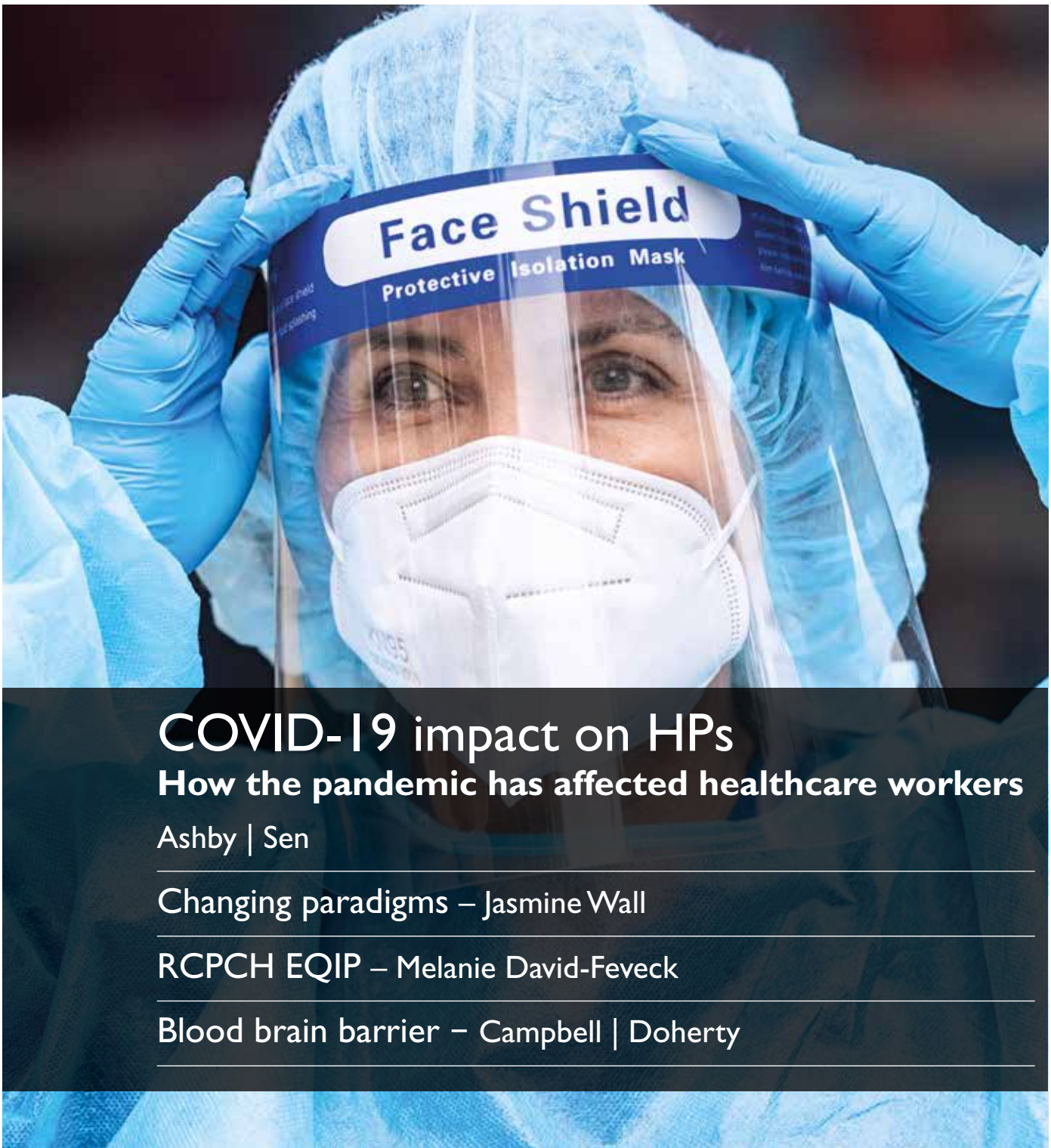
epilepsy action

issue sixty six / Autumn 2022 £3.50
(Free to Epilepsy Action professional members)

epilepsy professional



COVID-19 impact on HPs

How the pandemic has affected healthcare workers

Ashby | Sen

Changing paradigms – Jasmine Wall

RCPCH EQIP – Melanie David-Feveck

Blood brain barrier – Campbell | Doherty

VNS Therapy®

SENTIVA®

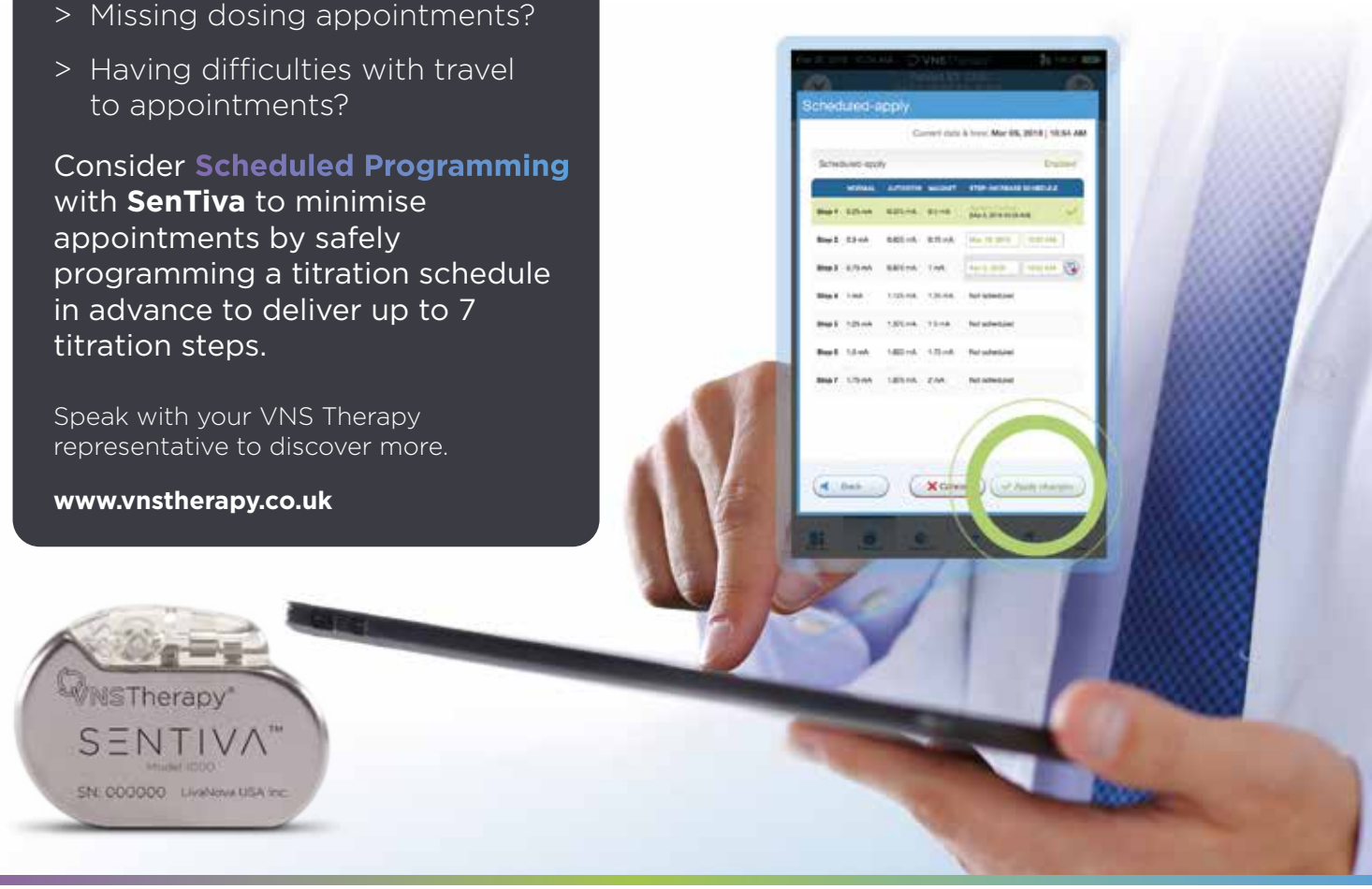
Are your patients:

- Concerned about visiting the hospital for appointments?
- Missing dosing appointments?
- Having difficulties with travel to appointments?

Consider **Scheduled Programming** with **SenTiva** to minimise appointments by safely programming a titration schedule in advance to deliver up to 7 titration steps.

Speak with your VNS Therapy representative to discover more.

www.vnstherapy.co.uk



LIVANOVA USA INC.,
100 Cyberonics Boulevard
Houston
Texas 77058 USA

LIVANOVA BELGIUM NV
Ikaroslaan 83
1930 Zaventem
Belgium

INTENDED USE / INDICATIONS:

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

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

Visit https://vnstherapy.co.uk/healthcare-professionals/brief-summary to view important safety information.

Not approved in all geographies, consult your labelling.

Please refer to the VNS Therapy System Epilepsy Physician's Manual August 2020 OUS version for complete information on programming and diagnostics. VNS Therapy Physician's Manuals. LivaNova USA, Inc.; Houston, Texas.

 IM-7600269-EPI

LivaNova
Health innovation that matters

Welcome to *Epilepsy Professional,* another bumper edition which reflects the rich tapestry of caring for people with epilepsy. We offer some thought-provoking articles, some education, some things to challenge and inspire. This edition brings you: The brain! COVID! Collaborative working! And older people!

It was once said, somewhat uncharitably, that a definition of the blood brain barrier is the 'ether screen' or the make-shift curtains that separate the anaesthetist from the surgeon. This tired old gag is as unstable and rickety as the elevated drapes connected to IV poles that construct said screen. For a more accurate and up-to-date review of this fascinating physiological feature, see Prof Campbell and Prof Doherty's review. This barrier is important to us for many reasons, but one is that it literally is an obstacle preventing medications that we deliver from reaching the organ of importance for seizures.

Talking of impediments to safe delivery of medication and healthcare... did someone mention the COVID-19 pandemic? We thank the Oxford and SUDEP Action research team, and authors Prof Sen and Sammy Ashby, for a contemporary and timely article on COVID-19, with a focus on how it has had an impact of the architects of healthcare delivery – namely you and me. They conclude by saying "Our findings show that there is an enduring need to support healthcare workers' mental and physical health" and I cannot echo this statement enough. There has never been a better time to heed the wise words of Jerry Springer – "Take care of yourselves, and each other."

What do you fantasise about? What are your darkest daydreams, the ones that you wouldn't share with even your spouse? Me? Probably to work in an adequately funded service, with systems that promote rather than resist change. So springing from collaborative work necessary because of the COVID-19 pandemic, Melanie David-Feveck shares some outcomes from the RCPCH Epilepsy Quality Improvement Programme. There is so much to love in this punchy article, including the ambition that NHS Trusts should incorporate time within job plans for teams to deliver quality improvement in their services – that sounds like nirvana to me.

And finally, Dr Wall discusses 'late onset epilepsy' with the bombshell that the "incidence of epilepsy increases after the age of 40". As a man on the wrong side of 40 (and unlikely to return to the right side) I am comfortable with feeling my age. But to be used as a touchstone for 'seizures in the decrepit' (not her words) or 'epilepsy in those who have been put out to pasture' (also not her words) was a bit too much for my delicate constitution. Thankfully her article is an excellent and thought-provoking piece that has important implications for all of us, particularly in the first seizure clinic.

Picking a theme across these four articles I would say that we should be, more than ever, working in supportive teams to deliver efficient and timely healthcare while continuing to be compassionate and innovative. Teams that do not discriminate against ropey old-timers like me who continue to work despite being critically post-40.

