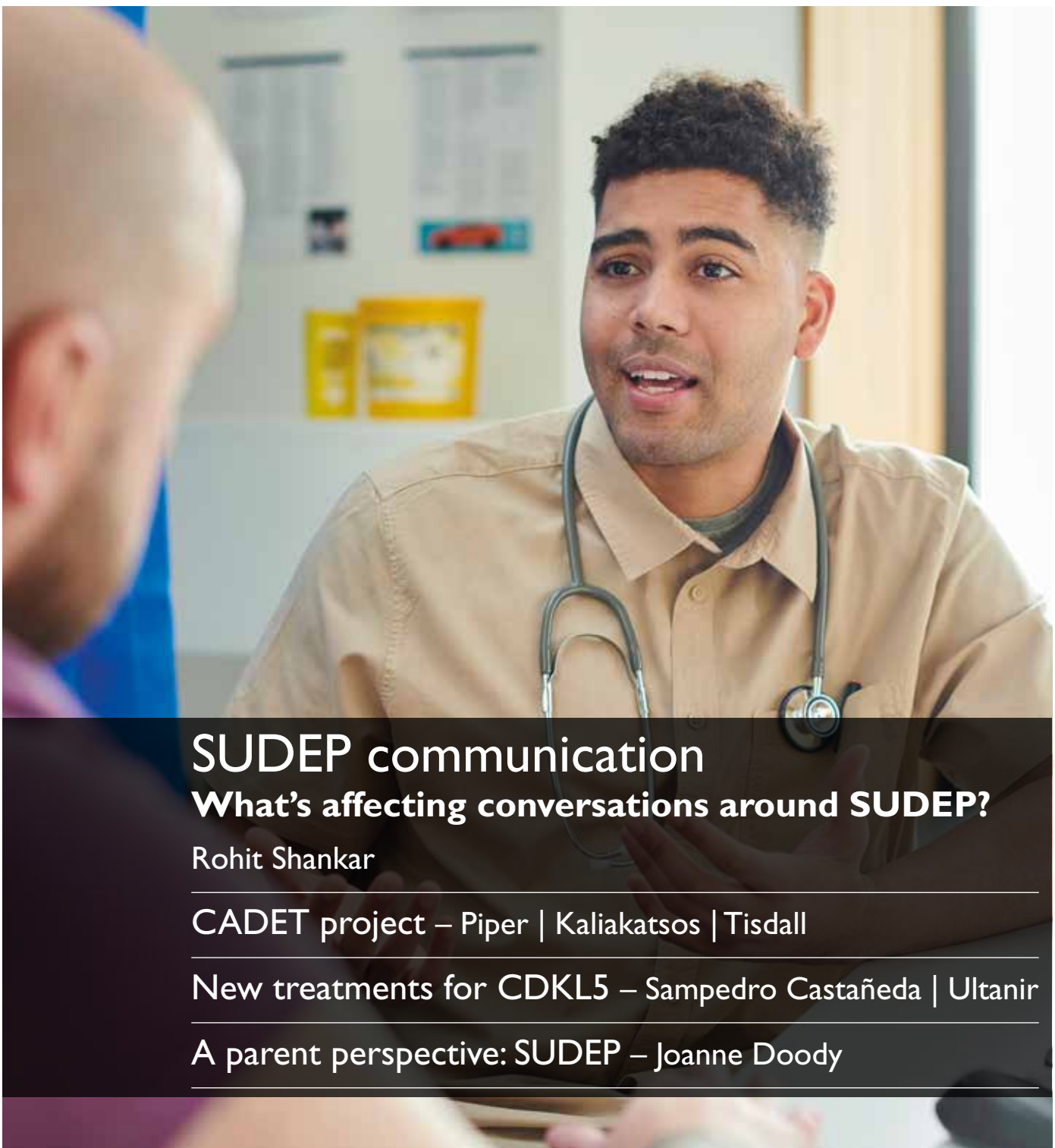
EPILEPSY ACTION

issue seventy five / Winter 2024
(Free to Epilepsy Action professional members)

epilepsy professional



SUDEP communication

What's affecting conversations around SUDEP?

Rohit Shankar

CADET project – Piper | Kaliakatsos | Tisdall

New treatments for CDKL5 – Sampedro Castañeda | Ultanir

A parent perspective: SUDEP – Joanne Doody

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1. Patient's Guide for Epilepsy 2021, LivaNova USA, Inc.
2. Ergene et al, 2000. Epilepsy & Behaviour, 2:284-287. Ryvlin et al, 2014. Epilepsia, 55(6):893-900

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LivaNova Epilepsy

You are in for a real treat this edition. I think these Epilepsy Professional articles have a theme of supporting the underdog and providing hope despite difficult circumstances. I cannot think of a better advocate than Prof Rohit Shankar for those important epilepsy issues that occur at the under-served, under-recognised fringes. Rohit is a titan of real-world data and, as such, his interview about SUDEP communication is required reading. Having had the pleasure of visiting Norway and attending epilepsy centres across this beautiful country, I am not surprised that the Nords were able to support his work with such enthusiasm, delivering a volume of responses to the survey. Their epilepsy network is a great example of how clinicians can bind together to work smarter, rather than harder; and something which we will look to bring you more on in a future edition.

Continuing the theme of under-served patient groups – children and adults with Lennox Gastaut syndrome (LGS) are in desperate need for impactful new therapies, particularly those that are minimally sedating. Colleagues from Great Ormond Street Hospital discuss the 'Children's Adaptive Deep brain stimulation for Epilepsy Trial' in detail, and how it could help children with LGS. I remember seeing news around the CADET Project, which really captured the imagination earlier this year. Deep brain stimulation for epilepsy is something that very few of us have significant experience with, but knowing who could or should be identified for this promising treatment is a positive forward step.

Some rare genetic epilepsies cause a spectrum of neurodevelopmental disorders with seizures, and some cause a more distinct clinical picture. Similarly, some genetic answers lead to a specific 'precise' therapy, either because we know what the gene should do biologically, or because clinicians have stumbled across specific therapies that are preferable. The super article on CDKL5 deficiency disorder not only meticulously unpicks the biology of the disorder, but leads us to think about how this evolving knowledge can help us to best treat this common but uncommon childhood-onset disorder.

Finally, as a companion piece to Rohit's interview, can I commend to you the poignant interview with Peter Doody's mother Jo. Here I must reveal that I too have had the opportunity to speak with Peter's parents and so have heard first-hand of his life and his untimely death. Jo's brave discussion of the topic continues to deliver in their mission to confirm that "Peter is, not Peter was", as they carve out a legacy for him.

Two messages arise from these similar but dissimilar articles. The first is to discuss SUDEP risk and how to mitigate against it, and to make this a regular part of your care. The second is that even the most desperately difficult to treat epilepsies may be helped, but we may need to take a left-field, research-driven approach to deliver the next breakthrough.

Enjoy this Winter edition of Epilepsy Professional.

Dr Rhys Thomas
Consultant neurologist
Chief medical adviser
Epilepsy Professional

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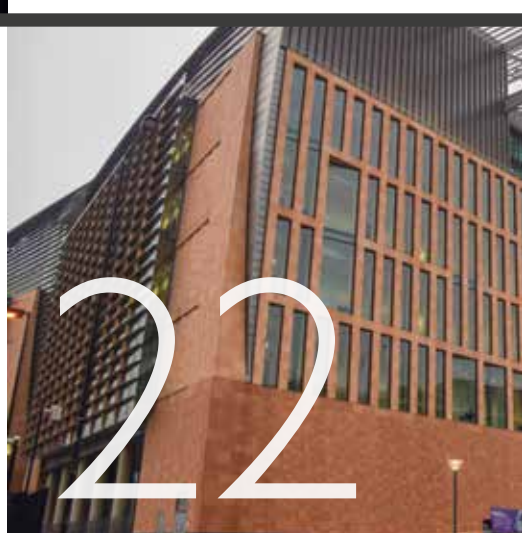

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New treatments for CDKL5

Sampedro Castañeda | Ultanir

Dr Castañeda and Dr Ultanir discuss the mechanisms around CDKL5 and what new treatment opportunitiies they provide.

I expect most people want to get into medicine because they want to 'help people'. It's a noble wish, and it shows strength of character to persevere through years of learning, training, gruelling exams and long shifts to realise that wish.

I expect, therefore, that most people didn't get into medicine because they want to 'deliver bad news'. But, unfortunately, that is part and parcel of the job. It's a part that you can definitely get really good at, but probably still one that never gets easier.

In this issue, we discuss the importance of communicating about sudden unexpected death in epilepsy (SUDEP) with patients with epilepsy. It might not be an easy conversation, but it needs to be had with everyone − Prof Rohit Shankar explains why on page 10.

Continuing on this theme, our patient perspective this issue comes from Joanne Doody, a bereaved parent whose son Peter died from SUDEP in 2019. Joanne and her whole family had never been told about SUDEP until after Peter's death. She shares her honest thoughts about what it would have been like to hear about SUDEP when Peter was first diagnosed, what it would have meant to know about it and what she'd like to see in place in the future (page 26).

Other topics covered this issue include deep brain stimulation for Lennox-Gastaut syndrome (page 16) and new treatments for CDKL5 (page 22).

Despite first appearances, I think this issue is full of promise and opportunities to help people, whether that is through delivering difficult news that can help people reduce risk, or whether that is the hope of new treatments on the horizon.

Kami Kountcheva
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Darzi report highlights 'critical state' of NHS

The NHS is in a "critical state, but the vital signs are strong", according to the Darzi report into the state of the UK's health service, published today.

The Independent Investigation of the National Health Service in England report was commissioned by the Secretary of State for Health and Social Care, Wes Streeting earlier this year.

Conducted by Professor Ara Darzi, the investigation has concluded that the NHS is "in serious trouble".

In a response to the report, Prime Minister Kier Starmer said that the public have a right to be angry. He added that the NHS is broken, but not beaten.

He announced three "big shifts" are planned over the next 10 years to improve the state of the NHS. They include investing more in community care rather than hospitals.

However, Epilepsy Action has stressed that historically, neurology services have been "severely underfunded".

The Darzi report highlighted a number of issues. It referenced 'ballooning' wait times, health inequalities in areas like maternity care, and an A&E in an "awful state" which could be contributing to an additional 14,000 deaths a year.

The investigation found that people are struggling to see GPs and waiting lists for community care and mental health services are "surging". Meanwhile, the health of the nation has deteriorated, the report added.

The report found that the NHS is "starved of capital", is still feeling the effects of the pandemic and the austerity of the 2010s.

Prof Darzi also concluded that the patient voice is not loud enough, with patients' concerns not being heard or acted upon.

