seizures is associated with preventable injuries, such as motor vehicle accidents

Epilepsy diagnosis dramatically affects patients' daily lives. Even today, there is a stigma associated with epilepsy that, in some cases, might prevent patients from seeking medical care. Some might deny their symptoms out of fear of losing their driving licence or occupation. Socioeconomic disadvantages have also been associated with lengthier delays [Firkin *et al*, 2015].

Why is it important to study diagnostic delay? The question of whether active chronic epilepsy may lessen the possibility of attaining remission was raised in 1984 [Shorvon 1984]. In his article, Prof Shorvon also pondered whether early, effective treatment with anti-seizure medication could affect the long-term outcomes of epilepsy. Studies have been unable to show the negative effects of delays on long-term seizure freedom. However, if we look at short-term effects, diagnostic delay of nonmotor seizures is associated with preventable injuries, such as motor vehicle accidents [Pellinen *et al*, 2020].

In our study at the Kuopio Epilepsy Center, we assessed diagnostic delay in a cohort of 176 newly diagnosed adult patients with focal epilepsy. We also analysed the effects of diagnostic delay on long-term prognosis at five years. The

study material was compiled from eight clinical anti-seizure medication trials conducted at our centre between 1995 and 2016. The main finding was that even in a developed country and a region with a well-defined epilepsy care pathway, public healthcare and long-standing work for epilepsy advocacy, such as in Eastern Finland, patients experience significant delays in the diagnosis of epilepsy. In our cohort, diagnostic delay ranged from 0 to 362 months (median 12 months, mean 50 ± SD 77). The delay was significantly shorter (median 6 months, mean 35 ± SD 72), if the patient had only focal to bilateral tonic-clonic seizures. The longest delay was over 30 years, and for 15% of the patients, the delay was over 10 years. The median number of seizures before diagnosis was 5 (range 2–2000); 23% had 2 seizures, 45% had 3–10 seizures and 32% had over 10 seizures. Four patients had over 100 seizures before diagnosis.

Despite lengthy delays in part of our cohort, the overall prognosis of epilepsy was good. Seventy-one patients (40%) remained seizure free throughout the five-year follow-up. In another 71 patients (40%), seizure freedom was achieved by either increasing the dosage or changing medications. Only 24 patients (14%) continued to have seizures despite medication. Diagnostic delay alone was not associated with a poor response to treatment ($p = 0.35$). However, when accompanied with recurrent seizures before diagnosis, the effect on prognosis was significant ($p < 0.001$). The latter finding is in line with previous reports that assessed the effect of seizures prior to diagnosis [Kwan *et al*, 2003; Camfield *et al*, 1993; Kwong *et al*, 2003; MacDonald *et al*, 2000; Beghi *et al*, 2019].

Our study illuminates the consequences of diagnostic delay in epilepsy. Numerous factors may constitute obstacles to the timely diagnosis of epilepsy. Impaired peri-ictal memory may play an important role in affecting patients' ability to accurately recognise both the occurrence and nature of their seizures. Patients or family members might also not recognise subtle events as being of concern. Moreover, despite having sought help for these symptoms, physicians may have discounted their seizures as normal. Increasing both public health awareness and physician knowledge, particularly among non-neurologists, about the diversity of seizure types and the impact of epilepsy is an important step, as both are clearly areas for educational interventions.

The high inherent risk of both positive and negative misdiagnosis in epilepsy means that clinicians should always be mindful that diagnoses may be wrong and adopt a practice that involves routinely reviewing diagnoses

Diagnosis of epilepsy depends heavily on detailed history and eyewitness accounts of symptoms and, to a lesser extent, on diagnostic tests. The high inherent risk of both positive and negative misdiagnosis in epilepsy means that clinicians should always be mindful that diagnoses may be wrong and adopt a practice that involves routinely reviewing diagnoses. It is also crucial that we support our patients, their caregivers and family members throughout the diagnostic and care pathway with

understandable information, and share our decision making with them.

We suggest that increasing both public health awareness and physician knowledge about the diversity of epileptic symptoms is crucial to shortening diagnostic delay and increasing awareness of morbidity and mortality related to untreated epilepsy. More work is still needed also to understand and overcome stigma that impairs access to healthcare and medical treatment. Attention needs to be paid on implementing effective diagnostic and care pathways with the aim of reducing the delays and with genuine patient involvement in the process.

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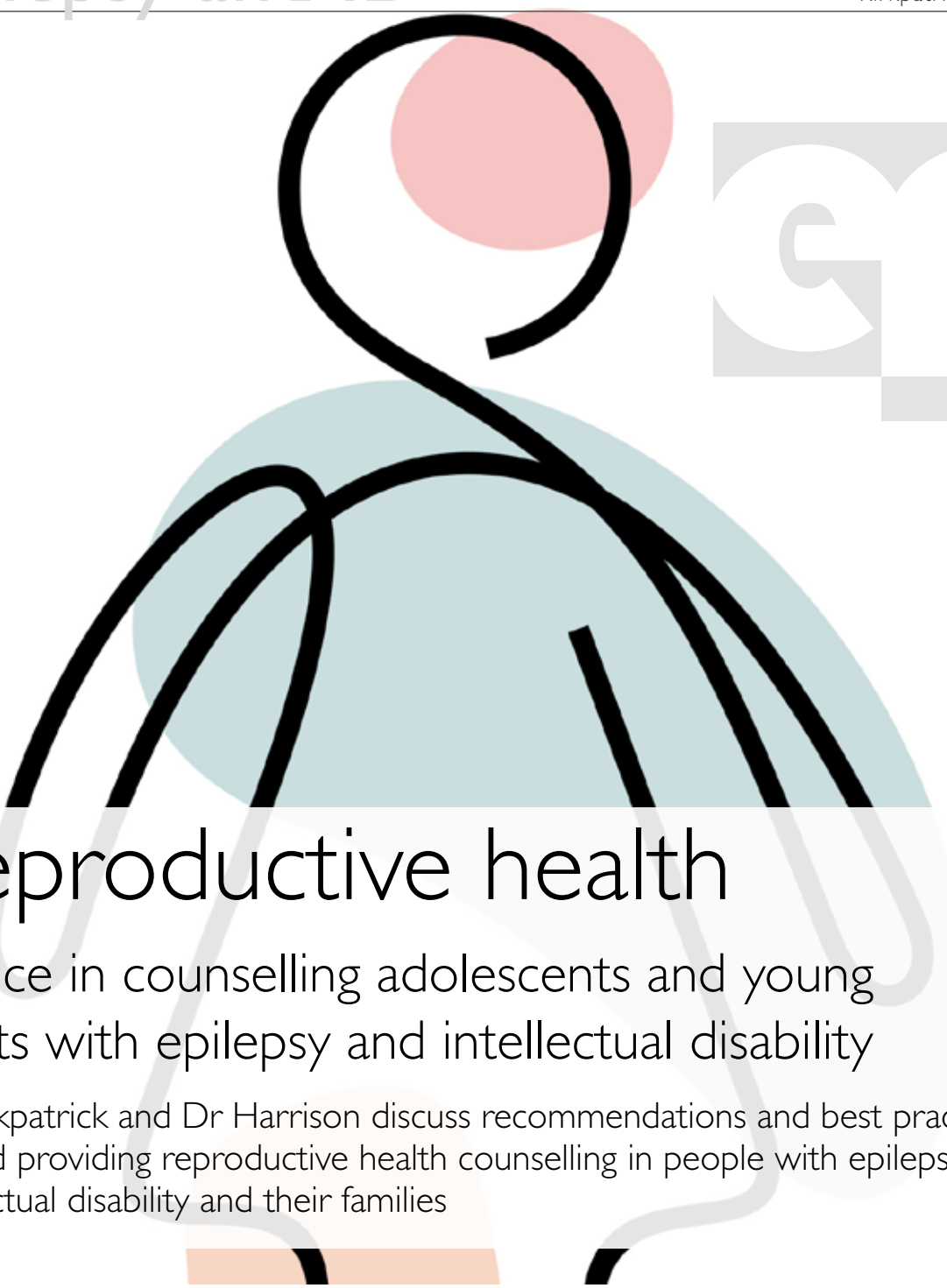