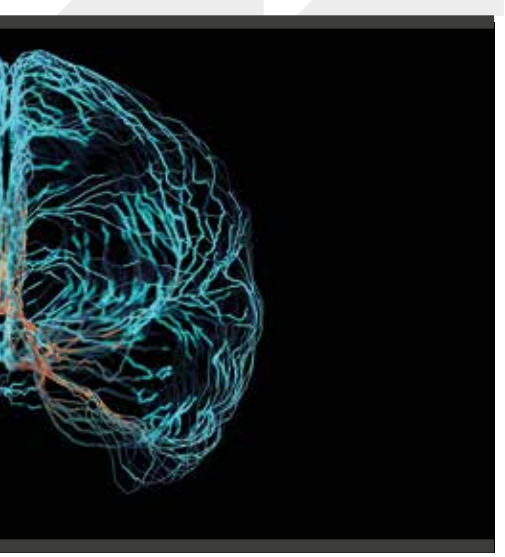
Rhys Thomas
Consultant neurologist
Chief medical adviser
Epilepsy Professional

contents

22
RCPCH EQIP

Melanie David-Feveck

Melanie David-Feveck shares outcomes of the Epilepsy Quality Improvement Programme and the different ways that participating epilepsy teams benefitted from it



I genuinely can't put into words how grateful I am for the NHS and all the brilliant people who work there. These are the people who removed my mum's cancer, safely delivered my child, and saved me from regular cold-sweat-inducing pain in the night by taking out my gall bladder.

I'm not sure it's as talked about as it should be that all the delays, lack of referral pathways, lack of specialists and everything else we read in the news about the NHS, all weighs heavy on the shoulders of healthcare workers. You are the people who face patients' concerns and frustrations and who work long shifts and extra hours to compensate for a lack of funding and staff. And I won't even mention the strain that the COVID-19 pandemic added to healthcare workers everywhere – because Sammy Ashby and Dr Arjune Sen do a great job of covering it on page 10. Their message is that support for healthcare workers in epilepsy is essential going forward.

This issue we also have great articles by Prof Matthew Cmpbell and Prof Colin Doherty covering the blood brain barrier and the new seizure management targets it provides (page 30) and by Dr Jasmine Wall on late-onset epilepsy as an early marker, in some people, of other neurological conditions (page 16).

And lastly, Melanie David-Feveck talks us through the RCPCH's Epilepsy Quality Improvement Programme, showing many NHS Trusts striving for better – and achieving it – with the support of the programme (page 22).

Please enjoy this issue, and here's to the NHS and to you, the fantastic people who work there, from your number one fan.

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

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

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

Publishers: Epilepsy Action (Communications and Digital Engagement Department)

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

Epilepsy Professional is available on subscription to non-members – £13 a year to UK residents. Please send letters or articles to the editor. We are unable to acknowledge receipt of materials, due to cost. We cannot offer payment to authors. All income generated by *Epilepsy Professional* funds the Association's work.
Epilepsy Action is a working name of British Epilepsy Association. British Epilepsy Association is a Registered Charity in England and Wales (No. 234343) and a Company Limited by Guarantee (No. 797997).

 ISSN 1750-2233
New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
tel: 0113 210 8800 | **fax:** 0113 391 0300 | **Epilepsy Action Helpline freephone:** 0808 800 5050
email: epilepsy@epilepsy.org.uk **epilepsy.org.uk**

Lack of care plans and access to specialists, Neuro Survey finds

Around seven in ten people (69%) with epilepsy reported that they did not have a care plan, according to the Neurological Alliance Survey carried out in 2021/22.

The survey included over 8,500 people with neurological conditions, and for the first time included people from across the UK.

The findings also showed that of the respondents with epilepsy who did have a care plan, 29% said they did not have a say in theirs.

The results of the survey also showed that people with epilepsy want more access to specialists. Over a third (37%) said they find it difficult to contact specialists and 21% said they don't have access to an epilepsy specialist nurse but would like to be able to see one.

People with epilepsy also reportedly had trouble getting mental health support. Seventy one percent of people said their epilepsy affected their quality of life to a moderate or great extent. Sixty one percent said they would like to be referred for counselling but had not been and 59% said they had not been asked about their mental health during their epilepsy appointments in three years.

Alison Fuller, director of health improvement and influencing at Epilepsy Action, said: "It is vitally important that people with epilepsy are involved every step of the way with individual care plans which focus on treatment options and quality of care. Everyone's experience of epilepsy is different, and it is crucial people feel involved and confident in all aspects of their care.

"We also know people with epilepsy are more likely to experience mental health problems such as depression. We have highlighted the importance of mental health support for people with epilepsy as part of our response to the Department of Health's new 10-year plan to improve mental health.

"Epilepsy, if poorly treated and managed, can be fatal. It's more vital than ever that we have a joined-up approach to healthcare to ensure both the physical and mental wellbeing of patients. We will be writing to the new Secretary of State, when they are appointed in September, to call for the necessary improvements to epilepsy services. Together with the Neurological Alliance, we're also calling on UK governments to establish a Neuro Taskforce to address common problems including health and care workforce shortages, growing waiting lists and barriers to accessing mental wellbeing support. You can sign the petition on the MS Society website: ***bit.ly/3cCl4Mj***."

The full Neuro Survey report is available at ***neural.org.uk/togetherforthe1in6/***.

Epilepsy Action has a care plan template available at: ***bit.ly/3TtWTQZ***.

NICE recommends fenfluramine for Dravet syndrome

Fenfluramine has been recommended by the National Institute for Health and Care Excellence (NICE) as an adjunctive treatment for Dravet syndrome.

Fenfluramine is a serotonin-releasing agent that stimulates serotonin receptors in the brain. Research has shown that fenfluramine added to other epilepsy medicines can reduce the number of convulsive seizures. Some evidence also suggests that it can help improve the quality of life of people with Dravet syndrome and their carers.

NICE recommended fenfluramine in July for treating Dravet syndrome in anyone aged two years and older if two or more anti-seizure medications (ASMs) have been unsuccessful, NICE says.

However, the frequency of convulsive seizures should be checked every six months, and fenfluramine should be stopped if they have not reduced by at least 30% compared with the six months before starting the ASM.

Fenfluramine has been previously used as an appetite suppressant in treating obesity. It was approved for use in Dravet syndrome in the US in 2020.

MHRA launches safety review into topiramate

The Medicines and Healthcare products Regulatory Agency (MHRA) has launched a safety review into topiramate, announced on 21 July. The review comes after a study reported an increased risk of problems with development in babies exposed to the medicine in the womb.

The study in *JAMA Neurology*, which triggered the safety review, has shown that topiramate may increase the risk the risk of autism and problems with learning and development in children whose mothers took it during pregnancy.

Researchers, Marte-Helene Bjørk and colleagues, found that topiramate and valproate, when taken on their own, are associated with a 2-4 times higher risk of autism (4.3% compared to 1.5% in babies who were not exposed) and intellectual disability (3.1% compared to 0.8%). A higher risk of neurodevelopmental disorders was also found with some combinations of anti-seizure medications (ASMs) – levetiracetam with carbamazepine and lamotrigine with topiramate.

The MHRA review will look at all available information about the safety of topiramate and decide if more needs to be done to increase awareness and reduce the risks posed. It will also look at what future research is needed to fully understand the impact of the ASM, and offer recommendations to the Commission on Human Medicines (CHM). This is expected to happen in October this year.

Last year, the MHRA published updated safety advice around many ASMs, after a review by the CHM into the safety of ASMs in pregnancy. This found topiramate could increase the risks of congenital malformations at birth, as well as cause babies to be born smaller. Concerns were raised then about the medicine's effect on development, but there were not enough data at the time to reach a conclusion.

Epilepsy Action has said in a statement: "We are pleased to see the MHRA is reviewing the available safety data on topiramate. We will monitor the progress of the review and keep everyone updated on the results."

The organisation is pushing for this information to be quickly circulated to doctors and nurses so they can help people make informed decisions about their healthcare.

There is more information on the safety review at: ***bit.ly/3TBKkTH*** and the study that triggered the review can be found on at: ***bit.ly/3edumPo***.

Brand name ASM prices skyrocket from 2010-2018

The cost of brand-name anti-epilepsy medications (ASMs) has increased more than two-and-a-half times between 2010 and 2018, according to a new US study from *Neurology*.

Researchers Samuel Terman and colleagues set out to better understand the trends in ASM prescriptions and costs from 2008-2018. The team looked at a sample of people in the US health insurance programme Medicare.

There were between 77,000 and 133,000 people with epilepsy included a year. In 2008, phenytoin was the most commonly prescribed ASM. This changed to levetiracetam in 2018. Brand name ASMs, older ASMs, and enzyme-inducing ASMs all reduced over the time period.

The researchers found that in 2018, brand name ASMs accounted for 79% of the cost of ASMs, but only 14% of prescriptions.

The cost of brand-name ASMs increased more than two-and-a-half times (277%) from 2010 to 2018, while generic ASMs reduced in price by two-fifths (42%) in that time.

The study authors found that many common brand-name ASMs cost 10 times more than the generic versions. The study authors said previous studies have shown that ASMs are the most expensive part of neurology care. They added that ASMs were the second most expensive medicines prescribed by neurologists.

The study is available at: ***bit.ly/3RAv7R3***.

Charity calls out "government inaction" two years after Cumberlege review

Epilepsy Action has said it is "alarmed at the worrying lack of progress" the government has made in the last two years, following the safety review published two years ago today by Baroness Cumberlege in 2020.

The Independent Medicines and Medical Devices Safety Review acknowledged major failings in the health system around three separate healthcare scandals, dating back decades, including around sodium valproate.

Over many years, women took sodium valproate for conditions including epilepsy, without being made aware of the risks to unborn babies if taken during pregnancy. The organisation said this has led to years of "avoidable suffering" for families affected.

The report made a series of recommendations, some of which the government is still considering, two years on, and others which have been rejected. This includes a redress scheme to "meet the costs of providing additional care and support to those who have experienced avoidable harm". Other recommendations that have been rejected include creating specialist centres for people affected by sodium valproate.

The government has made recent progress on one of the nine recommendations, appointing a Patient Safety Commissioner. However, the charity says this new role "will do nothing to help families that have already been harmed by valproate".

Alison Fuller, director of heath improvement and influencing at Epilepsy Action, said: "Families who live with the impact of taking sodium valproate in pregnancy often have to meet the costs of the additional care and support their children need. Some of these children are now adults with even more complex needs.

"As the cost-of-living crisis deepens, it is more vital than ever they receive the financial redress they deserve. We urge the government to reconsider its position on this.

"Much more needs to be done to ensure women with epilepsy are aware of the risks of the medication they are taking. Every woman must have access to specialist preconception counselling. It is also unclear whether the risks posed by other medicines are being properly communicated to health professionals and women with epilepsy.

"We cannot be having these same conversations another two years down the line. The government needs to show that it is taking patient safety seriously and the patient safety commissioner must now step up and prove they are committed to this issue as a priority.

"We will continue to seek assurances from all parties involved to ensure they implement the report recommendations and maintain patient safety and quality of service. Past mistakes must never be repeated."

Sulthiame for myoclonic atonic epilepsy

Adjunctive use of sulthiame may reduce seizures in children with myoclonic atonic epilepsy, according to a new study from Argentina.

Dr Roberto Caraballo and colleagues wanted to find out if sulthiame was effective and well tolerated in children.

The research, published in *Epilepsy & Behavior*, included 35 children with myoclonic atonic epilepsy, or Doose syndrome, who had all tried at least four other anti-seizure medications (ASMs) unsuccessfully. The effectiveness of sulthiame was assessed by comparing the number of seizures before and after using the medicine.