Despite all of this, Prof Darzi said the "vital signs are strong".

He said: "The NHS has extraordinary depth of clinical talent, and our clinicians are widely admired for their skill and the strength of their clinical reasoning.

"Our staff in roles at every level are bound by a deep and abiding belief in NHS values and there is a shared passion and determination to make the NHS better for our patients. They are the beating heart of the NHS.

"It is not a question… of whether we can afford the NHS. Rather, we cannot afford not to have the NHS, so it is imperative that we turn the situation around."

The government's three 'big shifts' programme to lead to the major recovery of the NHS include moving from hospital to community care, becoming more digital and focusing more on preventing sickness rather than treating it.

Epilepsy Action is campaigning for epilepsy to be prioritised within health and social care. The organisation says the UK has one of the worst ratios of neurologists to patients among high income countries. There are 1.1 full-time-equivalent neurologists per 100,000 people in England. Both France and Germany have one consultant for every 25,000 people or fewer.

Also, guidelines recommend that there should be nine epilepsy specialist nurses per 500,000 people. But in England there are two per 500,000.

Alison Fuller, director of Health Improvement and Influencing at Epilepsy Action, said: "The findings from the Darzi report are disappointing but not surprising. It's a harsh truth that the NHS has faced major challenges since way before the pandemic.

"We welcome aspects of the government's vision such as getting more people with long-term conditions into work, and empowering community care. At the same time, we still think there is investment needed into hospitals when it comes to specialist workforces, and it's concerning to hear this doesn't seem to be a part of the 10-year plan.

"Our country's neurology services have historically been severely underfunded. There just hasn't been enough resource. Lack of access to specialists has a major impact on people with a long-term condition like epilepsy, who are already faced with a life-changing diagnosis and need all the support they can get.

"There are huge regional disparities in the numbers of specialists available in our country, and even the better-served areas are not keeping up with the rest of Europe.

"We know there are major NHS-related issues that need addressing, including improving A&E waiting times and investing in digital technologies. But we were hoping for more support for people with long-term conditions."

Centre for Global Epilepy lanched to address global challengees

The University of Oxford is launching the Centre for Global Epilepsy to address the global epilepsy challenges.

Led by consultant neurologist and professor of Global Epilepsy at the University of Oxford, Arjune Sen, the new centre will drive advancements in epilepsy research, diagnosis, treatment and care by linking expertise from high-income settings to lower-resource areas.

Research by Simon Wigglesworth and colleagues showed that even within the UK, there is a higher prevalence and incidence of epilepsy in more deprived areas, compared with more affluent areas.

The centre will act as a global epilepsy hub, linking research institutions with epilepsy clinics across the world, and facilitate "bidirectional knowledge transfer".

It will also aim to inspire clinicians and trainees to help transform global epilepsy care.

Prof Sen said: "The need for epilepsy research and improved care is crucial. Most people in lower-income countries are currently undiagnosed, or incorrectly diagnosed, lack access to treatment, and face severe stigma.

"Through its holistic approach to sustainable global partnerships, and commitment to empowering local stakeholders, the Centre for Global Epilepsy has the potential to transform the lives of millions affected by this neurological disorder, especially those who happen to be born in less well-resourced settings."

The establishment of the new centre is part of the University of Oxford's commitment to "addressing global mind-brain health challenges and promoting equitable access to quality healthcare worldwide". It will be based at the university's Wolfson College.

Sir Tim Hitchens, president at Wolfson College said: "Wolfson College knows at first hand the tragedy of epilepsy related deaths and warmly welcomes the Centre for Global Epilepsy, with its particular focus on understanding and removing stigma from epilepsy in the Global South.'

Senior consultant neurologist and lecturer in internal medicine at University of Zimbabwe, Dr Gift Ngwende, added: "Having partnered with Arjune and the Oxford team for many years, we have seen the substantial benefits that associate with equitable, collaborative effort.

"We look forward immensely to working with multiple friends across the world to improve the care of those living with epilepsy in lower income settings."

The Centre for Global Epilepsy is supported by the BAND Foundation.

More epilepsy education and specialists needed

The UK needs more epilepsy nurses, better social care and empowerment of patients to help address health inequalities, say researchers.

In a new comment in The Lancet Public Health, Prof Angela Hassiotis and Prof Rohit Shankar said that prevention strategies should focus on three aspects: clinicians, patients and society.

The researchers explain that the prevalence of epilepsy is "unevenly distributed by population and geography". They say 2-3% of all A&E visits are suspected to be related to seizures and linked factors. These include poor quality of life, social deprivation, mental health issues and lack of seizure management knowledge.

The researchers cited another study by Dr Kathryn Bush and colleagues, also published in The Lancet Public Health. This investigated health inequalities in epilepsy. The researchers found that high levels of deprivation were linked to a higher level of new cases of epilepsy.

Prof Hassiotis and Prof Shankar said the first challenge to address is the lack of neurologists and epilepsy specialists. We also need to reduce the difference in the number of specialists in different areas of the country. They say it should be a priority to employ more epilepsy nurses, have joint professional case reviews and involve pharmacists in prescribing medicines.

They added that there is also an "urgent need" to help educate and counsel people about managing their condition. Finally, they say social care staff has an important part to play and needs training and education. These population-wide approaches need to be implemented to tackle issues linked to socioeconomic inequalities.

Men taking valproate advised to use contraception - MHRA

Men taking the medicine sodium valproate are advised to use effective contraception by the Medicines and Healthcare Products Regulatory Agency (MHRA) in a release published yesterday in the UK.

The MHRA advises that men taking sodium valproate use condoms and ask female partners to use contraception to prevent an unplanned pregnancy.

This is because taking the medicine may cause a "potential small increased risk" of neurodevelopmental disorders in children born to fathers taking sodium valproate.

Sodium valproate is an epilepsy medicine which people may know by its brand names: Epilim, Episenta, Epival, Dyzantil or Depakin.

The MHRA says no one should stop taking valproate without advice from their specialist, so doing so could worsen their seizures.

However, it advises that health professionals should discuss the risks with men taking the medicine at their next epilepsy appointment. They should also discuss available options with their patients.

The new advice also encourages patients to attend their routine appointments to discuss their treatment plans and ask any questions.

The organisation says men shouldn't donate sperm while taking sodium valproate and three months after stopping the medicine.

For anyone not currently taking sodium valproate, but wanting to have it prescribed, the restrictions brought in in January 2024 will apply.

These say that no one under the age of 55 will be prescribed sodium valproate unless two specialists agree there is no other effective or tolerated treatment, or unless there are "compelling reasons that the reproductive risks do not apply".

The new guidance is precautionary and is based on a study from a few Scandinavian countries. This research looked at health records and found that around five in 100 children whose fathers were taking sodium valproate at conception had a developmental disorder, according to the MHRA.

The researchers compared this to around three in 100 children born to fathers who were taking lamotrigine or levetiracetam.

The MHRA said that "this study does not prove that valproate use in men increased the risk of problems in children". However, it said that it is "an important safety issue", which needs "precautionary" action.

Alison Fuller, director of health improvement and influencing at Epilepsy Action, said: "When the MHRA introduced regulations for new sodium valproate prescriptions in January 2024, we raised concerns about adding additional restrictions to a potentially effective medication.

"We know there are around 65,000 boys and men currently on sodium valproate in the UK. The measures are precautionary, meaning they will not require two signatories to stay on their medication. That said, they will still need to have an in-depth conversation with a healthcare professional. We think healthcare professional capacity is still going to be a real issue.

"At Epilepsy Action we are working with the information we have been provided to support people this has a potential impact on, but we know these changes will raise questions within the epilepsy community. We are concerned people with epilepsy will feel confused at best, and very worried about what this means for their treatment at worst.

"We'll continue to monitor the implementation of the new rules closely and ask for more information from the MHRA."

Tiny folding implants improve epilepsy surgery and diagnosis

Picture by Lawrence Coles

Tiny folding implants could make epilepsy surgery safer and improve diagnosis, say UK researchers.

In a new study, the University of Oxford-led research team said that its electrodes, inspired by the Japanese art of origami, can fit through a surgical hole as small as 6mm.

The device is a flat, rectangular silicone wafer with 32 embedded electrodes. It folds up like an accordion and surgeons can then unfurl it on the brain's surface to a size five times larger.

The researchers hope that this folding electrode will help to find where seizures start in the brain and make diagnosis safer and more efficient.

The researchers said this technology could also cut down recovery times and lower infection risk of surgery.

At the moment, surgeries performed to monitor electrical activity in the brain are either very invasive or only cover a small surface area of the brain. According to Christopher Proctor, associate professor at the University of Oxford, this technology represents a "new approach" to connect with "large areas of the brain through a keyhole-like surgery".

Inquest – woman died after seizure in A&E waiting room

A woman died days after a seizure caused "significant, irreversible" brain damage while she waited in A&E, an inquest has heard.

Inga Rublite, 39, was found unconscious and appearing to be having a seizure under her coat in the Queen's Medical Centre (QMC) in Nottingham on 20 January 2024.

Staff discovered her "tucked behind a door" and "seemingly asleep" under her coat.

The inquest was told that there were "missed opportunities" to check on the mother of two, during the eight hours that she waited in the crowded A&E waiting room.

On 19 January, Ms Rublite had called 111 after getting a sudden headache, neck pain and blurry vision. She had described it as feeling like she was "hit by a brick". She was advised by a clinician on the phone to go to hospital.

She arrived at 10:30pm and staff called out three times for her in A&E and called her mobile phone. She wasn't found until 7am the next day.

Nottinghamshire coroner Elizabeth Didcock said: "There were three opportunities for the headache to be recognised as something more dangerous than it was thought to be."

The inquest continues.

Spider venom-derived drug promising for genetic epilepsy

Experts at the University of Queensland, Australia, have developed a drug based on spider venom which could help treat some forms of genetic epilepsy.

Professor Glenn King from the university's Institute for Molecular Bioscience developed the drug using peptides from the venom of the K'gari funnel web spider.

Prof King said: "We believe these venom peptides can be very precise, personalised drugs for specific epilepsy patients."

Additionally, the researchers are using a synthetic brain 'organoid' the size of a lentil to test the medicine. These are produced by Professor Ernst Wolvetang from the Australian Institute for Bioengineering and Nanotechnology using stem cell technology.

Prof Wolvetang said the venom-derived treatment has "proven efficacy" for some types of genetic epilepsy which are "in dire need" of better medicines.

He said that testing new treatments is challenging for ethical, practical and commercial reasons. Thus, the organoids are an ideal way to speed up the process, as well as help with the development of precise and tailored treatments. He added that testing on the organoids is also helping to build the case for their use in future testing.