Reproductive health

Advice in counselling adolescents and young adults with epilepsy and intellectual disability

Dr Kirkpatrick and Dr Harrison discuss recommendations and best practice around providing reproductive health counselling in people with epilepsy and intellectual disability and their families

Epilepsy and intellectual disability (ID) frequently co-occur. Nearly 25% of people with epilepsy have some degree of ID, and nearly 20% of people with ID have epilepsy [Doran *et al*, 2016; Robertson *et al*, 2015; Devinsky *et al*, 2015; Kerr *et al*, 2014; McGrother *et al*, 2006; Ring 2013]. Neurologists (both paediatric and adult) caring for patients with epilepsy therefore must be prepared to address the comprehensive needs of people with ID, including reproductive health needs for patients with gestational capacity. The American Academy of Neurology advises annual counselling about reproductive health to all people of gestational capacity with epilepsy beginning at menarche regardless of their neurodevelopmental status [American Academy of Neurology].

Therefore, paediatric neurologists must be prepared to offer reproductive health counselling to adolescents and young adults with epilepsy and ID.

The American Academy of Neurology's recommended topics for reproductive health counselling include pregnancy, teratogenic effects of anti-seizure medications (ASMs), adverse interactions between ASMs and contraception, and folic acid supplementation [American Academy of Neurology]. Despite these recommendations, our research group's earlier work has demonstrated that US paediatric neurologists may, at times, struggle with delivery of reproductive health information to adolescent and young adult women with epilepsy in general [Kirkpatrick *et al*, 2020; Kirkpatrick *et al*, 2022]. However, they might struggle especially to provide counselling to people with co-occurring ID [Kirkpatrick *et al*, 2022].

In qualitative interviews, paediatric neurologists revealed that they sometimes overlook the reproductive health needs of adolescent and young adult women with epilepsy and co-occurring ID. Some perceived this population as categorically lacking needs for reproductive healthcare [Kirkpatrick *et al*, 2020; Kirkpatrick *et al*, 2022]. In a national survey among paediatric neurologists, respondents indicated that they were significantly less likely to address any reproductive health topic with an adolescent and young adult woman with epilepsy and ID compared to one without ID [Kirkpatrick *et al*, 2021]. Paediatric neurologists are not alone in these struggles; primary care paediatricians have also been shown to be less likely to address reproductive health topics with their patients with disabilities compared with their patients without disabilities [Roden *et al*, 2019].

Our research group is currently studying how patients with epilepsy and ID, as well as their parents and caregivers, would prefer to receive reproductive health information from their physicians, including neurologists. Although this investigation is ongoing, we thought it would be useful to outline some basic advice for neurologists caring for adolescents and young adults with epilepsy and ID when addressing their patients' reproductive health needs.

In qualitative interviews, paediatric neurologists revealed that they sometimes overlook the reproductive health needs of adolescent and young adult women with epilepsy and ID

Firstly, we must be aware that the adolescent and young adult patients with epilepsy and co-occurring ID do have reproductive health needs. For example, adolescent and young adult women with ID have been shown to have similar fertility rates as peers with typical development [Brown *et al*, 2016]. For that reason, as advised by the American Academy of Neurology, it is a good idea to offer epilepsy-specific reproductive health counselling to these patients [American Academy of Neurology]. Discussions should include, as previously mentioned, teratogenic risks of ASMs and their possible interactions with contraception, as well as the benefits of folic acid supplementation [American Academy of Neurology]. Neurologists can frame conversations as ones that they conduct with people with epilepsy and their families regardless of their neurodevelopmental status in order to make these conversations as 'normal' and routine as possible. In the UK, these conversations may also be led by a patient's epilepsy specialist nurse (ESN).

Even when contraceptive methods are used for menstrual regulation, instead of for pregnancy prevention, neurologists or ESNs should discuss interactions with ASMs. Enzyme-inducing ASMs that reduce contraceptive efficacy can also increase the risk of breakthrough bleeding. In addition, lamotrigine can increase the risk of breakthrough bleeding with hormonal contraception, and oestrogen-containing contraception can also reduce lamotrigine levels, potentially resulting in worse seizure control [Sidhu *et al*, 2006; Christensen *et al*, 2007]. They should discuss both the risk of interactions between already prescribed medications and provide anticipatory guidance about potential interactions between ASMs and common methods of contraception in case the patient initiates a contraceptive method. Patients and families should also be advised to call their neurologist to notify them if they are considering starting a method of contraception.

If the patient or family is interested in learning more about contraceptive methods, the specialist can provide brief counselling about different options. However, they should be referred to a paediatrician or reproductive health provider in the US, or their general practitioner (GP) in the UK for more thorough discussion and prescription of contraception. Hormonal and copper intrauterine devices are worth highlighting as highly effective methods with no known adverse drug interactions with ASMs. However, such methods should be presented as one option among many and not aggressively pushed, as directive counselling might be considered coercive. Contraceptive

counselling should respect the autonomy of the patient (and family, when the patient does not have decision-making capacity). Providers should neither avoid nor force discussions of contraception with their patients, but they can ask permission to initiate such a discussion, elicit the patient or family's goals for discussing contraception, and proceed accordingly.