Seizures reduced by more than half in 60% who took sulthiame as an adjunctive treatment. Two of the children became seizure free. In the remaining 40%, seizures reduced by 25-50%.

The researchers noted that 31.4% had side effects. These included shortness of breath or unusually fast breathing, a loss of appetite, headaches, or feeling sick, drowsy or irritable. However, the authors said these were mild and passed in all cases, and no one withdrew because of these.

The study concluded that sulthiame was effective and was well tolerated. It was especially effective for myoclonic-atonic and myoclonic seizures, but also helped with atypical absences and tonic-clonic seizures, the researchers said. However, they added that further studies are needed to better understand the long-term outcomes. The full research is available at: ***bit.ly/3wQPsJS***.

Sulthiame is available in Australia, the US, Europe and Israel, but not yet in the UK.

Early epilepsy surgery may prevent drug-resistance

Epilepsy surgery is a successful treatment, especially in people with non drug-resistant focal epilepsy, according to a recent study from Italy published in *Epilepsy & Behavior Reports*.

Researchers Veronica Pelliccia and colleagues explained that epilepsy surgery is typically offered to people with drug-resistant epilepsy.

But the authors suggested that this treatment can also benefit people with non drug-resistant epilepsy. They said that if offered earlier, especially in children, surgery can be more successful and could prevent some epilepsies from becoming drug-resistant.

The researchers wanted to find out whether the outcomes of surgery are different between drug-resistant and non drug-resistant epilepsy.

They studied 250 people with focal epilepsy who had at least three months of seizure freedom after starting treatment with anti-seizure medications (ASMs). The participants were split into two groups. One group comprised those who had epilepsy surgery during the period of seizure freedom (74 people). The other included those who had surgery later, when their seizures had returned and their epilepsy had become drug resistant (176 people).

Almost everyone (95.9%) in the group who had surgery during the period of seizure freedom stayed seizure free, and the rest had only focal aware seizures for at least two years after surgery. In the group who had become drug-resistant, this was the case in 77.3% of people. Also, 83.8% in the group who had early surgery were able to come off their ASMs after surgery. In the group with drug-resistant epilepsy, this was 49.4%.

The researchers concluded that epilepsy surgery should be considered earlier and may help prevent epilepsy becoming drug-resistant in some people. This echoes the updated guidelines on epilepsy by the National Institute for Health and Care Excellence (NICE). They say people with non drug-resistant epilepsy should be referred for surgery assessment if an MRI shows a high risk of their epilepsy becoming drug-resistant.

The full research is available at: ***bit.ly/3q8bUdQ***.

Returning seizures after ASM withdrawal

Adolescent age at diagnosis and unusual EEG findings are among the factors that predict breakthrough seizures after withdrawal of anti-seizure medications (ASMs) in children, according to a new *Epilepsy & Behavior* study.

The research, by Miraç Yıldırım and colleagues, wanted to find out if any factors could be used to predict whether the seizure free children would end up having returning seizures after withdrawing ASMs They included 269 children who were seizure free and able to come off their ASMs. They were followed up for at least 18 months after withdrawal.

The researchers found that 33.5% of children ended up having breakthrough seizures. Of them, 45.6% had had their seizures return at six months, and 74.4% had had seizures at two years. Almost all (94.4%) of this group had returning seizures five years after ASM withdrawal.

Among the characteristics studied, adolescent age at diagnosis, unusual EEG findings after ASMs were stopped, and having a high number of seizures while taking ASMs predicted a higher chance of having returning seizures after withdrawal.

The researchers also identified malformations of cortical development and hydrocephalus that could be used as MRI biomarkers for returning seizures after ASM withdrawal.

However, the researchers also found that the vast majority (93.3%) of the children who had returning seizures got seizure control again with monotherapy.

The study is available at: ***bit.ly/3RwT4Zg***.

COVID-19 impact on HPs

How the pandemic has affected healthcare workers

Sammy Ashby and Prof Arjune Sen discuss how the COVID-19 pandemic has affected healthcare workers in epilepsy, and the delivery of care to patients

Since 2020, there have been seismic shifts in how healthcare workers interact with people with epilepsy. The burden of working during a pandemic, illness of colleagues and healthcare workers needing to self-isolate placed further pressure on an already stretched system. As we now, hopefully, begin to fully reconstitute epilepsy services, it is worth reflecting on the ways in which COVID-19 has changed clinical practice and affected those helping in the management of those with epilepsy.

To understand how SARS-COV-2 impacted on the epilepsy community, University of Oxford and SUDEP Action launched the COVID-19 and Epilepsy (COV-E) Study in March 2020 to capture the impact of the pandemic in real-time [Thorpe *et al*, 2021a]. The study collected 3,421 responses over an 18-month period (April 2020-December 2021), from the UK and 52 other countries. It is one of the largest worldwide datasets exploring the impact of the pandemic on the epilepsy community. Much can be gleaned from the data, which not only provide a snapshot of experiences during the pandemic, but offer insights into lessons which can be learnt by the epilepsy community going forwards.

Seventy-nine UK healthcare workers, who support people with epilepsy, contributed to the COVID-19 and Epilepsy (COV-E) study

Seventy-nine UK healthcare workers who support people with epilepsy contributed to this study. This included 36 epilepsy specialist nurses, 18 general neurologists, seven neurologists specialising in epilepsy, six general practitioners, five learning disability clinicians and four medical trainees. Fifty-one percent of responses for this study were captured during the first wave of the pandemic (n = 40), between 5 May and 1 June 2020. The information they shared showed how healthcare workers have been personally affected, logistical changes in the delivery of care, and how these factors impact the ability to deliver optimal individual care [Thorpe *et al*, 2021b].

Wellbeing

Many healthcare workers across the UK faced change to their role during the COVID-19 pandemic. For some, this change was significant; altering not only their daily routine, but also their role, workplace and the expectations placed on them [Mehta

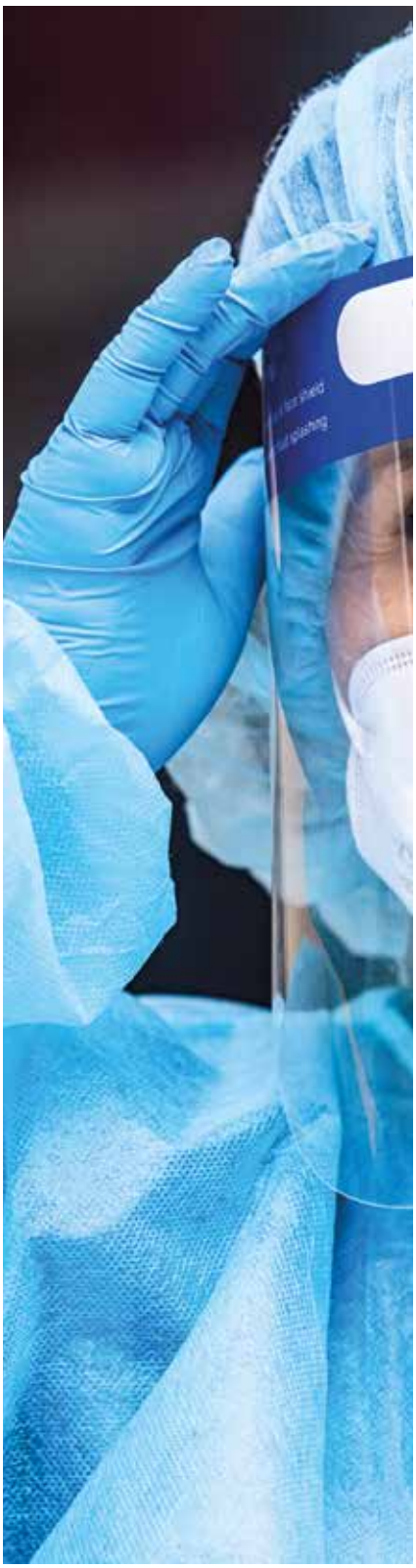
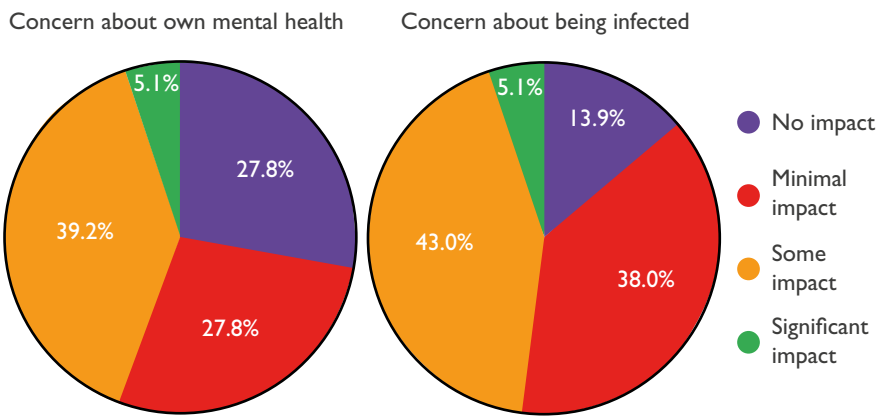


Figure 1: Impact of COVID-19 on UK healthcare workers' own health and perceptions. UK healthcare workers managing people with epilepsy reported marked concerns over COVID-19 with almost 75% having some worries about their mental health and just over 85% being concerned about contracting COVID-19 [Thorpe et al, 2021b]



et al, 2021]. There was a lot of reporting on this both in the media and in academic journals.

While 67% of our healthcare respondents reported no impact on their physical health, 43% reported some or significant impact on their mental health

The WHO reported in 2021 that between Jan 2020 and May 2021, 6,643 healthcare workers had died due to COVID-19, though they acknowledged that this figure is likely a significant underestimation of the worldwide figure [WHO, 2021]. In our survey, nearly 50% shared concerns about being infected with COVID-19 (which at the time of data collection would have been with one of the earlier strains of the virus, namely alpha or beta). With this comes the fear of transmitting the virus (to patients and family), as well as knock-on effects on the wider team – potentially placing additional burden onto others [Mehta *et al*, 2021; Shreffler *et al*, 2020].

While 67% of our healthcare respondents reported no impact on their physical health (and existing systemic comorbidities), 43% reported some or significant impact on their mental health. This compares to 40% of people with epilepsy who reported changes in their health during the pandemic, noticing, for example, changes in seizure frequency, sleep disruption and mental health challenges [Thorpe *et al*, 2021a]. The adverse impact on mental health and wellbeing among healthcare workers associated with the pandemic seems to persist and may continue into the future [De Kock *et al*, 2021]. The importance of addressing and alleviating mental health strain on healthcare workers is vital to ensure that optimal care delivery can be maintained and retention within the health service is assured.

Figure 2: Summary of overall findings from people with epilepsy during the COVID-19 pandemic.
Data from the first year of the pandemic suggests that people with epilepsy were more exposed to epilepsy-related risk at a time when there was less access to healthcare and less discussion about those risks. This could create a 'perfect storm' to consolidate risks for people resulting in increased harm

Changing practice
Redeployment of epilepsy healthcare workers occurred at varied rates across healthcare settings, roles and geographies in the UK during the first wave of the pandemic. In the early phase (March-Dec 2020), when compared with the same period in 2019, nationally there were:

Redeployment of epilepsy healthcare workers occurred at varied rates across healthcare settings, roles and geographies in the UK

- 2.9 million (34.4%) fewer elective in-patient admissions
- 1.2 million (21.4%) fewer non-Covid-19 emergency in-patient admissions
- 17.1 million (21.8%) fewer out-patient appointments [Karjalainen, 2021]

"Wards and investigations and surgery were closed. I am used to seeing excess mortality in normal times but reported deaths already show epilepsy deaths rising sharply during the first peak of the pandemic. We also saw a surge in requests from Coroners at this time to look at anti-epilepsy medications in the blood of those who likely have died suddenly, which suggested very early on that there was a rise in excess deaths."