Prof King and associate professor Nathan Palpant have previously developed stroke and heart disease drugs from the same spider venom.

SUDEP communication

What is affecting conversations around SUDEP?

Prof Rohit Shankar MBE, professor in Neuropsychiatry at the University of Plymouth Medical School, discusses his latest paper on SUDEP communication from epilepsy professionals in the UK and Norway. He explains some of the reasons for the disparities and challenges some of the issues standing in the way of better communication

Epilepsy Professional: Can you tell me a bit about your study?
Rohit Shankar: The preamble to the study is that there have been around 16 sudden unexpected death in epilepsy (SUDEP) surveys of clinicians – neurologists, epilepsy nurses, psychiatrists etc – generally done worldwide. These aim to understand if they are communicating SUDEP risk, what are the challenges or barriers are and other aspects, such as issues with regards to resources.

One of the big things is that every single guideline since the National Institute for Health and Care Excellence (NICE) [2004], and now the American Academy of Neurology (AAN) [AAN.com, 2017], makes it mandatory – it's not even good practice, it's mandatory – that we should be talking about SUDEP. At its most basic level, you have to tell people with epilepsy about SUDEP, but also you follow it up over the course of treating the patient.

One of the big goals was that we wanted to consolidate all these surveys – and identify the top 10 questions – so that from now on, we can have a validated tool to take forward. We published that research in Seizure [Watkins et al, 2023] last year.

The next step was to use that survey. In the UK, the last survey that had been done was in around 2015, and that had shown significant gaps in SUDEP communication. So, we thought that now is a good time to do another survey, as the AAN guidelines came out in 2017, it was post-pandemic, and we had a validated tool to help capture thoughts and opinions.

Every single guideline makes it mandatory – not even good practice, it's mandatory – that we should be talking about SUDEP

We did that in the UK, and we had 197 responses from professionals working with people with epilepsy. Then, a colleague, Dr Oliver Henning, in Norway showed an interest in doing the survey there too.


Prof Rohit Shankar

From the UK, we had 197 out of a population of generally around 60 million, and from Norway, we had around 110 responses from a

population of around five million. It's worth noting that there are fewer health professionals, like neurologists, working in epilepsy in the UK, than somewhere like Norway.

So overall, we could assess how each country was doing, but we could also compare the two, as both are socioeconomically advanced countries and pretty much neighbours.

It was quite an interesting journey. What we identified is that in the UK, we had only two people who said they don't talk about SUDEP with their patients i.e. people with epilepsy. It seems like awareness of SUDEP has become part of the larger culture of epilepsy management in the UK. So that's the positive thing.

The worrying bit for the UK is that there was a subjective inclination on the part of many professionals to decide who is at risk. So, clinicians would talk about SUDEP if they decide the risk is high. The question is, how do you know who is high risk? There is no exact science for that. The other thing is that it might be that at that time, seizures might be low, so if you are judging it on that, you might decide risk might be low. But you are not taking into account aspects like psychological and social factors, which might be impacting subsequently on the person and might change the risk level. So, it's best to avoid quantification of risk. It is best practice that we communicate the risk factors, and we hope that people will change their habits and lifestyle accordingly to help mitigate that.

I think the sense that one can define risk, especially sitting in a clinic in a 20-minute appointment, and then decide whether they want to tell somebody about SUDEP or not, is a significant clinical blind spot. Patients might not even share what they're going through outside the realms of their seizure issues, and they might just focus on the seizures. So, there might be other factors which clinicians might not be aware of or asking about, and they might be making a judgement based on an insufficient number of facts. Also, if it's not part of your framework and you're running late or if you're busy with other things, you might skip discussing SUDEP holistically.

The worrying bit for the UK is that there was a subjective inclination on the part of many professionals to device who is at risk

The issue is that risk is a very dynamic thing and depends on the individual and their environment. From seeing someone once, you can't actually say how at risk they are. Five years later, you might be able to say if the risk has changed for them relative to their original presentation if, say, their seizures have worsened, or their situation has changed and now they live on their own, perhaps.

Even when people are at a lower risk, we should still need to be talking to them about SUDEP, so that they can continue behaviours that help to reduce the risk.

Norway was quite some steps behind the UK in that the epilepsy professionals there did not even feel, to a degree, that SUDEP needs to be communicated. I think that did take our Norwegian co-author by surprise.

Health professionals in both countries cited problems with time and resources, and some of the Norwegian clinicians used the old

arguments that this might upset patients. And, of course, it might. No one likes to be told that they are at risk of dying suddenly. But that's the job that we've signed up to and needs to be done in a person-centred manner, providing a balanced view of mitigators, like being compliant with medication, while also discussing the factors that lower the threshold of harm, such as generalised seizures, sleep seizures and so on. So, there is a significant gap between UK and Norwegian attitudes to SUDEP.

EP: What about countries that are not as socioeconomically advanced?

RS: Our group published a paper on this a few years ago [Kinney et al, 2019]. For this research we asked all 114 ILAE branches about SUDEP research, practice and diagnosis in the last 10 years. Seventy-seven branches fed back. It was fascinating because what we realised was that SUDEP is quite an 'economically developed country' concept. In many places, there are no resources for things like autopsies, so there is no learning, and death by epilepsy is a not a big issue. In many developing countries, there is also no proper recording of cause of death, so you can't even find out if it was an epilepsy death or not. In some other countries, religious practices prevent pathological autopsies, so you cannot find out if a death is due to SUDEP.

There is currently no debate in the UK about whether we should or shouldn't talk about SUDEP. Not discussing SUDEP goes against best practice

EP: What makes attitudes to SUDEP communication different between the UK and Norway?

RS: I think you can divide the reasons into patient reasons, clinician reasons and then the third sector.

The first thing is that the UK was way ahead in terms of developing guidelines. So NICE 2004 was one of the seminal guidelines focusing on introducing SUDEP communication into epilepsy care. The AAN, the American guidelines, only came out over a decade later. So, I think the UK was at the forefront of that, mainly because a lot of the early research developed in the UK. Professor Lina Nashef actually deduced sudden death in epilepsy in 1995 in residential homes [Nashef et al, 1995a; Nashef et al, 1995b]. The first classification of SUDEP came from Prof Nashef [Nashef 1997] and Dr Annegers [Annegers 1997] in 1997, which got firmed up by Nashef in 2012 [Nashef et al, 2012]. Very importantly, the epilepsy charities, particularly SUDEP Action I believe, played a significant role to keep this issue in people's consciousness.

There is currently no debate in the UK about whether we should or shouldn't talk about SUDEP. That has been put to bed in that SUDEP has to be talked about with people with epilepsy. Not discussing SUDEP goes against best practice. I think the battle has been won on this, which is good, so there is the positive influence of that for which we need to give due credit to.

Another observation of mine is that the NHS is a much more a democratic health system than the health systems in many other

countries, and thus more patients are more aware and much more knowledgeable about their condition. They like to know about it and there is a culture of communication here. It can be improved, of course, but it is there.

The influence of epilepsy specialist nurses (ESNs) is another major positive. The UK is one of the few places which has ESNs. In most other countries, there is a medical model for epilepsy led and delivered by neurologists. While of course neurologists are essential, at the grassroots, ESNs are the clinicians who actually do the epilepsy awareness training, engage patient lobbies and, at a much more informal level, tend to be much closer to the patient needs. So, ESNs are people who are much more receptive of the need to communicate and appearing to do so as per our study.

Another thing, which I think has also helped, is research. We in the UK are very research oriented in this area and we are working on it and largely leading on it. The US is now doing a lot of work on it too, but generally, SUDEP especially around communication and risk factors is very topical in the UK. Another finding of our study was the use of the SUDEP and seizure safety checklist. Many professionals use it to understand risk. This too could have helped defuse the perceived tension of such sensitive conversations.

So, all these things play a role in creating an ecosystem which is much more evolved for SUDEP communication.

EP: Is there any circumstance where it might be appropriate not to speak about SUDEP at all?
RS: None that I can think of. I speak about it with every person with epilepsy. Every patient is different, of course, but the main thing is that you can't just mention SUDEP and leave it hanging in the air and send the patient off. We have to follow the thread through and explain it, tailor the conversation to the individual and spell out the positives and give opportunities for the person to raise their views and maybe even vent their anxiety and frustration. Of course, the patient might feel anxious and frightened, but that's where the clinician's role comes in to help make sense of the evidence viz a viz their individual need. We have a duty to tell people what the risks are. One of the issues our study raised was that

The main thing is that you can't just mention SUDEP and leave it hanging in the air and send the patient off. We have to follow the thread through and explain it

clinicians generally felt they did not have enough time to discuss SUDEP comprehensively in their clinics due to pressures of time.

EP: What is needed to help facilitate more of these conversations?
RS: This is where something like EpSMon, the SUDEP Action app, comes in. It's got around 5,000 users presently, which is the largest sample size of users, and every three months or so they update their risk information. With this data, we did a research paper focused on childbearing women with epilepsy, trying to find out whether they

understood the risk of SUDEP and the harm that epilepsy can cause in pregnancy [Zhou et al, 2023].

What we found was that, in the first instance, a significant group of women were clearly unaware of SUDEP as a concept. So, they were made aware of it during their assessment and the associated risks by EpSMon. But, three months later, when they took the questionnaire again, many had forgotten about it. This showed that it's a presumption that if we just talk about SUDEP once that somebody will register it or even go away and think about it.

On their third go on the app, it suggested that awareness started to change. While the study had it's biases, it showed that we have to repeat the message again and again to get it into people's active consciousness.

Also, in our recent study there was a high number of clinicians who had lost patients to SUDEP. I expect that that's quite a gut-wrenching moment. Possibly because of this, one would be more likely to speak about SUDEP to patients. I wouldn't want to wish clinicians to have a SUDEP to become more receptive to discuss it, but I think there is something to be said about peer learning. I don't think we've done that enough, especially around SUDEP. For clinicians, such as loss might induce a sense of failure or worry about their clinical judgements. But they shouldn't! I think we have to develop a therapeutic community or a community of practice, where clinicians can share their thoughts and experiences with others, who might be new to the field or sceptical of SUDEP risk. I think a missing link is that regular clinician to clinician learning, and it would be great to bring that change.

EP: What's next?

RS: The next thing is that we've got data using the same survey on SUDEP communication from Spain and Sweden, and hoping to collect some from Finland, Hungary and Italy as well. We can build up the picture, and look to benchmark the UK accordingly.

RS is the medical lead and partner of the EpSMon app (non-commercial)

Prof Rohit Shankar MBE
Professor in Neuropsychiatry
University of Plymouth Medical School

Further reading

AAN.com. (2017). Sudden Unexpected Death in Epilepsy Incidence Rates and Risk Factors. [online] Available at: *https://www.aan.com/Guidelines/home/GuidelineDetail/850* [Accessed 3 Sep. 2024].