Healthcare professionals should particularly avoid potentially coercive contraceptive counselling with patients and families affected by ID due to a relatively recent history of forced sterilisation in people with ID. Paediatric neurologists might, at times, be asked by parents or caretakers to give their opinion on proposed sterilisation of patients with ID, either for definitive menstrual regulation or pregnancy prevention [Kirkpatrick *et al*, 2022]. In these situations, it would be reasonable, if not entirely appropriate, for the neurologist to decline to participate in decision-making around sterilisation. In the UK, most neurologists and paediatric neurologists would not get involved in sterilisation discussions. Rarely, it may even be necessary for the neurologist to refer such cases to a medical ethics committee associated with their institution. If involved in the decision-making, the neurologist should ideally communicate with:

1. The patient (if verbal) to ensure that they understand the risks and benefits of the procedure and that it is congruent with their wishes.
2. The family (if the patient is non-verbal or does not have decision-making capacity) to ensure their understanding and explore the reasons for pursuing sterilisation.
3. The reproductive health provider involved in performing the procedure, particularly to understand what alternatives (if any) have already been discussed or pursued.

At least once a year, neurologists should take a menstrual history and inquire about any pattern of linkage between patients' seizures and their menstrual cycles. This is particularly important in patients with uncontrolled seizures given that catamenial epilepsy is a common cause of refractory epilepsy in the menarchal population [Shakeshaft *et al*, 2022]. A recent Cochrane review found that there was insufficient evidence to recommend any specific therapy for catamenial epilepsy [Maguire and Nevitt, 2021]. Strategies that have been tried, but which are not always successful, include intermittent alterations in dosages of ASM regimens, addition of acetazolamide or clobazam during high-risk times, and progesterone supplementation [Maguire and Nevitt, 2021].

Discussions should include teratogenic risks of ASMs, their possible interactions with contraception, and the benefits of folic acid supplementation

Neurologists and ESNs should be aware that taking a menstrual history in young women with epilepsy and co-occurring ID may reveal psychosocial challenges associated with the menstrual cycle. This could include hygienic and behavioural difficulties, as well as challenges with discomfort or pain [Houtrow *et al*, 2021]. Patients with such challenges can be referred to their primary care paediatrician and/or an adolescent medicine provider and/or a paediatric gynaecologist for further

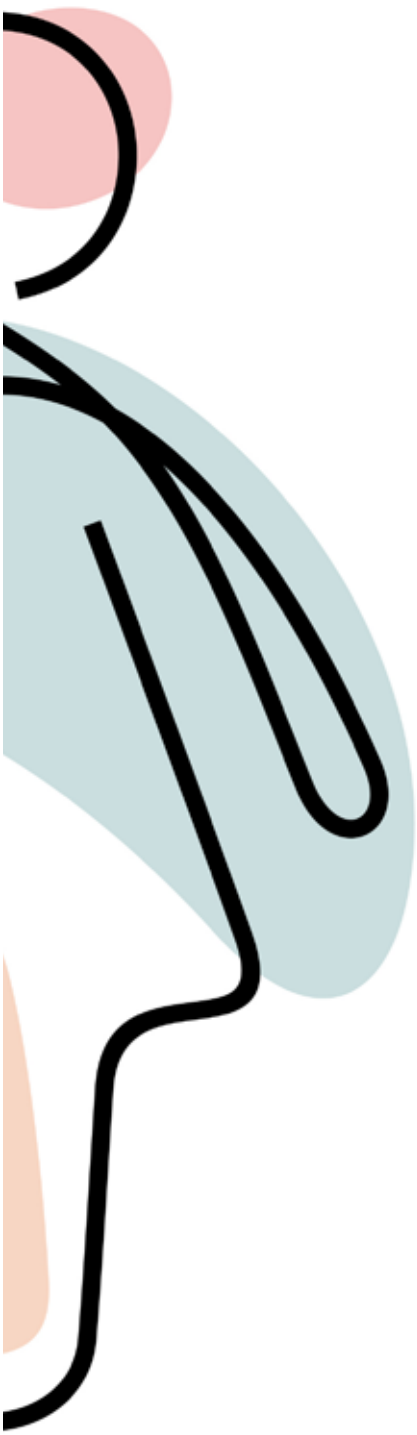
evaluation and treatment. Neurologists and ESNs should be aware of these kinds of specialists or providers in their communities when making these referrals. It might also be useful to have a database and develop a close working relationships with such providers.

By being aware or having a close working relationship with these specialists and providers in their communities, neurologists can also ensure that their patients are receiving appropriate preventive care. Appropriate preventive care for adolescents includes Human Papilloma Virus vaccination, as well as regular testing for sexually transmitted infections if sexually active [Houtrow *et al*, 2021]. Not all paediatricians and reproductive health providers in the community have the same levels of comfort and experience with people with disabilities. Neurologists may want to communicate with these practices to identify whether particular providers have interest and expertise with this population.

Healthcare professionals should be aware that children with ID may be sexually vulnerable, including being groomed, and face substantially increased risks of sexual abuse compared to peers without ID

Neurologists or ESNs can also follow best practices in adolescent healthcare by offering verbal patients confidential time apart from their parents or guardians to speak privately [Maslyanskaya and Alderman, 2019]. However, this may also depend on the level of the adolescent's ID. Neurologists or ESNs can inform families that they universally offer this opportunity to their adolescent patients and that it is part of learning how to interact with the medical system more independently while transitioning from adolescence to adulthood. Ideally, during confidential time, neurologists should take a detailed social history, following a HEEADSSS (Home, Education/Employment, Eating Activities, Drugs, Sexuality, Suicide/Depression, and Safety) or SSHADESS (Strength, School, Home, Activities, Drug/Substance Use, Emotions/Eating/Depression, Suicidality, Safety) model [Ginsburg, 2022; Smith and McGuinness, 2017]. The patient should also be given an opportunity to ask any confidential questions. Neurologists should also be sure to communicate in plain, developmentally appropriate language.

Healthcare professionals should be aware that children with ID may be sexually vulnerable, including being groomed, and face substantially increased risks of sexual abuse compared to peers without ID [Wissink *et al*, 2015]. While it is not necessarily recommended for neurologists or ESNs to screen for or elicit disclosures of abuse, at a minimum, they should be prepared to address concerns volunteered by patients or parents about abuse. Providers should maintain appropriate lists of community referrals for people who have experienced abuse or violence, including having procedures in place should a patient confidentially disclose abuse in the home. Healthcare professionals should also be familiar with mandatory reporting procedures to both child and adult protective services. From a preventive standpoint, while gathering an adolescent's social



history, neurologists can inquire whether patients have ever received education about safety and sexuality, and provide referrals to community resources offering such education.