Professor Ley Sander, Consultant Neurologist, National Hospital for Neurology and Neurosurgery and Head of the Department of Clinical & Experimental Epilepsy at UCL, Queen Square Institute of Neurology, London. (Quote given in October 2020 from the Lives Cut Short, report created in response to this research project) [Hanna and Ashby, 2020]

"I find it hard to get out what I needed to ask or get help on. Realised after the phone call I forgot to tell the specialist a lot of things I think they needed to know. Phone calls give me anxiety."[Hanna and Ashby, 2020]

"Telephone appointments do not work for me. My neuropsychology exercises need to be face to face so I have lost this support... I was not given enough time to talk with the on call GPs… and they didn't know how complex my epilepsy was."[Hanna and Ashby, 2020]

In person vs remote

Thirty nine percent of our UK healthcare worker survey respondents switched entirely to remote consultations during the first waves of the pandemic. This would be almost unthinkable in 2019. There were definite benefits, enabling ongoing access to routine appointments and care. More vulnerable people, those without easy access to phone/internet technologies and people with complex needs may, though, have been less able to access clinicians through remote platforms. Some may also have been less able to communicate nuances in their health requirements outside of a face-to-face visit [Thorpe *et al*, 2021a].

Diagnosis of epilepsy

Nineteen percent of our survey participants reported they were significantly less confident diagnosing epilepsy when working remotely and half of healthcare workers specified that the pandemic had negatively impacted their ability to deliver care. Concern was also expressed by healthcare workers that some people with epilepsy might be reluctant to engage with services for support.

"We are wondering where have all the patients gone… you have a legitimate concern that patients might not be reporting…. and might not make an appointment for an annual epilepsy review." Research survey respondent (GP) [Hanna and Ashby, 2020]

Prescribing

Most healthcare workers did not change their approach to prescribing substantially. Three reported an increase in prescribing rescue medication to reduce hospitalisation of people with epilepsy and there was some additional reluctance to reducing/withdrawing anti-seizure medications. However, of people with epilepsy, 25% reported difficulties in accessing their epilepsy medication during the same period [Thorpe *et al*, 2021a]. Given the importance of medication in seizure control and to help reduce risk of sudden unexpected death in epilepsy (SUDEP) or other causes of premature mortality, addressing these medication supply issues is essential to minimise future impact on safety.

Careful consideration and a personalised approach will be required in service delivery as we move to a hybrid model of care

Going forward, careful consideration and a personalised approach will be required in service delivery as we move to a hybrid model of care which tries to support services, meet demand and ensure patient engagement remains high

[Abel, 2020; Verghese and Carr, 2021]. This is particularly vital during the pandemic given people with epilepsy have reported an increased risk of epilepsy mortality and SUDEP, a decreased awareness of these risks and a worsening of their mental wellbeing. Such factors, regrettably, sow the seeds for a potential increase in premature epilepsy deaths [Thorpe *et al*, 2021a; Hanna and Ashby, 2020].

Transitioning beyond the pandemic

Moving ahead, planning will be required for how epilepsy services can be supported to tackle their part of the anticipated backlog of 227,000 neurology and 58,000 neurosurgery appointments. These numbers were estimates from the end of 2020, and are likely to have increased significantly. This is a backlog that has now been added to the already pressured caseload of many epilepsy healthcare workers [Abel, 2020]. In the longer term, a national plan for neurology to provide coordination of initiatives, workforce and increased access to neurology services could help with this issue [The Neurological Alliance, 2022]. The shortages of healthcare staff going into the pandemic created a context which led to decision-making regarding the extent of redeployment and impact on epilepsy services.

Our findings show that there is an enduring need to support healthcare workers' mental and physical health. A dependence on consultations should also perhaps be reconsidered to ensure that people with epilepsy can be empowered in self-management while still receiving prompt, reliable, comprehensive and high-quality clinical care when required. Mindful of the responses from our surveys examining impacts on people with epilepsy [Thorpe *et al*, 2021a] and the Lives Cut Short Report [Hanna and Ashby, 2020], it will be vital to properly support health professionals working in epilepsy. This can help reduce risks, improve outcomes and ensure premature mortality is avoided.

Sammy Ashby
Deputy chief executive
SUDEP Action

Prof Arjune Sen
Consultant neurologist
The University of Oxford

Further reading

Abel J. (2020). Restarting services for people with neurological conditions after the COVID-19 pandemic and planning for the longer term. [online] Available at: https://www.neural.org.uk/wp-content/uploads/2021/07/20200703-Final-Restarting-Services-for-People-with-Neurological-conditions-v3.pdf.

De Kock JH, Latham HA, Leslie SJ, *et al.* (2021). A rapid review of the impact of COVID-19 on the mental health of healthcare workers: implications for supporting psychological well-being. BMC Public Health 21, 104. [online]. Available at: https://doi.org/10.1186/s12889-020-10070-3

Hanna J and Ashby S. (2020). Lives Cut Short – a report on urgent measures to tackle deaths in epilepsy and support the bereaved during the COVID-19 pandemic, SUDEP Action. [online] Available at: https://sudep.org/sites/default/files/lives_cut_short_-_final.pdf

Karjalainen H. (2021). Update: How is the Covid-19 crisis affecting the NHS? [online] Economics Observatory. Available at: https://www.economicsobservatory.com/update-how-is-the-covid-19-crisis-affecting-the-nhs.

Mehta S, Machado F, Kwizera A, Papazian L, Moss M, Azoulay É and Herridge M. (2021). COVID-19: a heavy toll on health-care workers. The Lancet Respiratory Medicine, [online] 9(3), pp.226–228.

The Neurological Alliance. Together for the 1 in 6: UK Findings from My Neuro Survey 2 Together for the 1 in 6: UK Findings from My Neuro Survey. (2022). [online] Available at: https://www.neural.org.uk/wp-content/uploads/2022/05/Together-for-the-1-in-6-UK-Findings-from-My-Neuro-Survey-v6.pdf.

Shreffler J, Petrey J, Huecker M. (2020). The Impact of COVID-19 on Healthcare Worker Wellness: A Scoping Review. West J Emerg Med. 21(5):1059-1066.

Thorpe J, Ashby S, Hallab A, Ding D, Andraus M, Dugan P, Perucca P, Costello D, French JA, O'Brien TJ, Depondt C, Andrade DM, Sengupta R, Delanty N, Jette N, Newton CR, Brodie MJ, Devinsky O, Cross JH and Sander JW. (2021a). Evaluating risk to people with epilepsy during the COVID-19 pandemic: Preliminary findings from the COV-E study. Epilepsy & Behavior, p.107658.

Thorpe J, Ashby S, Cross JH, Sander JW, Newton C, Hanna J and Sen A. (2021b). The impact of COVID-19 on epilepsy care: Perspectives from UK healthcare workers. Epilepsy & Behavior Reports, 16, p.100487.

Verghese H and Carr G. (2021). Lessons learnt from the COVID-19 pandemic Priorities in care for people with neurological conditions after the pandemic A report by the National Neurosciences Advisory Group (NNAG). [online] Available at: https://static1.squarespace.com/static/5f1021faf6248b39f4c64f5d/t/607d5ef837ac504ec37b00cb/1618829052526/Lessons+learnt+from+the+COVID-19+pandemic++Priorities+in+care+for+people+with+neurological+conditions++A+report+by+the+National+Neurosciences+Advisory+Group+%28NNAG%29+2021+x.pdf

World Health Organization Health Workforce Department. (2021). The impact of COVID-19 on health and care workers: a closer look at deaths. [online] Available at: https://apps.who.int/iris/bitstream/handle/10665/345300/WHO-HWF-WorkingPaper-2021.1-eng.pdf.

Jasmine Wall

Changing paradigms

Late onset epilepsy as an early sign of brain frailty

Dr Jasmine Wall discusses late-onset epilepsy as a possible sign of brain frailty which may in some cases herald development of future conditions, such as stroke and dementia.

Introduction

Incidence of epilepsy increases after the age of 40. In some cases there is a clear cause, such as head injury or stroke. These causes of epilepsy in adulthood are sometimes referred to as 'lesional' epilepsy. In some cases, however, there is no 'lesion' or cause identifiable through history or brain imaging. As we begin to understand the causes of non-lesional epilepsy, or late-onset epilepsy, it has become evident that in a proportion of these cases, epilepsy may be a sign of invisible, unidentified disease. This is important because if we recognise the significance of this kind of epilepsy, then we may be able to act to prevent further disease.

It is likely that there are many causes of late-onset epilepsy, only some of which are understood. In the course of this article, we will discuss:

- The phenotype of late-onset epilepsy
- The theoretical basis behind the understanding that late-onset epilepsy is due to invisible brain insult
- Recognised associations with late-onset epilepsy
- The importance of brain frailty in managing people with late-onset epilepsy

It is likely that there are many causes of late-onset epilepsy, only some of which are understood

Late-onset epilepsy commonly presents as focal-onset seizures

Epilepsies involving generalised seizures often commence in childhood and early adolescence. Generalised seizures are often related to diseases of brain excitability, for example due to sodium channel diseases, which involve broadly distributed brain networks.

By contrast, epilepsy in adulthood most commonly features focal-onset seizures [Josephson *et al*, 2016]. This implies an acquired insult, such as trauma, stroke or brain injury.

However, in late-onset epilepsy, there is no clearly identifiable brain insult. In these cases, it is therefore likely that there is an 'invisible' insult, not detectable through conventional neuroimaging or history, from which the epilepsy arises.

Jasmine Wall

Multiple causes of late-onset epilepsy

It is likely that late-onset epilepsy or 'late-onset seizures of unknown aetiology' is not a single disease, but a syndrome underpinned by many different aetiologies. Progress has been made in recent years towards understanding some of these cases. There are three tentative areas of interest in late-onset epilepsy:

- Autoimmune epilepsy
- Cerebrovascular disease
- Dementia

Of these areas, autoimmune epilepsy is perhaps the most well-understood. Antibodies against cell-surface markers can produce an autoimmune phenomenon which manifests as late-onset epilepsy. In these cases, epilepsy is not amenable to treatment with immunomodulating treatment, but benefits most from treatment with conventional anti-seizure medications (ASMs).

The link between late-onset epilepsy and vascular supply to the brain is not well understood, however, there are a few clues from existing research, which help to understand the nature of this connection

The discovery of autoimmune-associated epilepsy has changed the way that late-onset epilepsy has been understood. While late-onset epilepsy was previously considered to be an idiopathic disease of age, it is increasingly recognised as an early sign of brain disease.

Late-onset epilepsy and increased stroke risk

Cerebrovascular disease comprises any form of disease affecting the vascular system of the brain – including stroke, small vessel disease and cerebral amyloid angiopathy.

Early cerebrovascular disease may be one cause of late-onset epilepsy. The link between late-onset epilepsy and vascular supply to the brain is not well-understood, however, there are a few clues from existing research, which help to understand the nature of this connection.

A recent meta-analysis of existing studies has shown that people have a four-fold risk of developing stroke subsequent to a diagnosis of late-onset epilepsy [Wall *et al*, 2021]. Recently, the Atherosclerosis Risk in Communities (ARIC) study has shown that even at the time of diagnosis, people with late-onset epilepsy have increased chance of carrying risk factors for vascular disease in the brain. These risk factors include high blood pressure, high cholesterol, diabetes and smoking [Koubeissi, 2019]. This suggests that late-onset epilepsy is an early warning sign for high stroke risk and may be caused by early, invisible damage. We might imagine, therefore, that late-onset epilepsy may be caused by network disruption as a result of early cerebrovascular disease.