Annegers JF. (1997). United States perspective on definitions and classifications. *Epilepsia*, 38 (**11 Suppl**):S9-12 DOI: 10.1111/j.1528-1157.1997.tb06137.x

Kinney MO, McCluskey G, Friedman D, Walker MC, Sander JW and Shankar R. (2019). Investigative practice into sudden death in epilepsy: A global survey. *Acta Neurologica Scandinavica,* 139(**5**), pp.476–482. doi: https://doi.org/10.1111/ane.13080

Nashef L, Fish DR, Garner S, Sander JW and Shorvon S. (1995). Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia*, 36(**12**): 1187-1194. DOI: https://doi.org/10.1111/j.1528-1157.1995.tb01061.x

Nashef L, Fish DR, Sander JW and Shorvon SD. (1995). Incidence of sudden death in an adult outpatient cohort with epilepsy at a tertiary referral centre. *BMJ*, 58(**4**): 462-464. DOI: https://doi.org/10.1136/jnnp.58.4.462

Nashef, L. (1997). Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia*, 38: S6-S8. DOI: https://doi.org/10.1111/j.1528-1157.1997.tb06130.x

Nashef L, So EL, Ryvlin P and Tomson T. (2012). Unifyingg the definitions of sudden unexpected death in epilepsy. *Epilepsia*, 53(**2**):227-33 DOI: 10.1111/j.1528-1167.2011.03358.x

NICE (National Institute for Health and Care Excellence NICE). (2004). The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care | Guidance | NICE. [online] Available at: *https://www.nice.org.uk/guidance/cg20*.

NICE (National Institute for Health and Care Excellence NICE). Epilepsies in children, young people and adults: diagnosis and management [19] Evidence review: Reducing the risk of seizure-related mortality, including SUDEP NICE guideline NG217. (2022). Available at: *https://www.nice.org.uk/guidance/ng217/evidence/19-reducing-the-risk-of-seizurerelated-mortality-including-sudep-pdf-398366282808*.

Watkins LV, Ashby S, Hanna J, Henley W, Laugharne R and Shankar R. (2023). An evidence-based approach to provide essential and desirable components to develop surveys on Sudden Unexpected Death in Epilepsy (SUDEP) for doctors: A focused review. *Seizure*, 106: 14–21. https://doi.org/10.1016/j.seizure.2023.01.007

Watkins L, Henning O, Bassett P, Ashby S, Tromans S and Shankar R. (2024). Epilepsy professionals' views on sudden unexpected death in epilepsy counselling: A tale of two countries. *European Journal of Neurology*. doi:https://doi.org/10.1111/ene.16375.

Zhou SM, McLean B, Roberts E, Baines R, Hannon P, Ashby S, Newman C, Sen A, Wilkinson E, Laugharne R and Shankar R. (2023). Analysing patient-generated data to understand behaviours and characteristics of women with epilepsy of childbearing years: A prospective cohort study. *Seizure*, 108, 24–32. https://doi.org/10.1016/j.seizure.2023.04.008

CADET project

Deep brain stimulation for children with Lennox-Gastaut syndrome: an update

Great Ormond Street Hospital clinical lecturer in neurosurgery Rory Piper, consultant paediatric neurologist Dr Marios Kaliakatsos and consultant paediatric neurosurgeon Martin Tisdall introduce the CADET Project, discuss deep brain stimulation opportunities in children with Lennox-Gastaut syndrome and share a recent case study.

What is CADET?

The CADET Project is the 'Children's Adaptive Deep brain stimulation for Epilepsy Trial' – a series of clinical device trials that will investigate the safety and effectiveness of deep brain stimulation to reduce seizure frequency in children with Lennox Gastaut Syndrome (LGS) (NCT05437393) [Piper and Tisdall, 2023]. If this therapy is effective, our overall intent is to be able to provide a successful therapy to children with LGS – one that significantly improves their quality of life.

LGS is a rare, yet severe, form of childhood-onset epilepsy that affects 1-2% of children with epilepsy. LGS is associated with multiple, drug-resistant seizure types, classical electroencephalography (EEG) patterns and intellectual disability. More than 90% of children with LGS have drug-resistant epilepsy and other treatments are often offered, such as ketogenic diet, corpus callosotomy for drop seizures, or vagus nerve stimulation (VNS).

Deep brain stimulation (DBS) has more recently become of interest as a treatment that may reduce seizure frequency for patients with LGS. Stimulation of the thalamus of the brain – a key relay hub for neuronal networks – is proposed to interfere with seizure propagation in the brain [Piper et al, 2022]. Data from adult [Dalic et al, 2022] and a small number of childhood [Khan et al, 2022] studies of DBS for LGS has shown the potential of this therapy, but larger and robust studies are required.

Deep brain stimulation has more recently become of interest as a treatment that may reduce seizure frequency for patients with LGS

Teams from Great Ormond Street Hospital for Children and King's College Hospital, both in London, will be enrolling and treating 26 children with LGS into the study over the next three years. A simplified version of the eligibility criteria is provided in Table 1. The trial design consists of a one-month baseline assessment period, surgical implantation of the DBS device, and then a follow-up period. Pre- and post-operative assessments include parent-recorded seizure diaries, EEG, cognitive assessments and quality-of-life questionnaires. After the trial, children transition to NHS care with the option to continue with DBS therapy long term.

The DBS device: Picostim DyNeuMo

Current DBS devices have been designed for adults and have disadvantages for paediatric practice [Piper et al, 2022]. For example, the implanted pulse generator and battery of DBS devices are typically placed in the chest wall and connected to the wires in the brain. For growing children, there is a risk of the fixed wires between the head and the chest wall tightening, causing pain or breaking. Another example of deficiency of current DBS systems is the device lifetime, with batteries that need surgical replacing within every five years. Frequent surgical battery replacement is suboptimal, and

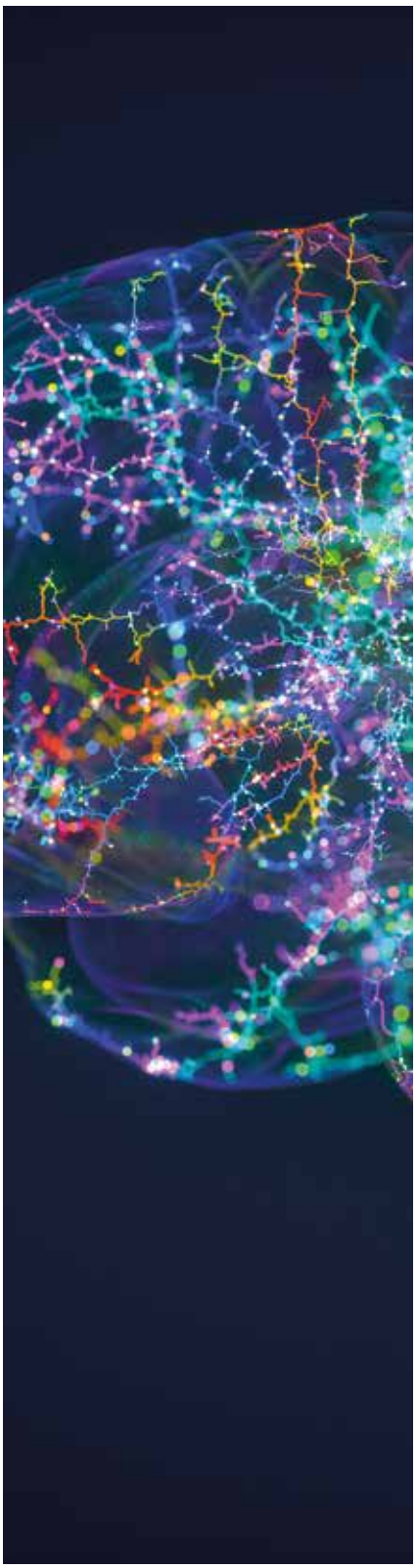


Table 1. Simplified version of the eligibility criteria for the CADET Project.

Inclusion Criteria*	Exclusion Criteria*
• 5-14 years of age • Formal diagnosis of LGS • Baseline seizure frequency of >10/ month • Have tried and not responded to >2 anti-seizure medications • Stable (>4-weeks) prescription of anti-seizure medications or ketogenic diet	• Prior treatment with deep brain stimulation (DBS) • Active vagus nerve stimulation • Abnormal brain scan, bleeding disorder or medical conditions that would make DBS procedure infeasible or unsafe
* Not an exhaustive list	

rechargeable systems would be preferable, particularly for being able to deliver continuous stimulation where battery depletion is faster.

The deficiencies of current, market-available devices have motivated our project to trial a new device called the Picostim DyNeuMo, which is manufactured by UK company Amber Therapeutics. The Picostim device is entirely implanted in the skull and has a generator and battery that replaces a craniectomy in the parietal bone. The device is non-invasively rechargeable and therefore has a longer battery duration before needing replacement. Furthermore, the advanced capabilities of the device will, in the future, allow us to deliver adaptive stimulation – tailored stimulation settings that respond to the patients' individualised seizure activity detected in the brain in real time.

Case study: Oran's story

Oran is a 13-year-old boy with Lennox-Gastaut Syndrome. Oran started having seizures when he was three years old and epilepsy has had a profound and deleterious impact on his and his family's lives ever since. He had daily seizures, often requiring resuscitation or hospital admission, lost cognitive skills, and in the words of his mother was "robbed of all of his childhood".

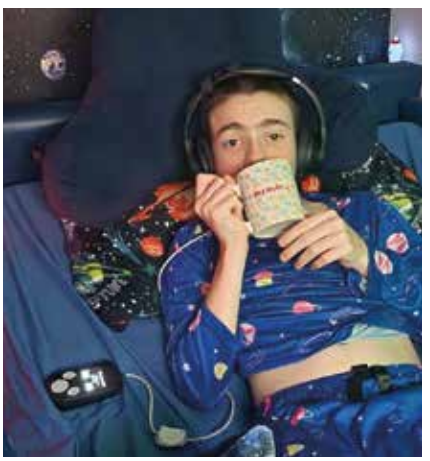
In October 2023, at the age of 12, Oran became the first child treated within the CADET Project and the first child in the world to receive the Picostim DBS device. Six months after device activation, Oran and his family were delighted with the benefits received. His daytime seizures were reduced by over 80% and he experienced a dramatic improvement in his mood and overall quality of life.

In May, Oran and his family bravely shared their success story in a news piece by Fergus Walsh (BBC health correspondent), and gained international attention [Walsh, 2024]. We thank Oran and his family for allowing us to share his story here too.