In summary, people with epilepsy and ID have reproductive health needs – some distinct from and some shared with their peers without ID. Paediatric neurologists and ESNs should be prepared to offer counselling about reproductive health to patients with epilepsy, both with and without co-occurring ID (or to their families if patients are nonverbal or who have severe ID). Paediatric neurologists should follow best practices for adolescent-friendly care, such as offering confidential time and conducting a detailed social history, with verbal patients regardless of neurodevelopmental status. Having this become routine is a helpful strategy to proceed with this counselling.

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Can epilepsy specialists become extinct?

Are we slowly slipping in to an epilepsy staffing crisis, just when we need it least?

A generation or two ago (and this is extrapolated from poorly remembered anecdotes misheard late at night), there would be a neurologist for the North of England, one for the West country and sixty or so for central London. A generation or two ago, there was little epilepsy surgery and treatment was low-dose or high-dose bromide. A generation or two ago, patients might have faced a more paternalistic or patronising approach to diagnosis. In short, neurologists were a scarce resource, and they flipped a coin for diagnosis (one side 'epilepsy', the other 'probably not epilepsy, but let's treat just in case'). All jokes aside, things were certainly different.

We are now in 2022. We have international recommendations for epilepsy (World Health Organisation Intersectoral Global Action Plan), NHS England guidance with the National Institute for Health and Care Excellence (NICE), and there are shiny and exciting medications waiting to be prescribed. We have superb epilepsy charity partners (and yes I include you here, Epilepsy Action). People with epilepsy quite rightly demand a lot from us, and personally, I feel that they should be demanding a lot more. Wouldn't it be nice to clone yourself and have another epilepsy buddy to cover your work? But even if the NHS funding fairy made all my wishes come true, could we even come close to plugging the gaps?

As my mother used to say, "Epilepsy specialist nurses do not grow on trees, you know." This was one of her favourite aphorisms, along with "EEG technicians, like Rome, were not built in a day." And if she offered me advice about becoming an epilepsy consultant, I did not heed it. Not only are specialists relatively expensive to employ (not as expensive to the NHS and UK PLC as badly controlled epilepsy, I'd wager), but they are not trained overnight. There is not a cohort of 'oven ready' trainees looking for posts currently.

I am very concerned about the impression we make on trainees in clinic. Can we inspire people with phone clinics? Can we sell visions of excellence when our video telemetry beds are empty or the surgeon's knife gathers dust waiting for theatres to reopen? Are massively overbooked clinics a good example to set our juniors? They support our clinics and think, 'Gosh I was interested in epilepsy, but I'd rather do something a little easier, like work in an illegal South African diamond mine.'

There is no reason why we should accept being a Cinderella speciality, and being adequately staffed is the absolute minimum we should aspire for. Or is the answer staring us in the face? Do we need to re-energise GPs? Teach epilepsy care differently? Help them become an expert in the four or so major drugs we prescribe (bye-bye bromide) and the side effects, monitoring thereof – and we take on the rest? Supercharge the annual GP review to make it impactful, meaningful and give GPs the funding back for this? Would a nationally acknowledged educational platform allow people to be reassured that they are working within their competence, and then support GPs with an accessible specialist?

Can epilepsy specialists become extinct? I am not sure how I'd feel if the WWF starts campaigning against the destruction of my habitat. It is not that we are leaving or that we are losing big numbers of us – rather that we have tolerated such low staffing levels for so long. I am certain that if we do nothing, we will become a case study of what happens when good will and good intentions are not enough.

Markus Reuber

Highlights

Top picks from *Seizure*

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

It's widely understood that about one third of all individuals with epilepsy fail to become seizure-free with anti-seizure medications in the long term, even with our ever-expanding ASM choices. In economically developed countries, epilepsy surgery has become an established treatment option for (older) children and (younger) adults with such epilepsies. There is evidence from randomised controlled studies of the many potential benefits. However, there are ongoing uncertainties about the role of epilepsy surgery in the youngest children (as well as in older adults).

My editor's choice from issue 96 of Seizure is a systematic review and meta-analysis of epilepsy surgery in the first year of life by Konstantin Makridis *et al* [2022]. In addition to outcomes around seizure control, quality of life and reduced risk of death, the ability of the child to develop to their full potential is a consideration that is especially important in the treatment of very young children. The potential to recover from brain surgery and to optimise the opportunities for normal intellectual and social development are greatest when epilepsy surgery is carried out early in life. The high level of plasticity of the brain may protect children operated on at this time in their lives without the sort of neurological deficits that would be unavoidable if surgery is postponed until they are older. However, for several reasons, epilepsy surgery is also most challenging in the youngest children.

Makridis *et al* found a total of 158 reported outcomes of epilepsy surgery in infants up to six months of age in 16 scientific publications. Most children had undergone hemispherotomies rather than focal resections. The rates of achieving seizure freedom were impressive and similar to those reported in adults (although adults would rarely be candidates for hemispherotomies). While 71% became seizure free following hemispherotomy, 58% achieved this status after focal surgery. However, the number of complications was also quite high (27.7%). Hydrocephalus was particularly common, affecting one in six infants postoperatively. Five of every six patients had shown signs of cognitive impairment preoperatively. After surgery, some cognitive improvements were seen, especially among those infants who had become seizure free. One in every five infants who had undergone epilepsy surgery could subsequently stop ASM treatment.

These findings suggest that epilepsy surgery should definitely be considered in infants with focal seizure disorders amenable to epilepsy surgery. However, the authors conclude that it should only be carried out at specialised centres with experience of epilepsy surgery in this age group.

Non-persistence with ASMs

The regular ingestion of antiseizure medicines (ASMs) continues to be the mainstay of epilepsy treatment. With optimal use, ASM treatment should allow seven out of every ten people with epilepsy to achieve full seizure control. Epilepsy is not always a lifelong disease, but ASM treatment typically has to be continued for several years. This is needed to achieve and maintain seizure control and to protect people with epilepsy from the harms of uncontrolled seizures, including injury, disability and death. Unfortunately, in reality the proportion of individuals who actually achieve full control of their seizures, even in countries like the UK with free access to diagnostic facilities and treatments, has been estimated to be as low as 50% [Joint Epilepsy Council, 2011].

Non-adherence to ASMs is likely to make an important contribution to the gap between what medication could achieve in an ideal world and what it does achieve in reality. A systematic review previously published in Seizure related non-adherence to a number of factors. These were specific beliefs about medications, comorbid depression and anxiety, poor medication self-administration management, uncontrolled recent seizures, frequent medication dosage times, poor physician-patient relationship and social support [O'Rourke and O'Brien, 2017].