Late-onset epilepsy and increased dementia risk

There is an established link between advanced dementia and epilepsy. The commonest forms of dementia are Alzheimer's disease and vascular dementia. The ARIC study has additionally identified that people with late-onset epilepsy have a twofold increased risk of developing dementia following a diagnosis [Johnson *et al*, 2020]. Although the

relationship between dementia and late-onset epilepsy has not been the subject of a dedicated study, it is perhaps not a surprise to discover that they are connected.

Mental health and cognitive issues are associated with epilepsy [Tellez-Zenteno *et al*, 2007]. Common diseases of mental health include depression and anxiety; but a commonly neglected aspect of mental health is dementia, particularly in older age. The World Health Organisation identifies dementia and depression as the two most common mental disorders in the age group over 60, affecting between 5% and 7% of the world's older population [World Health Organisation, n.d.]. Identifying which people with late-onset epilepsy are at risk of dementia is an important subject for future research.

There are also hypothetical explanations as to why late-onset epilepsy may, in some cases, be the earliest sign of Alzheimer's disease. There is a close relationship between vascular disease and Alzheimer's disease

As vascular dementia and cerebrovascular disease are related, it may be unsurprising that both diseases are found in association with late-onset epilepsy. There are also hypothetical explanations as to why late-onset epilepsy may, in some cases, be the earliest sign of Alzheimer's disease. There is a close relationship between vascular disease and Alzheimer's disease. The development of amyloid plaques in Alzheimer's disease is also related to cerebrovascular disease [Love and Miners, 2016]. Additionally, amyloid is itself epileptogenic [Irizarry *et al*, 2012]. These factors may contribute to the genesis of late-onset epilepsy as a prequel to Alzheimer's disease.

We do not, however, know if it is possible to predict which people with late-onset epilepsy will go on to develop stroke or dementia. In the future, it may be possible to predict this either by examining risk factors, or through identifying early changes in the brain which are associated with developing these diseases in late-onset epilepsy.

Impact on clinical practice

There is not enough evidence yet in this area to support change in the guidelines around late-onset epilepsy. However, the association of late-onset epilepsy with a fourfold increased risk of stroke, may influence practice. A diagnosis of late-onset epilepsy is an impactful time to advocate lifestyle modification: particularly cessation or reduction of alcohol, smoking and recreational drug use. A diagnosis of epilepsy often coincides with lifestyle uncertainty: suspension of driving privileges, and wariness around exercise. Proactively addressing the role of exercise to improve mood, and prevent stroke and dementia, may be valuable. Epilepsy is closely related to depression which is a risk factor for dementia, and signposting people at the time of a diagnosis of epilepsy contributes to dementia prevention.

Although there is little evidence on the role of preventative medicine following a diagnosis of late-onset epilepsy, fortunately there is research planned in order to answer these questions [Health Research Authority, n.d.]. When a person receives a life-changing diagnosis such as late-

onset epilepsy, this can prove an impactful time when people are receptive to lifestyle modifications which may prevent later disease.

Late-onset epilepsy is an early sign of brain frailty

Frailty is a state of vulnerability to decline, which arises as a result of the effect of persistent exposure to risk factors. Brain frailty refers to the state of vulnerability to stroke and dementia, the two monoliths of aging in the brain. Brain frailty stands in opposition to 'brain health' [Hachinski *et al*, 2021]. If late-onset epilepsy is an early sign of otherwise invisible disease, leading to increased risk of stroke and dementia, it is also an early sign of brain frailty. Patients with late-onset epilepsy may benefit particularly from interventions to reduce the risk of subsequent stroke and dementia, given that late-onset epilepsy may be a sign of early, pre-morbid disease. As ever, further research will be key to understanding more about this relationship, and the ways in which we can prevent stroke and dementia in this cohort. In the interim, a diagnosis of epilepsy can be an impactful time for interventions which reduce vascular risk, such as smoking cessation, and for optimising management of other risk factors such as diabetes and hypertension.

Dr Jasmine Wall
NIHR Academic Clinical Fellow in Neurology
Lancaster University

Further reading

Hachinski V, Avan A, Gilliland J, and Oveisgharan S. (2021). A new definition of brain health. In The Lancet Neurology. 20(5):335-336 https://doi.org/10.1016/S1474-4422(21)00102-2

Health Research Authority. (n.d.). Neurofrailty: A study of late-onset epilepsy and its associations. Retrieved August 12, 2022, from Neurofrailty: A study of late-onset epilepsy and its associations.

Irizarry MC, Jin S, He F, Emond JA, Raman R, Thomas RG, Sano M, Quinn JF, Tariot PN, Galasko DR, Ishihara LS, Weil JG, and Aisen, P. S. (2012). Incidence of new-onset seizures in mild to moderate Alzheimer disease. Archives of Neurology. 69(3):368-372. https://doi.org/10.1001/archneurol.2011.830

Johnson EL, Krauss GL, Kucharska-Newton A, Albert MS, Brandt J, Walker KA, Yasar S, Knopman DS, Vossel KA, and Gottesman RF. (2020). Dementia in late-onset epilepsy: The Atherosclerosis Risk in Communities study. Neurology. 95 (24):e3248-e3256 https://doi.org/10.1212/WNL.0000000000011080

Josephson CB, Engbers JDT, Sajobi TT, Jette N, Agha-Khani Y, Federico P, Murphy W, Pillay N, and Wiebe S. (2016). Towards a clinically informed, data-driven definition of elderly onset epilepsy. Epilepsia. 57(2):298-305. https://doi.org/10.1111/epi.13266

Koubeissi M. (2019). Seize the Day for a Day With No Seizures: Modifiable Midlife Risk Factors Identified. In Epilepsy Currents. 19(1):27-28 https://doi.org/10.1177/1535759718822041

Love S, and Miners JS. (2016). Cerebrovascular disease in ageing and Alzheimer's disease. In Acta Neuropathologica. 131:645–658. https://doi.org/10.1007/s00401-015-1522-0

Tellez-Zenteno, J. F., Patten, S. B., Jetté, N., Williams, J., & Wiebe, S. (2007). Psychiatric Comorbidity in Epilepsy: A Population-Based Analysis. Epilepsia, 0(0), 070728063136006-??? https://doi.org/10.1111/j.1528-1167.2007.01222.x

Wall, J., Knight, J., & Emsley, H. C.A. (2021). Late-onset epilepsy predicts stroke: Systematic review and meta-analysis. In Epilepsy and Behavior. https://doi.org/10.1016/j.yebeh.2020.107634

World Health Organisation. (n.d.). Mental Health of Older Adults. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Mental-Health-of-Older-Adults. Retrieved August 12, 2022, from https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults

Health by numbers

One of the first things we learn as young children is to count. It's also one of the first aspects of a foreign language which we master. And, as illustrated here in this simple opinion piece, numbers and counting are vital in epilepsy care. In this edition of Epilepsy Professional, I thought I would look at epilepsy in numbers and how we use numbers in the diagnosis, the investigation, therapeutics and ongoing care of epilepsy.

I have recently been thinking about the numbers we use in our epilepsy consultations, clinics and care. As clinicians, we tend to count seizures in which we consider there to be a significant risk of harm – tonic-clonic seizures, prolonged seizures, seizures from sleep, episodes of status epilepticus and intensive care admissions. Patients and families often count all seizure types and we encourage them to keep diaries and record seizure numbers on smart phones. We also encourage families and carers to count the duration of a seizure, as a marker as to when to call for paramedic assistance.

As part of our diagnostic evaluation, we also count electrographic seizures on standard and prolonged EEG monitoring, on the lookout for several stereographed seizures and subclinical seizures following drug withdrawal in our surgical programmes.

The number of seizures is also useful when there is diagnostic uncertainty. Multiple seizures counted within one day, or over serial days in a week, combined with other clinical markers, may point towards dissociative seizures or non-epileptic attack disorder.

As part of ongoing clinical care, numbers play a role in the therapeutics of epilepsy. With the evolving number of anti-seizure medications (ASMs) available, we monitor the number used per patient, the doses prescribed, titration schedules, and the doses at which side effects are encountered. Numbers are also employed in the definition of drug-refractory epilepsy and so play a part in epilepsy surgery discussions. When reviewing unwell patients with epilepsy in hospital, we often also count and sometimes gasp at the amount of benzodiazepines used.

I think we also often wonder what is the ideal time interval for out-patient review? Every four months, twice a year, annually? Modern technology has certainly eased this, as has the work of epilepsy nurses.

One other crucial area in which numbers are used in epilepsy is as a contact point to the local epilepsy nursing team. I know I, for one, have their telephone number etched onto my brain. The epilepsy nursing teams across the country are a vital source of support and information for patients and clinicians alike. Their numbers, whether contactable via telephone, bleep or pager, are an important set to remember.

We all know we can't boil down a patient and their epilepsy experiences to a set of numbers alone, and so we take care to take detailed histories, listen to concerns and strive to give everyone *their* optimal outcomes. But fundamentally, numbers play a role even in this. In epilepsy, they can be descriptive, can point towards a certain diagnosis, can illustrate the degree of, or lack of seizure freedom, and form part of the workup and management. Finally, observing the trend in seizure numbers over weeks and months might also prove helpful, or even lifesaving, and serve as a trigger point for intervention.

Melanie David-Feveck

RCPCH EQIP

2021/2022 RCPCH Epilepsy Quality Improvement Programme

Melanie David-Feveck discusses the EQIP programme and shares the different ways that participating epilepsy teams benefitted from it.

The RCPCH Epilepsy Quality Improvement Programme (EQIP) pilot programme delivered in 2019-20 involved multi-disciplinary paediatric epilepsy teams from 11 NHS Trusts in England and one Health Board in Wales [RCPCH, 2021]. Their response to the emerging Covid-19 pandemic in the latter stages of their training demonstrated their commitment to improving the care provided to children and young people within NHS paediatric epilepsy services.

Following the success of the 2019-20 pilot, the programme was extended in 2021 to a second cohort of teams involving 17 new multi-disciplinary paediatric epilepsy teams. Of these, 11 were from individual NHS Trusts and one was an Integrated Care System (ICS) network structure of six NHS Trusts. Over a seven-month period between August 2021 and April 2022, online practical training and support helped teams uncover areas requiring improvement within their local context (Table 1).