Next steps

The next phase of our project is to complete the recruitment of 26 children into the CADET Project and to determine the clinical efficacy of DBS in reducing seizure frequency.

Oran in charging headset (left) and on his bike (right).



Our future plans are to develop the device further and investigate its potential to deliver individualised and precision brain stimulation.

Patient involvement in CADET

The CADET team welcome referrals to the trial. The best route to referral is by the child's primary neurologist writing to Dr Marios Kaliakatsos and Mr Martin Tisdall at Great Ormond Street Hospital for Children.

This is work is made possible by funding from: The Royal Academy of Engineering, LifeArc, GOSH Children's Charity and NIHR

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Further reading

Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial). Ann. Neurol. 2022;91(2):253–267.

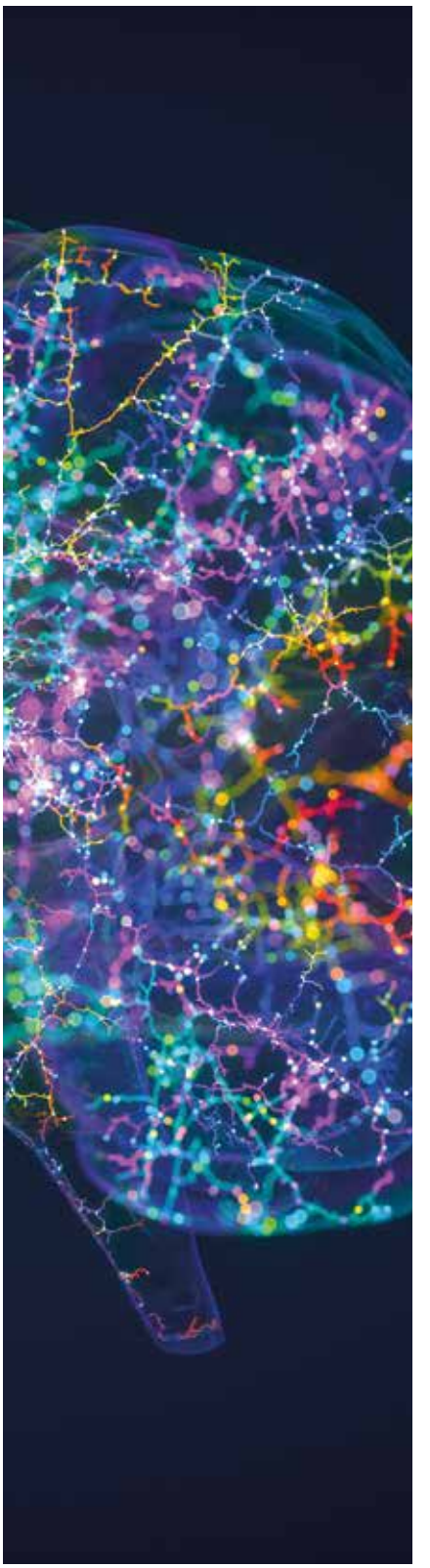
Khan M, Paktiawal J, Piper RJ, et al. Intracranial neuromodulation with deep brain stimulation and responsive neurostimulation in children with drug-resistant epilepsy: a systematic review. J. Neurosurg. Pediatr. 2022;29(2):208–217. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34678764

Piper RJ, Richardson RM, Worrell G, et al. Towards network-guided neuromodulation for epilepsy. Brain 2022;145(10):3347–3362. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35771657

Piper RJ, Tisdall MM. Children's Adaptive Deep Brain Stimulation for Epilepsy Trial (CADET): Pilot (CADET Pilot). ClinicalTrials.gov 2023;Available from: https://clinicaltrials.gov/ct2/show/NCT05437393

Piper RJ, Fleming J, Valentín A, et al. Neurostimulation devices for children: lessons learned. Lancet Child Adolesc. Heal. 2022;6(6):359–361. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2352464222001237

Walsh F. World first epilepsy device fitted in UK boy's skull. BBC 2024;Available from: https://www.bbc.co.uk/news/articles/cg33kgd81mvo



Michael Tittelbach, CTO, Precisis

Neuromodulation and Innovation: Pioneering the Future of Epilepsy Treatment

Neuromodulation is heralding a transformative era in medical treatment. This technique, involving the alteration of nerve activity through targeted electrical stimuli, is anticipated to see the global market grow to over $11 billion within five years. The technology is advancing rapidly, offering alternative treatments for various conditions including pain, depression, and urinary incontinence. Specifically for epilepsy, neuromodulation provides a beacon of hope, particularly for the 30% of patients who are resistant to conventional drug therapies.

Around 80 million people globally suffer from epilepsy, with approximately 24 million not finding adequate relief from standard medications. Neuromodulation's potential to offer precise, adjustable, and reversible interventions makes it an attractive option, particularly when traditional methods such as medication or surgery fall short. For instance, Onward Medical in the Netherlands and Precisis in Germany are pioneering less invasive neuromodulation devices that could potentially restore function in spinal cord injury patients and treat focal epilepsy without major surgery.

In Europe, over six million people live with epilepsy, with 30% experiencing drug-resistant forms. Traditional treatment for these patients might involve resective surgery, which can have significant implications for motor skills, speech, and memory depending on the brain area removed.[1] Neuromodulation offers a less invasive alternative, with several methods already in use, including Deep Brain Stimulation (DBS) and Vagus Nerve Stimulation (VNS), but both come with potential side effects like infection or speech impairment. [2,3,4]

The newer Responsive Neurostimulation (RNS) method involves placing electrodes directly onto the brain's surface, allowing for real-time seizure detection and response. Although promising, it shares some risks with DBS, such as surgical complications and technical issues like battery replacement. Despite its benefits, RNS is not yet planned for introduction in Europe.[5]

Technological advancements are continuously emerging in the field. For example, Focal Cortex Stimulation (FCS) involves placing stimulation electrodes under the skin without drilling into the skull, showing significant improvement in patients unresponsive to other treatments.

One such system by Precisis is EASEE – short for Epicranial Application of Stimulation Electrodes for Epilepsy. This new device for individualised brain stimulation is anatomically positioned precisely over the epileptic focus in the brain and surgically placed just under the scalp.

Based on a dual principle of action, EASEE provides a disruptive, acute effect with high-frequency pulses every two seconds against emerging seizures and direct current-like phases applied every day for 20 minutes, which regulate over-excitable brain areas in the long term to prevent seizures.

Early outcomes suggest that 65% of patients previously unresponsive to conventional medical management experience clinically meaningful improvements.

Looking forward, the focus is on developing closed-loop systems and AI technologies to better predict and respond to seizures, tailoring treatments to individual needs more effectively. Neuromodulation not only offers hope for those traditionally underserved by existing treatments but also stands at the forefront of innovative, less invasive, and more effective medical interventions for epilepsy, promising a future where patients can lead healthier, fuller lives free from the debilitating effects of seizures.

To find out more about EASEE visit easee.precisis.de/en.

Michael Tittelbach
Chief Technology Officer
Precisis GhbH

References

1. Katella K. 2023. Seizure Treatment: Major Advances in Epilepsy Surgery Cure More People. *Yale Medicine*.
2. Mayo Clinic. Deep brain stimulation. [online] *https://www.mayoclinic.org/tests-procedures/deep-brain-stimulation/about/pac-20384562*
3. NIH. Brain stimulation therapies for epilepsy. [online] *bit.ly/3ZJ3fRV*
4. Epilepsy Foundation. Vagus Nerve Stimulation (VNS) Therapy *www.epilepsy.com/treatment/devices/vagus-nerve-stimulation-therapy*
5. Bergey GK et al. 2015. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*. 84(**8**): doi: 810-817. 10.1212/WNL.0000000000001280

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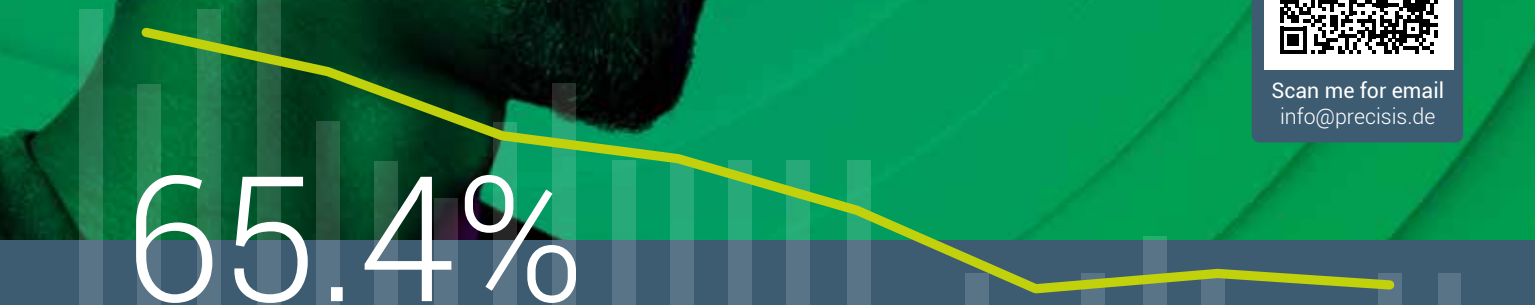

65.4%

Responder Rate after 2 years of stimulation

Schulze-Bonhage et al. 2023 „Focal Cortex Stimulation with a Novel Implantable Device and Antiseizure Outcomes in 2 Prospective Multicenter Singel-Arm Trials"

Schulze-Bonhage et al. 2024 "Long-term outcome of epicranial Focal Cortex Stimulation with the EASEE® system in pharmacoresistant focal epilepsy"

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PRECISIS

New treatments for CDKL5

New therapeutic targets for CDKL5 deficiency disorder

Marisol Sampedro Castañeda and Sila K Ultanir discuss the mechanisms around CDKL5 and what new treatment opportunities they provide.

Mutations in the gene encoding Cyclin-Dependent Kinase Like 5 (*CDKL5*) have been causally linked to developmental and epileptic encephalopathy (DEE) for over two decades [Kalscheuer et al, 2003]. The mutations are usually *de novo* and lead to loss-of-function and reduced substrate phosphorylation by CDKL5. The disease, commonly known as CDKL5 deficiency disorder (CDD, DEE2), presents as early onset epilepsy with developmental comorbidities, including global delay, motor, sensory and autonomic disturbances. *CDKL5* is an X-linked gene with highly enriched expression in the brain. *CDKL5* transcription is regulated during development, rising in embryonic stages, and peaking in the first postnatal week in mice [Hector et al, 2016]. However, the role of this protein kinase in cell signalling and the stimuli that control its activity are incompletely understood.