My editor's choice from issue 97 of Seizure is a research study by Alex Marshall *et al* using routinely available health service data from a total of 6,449 patients to explore one particular manifestation of non-adherence: the non-persistence with a newly started ASM [Marshall *et al*, 2022]. The authors focussed

particularly on the effects of sociodemographic variables and comorbidities but also looked at the effects of ASM choice on persistence. The most striking finding is that only 45% of patients who were started on a first ASM after they had received a diagnosis of epilepsy persisted for at least one year. Persistence rates were not higher in the 46% of patients who received a second ASM during the eight-year study period. Almost 10% of patients never persisted with any ASM for at least one year. Persistence for at least three months ranged from 25.7% to 78.6% between different ASMs, with lacosamide, lamotrigine and levetiracetam faring much better than carbamazepine or topiramate. To some extent, non-persistence may have reflected the efforts of clinicians to achieve seizure control with as few side effects as possible. However, persistence was significantly lower in younger people and those who had previously been non-persistent with ASMs. This suggests that attitudes towards medication taking, risk, and social and educational factors may also have been relevant.

This paper demonstrates that epilepsy management models restricting the input of specialist service to the diagnosis and prescription of a first ASM are likely to fail many people with epilepsy. In particular, those who need more time, education and expert input after the diagnosis of epilepsy and before they have found a treatment that suits them and that they are able and willing to take.

Postictal generalised EEG suppression

Bilateral tonic-clonic seizures (BTCS) are commonly considered as the 'final common pathway' of epileptic activity in the brain, and as if they were not only stereotyped in one individual but across all patients with epilepsy. This may be one of the reasons why, in clinical practice and research studies, the number of BTCS is considered a meaningful measure of the effectiveness of medical or other therapeutic interventions for epilepsy.

In reality, things are more complicated, of course. Firstly, the subjective impact of BTCS on a person with epilepsy is likely to vary depending on the circumstances in which the seizure has occurred. In addition, there are also major objective differences between BTCS. Some BTCS are associated with injuries or incontinence, others are not. BTCS may only last 30 seconds or continue for over two minutes. What is more, electroclinically definable phases within a single BTCS (including those characterised by the focal build-up of epileptic activity, tonic or clonic manifestations) differ in length intra- and inter-individually [Pan *et al*, 2016]. And, importantly, BTCS differ in terms of the occurrence and duration of postictal generalised EEG suppression (PGES), a recognised risk factor for Sudden Unexpected Death in Epilepsy (SUDEP) [Lhatoo *et al*, 2010].

My editor's choice from issue 98 of Seizure is a systematic review and meta-analysis by Yang *et al*, which examines factors determining the likelihood of PGES development [Yang *et al*, 2022]. The first finding is that PGES is a common phenomenon, having been identified after 23-86% of BTCS across the 15 studies contributing to this meta-analysis. Factors associated with the occurrence of PGES included a longer tonic phase duration, sleep at BTCS onset, and an older age at epilepsy onset. The duration of the whole tonic-clonic or clonic phases, and the length of the epilepsy history, were not associated with PGES. Another factor which had no impact on the PGES risk was early oxygen – this meta-analysis therefore provided no justification for postictal oxygen administration.

Given that seizure phases have become easier to measure using wearable technology, it should now be technically possible to capture the duration of the tonic phase of BTCS in more naturalistic settings over the longer term. The findings of this study suggest this may be a more meaningful objective treatment outcome for future studies than the measures listed above.

Further reading

Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics, 2011. https://d3imrogdy81qei.cloudfront.net/instructor_docs/373/29_05_2016_Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11.pdf

Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol 2010;68:787-96.

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Marshall AD, Pell JP, Askarieh A, Leach JP, Heath C. The influence of demographics and comorbidity on persistence with anti-seizure medication. Seizure 2022; 97:88-93.

O'Rourke G, O'Brien JJ. Identifying the barriers to antiepileptic drug adherence among adults with epilepsy. Seizure-European Journal of Epilepsy 2017;45:160-8.

Pan S, Wang F, Wang J, Li X, Liu X. Factors influencing the duration of generalized tonic-clonic seizure. Seizure 2016; 34:44-7.

Yang X, Yang X, Liu B, Sun A, Zhao X-H. Risk factors for postictal generalized EEG suppression in generalized convulsive seizure: a systematic review and meta-analysis. Seizure 2022;98:19-26.

The 'killer' questions

The questions that stop us in our tracks – and their answers!

After a fascinating Epilepsy Research UK (ERUK) Share Network Conference, we share the 'killer' questions from the audience of the organisation's volunteers. They got right to the heart of the topics in the session – and here we bring you the answers. Kami Kountcheva reports

The Epilepsy Research UK Share Network Conference took place on 17 May 2022, sharing recent research advances, and information on the research process and the underlying mechanisms involved. The conference brought together many of the volunteers and supporters of ERUK, and offered a programme of expert speakers, including researchers and clinicians.

Dr Rhys Thomas, our very own medical editor and consultant neurologist at the Royal Victoria Infirmary in Newcastle, spoke at the conference. In true form, he championed patients for all their invaluable involvement in research. Not only are patients at the core of research – their conditions, their experiences, their participation, their perseverance – but they often bring what Dr Thomas called "the killer question". The one where you think: 'I don't actually have an answer for that. Why don't I have an answer for that?" They're often the spark that lights a fire in researchers to answer some of these missing questions and advance our understanding of epilepsy further.

The research process: Lab-based research

In this session, Prof Stephanie Schorge from University College London (UCL) talked about animal models in research. To describe the importance of animal models, she first gave an example of a condition with poor animal models – Alzheimer's disease. She said cells and mice don't model memory loss, and this can stifle

research on these very key aspects of the disease.

Prof Schorge said we are lucky in epilepsy that we have a lot of animal models – allowing us to study different forms of epilepsy, both acute and chronic, and monitor things like EEG. Animal models can also help with the other aspects of epilepsy, often of more concern to patients than seizures, such as learning and memory, anxiety and adverse effects of treatments. Work at the moment is looking at treatments that stop epilepsy itself, rather than treating seizures.

Addressing the elephant in the room, Prof Schorge also discussed ethics around animal models, in her capacity as the Head of the Ethics Committee at UCL. She said that there have been enormous changes in the last 30 years, and today researchers make sure their animals are safe, comfortable and happy. This is partly because healthy animals make better models, but also because researchers feel compassion for their animals. She added that someone is in charge of ensuring the animals are being properly looked after, and groups of people are invited to visit the research facility and see the animals.

Prof Mike Cousin from the University of Edinburgh presented next on the role of cell biology in epilepsy research. He established cells as the "basic unit of physiology" and discussed intra- and intercellular communication. He said that 10-15 years ago, anyone would have been surprised by the suggestion that defects in neurotransmission may underlie certain forms of epilepsy. However, he shared an example of a mutation in the Dnm1 gene affecting proteins involved in neurotransmission.