Following the success of the 2019-20 pilot, the EQIP programme was extended in 2021 to a second cohort of teams involving 17 new multi-disciplinary paediatric epilepsy teams

EQIP teams were provided with high standard quality improvement (QI) training by distance learning in a virtual format. This was co-designed and delivered with an expert QI trainer and facilitator, and offered flexible remote learning options that were adaptable to the pace of individual teams. Team members could attend live training webinars with access to digital pre-course materials, case studies and real-world training examples through a dedicated online microsite. A framework of support was offered to

Table 1:The 2021/2022 participant EQIP teams and their QI project aims

Team	Project aim
Developing mental health pathways	
Epsom and St Helier University NHS Trust	Identify and implement a mental health screening tool for CYP with epilepsy to identify those at risk
North-West Anglia Foundation Trust	Improving mental health pathway using signposting
Warrington and Halton Teaching Hospitals NHS Foundation Trust	Engage with families to improve the mental health care pathway for young people with epilepsy
Improve and adapt transition process to adult services	
Croydon Health Service NHS Trust	Improve and adapt the transition process for young people with epilepsy
East Lancashire Hospital Trust	Develop the transition service for young people with epilepsy
Developing an integrated care pathway and increasing specialist input	
North Tees & Hartlepool NHS Foundation Trust	Reduce referrals from 12 to four weeks for 50% of patients following first epileptic seizure
Salisbury NHS Foundation Trust	Seventy-five percent of CYP with first afebrile seizure will be seen in clinic within two weeks of referral
Improving patient engagement processes	
Barts Health NHS Trust	Obtain meaningful feedback on our service from 50% children, young people and families by March 2022
Doncaster and Bassetlaw NHS Foundation Trust	By March 2022, 70% of children aged 11-19 years with epilepsy will have digital feedback forms offered in clinics (consultant and nurse led) and on acute wards
SUDEP risk	
Oxford University Hospitals NHS Foundation Trust	Develop a patients standardised toolkit for clinicians to use to provide information on SUDEP to families enabling a personalised annual discussion on SUDEP with for at least 80% of children with epilepsy
Digitalisation of epilepsy passport	
University hospitals of Morecambe Bay NHS Foundation Trust	Produce epilepsy passport electronically for 50% of our patients with epilepsy and complex comorbidities
ICS - Improving the first year of care	
West Yorkshire & Harrogate Health and Care Partnership (six NHS Trusts)	Establish a standardised first year of care pathway for patients with epilepsy diagnosis (sub-projects include the areas of transition, mental health, reducing waiting times for first referral)

Table 2: Service-level outcomes of the EQIP

Status pre-EQIP	Changes and benefits post-EQIP
Participant teams initially focused on the negative barriers they faced, in comparison to the successes they achieved as a service.	By using QI methodology, service teams gained skills in how to break down challenges and find solutions. Trusts were therefore able to achieve outcomes meeting their specific service goals. For example, the successful development of an integrated digital Epilepsy Passport - co-designed with patients and their families - shows the barriers that can be overcome when working with multi-faceted teams.
Few teams had prior knowledge of quality improvement methods.	All teams have now been trained in the use of QI tools to help diagnose and test solutions when making service im-provements. This resulted in multiple teams reporting a reduction in new patient referral waiting times, for example, above 16 weeks to within six weeks or 12 weeks to four weeks.
Some service teams struggled to communicate effectively; especially when working across different sites within their NHS Trust, or across multiple Trusts in ICS structures. Many were unsure what an effective epilepsy service team looked like beyond the roles of the consultant and ESN.	The ICS team have increased their outputs by working on improving effective communication methods across six sites. The group shared knowledge in developing pathways in mental health support, establishing effective transition clinics and reporting on a reduction in waiting times for first seizure referrals. Further examples of incremental changes to services has led to the implementation of new emergency department patient referral processes to paediatric epilepsy clinics. These have been embedded within Trust guidelines.
Some of the service teams were not participating in Epilepsy12.	All teams on the programme participated in the Epilepsy12 audit by the end of the programme cycle. They had a great-er understanding of its value, and how to use the data in local QI activity.
Services lacked clear processes to meet national standards, measured in Epilepsy12's key indicators.	Teams used the audit data to review areas for improvement and help plan their projects. Several projects focused on building new processes, for example to ensure discussion of SUDEP risk with patients and their families, establish a new mental healthcare pathway, developing screening tools and methods of signposting information or services.
Some teams were not able to effectively engage with children and young people, or to include them in the co-design of services.	All teams have reported an increase in regular patient and family engagement, using tools and techniques they have learnt. Teams focusing on transition to adult services have worked with children and young people on capturing their needs and wants. This helped to structure and establish an efficient referral pathway for young children aged from 14 years old onwards.
All teams wished to improve aspects of their culture and clinical services.	All teams experienced a transformation in terms of the skills learnt from expert trainers and each other. Teams bene-fited from the knowledge provided through monthly coaching and support. All teams experienced incremental changes within team interactions and improvements in how they deliver their service to children and young people.

each identified team champion. Additional one-hour monthly support calls were offered to all teams alongside 1:1 team meetings with QI facilitators to support them to achieve their project aims.

The 2021-2022 programme was designed to offer more flexibility and work around the current capacity of participant teams. The programme encouraged a multi-disciplinary whole-team approach to service improvement with a particular focus on children and young people's engagement and measurement for improvement. It was recommended that teams devoted at least 1-2 hours of time per week to work on team projects.

The progrmme encouraged a multi-disciplinary whole-team approach to service improvement with a particular focus on children and young people's engagement and measurement for improvement

Lessons learned

Team working and communication – Services need the time and space to define what makes an effective team and agree a shared purpose when developing service improvements. It is important the teams strengthen their team building and improve communication processes to see significant improvement and meet national standards.

QI training and support – NHS Trusts should incorporate time within job plans for teams to deliver quality improvement in their services and share learning within the organisation, whether through programmes such as EQIP or independently.

In EQIP, teams found the monthly coaching and support crucial in helping to keep momentum through incremental changes, as well as providing guidance to help resolve barriers.

Patient and family engagement – EQIP's new training and structure placed a greater emphasis on patient engagement, and, for many of the 2021/22 teams, this was at the centre of their project interventions. Teams had a better understanding of how to include patients and families in service redesign. EQIP teams were able to identify where assumptions made about patient preferences were unproductive. They tested and quickly abandoned practices where these did not result in engagement.

In EQIP, teams found the monthly coaching and support crucial in helping to keep momentum through incremental changes, as well as providing guidance to help resolve barriers

Overcoming challenges – Due to the COVID-19 pandemic, at times, some of the improvement projects lost momentum when the service or the wider NHS were under significant pressures. In challenging conditions, the teams and individuals demonstrated dedication to their continued efforts to improve the care for children and young people.

The pandemic also prompted significant change, and teams found the importance of using data to evidence and understand change, with both local and national data providing insights into variation between and within services.

Network links and sharing of good practice – There is a need for platforms, such as OPEN UK, where service teams can share best practice across different Trusts, ICSs or regions. These connections may assist in reducing variation in practice and develop standardised processes and procedures to improve the quality of care.

Visit the RCPCH EQIP website ***eqip.rcpch.ac.uk*** or Twitter #RCPCHEQIP to access presentations by the teams from the shared learning event that took place on 17 March 2022. EQIP teams shared their QI journey and outcomes with their peers and wider epilepsy community. Posters of their project interventions are also available.

Teams found the importance of using data to evidence and understand change, with both local and national data providing insights into variation between and within services

We would like to say a huge thanks to all the participant teams. It has been a pleasure supporting their QI journey and seeing the teams' growth. We would like to say a special thanks also to the advisors and faculty for their valuable input for this programme

ESN advisors: Alison Mollett, Amanda Tomlin, Carolyn McAskil, Christine Bennett, Debbie Dean, Emma Hassan, Jill Conium, Laura Neely.
QI Trainer: Dr Patricia O'Connor, CEO QI Discovery.
Faculty team: Ms Angie Pullen, Dr Colin Dunkley, Ms Emma Sparrow, Dr Megan Peng, Mr Mirek Skrypak, Dr Richard Brown, Ms Rosemarie Pardington, Dr Sreenivasa Tekki-Rao, Ms Helen Stacey
The Healthcare Quality Improvement Partnership (HQIP) is led by a consortium of the Academy of Medical Royal Colleges, the Royal College of Nursing, and National Voices. Its aim is to promote quality improvement in patient outcomes, and in particular, to increase the impact that clinical audit, outcome review programmes and registries have on healthcare quality in England and Wales. HQIP holds the contract to commission, manage, and develop the National Clinical Audit and Patient Outcomes Programme (NCAPOP), comprising around 40 projects covering care provided to people with a wide range of medical, surgical and mental health conditions. The programme is funded by NHS England, the Welsh Government and, with some individual projects, other devolved administrations, and crown dependencies. www.hqip.org.uk/national-programmes

Melanie David-Feveck
RCPCH EQIP project manager
Royal College of Paediatrics and Child Health

Further reading

RCPCH. (2021). Epilepsy12 - national organisational audit and clinical audit - 2021. [online] Available at: https://www.rcpch.ac.uk/resources/epilepsy12-national-organisational-audit-clinical-audit-2021 [Accessed 22 Aug. 2022].

Markus Reuber

Highlights

Top picks from *Seizure*

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

It is now widely recognised that the disability related to epilepsy is not simply the sum total of all epileptic seizures a person has experienced. Of course, most seizures are disabling, but they are merely one – albeit important – manifestation of epilepsy [Olusanya *et al*, 2020]. The disability related to seizures is often complicated by immediately pre- and postictal symptoms, by their more persistent effects on physical and mental health, and by responses to the seizures – at personal, family and societal level. While this seems complex enough, the disability experienced by people with epilepsy is also influenced by the underlying cause of their disorder and how this changes over time. In children, there is the additional dimension of the effects of epilepsy on education. The suboptimal treatment of epilepsy in childhood and adolescence may not only cause disability and disadvantage at this particular time of a person's life but also lead to permanent effects on the life chances of those affected.

My Editor's Choice from the issue 99 of *Seizure* summarises the findings of an original research study by Reidar Lystad *et al*, which characterises how profoundly epilepsy affects formal education in childhood and adolescence [Lystad *et al*, 2022]. This population-based study compares the educational performance in children hospitalised with epilepsy in New South Wales, Australia, with that of children not hospitalised with this disorder. Hospitalisation statistics provide the most reliable statistical data about epilepsy in childhood and adolescence in Australia because about 80% of young people with epilepsy in this country are hospitalised after their initial presentation with seizures. This patient group is, therefore, considered fairly representative of all children and adolescents with epilepsy.

Young people hospitalised with epilepsy were found to be three times more likely not to have achieved the national minimum standard for numeracy (ARR: 3.40; 95%CI 2.76?4.18) and reading (ARR: 3.15; 95%CI 2.60?3.82), compared to non-hospitalised peers, matched for age, sex and socioeconomic status. Young people hospitalised with epilepsy had a 78% higher risk of not completing year 10 (ARR: 1.78; 95%CI 1.14?2.79), 18% higher risk of not completing year 11 (ARR: 1.18; 95%CI 0.97?1.45), and 38% higher risk of not completing year 12 (ARR: 1.38; 95%CI 1.14?1.67), compared to non-hospitalised controls.

This population-based study cannot tell us about the specific reasons for the poor educational achievements of young people with epilepsy, such as the extent to which

seizures, medication, stigma, comorbid disorders or the underlying pathology causing the epilepsy are to blame. However, its stark findings draw attention to the potentially avoidable damage done to the life chances of young people with epilepsy and call for further research exploring causation and testing interventions.

Could 'anti-seizure' medications be 'anti-epileptic'?

While the number of medical treatment options in the epileptological toolbox continues to increase every year, treatments capable of affecting the course of epilepsy remain elusive. The ILAE recently recognised this continuing major gap in our therapeutic arsenal by encouraging clinicians and researchers to talk of the pharmaceuticals we routinely use to treat epilepsy as anti-seizure medicines (ASMs) rather than anti-epileptic drugs (AEDs). The abandonment of the term AED was not meant to indicate that truly "anti-epileptic" medications would not be of interest. The opposite is true: the fact that we suddenly have no actual "AEDs" at our disposal at all should stimulate interest in the development of a new class of drugs with proven disease-modifying potential.

Unfortunately, there are many reasons for the lack of drugs with well-documented anti-epileptic (or anti-epileptogenic) properties. Epilepsy is a highly heterogeneous disease, and it is unlikely that a single anti-epileptogenic mechanism would work in the context of the broad range of possible aetiologies of epilepsy. Similarly, potential biomarkers of the development of epilepsy may only be predictive of its development in particular circumstances. In the absence of reliable biomarkers, studies of anti-epileptogenic drugs have to be quite long and capture the proportion of the treated population who ultimately develop epilepsy after a given insult (or in the presence of a particular risk factor).