Despite the rarity of this disorder, research and awareness in the field has advanced rapidly thanks to the commitment and hard work of patient-led organisations and a growing number of clinical, academic and industry scientists dedicated to changing the therapeutic landscape in

rare diseases. As a result, CDD is now among the top five most frequently diagnosed genetic epilepsies in children.

To understand CDKL5 epilepsy, researchers have generated multiple animal models by either disrupting the expression of the CDKL5 gene (knock-out, KO) or introducing human disease mutations (knock-in). These models, including mouse, rat, fish, and fly mutants, recapitulate some aspects of the clinical spectrum of CDD, but epilepsy remains difficult to investigate, as no single genetically altered model consistently exhibits spontaneous seizures. Despite these limitations, animal models and CDKL5 deficient cell systems are enabling the characterisation of the cellular and molecular players in the disease. In the last 10 years, multiple CDKL5 phosphorylation targets have been discovered, shedding light on the cellular pathways affected in CDD. These include proteins linked to the cell cytoskeleton like EB2 and MAP1S, and gene expression regulation such as SOX9, ELOA and EP400 [Baltussen et al, 2018; Katayama et al, 2020; Khanam et al, 2021; Kim et al, 2020; Muñoz et al, 2018].

CDKL5 deficiency leads to a calcium channelopathy

In addition, our recent research, published in Nature Communications, described the first CDKL5 substrate directly involved in neuronal electrical activity, highlighting a potentially critical target for CDKL5 epilepsy [Sampedro-Castañeda et al, 2023]. This work was a collaborative effort with the UCL Queen Square Institute of Neurology and MSD.

Neurons from *Cdkl5*-deficient and control mice were grown in media with or without labelled amino acids. Because of the differential protein labelling, we were able to compare protein and phosphorylation abundance in isolates from both groups. Our data showed that the voltage-dependent ion channel Cav2.3 is significantly less phosphorylated at position Serine 15 in absence of CDKL5. The target amino acid sequence in Cav2.3 is a perfect match to CDKL5 target recognition sites in other validated cellular substrates [Baltussen et al, 2018; Muñoz et al, 2018], suggesting direct phosphorylation of Cav2.3 by CDKL5. Using an alternative methodology, we also validated this substrate in neurons derived from CDD patients, highlighting the translational relevance of this target.

In the last 10 years, multiple CDKL5 phosphorylation targets have been discovered, shedding light on the cellular pathways affected in CDD

Cav2.3 is expressed in select neurons in the central nervous system and is involved in Ca^{2+} entry and regulation of action potential firing. Its activity can be modulated by neurotransmitters such as acetylcholine, acting via membrane receptors. This ensures adequate neuronal activity in response to behavioural demands. To investigate how CDKL5 affects channel function, we generated channels with a point mutation in the CDKL5 phosphorylation site (Serine is mutated to Alanine) and also transgenic mice harbouring this mutation (phosphomutant mice). Our electrophysiological studies demonstrate that in the absence of CDKL5 phosphorylation, Cav2.3 mediates longer-lasting Ca^{2+} currents that are also overly sensitive to cholinergic stimulation. Consequently, our phosphomutant mice exhibit behavioural deficits and seizure susceptibility, which partially mirror the human phenotype. Finally, human genetic evidence has directly implicated Cav2.3 overactivity to a different and ultrarare early-onset epilepsy [DEE69; Helbig et al, 2018] and there are some indications of disrupted functional expression of this channel in Juvenile Myoclonic Epilepsy [Suzuki et al, 2004] and Fragile X [Gray et al, 2019]. This combined evidence suggests that CDD is partially a channelopathy and that directly or indirectly targeting this channel could be therapeutic. Current anti-epileptic medication with partial effects on Cav2.3 include topiramate and lamotrigine. The development of specific inhibitors of this channel is underway.

Could other protein kinases replace CDKL5?

Another line of research for CDD therapeutics concerns the possibility to restore CDKL5 activity in patients. This could be achieved by either replacing the CDKL5 protein [Colarusso et al, 2022; Gao et al, 2020; Medici et al, 2022], increasing the expression of the non-mutant allele in females [Halmai et al, 2020], correcting the gene defects by gene editing or harnessing an alternative protein kinase that shares some of the cellular targets of CDKL5.

In relation to alternative kinases, our group has conducted a screen with kinases belonging to the same evolutionary group as CDKL5, with the expectation that they share some of its structural and functional features. Our work, published earlier this year in

Molecular Psychiatry, revealed for the first time two kinases that are able to phosphorylate the same target sites as CDKL5 on the microtubule-interacting proteins EB2 and MAP1S [Silvestre et al, 2024]. The most promising kinases were CDKL2 and ICK.

Our initial experiments were conducted in vitro, by individually expressing each kinase (in its active or inactive form) and the target protein EB2 in mammalian cells. We then compared the phosphorylation levels on EB2 using a phospho-specific antibody that recognises the phosphorylated sequence. To corroborate our findings in a mouse brain, we carried out a similar experiment in CDKL5 KO and double CDKL5/CDKL2 deficient animals. In the absence of CDKL5, the same phospho-antibody can detect leftover phosphorylation signal on EB2 and MAP1S, which is almost completely abolished in brains when CDKL2 is concomitantly deleted.
These mouse models suggest that, although CDKL5 is the main kinase regulating EB2 and MAP1S as previously described, CDKL2 is responsible for around 15-20% of phosphorylation of these brain proteins at the same sites. We propose that if CDKL2 expression was boosted, it could compensate for the absence of CDKL5 in CDD by increasing phosphorylation of its substrates. Thus, these findings highlight two new potential therapeutic targets. Further investigations will address the extent of functional overlap between these kinases and CDKL5, as well as the mode and optimal window for intervention. Safety considerations regarding potential side effects of increasing the activity of alternative kinases should also be addressed.

Perspectives

Scientific research is swiftly informing and advancing the development of new therapies, which can be tested on existing CDKL5 deficient animal and cellular model systems. Drug-resistant

Further reading

Baltussen LL, Negraes PD, Silvestre M, Claxton S, Moeskops M, Christodoulou E, Flynn HR, Snijders AP, Muotri AR, Ultanir SK. 2018. Chemical genetic identification of CDKL5 substrates reveals its role in neuronal microtubule dynamics. *EMBO J*. 37, e99763.
Barbiero I, Zamberletti E, Tramarin M, Gabaglio M, Peroni D, Rosa RD, Baldin S, Bianchi M, Rubino T, Kilstrup-Nielsen C. 2022. Pregnenolone-methyl-ether enhances CLIP170 and microtubule functions improving spine maturation and hippocampal deficits related to CDKL5 deficiency. *Hum. Mol. Genet*. 31, 2738–2750.
Colarusso A, Lauro C, Calvanese M, Parrilli E, Tutino ML. 2022. Active human full-length CDKL5 produced in the Antarctic bacterium Pseudoalteromonas haloplanktis TAC125. *Microb. Cell Factories* 21, 211.
Gao Y, Irvine EE, Eleftheriadou I, Naranjo CJ, Hearn-Yeates F, Bosch L, Glegola JA, Murdoch L, Czerniak A, Meloni I, Renieri A, Kinali M, Mazarakis ND. 2020. Gene replacement ameliorates deficits in mouse and human models of cyclin-dependent kinase-like 5 disorder. *Brain* 143, 811–832.
Gray EE, Murphy JG, Liu Y, Trang I, Tabor GT, Lin L, Hoffman DA. 2019. Disruption of GpI mGluR-Dependent Cav2.3 Translation in a Mouse Model of Fragile X Syndrome. *J Neurosci* 39, 7453–7464.
Halmai JANM, Deng P, Gonzalez CE, Coggins NB, Cameron D, Carter JL, Buchanan FKB, Waldo JJ, Lock SR, Anderson JD, O'Geen H, Segal DJ, Nolta J, Fink KD. 2020. Artificial escape from XCI by DNA methylation editing of the CDKL5 gene. *Nucleic Acids Res*. 48, 2372–2387.
Hector RD, Dando O, Landsberger N, Kilstrup-Nielsen C, Kind PC, Bailey MES, Cobb SR. 2016. Characterisation of CDKL5 Transcript Isoforms in Human and Mouse. *Plos One* 11, e0157758.
Helbig KL, Lauerer RJ, Bahr JC, et al. 2018. De Novo Pathogenic Variants in CACNA1E Cause Developmental and Epileptic Encephalopathy with Contractures, Macrocephaly, and Dyskinesias. *Am J Hum Genetics* 103, 666–678.
Kalscheuer VM, Tao J, Donnelly A, Hollway G, Schwinger E, Kübart S, Menzel C, Hoeltzenbein M, Tommerup N, Eyre H, Harbord M, Haan E, Sutherland GR, Ropers H-H, Gécz J. 2003. Disruption of the Serine/Threonine Kinase 9 Gene Causes Severe X-Linked Infantile Spasms and Mental Retardation. *Am J Hum Genetics* 72, 1401–1411.
Katayama S, Sueyoshi N, Inazu T, Kameshita I. 2020. Cyclin-Dependent Kinase-Like 5 (CDKL5): Possible Cellular Signalling Targets and Involvement in CDKL5 Deficiency Disorder. *Neural Plast* 2020, 1–14.
Khanam T, Muñoz I, Weiland F, Carroll T, Morgan M, Borsos BN, Pantazi V, Slean M, Novak M, Toth R, Appleton P, Pankotai T,

seizures are a prominent burden of CDD. Although epilepsy modelling in rodents and other animals has presented substantial challenges, alternative strategies are being developed. The now advanced state of technologies like human induced pluripotent stem cells is enabling the generation of brain-like tissues derived from CDD patients. Dysregulated firing activity has already been reported in these neuronal assemblies [Negraes et al, 2021], suggesting that they could be a valuable platform to examine epilepsy treatment efficacy in human cells and possible variations due to specific mutations.

The discovery of ion channel Cav2.3 as a new CDKL5 substrate independently linked to human epilepsy, opens a highly promising therapeutic avenue. Some of the most effective anti-seizure medication used in CDD includes molecules known to inhibit Cav2.3 at therapeutic doses, such as topiramate and lamotrigine [Leonard et al, 2022; Olson et al, 2019], showing that it is safe to reduce these currents. However, their effects are compounded by their lack of specificity and the frequent use of combined anti-seizure medicines.

Testing of novel inhibitors of this ion channel is already ongoing, including on patient-derived neurons. Similarly, compensatory kinases like CDKL2 and ICK that phosphorylate some of the same substrates as CDKL5, represent important druggable targets for future therapies. Methodologies such as anti-sense oligonucleotides to increase their expression levels in neurons can be employed, although further research is needed to ensure that this is targeted to the right cell type and will not have major unwanted consequences.