The research team found that the mutation is a dominant negative, meaning that heterozygous individuals would have the negative effect. Looking at mouse models, the team saw that endocytosis was disrupted, the brain circuits were affected and that there was seizure activity. The team knew the gene mutation responsible and the exact deficit it created, so they could screen treatments on the cells in a dish until they found one that corrected the deficit and, importantly, didn't act on unaffected neurons and circuits. Prof Cousin concluded saying this all highlights that cell biology can answer a lot of questions we couldn't do with animal models alone.

Finally, Dr Gareth Morris, also from UCL, presented on gene therapy, drawing a unique parallel with Batman (hear him out). He discussed current challenges with treatments and said better treatment would:

The hope is that by restoring normal function to circuits, we would not only stop seizures but also restore the ability of that circuit to do its normal function

- Be long-lasting or permanent
- Be restricted in space to just the seizure focus
- Only affect the particular cells driving the seizures
- Be active only when seizures are likely to happen, and be inactive the rest of the time

He explained that gene therapy would be delivered with a viral vector carrying a helpful gene which would work with promoter specific to the target cells, which allows for targeted, long-lasting therapy. The team is currently working on ways to make treatments only active when they're needed, and inactive the rest of the time. Dr Morris is working on gene therapy affected by a natural molecular marker of seizures – microRNAs, which would act as the bat signal (to return to our Batman analogy). Batman (our therapy) would only become activated in response to this signal, and then inactivate and lie quietly in the shadows until the next film. I mean until it's next needed.

How would gene therapy help with symptoms of epilepsy outside of seizures, such as cognition and mood?

GM: We don't necessarily understand these aspects of epilepsy that well yet. A lot of these comorbidities occur because the circuits causing epilepsy also have another function. Memory is a good example. Seizures often occur in the part of the brain where memory occurs and that's why people have challenges with memory. So the hope is that by restoring normal function to these circuits, we would not only stop seizures but also restore the ability of that circuit to do its normal function.

It's something that we test in our animal models, we have behavioural tests in memory. It's equally important for us to address things like memory as well as seizures. Also, the whole idea of creating specific treatments is that the treatment itself doesn't have any further impact on other aspects, like memory.

How fast is gene therapy advancing so that it can be targeted at the masses rather than the few? What hope is there for people with chromosomal disorders where the pathogenic genes aren't always known?

GM: With the therapy I'm working on, what we're doing is inserting a potassium channel which will reduce the excitability of those cells. That reduction in excitability is regardless of the underlying mechanism, and that's

Dr Gareth Morris, Prof Stephanie Schorge and Prof Mike Cousin answering questions from the audience

one of the really promising things with this kind of gene therapy. We don't necessarily need to know the exact underlying genetic mechanism because we are still able to treat the condition. Also, we are starting to understand cell models better and we have tools called antisense oligonucleotides which can be used to manipulate specific genes in ways that can be quite helpful with those kinds of epilepsies.

SS: Looking back even just a few years, we'd have this feeling of 'are we just treating the very few? How much are these treatments going to get out to the world?' A very thin silver lining to the pandemic is the cold chain supply chain and the vast advancement in developing these viruses used in the vaccines, which are a form of gene therapy. They are using many of the same tools and the infrastructure that we hope one day to capture to deliver gene therapy [for epilepsy] throughout the world.

Also, most of the animal models I talked about did not have a genetic cause. In those animals, we're treating the epilepsy [regardless of] what has caused it. That won't happen in all genetic epilepsies, but it does give hope that this treatment may help independent of the cause of one gene or another, or an injury.

Another way to try to reduce cost is to repurpose drugs that are already approved for use in people. There is screening going on currently, at a cellular level, of drugs that are perfectly safe to use in people, and we are looking for anti-epileptic potential

MC: It's something we wrestle with all the time, that so few people in the world have a specific mutation. One strand of hope is that when more people look at these genetic epilepsies, you do tend to see convergence points, even at a cellular level. It might be that there will be maybe 10 different points where we could potentially intervene to help a far broader spectrum of people than just the 10 people in the world who have this particular mutation.

Would you be able to treat multiple types of seizures with gene therapy?

SS: It will be a challenge, but it is something we are looking at now. One of the big projects that we and different groups around the world are looking at, is how networks and circuits come together in focal epilepsy. It's something that we look at with caution, and the 'Batman' approach gives us much more hope about treating larger parts of the brain. With gene therapy you do want to be cautious, you don't want to treat the bit that isn't causing [the problems].

GM: I mentioned this idea about antisense oligonucleotides –what's exciting about those is they are really tiny molecules, which means that they spread quite far around the brain. In some situations that's not great, [if you have a single focus epilepsy], but in the case where you have a multi-focal epilepsy, that might actually be an advantage. So there are other [treatments] being developed which might have different characteristics and may be suitable to different types of epilepsy.

Is gene therapy cheap and would it end up stymied by pharmaceutical drugs that are cheaper even if they are less effective?

SS: We are advancing slowly towards trial, and gene therapy is notoriously expensive. One of the reasons is that it's stupidly hard to make, so that translates to stupidly expensive. The other is that most gene therapies are focused on treating rare genetic diseases. So, if you have a treatment that is targeted to a small number of people in the world, that cost of development is spread over a very small number of patients. In the sort of epilepsy that we, and other groups, are starting to treat, we estimate there's a prevalent population of people who could benefit of about 25,000 in the UK alone. So instead of dividing your £2m development fee across 10 patients, you are now dividing across thousands. If you extend that globally, it's a much bigger pool. We are hoping that the cost of

gene therapy will be less than the cost of resective surgery. We can't promise, but that is our goal, to make this a practical thing.

MC: Additionally, at the cell level, another way to try to reduce cost is to repurpose drugs that are already approved for use in people. There is screening going on currently, at a cellular level, of drugs that are perfectly safe to use in people, and we are looking for anti-epileptic potential.

The research process: research in a hospital setting

Dr Rhys Thomas, from Royal Victoria Infirmary, answered the question "What is clinical research?" He explained that to him, it's about being with people. He discussed the transfer of information – either giving information to patients, such as conversational therapy, or taking, in terms of things like information, DNA or biopsy.

The aim of this research is to change something, Dr Thomas said, such as treatment (does it work, is it safe?), policy or care (how to treat without causing damage to memory, for example). He highlighted the variability of clinical research, including treatment research, prevention research, screening, genetic, imaging, data analysis and more. He also highlighted natural history studies as a good source of data. Dr Thomas also added that the patient experience has so far been missing – what does research look like to the individual? He concluded that despite it being hard work and expensive, clinical research is really rewarding.

Dr Kate Baker, from the University of Cambridge, next discussed whether genetics research can solve unanswered questions in epilepsy. She said there has been a technological revolution in our ability making things like next generation sequencing possible. Now there is an up to 50% chance of finding a diagnosis, with the highest chance being in people with early onset, treatment resistant epilepsy, who have additional problems, such as learning difficulties.