Having said that, in animal studies of acquired epilepsies, several ASMs (including levetiracetam, brivaracetam, topiramate, gabapentin, pregabalin, vigabatrin and eslicarbazepine acetate) have shown anti-epileptogenic or disease-modifying effects [Klein *et al*, 2020]. Additionally, several studies designed to observe possible anti-epileptic properties of drugs, which can – to date – only be described as ASMs, are currently in progress [Nicolo *et al*, 2021; Clinicaltrialsregister.eu, 2012]. These studies follow on from previous (unsuccessful) studies exploring possible anti-epileptogenic effects of short courses of valproate or diazepam or of levetiracetam in the post-stroke setting [Chang *et al*, 2022; van Tuijl *et al*, 2011].

My Editor's Choice from issue 100 of *Seizure* is a retrospective study of post-stroke epilepsy by Yaroslav Winter *et al*. This paper, while not proving the anti-epileptogenic properties of any drugs studied, may generate hypotheses which future studies need to test. They analysed data from 207 patients with post-stroke epilepsy who did not change their initial anti-seizure monotherapy during 12 months of follow-up. Their findings suggest that complete seizure control was more likely to be achieved by ASMs acting via the slow inactivation of sodium channels, such as lacosamide and eslicarbazepine [Winter *et al*, 2022]. While the focus of this study was on secondary prevention, it suggests that these medications would also be particularly interesting drugs to test in primary epilepsy prevention studies in the post-stroke setting.

Further reading

Chang RS, Leung WC, Vassallo M, Sykes L, Battersby Wood E, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev. 2022 Feb 7;2(2):CD005398. doi: 10.1002/14651858.CD005398.

Clinicaltrialsregister.eu. (2012). Clinical Trials Register. Prevention of epilepsy in stroke patients at high risk of developing unprovoked seizures: anti-epileptogenic effects of eslicarbazepine acetate, EurdraCT number: 2018-002747-29. [online] Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002747-29/SE [Accessed 25 Aug. 2022].

Klein P, Friedman A, Hameed MQ, *et al*. Repurposed molecules for antiepileptogenesis: Missing an opportunity to prevent epilepsy? Epilepsia. 2020 Mar;61(3):359-386. doi: 10.1111/epi.16450

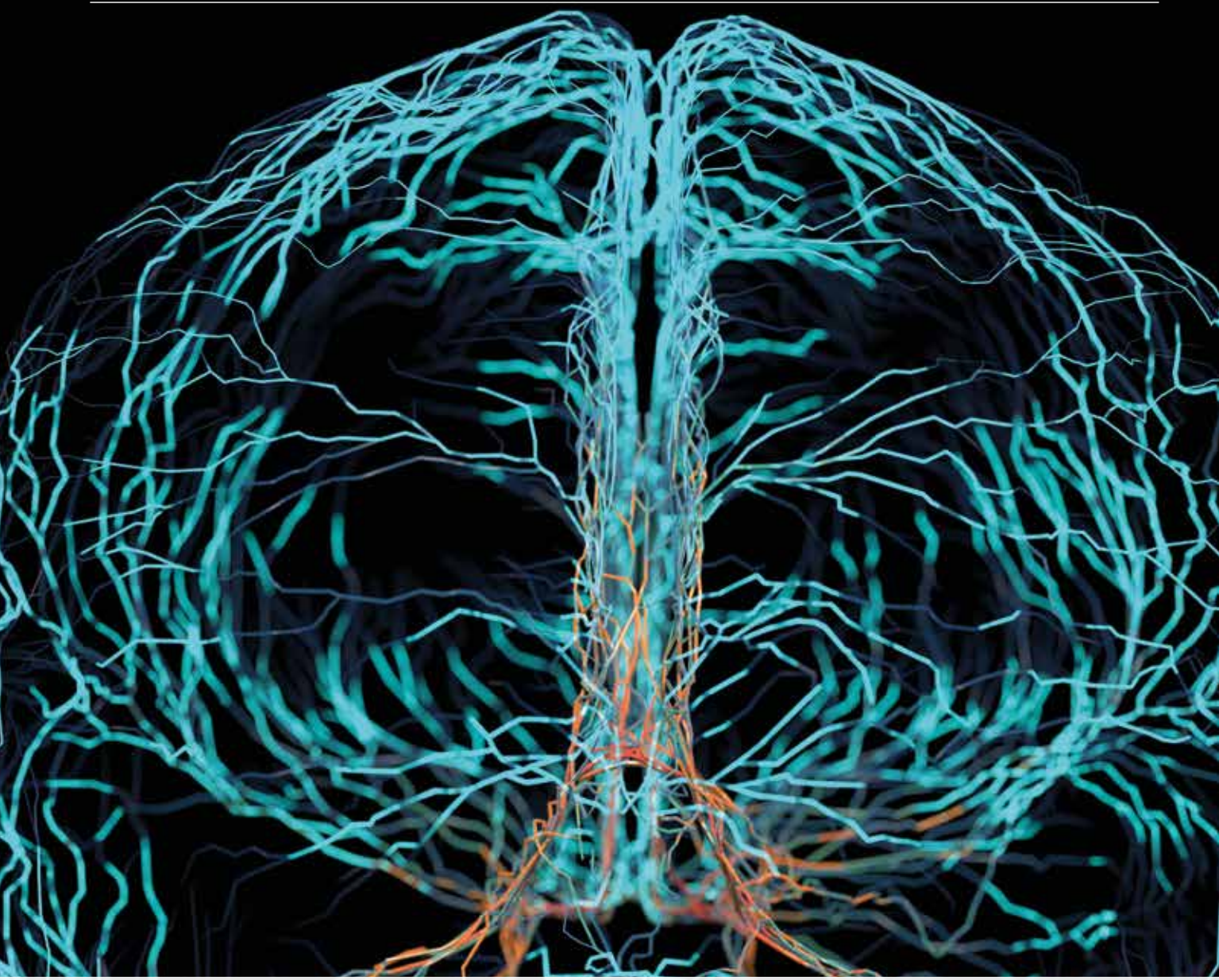
Lystad RP, McMaugh A, Herkes G, Badgery-Parker T, Cameron CM, Mitchell RJ. The impact of childhood epilepsy on academic performance a population-based matched cohort study. Seizure 2022; 99:91-98.

Nicolo J, Chen Z, Moffat B, *et al*. Study protocol for a phase II randomised, double-blind, placebo-controlled trial of perampanel as an antiepileptogenic treatment following acute stroke. BMJ Open 2021;11:e043488. doi: 10.1136/bmjopen-2020-043488

Olusanya BO, Wright SM, Nair MKC, *et al*. Global burden of childhood epilepsy, intellectual disability, and sensory impairments. Pediatrics. 2020;146(1):e20192623

van Tuijl JH, van Raak EP, de Krom MC, *et al*. Early treatment after stroke for the prevention of late epileptic seizures: a report on the problems performing a randomised placebo-controlled double-blind trial aimed at anti-epileptogenesis. Seizure. 2011 May;20(4):285-91. doi: 10.1016/j.seizure.2010.12.012.

Winter Y, Uphaus T, Sandner K, Klimpe S, v. Stuckrad-Barre S, Groppa S. Efficacy and safety of antiseizure medication in post-stroke epilepsy, Seizure 2022;100:109-114.



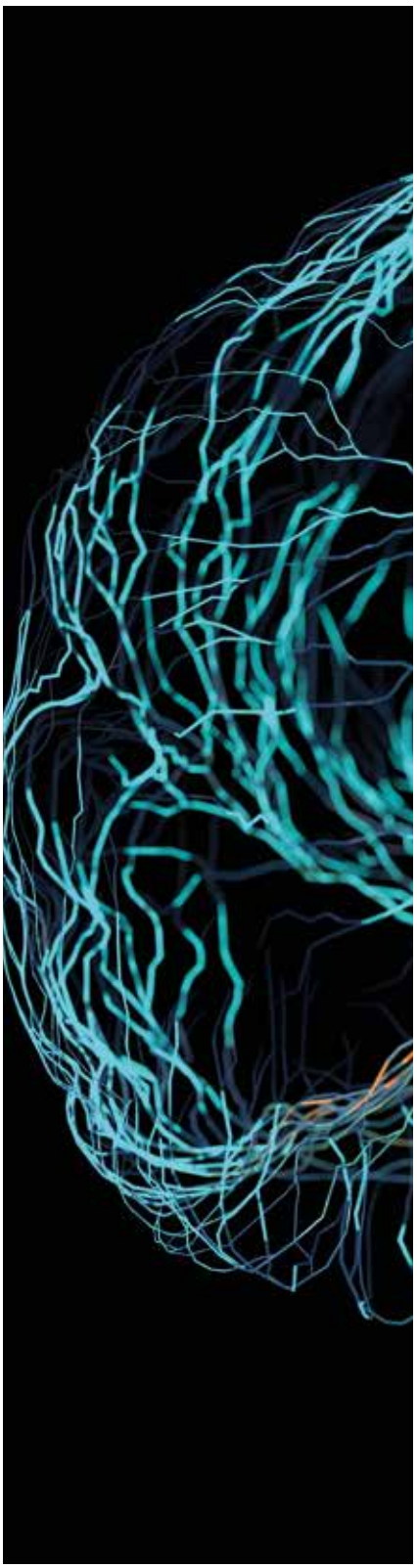
Blood brain barrier

A target for treating epilepsy

Prof Campbell and Prof Doherty describe the way the blood brain barrier can be implicated in some epilepsies, and share evidence showing that restoring its function could lead to seizure control.

The capillary network of the human brain is so vast that it covers a surface area of up to 20m2. If each of these capillaries were lined up next to each other, they would stretch to a distance of 600km. Such is the extent of vascularisation of the human brain, that no neuron is ever more than about 20µm from a capillary. Why does the human brain command such a dense network of blood vessels? This is largely due to the inability of the brain to store glucose at any great capacity. It therefore requires a constant energy supply and consumes up to 25% of the daily energy intake, an enormous amount given the size of the brain relative to the body. With this extensive vascular network also comes a need for tight regulation of transport of material from blood to brain and vice versa. In that regard, the endothelial cells lining the cerebrovasculature have properties unlike endothelial cells anywhere else in the body. The properties and attributes of these cells form what is know as the blood brain barrier (BBB). The BBB tightly regulates what gets into the brain and out of it. Specialised reporters on the luminal surface of endothelial cells can traffic glucose, transferrin and ions across the endothelial cells and into the brain. Additionally, efflux pumps can very effectively pump unwanted material out of the cells and back into the blood. Unfortunately, this is the fate of many potentially useful drugs which

Many neurological and neuropsychiatric disorders appear to have BBB disruption as a hallmark pathology



simply can't get access to the brain when administered systemically.

In recent years, however, it is becoming increasingly evident that drug delivery is not the only problem the BBB presents. Many neurological and neuropsychiatric disorders appear to have BBB disruption as a hallmark pathology. Post mortem analysis of donor human brain tissues who had Alzheimer's disease (AD), schizophrenia and major depression has shown a disruption to the endothelial tight junctions, the 'kissing point' of two contacting cells [Greene *et al*, 2020]. This disruption can cause exudative leakage at the BBB and long-term extravasation of serum components can ultimately lead to neurodegeneration and gliosis.