The last decade has seen significant steps towards a better understanding of disease mechanisms in many epileptic disorders such as CDD. We now know that CDKL5 is involved in a number of cellular processes and each discovery reveals new potential treatment targets. For example, the neurosteroid pregnenolone and derivatives have been put forward for CDD treatment based on their ability to rescue microtubule deficits in neurons and partially restore cognitive abilities in Cdkl5 KO mice [Barbiero et al, 2022]. Although strategies like this have not yet progressed beyond pre-clinical investigations, they raise the possibility that different and complementary forms of therapy could ultimately be combined to achieve disease modification or cure.

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Zhou H, Rouse J. 2021. CDKL5 kinase controls transcription-coupled responses to DNA damage. *EMBO J*. 40, e108271.

Kim JY, Bai Y, Jayne LA, Hector RD, Persaud AK, Ong SS, Rojesh S, Raj R, Feng MJHH, Chung S, Cianciolo RE, Christman JW, Campbell MJ, Gardner DS, Baker SD, Sparreboom A, Govindarajan R, Singh H, Chen T, Poi M, Susztak K, Cobb SR, Pabla NS. 2020. A kinome-wide screen identifies a CDKL5-SOX9 regulatory axis in epithelial cell death and kidney injury. *Nat. Commun.* 11, 1924.

Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. 2022. CDKL5 deficiency disorder: clinical features, diagnosis, and management. *Lancet Neurol.* 21, 563–576.

Medici G, Tassinari M, Galvani G, Bastianini S, Gennaccaro L, Loi M, Mottolese N, Alvente S, Berteotti C, Sagona G, Lupori L, Candini G, Baggett HR, Zoccoli G, Giustetto M, Muotri A, Pizzorusso T, Nakai H, Trazzi S, Ciani E. 2022. Expression of a Secretable, Cell-Penetrating CDKL5 Protein Enhances the Efficacy of Gene Therapy for CDKL5 Deficiency Disorder. *Neurotherapeutics* 19, 1886–1904.

Muñoz IM, Morgan ME, Peltier J, Weiland F, Gregorczyk M, Brown FC, Macartney T, Toth R, Trost M, Rouse J. 2018. Phosphoproteomic screening identifies physiological substrates of the CDKL5 kinase. *EMBO J*. 37, e99559.

Negraes PD, Trujillo CA, Yu N-K, Wu W, Yao H, Liang N, Lautz JD, Kwok E, McClatchy D, Diedrich J, Bartolome SM de Truong J, Szeto R, Tran T, Herai RH, Smith SEP, Haddad GG, Yates JR, Muotri AR. 2021. Altered network and rescue of human neurons derived from individuals with early-onset genetic epilepsy. *Mol Psychiatr* 1–22.

Olson HE, Demarest ST, Pestana-Knight EM, Swanson LC, Iqbal S, Lal D, Leonard H, Cross JH, Devinsky O, Benke TA. 2019. Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder: clinical review. *Pediatr Neurol* 97, 18–25.

Sampedro-Castañeda M, Baltussen LL, Lopes AT, Qiu Y, Sirvio L, Mihaylov SR, Claxton S, Richardson JC, Lignani G, Ultanir SK. 2023. Epilepsy-linked kinase CDKL5 phosphorylates voltage-gated calcium channel Cav2.3, altering inactivation kinetics and neuronal excitability. *Nat. Commun.* 14, 7830.

Silvestre M, Dempster K, Mihaylov SR, Claxton S, Ultanir SK. 2024. Cell type-specific expression, regulation and compensation of CDKL5 activity in mouse brain. *Mol. Psychiatry* 1–13.

Suzuki T, Delgado-Escueta AV, Aguan K, Alonso ME, Shi J, Hara Y, Nishida M, Numata T, Medina MT, Takeuchi T, Morita R, Bai D, Ganesh S, Sugimoto Y, Inazawa J, Bailey JN, Ochoa A, Jara-Prado A, Rasmussen A, Ramos-Peek J, Cordova S, Rubio-Donnadieu F, Inoue Y, Osawa M, Kaneko S, Oguni H, Mori Y, Yamakawa K. 2004. Mutations in EFHC1 cause juvenile myoclonic epilepsy. *Nat Genet* 36, 842–849.

A parent perspective

Helping to understand what is really important to our patients: SUDEP

Joanne Doody's son Peter died from sudden unexpected death in epilepsy (SUDEP) in May 2019 at the age of 21. Joanne shares why having SUDEP information is so important

Peter was our first born, big brother to Harry and loved deeply by many. He was someone who transcended individual friendship groups throughout school. He was so fondly thought of because of his kind nature that he fitted in everywhere. He was caring, thoughtful, sensitive and funny, and he wanted to make life better for others whenever he could. He was a talented musician and music producer, and there wasn't much he didn't know about technology! He had a wonderful enquiring mind. It is engraved on his headstone that he was too beautiful for this earth, and he truly was. We have always preferred to say, however,

"Peter is", not "was". We believe fervently that Peter still exists but not in the way we long for.

The first time we became aware of sudden unexpected death in epilepsy (SUDEP) was when we were informed of his cause of death. At no point while Peter was alive did any of the clinicians involved in Peter's epilepsy care mention SUDEP or provide us with any SUDEP literature.

In a recent film I made with the aim to stop the SUDEP silence, I refer to and acknowledge a considered unconscious bias around this. Would I really have wanted to know about SUDEP when Peter was alive? The answer is unequivocally yes. Of course, we would have been fearful and anxious as would have Peter, but, ultimately, we would have been empowered to help keep him safe. Any feelings of anxiety we may have felt at the time pale into insignificance compared to the trauma and finality of losing Peter forever.

If we had known about SUDEP from the start, all of us would have understood the seriousness of his condition. We believe it would have made a significant impact on medication adherence, for one. It would have also enabled us, as a family, to take safeguarding measures knowing about SUDEP and the risks associated with sleep seizures. We would have made adaptations to his sleeping arrangements and used a seizure detection device and an anti-suffocation pillow. We would have also had a far better understanding of Peter's vulnerability whilst being away from home at university.

What we would like to see happen in the future around SUDEP communication is for people living with epilepsy to be informed about SUDEP in clear terms. To not avoid using the word SUDEP, and what that means, by only talking about generic 'risk'. We would also like to see a nationally set, comprehensive, person-centred care plan with clear set pathways inclusive of a individual SUDEP plan, similar to a status plan, regularly updated at each appointment and a copy given to the patient. As an example, in Peters' medical records, a covering letter to his doctor with an accompanying checklist shows the SUDEP box as being ticked. We know it wasn't discussed because we were there. Peter also wasn't seen by a consultant in almost three years at one point. We were told 'he slipped through the net'. Had a comprehensive person-centred care plan been in place, this would have been picked up.

As epilepsy specialist nurse Neil Williamson comments in the film: "Why do we have a care plan for the second leading cause of death in epilepsy (status epilepticus), but not SUDEP?".

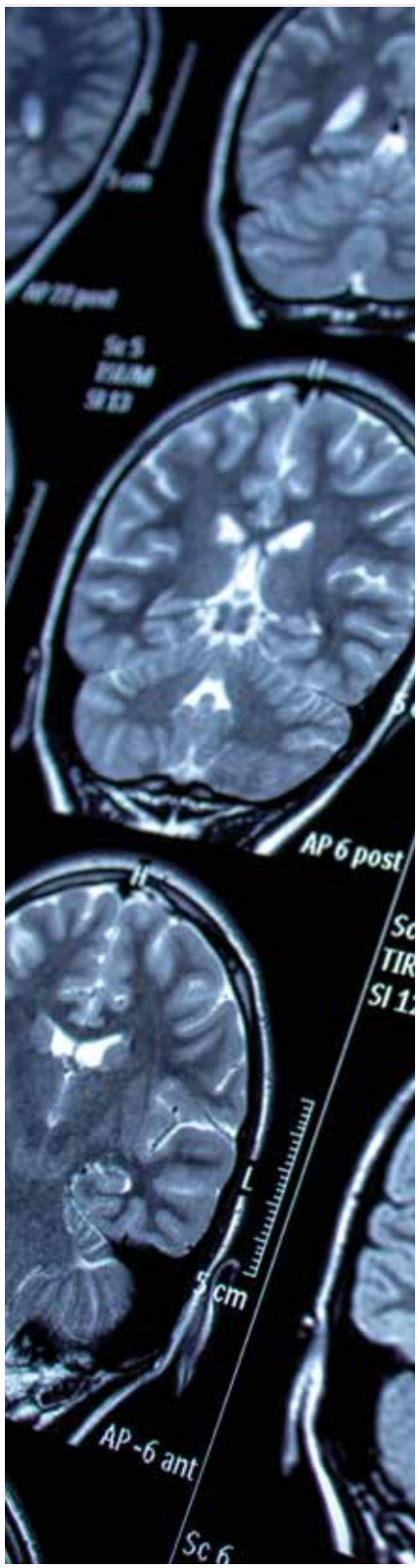
We would also wish to see increased clinician accountability with a recorded account of what information relating to SUDEP was specifically given and countersigned by the patient. Greater encouragement for parents/carers to attend appointments, with an emphasis on a shared care approach, would also be welcome and improve outcomes.

We are often asked how clinicians should deliver the SUDEP conversation. First and foremost, SUDEP just simply needs to be spoken. Similarly to discussions oncologists and cardiologists have with their patients, the informing of SUDEP will be extremely difficult and challenging, however this information must be given. There is no easy way, it is as simple as that. It just takes courage, kindness and time.

Explaining the mechanisms of SUDEP to the best of current understanding (heart and respiratory failure) is empowering and builds a clearer picture and increased understanding of this complex neurological condition. It would be wrong to assume that people automatically understand this. Another way to assist patients and families would be to inform of the varying aids and seizure detection devices which can increase the chance of a person being attended to who is having a potentially dangerous seizure.

It goes without saying that to achieve optimal SUDEP care, there is a great need for increased appointment times and availability of epilepsy specialists and nurses. But the present lack of time and resource mustn't continue to be a reason not to inform patients about it. As parents who are now experiencing the finality of this unimaginable loss, we would simply ask clinicians to please have the courage to inform and discuss SUDEP. We ask you to please push past any personal anxiety or lack of appointment time so that patients and families get a fighting chance to keep their child/loved one alive.