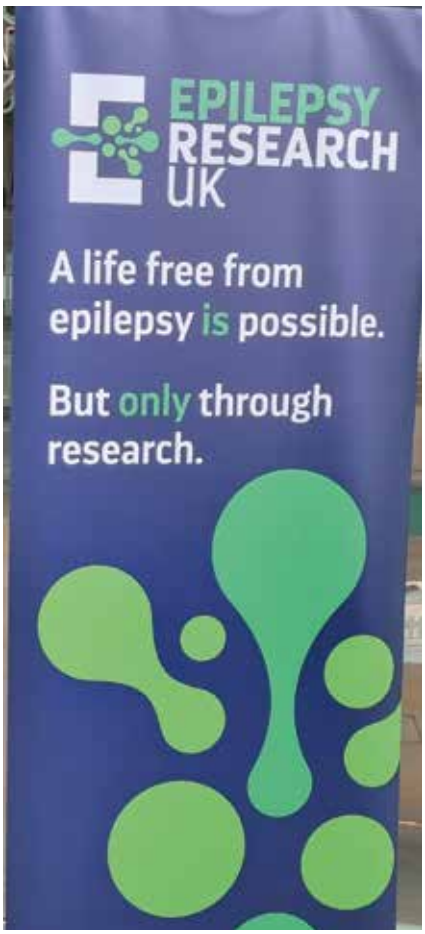
The genetics service in England has been organised to remove the postcode lottery, Dr Baker said. There is a National Genomic Test Directory, a centralised sequencing pipeline, seven laboratory hubs, 13 genomics medicine centres and a national genomics reference library. The benefits include patients being able to understand more about themselves, the history and background of their condition and what it means for the future. Dr Barker added that "diagnosis turns the key towards personalised treatment."

Dr Baker said her group is now looking at groups of epilepsies, and the similarities and differences within them. She is also going around with her team meeting with people and trying to understand how epilepsy really affects them. A focus for the team is also the mental health wellbeing of parents and carers to people with these kinds of epilepsies.

A focus for Dr Baker and the team is also the mental health wellbeing of parents and carers to people with more complex epilepsies

Last in this session, Prof Markus Reuber, from the University of Sheffield, discussed technology in epilepsy clinics. He described some of the ways technology has been integrated and has advanced in epilepsy clinics. They include tests and scans before surgery, imaging, deep brain stimulation (DBS) and vagus nerve stimulation (VNS), smart pills and smart medicine bottles. However, he also identified gaps, where technology could be developed and used. DBS and VNS don't stop seizures, for example, just aim to reduce them. Seizure diaries are still used to monitor frequency, which we know miss around a third of seizures. There is not yet a lot of technology involved in making a diagnosis, Prof Reuber said, and it relies on a doctor's knowledge.

Prof Reuber said that there is work going on to develop a digital doctor, using a computer program looking at diagnostic features and using a classifier to diagnose if symptoms are of epilepsy or not epilepsy. He said the biggest change



with technology is smart watches, which can identify tonic-clonic seizures well and are getting better at other seizure types too, and the potential of seizure forecasting.

How do you choose which clinical research questions to answer?

KB: This is one of the most fun and challenging parts of the work. I choose three things – the first essential ingredient for a clinical research question comes from the clinic, from a patient or family member asking you a question you can't answer. The second is, is there a chain of research I can build on? Because starting it from scratch is very hard. And the third thing is feasibility – is this a question I can answer? For that I need a method, people – partners, patients, participants and families – and skills in the collaborators around me. So these are the three components – the question, the research history and the feasibility.

RT: Sometimes we can get distracted by a 'new project' energy, that buzz, that feel you get with something new and shiny and exciting. And, unfortunately, the research funding landscape can reward that. Some of the more successful teams are the ones who pick a theme and become experts within that area.

MR: The only addition I have is that many of the advanced complex methodologies involve quite a lot of learning about the method. And once you've learned it, you're likely to look for questions you can answer with that same method. This can sometimes be a good thing, and sometimes, there's a risk that research funders could waste money on questions we can answer, even if they're not relevant.

Is there an overlap between epileptic and functional seizures and how do you go about researching these?

MR: There are overlaps and I think it's wrong for neurologists, who are experts in diagnosing different types of seizures, to regard functional seizures as not to do with them. There are still some neurologists with a view like this, but I'm hoping it's a diminishing number. Given that we are experts in diagnosis and have an increasing understanding in functional seizures, we should treat them just like we treat epilepsy, and it should just be a part of what neurologists do. We shouldn't just send people away after diagnosis.

In terms of overlap of epilepsy and functional seizures, I do think the mechanisms are different between functional seizures and epileptic seizures. But epileptic seizures, for instance, are a risk factor for developing functional seizures, so there is a group of people who will have both epileptic and functional seizures. There can be a range of different types of relationships between epilepsy and functional seizures. Sometimes people can have a focal epileptic seizure that immediately goes into a functional seizure. Or some have epileptic and functional seizures at different times. Some research in this area involves recording seizures with video EEG to better understand transitions, what kind of epileptic seizures are involved and what kind of brain structures might be involved in those who then go on to have functional seizures. Epidemiological and psychotherapy research can also be done. While the two different types of seizures are very different in nature, there is definitely overlap and I hope this will be increasingly recognised.

Given that we are experts in diagnosis and have an increasing understanding in functional seizures, we should treat them just like we treat epilepsy

Where do you see seizure forecasting in the next 5-10 years?

MR: There's really interesting research data from the research study that was done with an implantable device. It continuously records EEG and also stimulates the brain. We know very well, from the people who have had these devices, when exactly the brain has been producing these epileptic discharges and when they've had seizures. And what it turns out is that most of the time – maybe three-

quarters of the time – there is some kind of pattern to the seizures. They maybe happen in the morning, every 10 days, once a week, or once a month, for example, so there are certain clusters. And these rhythms were often unknown to the individuals who had the seizures before the research was done. So, just by recording seizures exactly with these devices, you often get some kind of rhythm or pattern.

I think in 10 years' time, a fair proportion of people with epilepsy could have wrist-worn devices that would tell them that they're either at low or high risk of an epileptic seizure

In addition, we are learning more about the autonomic nervous system and how it responds to epileptic activity. In many cases, but not all, with epileptic seizures which seem to just start one second, there is often a build-up to them. This is characterised by a certain state of the autonomic nervous system, which you can then measure with these devices. So, I think in 10 years' time, a fair proportion of people with epilepsy could have wrist-worn devices that would tell them that they're either at low risk or at high risk of an epileptic seizure. I think that is a realistic prediction.