Recently, our group has reported a detailed analysis of BBB integrity in patients being worked up for neurosurgical resection due to treatment-resistant epilepsy [Keaney *et al*, 2015]. Worldwide, only 70% of patients with epilepsy can expect to have their condition controlled by medication alone. Of the remining

Recently, our group has reported a detailed analysis of BBB integrity in patients being worked up for neurosurgical resection due to treatment-resistant epilepsy

30%, only a minority are suitable for other treatments like surgical resection. Despite the identification of more than 10 new compounds over the last 20 years to treat epilepsy, increased precision targeting the electrochemical environment has not yielded significant improvements in seizure control in refractory cases. There is an urgent need to identify new targets for treatment.

In the BBB field, there remains an open debate as to whether BBB disruption is a cause or effect of seizure activity. Our approach was agnostic to this debate. We sought to characterise the integrity of the BBB in patients pre-surgery and to then examine the resected material

It is tempting to suggest that some individuals may be more at risk of developing epilepsy due to low levels of claudin-5 at their BBB compared to others

microscopically for molecular components of the BBB associated tight junction. Our aim was to identify key components of the tight junction that might be therapeutically targetable to regulate seizure activity. While the initial study involved four patients, we have now gone on to show in eight patients that the BBB is significantly compromised in temporal lobe epilepsy based on evidence from dynamic contrast enhanced MRI (DCE-MRI). These scans involve an injection of a bolus of gadolinium which is known to only cross the BBB in pathological conditions such as glioblastoma multiforme (GBM) and multiple sclerosis (MS). Our scans were designed to observe more subtle changes at the BBB by extending the scan time to 20

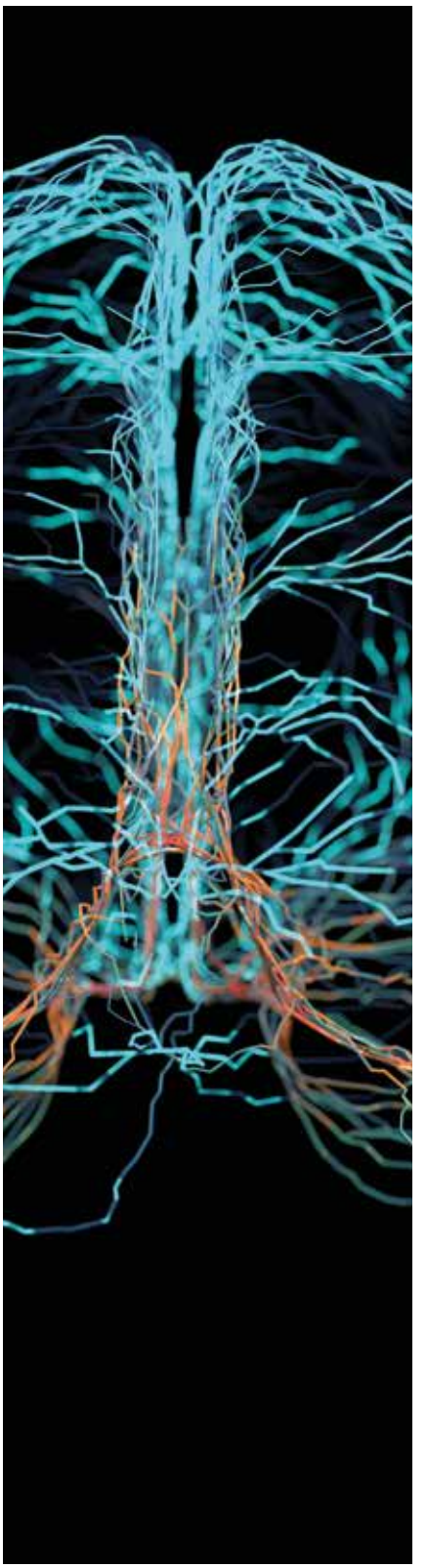
minutes, as opposed to diagnostic scans which take only five minutes. Clear evidence of BBB disruption was observed at the temporal lobe, the focal point of the seizure in these patients. However, intriguingly, BBB disruption was also observed at distal sites, suggesting a focal BBB disruption could propagate the entire brain and cause widespread depolarisation and BBB damage. In all cases, the patients went on to have surgical resection of the seizure focus, and in those who became seizure free, resolution of the brain-wide BBB disruption resolved.

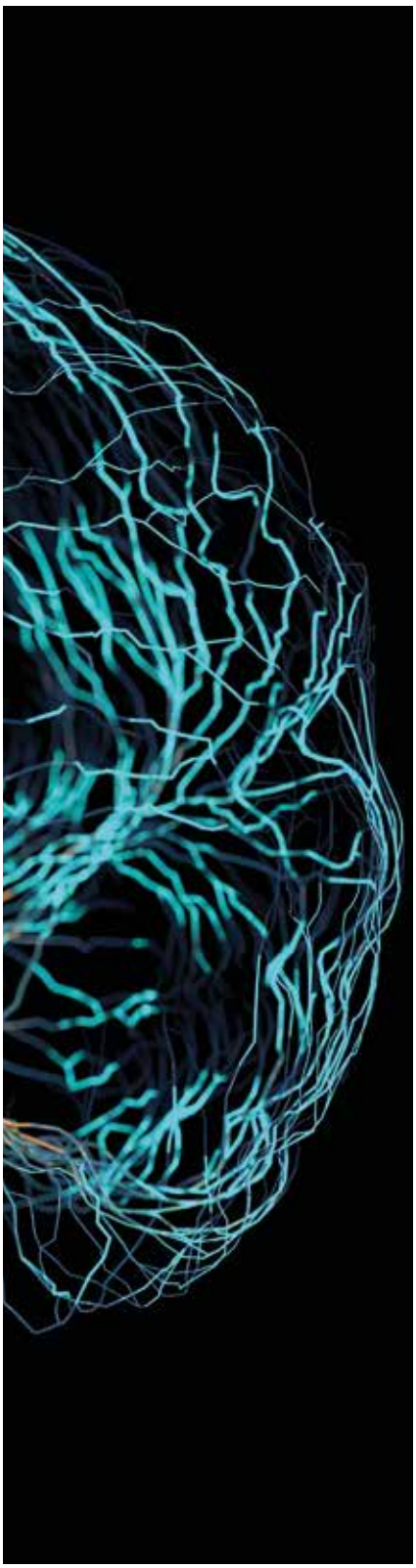
Interestingly, the resected tissues, while showing very evident gliosis, also showed a marked decrease of the key tight junction component claudin-5. Claudin-5 is the most enriched tight junction protein at the BBB and it regulates the paracellular pathway at the BBB strictly controlling what can pass between two contacting endothelial cells. Its pattern of expression should be at the cell borders in a strong linear and continuous band. However, in the resected material, it was very clear that claudin-5 expression was decreased and its localisation was compromised. This study represented the first molecular evidence of not only BBB disruption in treatment-resistant epilepsy, but also its rescue after seizure resolution. It raises the tantalising possibility that regulating BBB integrity may be a novel way of controlling seizure activity. To this end, we then turned to animal models of the condition.

Kainic acid has traditionally been used to induce seizures in mice by either systemic or direct injection into the brain. It is a glutamate analog and well defined doses are known to induce profound seizure activity in mice. Indeed, it is the gold standard model for screening novel anti-seizure medications (ASMs). Our first experiment showed that in mice with only one copy of the claudin-5 gene, injecting sub-convulsive doses of kainic acid could induce seizures [Greene *et al*, 2022]. This suggested that low levels of claudin-5 likely primed the brain and reduced the threshold to a level beyond which a seizure could occur. It is tempting to suggest that some individuals may be more at risk of developing epilepsy due to low levels of claudin-5 at their BBB compared to others.

This study represented the first molecular evidence of not only BBB disruption in treatment-resistant epilepsy, but also its rescue after seizure resolution

Our second experiment involved the generation of a mouse model where we could genetically decrease claudin-5. Such is the importance of claudin-5 that when it is removed completely from the genome of a mouse, the animals die within 10 hours of birth. Therefore, we developed a strain of mouse that allowed us to target the gene in adult animals. We engineered a molecular switch that was controlled by the antibiotic doxycycline. Feeding mice doxycycline in their drinking water would turn on the genetic machinery to decrease claudin-5 in the adult brain and, within two weeks, all the mice developed spontaneous seizures. The extent of these seizures was such that all the





animals died. However, upon withdrawal of doxycycline, the seizures stopped, providing direct evidence that regulating claudin-5 levels at the BBB can control seizure activity.

Finally, we tested this hypothesis in the kainic acid model. Mice exposed to kainic acid were treated with an experimental drug called RepSox. RepSox is a potent inhibitor of the TGF-beta receptor and is known to increase the production of claudin-5. Sure enough, animals treated with RepSox did not develop seizures after exposure to kainic acid, proving that a targeted increase in claudin-5 levels at the BBB can prevent seizures.

The next step in this journey is to begin to widen our search for molecules or therapeutic modalities that can regulate claudin-5 levels at the BBB with a view to prevent seizures

So, where do we go from here? The next step in this journey is to begin to widen our search for molecules or therapeutic modalities that can regulate claudin-5 levels at the BBB with a view to prevent seizures. In the age of advanced medicines such as gene therapies, it is very tempting to consider developing viral vectors that will specifically deliver BBB components to the damaged and disrupted endothelial cells. There may also be drugs already approved that can regulate BBB integrity. Suffice to say, we believe there is now a burgeoning field opening that considers the cerebrovascular nature of epilepsy and other neural malignancies. Excitement is building that a vast network of untapped therapeutic targets is now at our doorstep. We, and others, intend to fully exploit them to develop the next generation of medicines for these devastating diseases.

Prof Matthew Campbell
Professor in Genetics
Smurfit Institute of Genetics
Trinity College Dublin

Prof Colin Doherty
Consultant neurologist
St James's Hospital

Further reading

Greene C, Hanley N, Campbell M. Blood-brain barrier associated tight junction disruption is a hallmark feature of major psychiatric disorders. Transl Psychiatry. 2020 Nov 2;10(1):373.

Greene C, Hanley N, Reschke CR, Reddy A, Mäe MA, Connolly R, Behan C, O'Keeffe E, Bolger I, Hudson N, Delaney C, Farrell MA, O'Brien DF, Cryan J, Brett FM, Beausang A, Betsholtz C, Henshall DC, Doherty CP, Campbell M. Microvascular stabilization via blood-brain barrier regulation prevents seizure activity. Nat Commun. 2022 Apr 14;13(1):2003.

Keaney J, Walsh DM, O'Malley T, Hudson N, Crosbie DE, Loftus T, Sheehan F, McDaid J, Humphries MM, Callanan JJ, Brett FM, Farrell MA, Humphries P, Campbell M. Autoregulated paracellular clearance of amyloid-β across the blood-brain barrier. Sci Adv. 2015 Sep 4;1(8):e1500472

Dates for the diary

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

2022

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

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

17-20 September
8th Loncon-Innsbruck Colloquium on Status Epilepticus and Acute Seizures
Salzburg, Austria
statusepilepticus.eu/index.php

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

2023

29-31 March
International Congress on Structural Epilepsy & Symptomatic Seizures
Gothenburg, Sweden
bit.ly/3ezBJRs

5-8 May
Seventeenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVII)
Gothenburg, Sweden
bit.ly/3ezBJRs

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:

Prof Ramon Bautista

Prof Bautista discusses employment and epilepsy and the role of health professionals in supporting people with this.

Dr Marco Mula

Dr Mula shares information on managing psychosis in epilepsy.

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

kkountcheva@epilepsy.org.uk

Epilepsy Professional's advisory panel

optima

XLTEK

Diagnostic EEG

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

natus neurology

To find out more call 020 3058 0850

www.optimamedical.com