Markus Reuber



Highlights

Top picks from *Seizure*

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

We like to think of the history of medicine as one of steady progress in which public health measures (like the provision of clean drinking water), as well as medical discoveries (such as the use of vaccinations or antibiotics in the prevention or treatment of infections), increase population health and life expectancy. However, following many decades of steady improvements, life expectancy in several high-income countries has actually been falling in recent years [ONS, 2024; NCHS, 2019]. For instance, in the US, life expectancy was 47 years in 1900 and 68 years in 1950. By 2019 it had risen to 79 years [Kochanek et al, 2020]. Life expectancy then declined to 77 in 2020 and dropped further to 76 in 2021. The drops in US life-expectancy were greatest in Native Indian, Black and Hispanic American populations. While the identification of specific causes of these observations is difficult, two thirds of the recent decline in life expectancy in the USA have been put down to COVID, drug overdoses and accidental injuries [Arias et al, 2022].

My editor's choice paper from volume 120 of Seizure examines long-term US mortality trends when epilepsy was recorded as the underlying cause of death, for instance because deaths were attributed to sudden unexpected death in epilepsy (SUDEP) status epilepticus, accidents during seizures, surgical complications, and potential comorbidities [Liu et al, 2024]. Deaths will only be a subset of all of those who died with a diagnosis of epilepsy but of causes not directly associated with their seizure disorder. Based on cause-of-death and demographic data from the National Center for Health Statistics, the authors used a joinpoint regression model to describe changes in US mortality trends from 1979 to 2021. Age-adjusted mortality in all ethnic groups initially fell during the study period. However, since 2006 the number of those dying with a diagnosis of epilepsy has been on the rise.

The sustained increase in mortality attributed to epilepsy is clearly of concern. It may in part be explained by an increased awareness of epilepsy and causes of epilepsy-related causes of deaths (especially SUDEP), and by the American Population is getting older. However, the fact that mortality discrepancies between white and non-white Americans are increasing also hints at the effects of inequitable access to health and social care – or an uneven distribution of other risk factors for epilepsy-related deaths.

Most worrying of all is the fact that the increase in the epilepsy-related mortality is accelerating, and that the differences between white and other populations are increasing further. Further work will need to untangle what contributes to these trends and what can be done to reverse them.

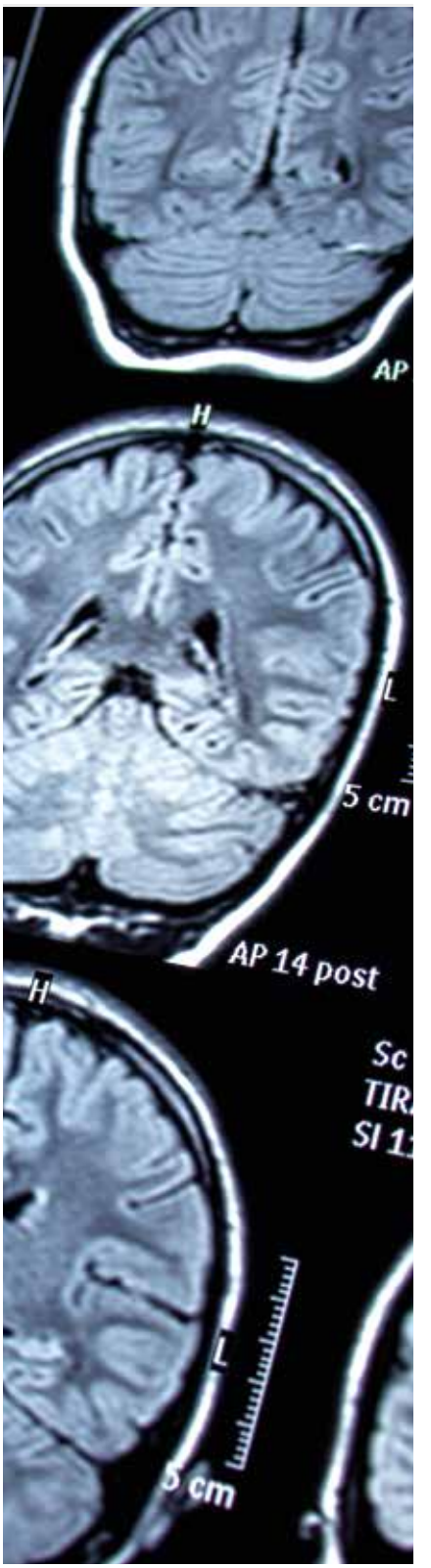
Status epilepticus outcomes

There are reasonable grounds for asking whether 'epilepsy' exists as a meaningful disease entity. The logical conclusion of the stress the current ILAE classification of epilepsy places on aetiology suggests that it would be more appropriate to talk of 'the epilepsies', or to abandon the concept of 'epilepsy' altogether and to think of diseases or clinical scenarios associated with epileptic seizures instead. The same considerations apply to status epilepticus (SE). Of course, the scenario in which an epileptic seizure fails to self-terminate is a clinical reality – in fact it continues to be one of the commonest serious neurological emergencies [Jackson et al, 2022]. However, it is not a neat clinical entity in terms of its causes, treatment or outcomes. This fact is reflected in the current definition and classification of the ILAE which recognises different manifestations of SE: Instead of a single temporal cut off defining all types of SE, this scenario is now defined by a time point one at which the failure of the mechanisms responsible for seizure termination has become clear (t1) and a second time point (t2) at which long-term consequences may be expected (e.g. neuronal death, neuronal injury or neuronal network alteration). This means that t1 and t2 are twice as long for focal SE with impaired awareness as for bilateral tonic SE [Trinka et al, 2015].

While beginning to distinguish between subtypes of SE, the current classification is still rather crude. Most importantly it fails to take account of the aetiology of SE. For instance, t1 and t2 may well be quite different depending on whether SE occurs in a patient with a non-progressive structural brain abnormality or a patient with a mitochondrial disorder.

My editor's choice from volume 121 of Seizure is a prospective cohort study of 367 consecutive patients diagnosed with SE in the Auckland region of New Zealand [Zhang et al, 2024]. This study contributes to our understanding of SE by demonstrating the great variability of the two-year outcome of SE presentations. Patients across the whole (paediatric to adult) age range were included. Outcomes varied from symptom-free with no further seizures, to death. Two-year all-cause mortality over the follow-up period was 14.9%. Univariate analyses revealed that SE presentations in children, patients of Asian ethnicity, with an SE duration <30mins and acute (febrile) aetiology were associated with lower mortality. Age >60 and progressive causes were associated with higher mortality in uni- and multivariate analyses. The risk of seizure recurrence was lower in those presenting <2 years of age and with an acute aetiology, it was higher in those with non-convulsive status epilepticus (NCSE) with coma and a history of epilepsy. Multivariate analyses revealed a history of epilepsy, as well as having both acute and remote causes, to be associated with a greater risk of seizure recurrence.

The classification of the epilepsies and of SE continues to be a work in progress. It is safe to say that improvements in the rapid determination of the aetiology of SE with consequences for acute treatment and outcome are likely to prompt further refinement of our thinking about SE in the future.



Are we broken?

The NHS used to be described as the envy of the world. Set up after the second world war in the late 1940's, the NHS aspired to Aneurin Bevan's dream that "illness is neither an indulgence for which people have to pay, nor an offence for which they should be penalised, but a misfortune the cost of which should be shared by the community". However, over the NHS' 76-year history, there have been several ups and downs, and there have always been those who detract from the good work done every day.

This is something many of us who have spent time in the NHS will be all too aware of. I remember as a first-year medical student in 1995, on an early clinic exposure day at the University Hospital of Wales in Cardiff, being appalled at the waits for patients in the emergency department. I have a vivid recollection of an elderly victim of a stroke being left for 12 hours, as the medical team perceived there was nothing they could do for her, so she was left until things were less busy. Not that the other patients waiting for a review were seen very much quicker.

By the time I was a pre-registration house officer (what would now be called a foundation year 1 resident doctor) in 2004 (having added some research time to my medical degree to postpone my inevitable entry to the workforce), things were on the up. Targets of a four-hour wait in the emergency department were starting to make a real difference. Patients with all types of neurological and other medical problems were seeing advances and improvements in care, with more timely reviews, new treatments and improvements in survival and quality of life.

By the time I took up my first substantive consultant post at the Wessex Neurological Centre in 2014, things were starting to look bleak again. Waiting times for outpatient appointments and the time taken to move through emergency services and inpatient care have worsened. The patients we look after have rightly come to expect more form their NHS, and, because of the success of new treatments, are surviving longer with more complex health needs. The pandemic and recent rounds of strikes from nurses, paramedics, junior doctors and consultants have added to these problems. Morale within the workforce is low.

But are we really broken? The new government certainly wants to portray us as such. Is this spin or is this the truth? Does it help, or does it just further crush an already demoralised work force? What does it mean for our patients with epilepsy who are caught in the middle of this?

I had a clinic recently and three of the follow-up patients had not been seen for three years – their clinic appointments had kept on being put back due to cancellations related to first COVID contingency and then because I had to cover several night shifts around the strikes. These patients had not called in, they had not complained. But they had needed support with their epilepsy and there had been things I could have done if I had known.

My fear, and a fear that has been expressed by others, is that patients will lose faith in the services that are actually working, because of all the doom mongering and not call for help when they need it.

Personally, I don't think we are broken. I think we have had difficult times, and we have work to do to make an NHS that works for our patients and for us, the people who work in it. There remain many in the NHS dedicated to improvement, as there always has been. We are not perfect, but we can and will do the best we can for our patients.

Dates for the diary

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

2024

21-23 October
2024 ILAE British Branch Annual Scientific Meeting
Liverpool, UK
ilaebritishconference.org.uk

9 November
2024 ILAE British Branch Clinical Epilepsy Course for Doctors in Training
Birmingham, UK
bit.ly/4gEKKUV

2-3 December
Encephalitis 2024
London, UK & online
encephalitis.info/encephalitis-conference

2025

20-24 January
14th ILAE School on Pre-Surgical Evaluation for Epilepsy and Epilepsy Surgery
Brno, Czech Republic
ta-service.cz/epodes2025

20-22 March
19th World Congress on Controversies in Neurology
Prague, Czech Republic
cony.comtecmed.com

2-4 April
International Congress on Structural Epilepsy & Symptomatic Seizures 2025
Gothenburg, Sweden
bit.ly/3X8FlOt

30 August-3 September
36th International Epilepsy Congress
Lisbon, Portugal
bit.ly/3uz1ARq

2026

3-6 May
18th Eilat Conference on New Antiepileptic Drugs and Devices
Madrid, Spain
bit.ly/3Wq6dcc

Next issues:

Prof Sanjay Sisodiya

Prof Sisodiya discusses the urgent problem of climate change and its effects on people with epilepsy and on epilepsy care.

Dr Sophie Bennett

Dr Bennett shares the findings of the Mental Health Invervention for Children with Epilepsy trial

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

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