Looking to the future

Dr Kathryn Bush, from the University of Edinburgh, spoke about understanding patient data in epilepsy. She explained that data research uses routinely collected data from places like medical records, prescriptions, A&E and blood tests. She called patient data a "precious resource", explaining that it shows more of a full picture than trial data, which may be subject to selection bias. Dr Bush said its uses extend to improving care for individuals and populations, including things like safety, diagnosis and services.

Dr Bush reassured the audience that their data is kept safe, secure and confidential, within secure IT systems with strict controls. She also shared research she is working on looking at why epilepsy is more common in the most deprived areas, and what can be done about this. She said patient data could be used to model what interventions might make the biggest change to this.

The last talk came from Prof John Terry, from the University of Birmingham, who discussed mathematical modelling in diagnosis. He explained how mathematical models work and explained that we have equations that can model some epilepsies. He explained brain network ictogenicity (BNI) – the ability of a given network to generate seizure-like activity – and said this could be calculated to show a risk of seizures developing.

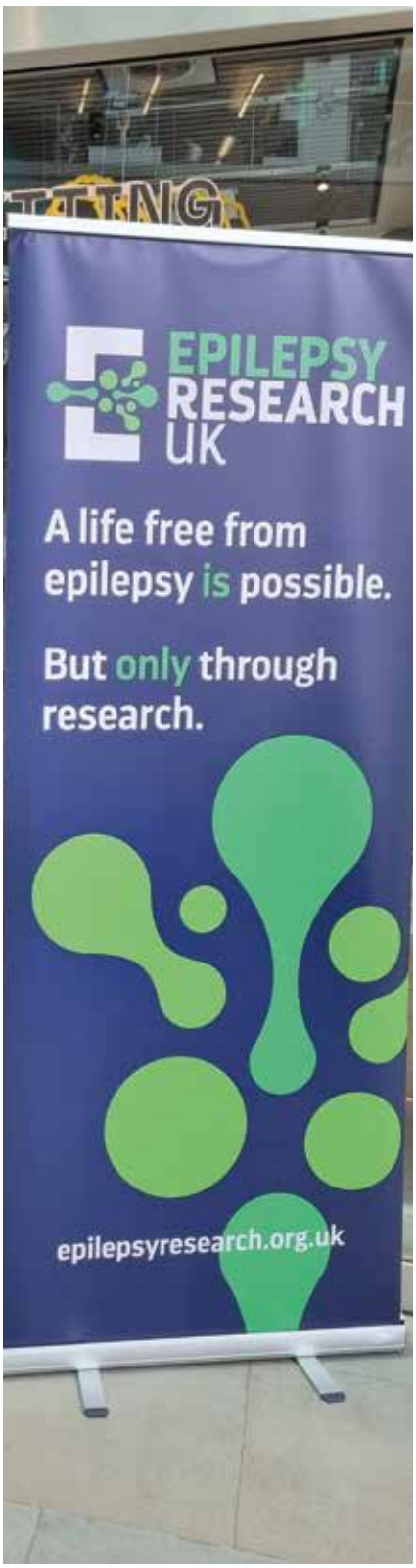
Prof Terry said with inconclusive EEGs, which comprise around 70% of EEGs in the first seizure clinic, short segments of normal EEG data can be used to inform a model. EEG can then be simulated – a year's worth of data in a matter of minutes. He said the model allows us to change the parameters and see how easy it is for seizure-like behaviour to emerge, which can be used to inform risk level.

How does socioeconomic data link with genetics in epilepsy?

KB: I think there are two different aspects to it. In the adult late onset epilepsies, we know that they are linked to underlying socioeconomic

Dr Kate Baker, Dr Rhys Thomas and Prof Markus Reuber joining the session remotely

Prof John Terry and Dr Kathryn Bush at the final Q&A session



factors. We see that it's more common in the most deprived communities, and we can make a really good guess about the reasons for that, because we've got data elsewhere. But we've never looked at it in the UK.

In terms of the genetic epilepsy, there are some data out there which show that in children who get epilepsy before the age of three there is social patterning. We don't understand why that is, and there are many different theories around genetics and epigenetic changes and things which pass on through generations. I think it's a really exciting area but it's an area that needs a lot more research – I don't have an answer.

Where else could we apply computer model techniques?

JT: I think there's a lot of potential, at least from network-based approaches, to understand other neurological conditions. There have been several research studies into pretty much every neurological condition that have shown if you take cohorts of those with a neurological condition and compare to those without you will find differences between them. But we don't know how that maps onto cohorts of people with a neurological condition versus cohorts of people who are suspected of having that neurological condition. And we want to try to go that step further and understand how that maps onto each individual. This is one of the important steps that you have to take to go beyond populations to individuals when it comes to diagnosis.

We're also interested in prognosis. We have some interesting pilot data that shows that when measuring the risk of seizures from segments of apparently 'normal' data, it changes in response to medication. In particular, after a few months of taking a medication, if you're responding well to the medication, the risk score appears to drop relative to the original score you had. And in cases where the treatment isn't working so well, that doesn't appear to happen. That's something we're excited about and looking into at the moment, but it is only pilot data.

Is better stratification in NHS coding systems needed to better understand different types of epilepsy and better use this data?

KB: I fully agree that we need a better coding system. There are different things that we can do to make sure that we're accurately identifying people with epilepsy. We can use different combinations of hospital codes, GP codes and medication codes, for example. There are a lot of validation studies looking at how accurate the code combinations are at identifying epilepsy and identifying causes of epilepsy, like stroke. I think we will be doing our own validation studies as well to make sure we're identifying the right people.

JT: And from a mechanistic perspective it's interesting to think how some of these approaches could add value. Traditionally epilepsy has been a kind of clinical phenomenology-based definition. The analogy I like to give is diagnosing epilepsy is like a mechanic observing your car drive down the road and when you have an accident concluding there's something wrong. What we're trying to achieve is actually to say 'is there a problem with your tyres? Is there a problem with your brakes?' prior to you having a crash. Tyres and breaks have different mechanisms even though the outcome is the same. Moving away from epilepsy as a single condition is going to be increasingly important in developing more appropriate treatments or better use of the existing treatments.

Dates for the diary

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

2022

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

4-8 July
XVI Workshop on Neurobiology of Epilepsy (WONOEP 2022)
Talloires, France
bit.ly/3NfPTU0

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

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

14-16 September
14th International Epilepsy Colloquium
Lausanne, Switzerland
epilepsy-colloquium2022.com

16 September
Irish Epilepsy League Annual Meeting
Dublin, Ireland
bit.ly/3M0dBlV

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

2023

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

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

Next issues:

Rachel Batchelor

Dr Batchelor talks about epilepsy and mental health in young adults

Matthew Campbell

Dr Campbell discusses the blood brain barrier and its role in epilepsy

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

kkountcheva@epilepsy.org.uk

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