epilepsy action

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epilepsy professional

Employment and epilepsy
Considerations for the 21st century

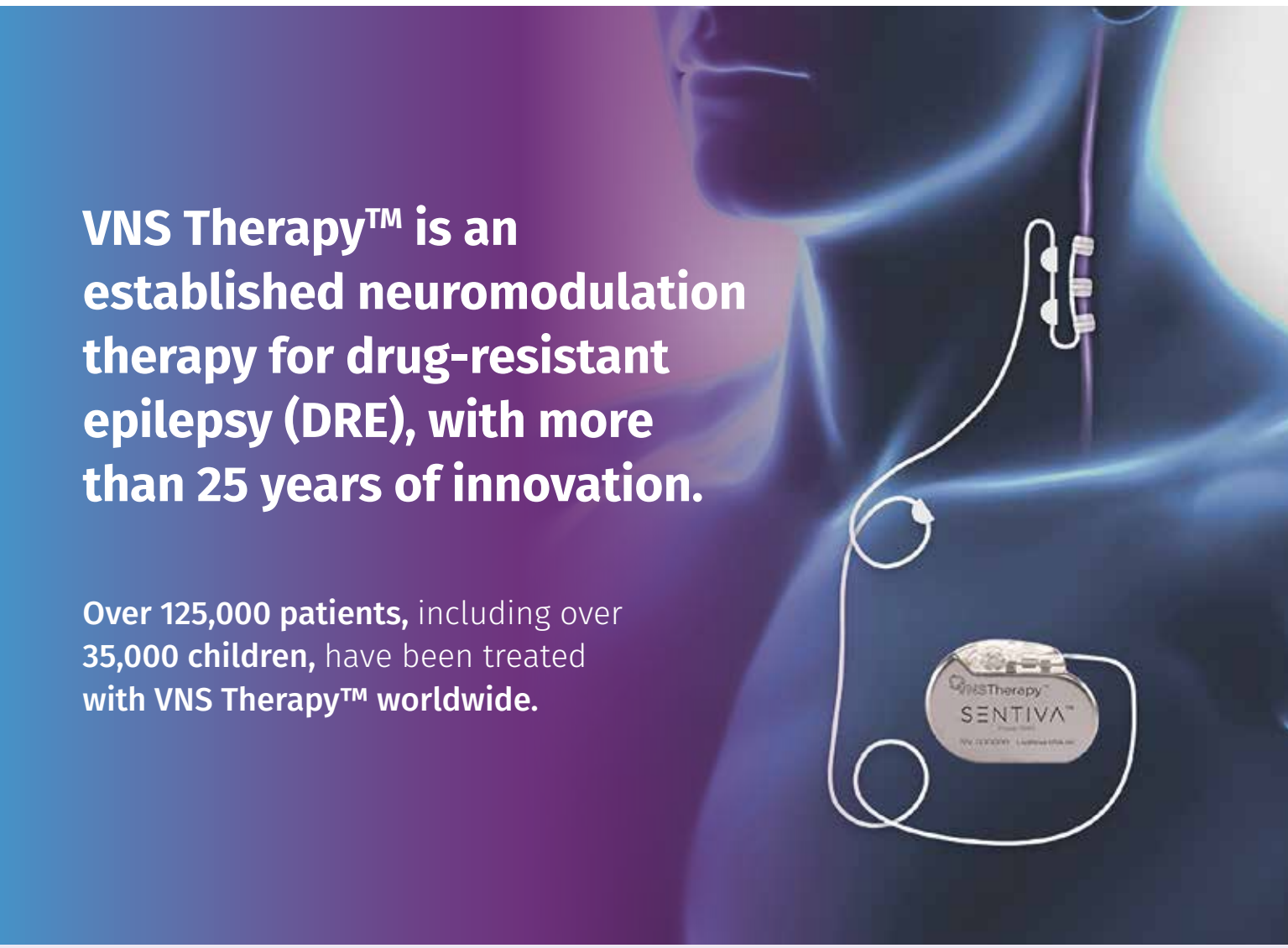
Ramon Bautista

Epilepsy and psychoses – Marco Mula

Seizure risk in Alzheimer's disease – Melissa Barker-Haliski

Improving care – Kami Kountcheva

VNS Therapy™



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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

Welcome to our winter edition of *Epilepsy Professional*. In this issue, there is a focus on comorbid conditions with epilepsy, employment for people with epilepsy and a conference overview, in case you missed it.

Marco Mula introduces us and gives us an excellent overview of the boundary zone of epilepsy and psychosis. I am sure I am not alone in feeling slightly uncomfortable when dealing with psychosis and epilepsy. Maybe this reflects training in the UK, with the disciplines of neurology and psychiatry maybe wrongly separated into semi-distinct specialities. Marco reminds us that although psychosis is rare, it can be a very serious complication of epilepsy and seizures. He walks us through the spectrum of psychosis in epilepsy from the most common – post-ictal states with the recognised lucid period – to the rarer situations. These include pre-ictal and interictal psychotic states, psychosis secondary to anti-seizure medications and as a consequence of vagal nerve stimulation and epilepsy surgery. There is a reminder that psychosis is more common in drug-resistant temporal lobe cases, and that management should focus on aiming to achieve seizure freedom. He adds that, if needed, there may be a role for second generation antipsychotics, or hopefully access to a friendly neuropsychiatrist and a functioning epilepsy-psychiatry MDT. Or maybe, for some, that's one for the Christmas list.

Melissa Barker-Haliski introduces us to the fastest growing demographic group of people with epilepsy – older adults – and explores seizures as an often under-recognised comorbidity of Alzheimer's disease (AD). Intriguingly, seizures have a high incidence in early onset AD, probably reflecting specific genetic risk factors, and also, in late AD seizure susceptibility is several times greater than similarly aged general population. She explores some interesting aspects of excitotoxic damage, neurodegeneration, neuronal hyperexcitability induced neuroinflammation which are characteristic of both epilepsy and AD. And she also considers how controlling the inflammatory response may be a therapeutic target for both epilepsy and AD.

Ramon Bautista discusses the problems people with epilepsy face when looking for and staying in work. He challenges certain beliefs around employment, saying the working horizon for people with epilepsy is bright and has improved in recent years. Increased social acceptance of individuals with epilepsy into the workforce, a consequence of increased acceptance, reduced stigma and improved seizure control coupled with increased flexibility of the workplace and of working hours has all contributed. However, there is still work to be done in this area as there is still evidence of higher rates of un- and under-employment in people with epilepsy than in the general population. I found this article quite stimulating and will use it to encourage my patients who would like to work.

And finally, in case you missed it (why did you?), is a roundup of the ILAE British Branch conference this year. I was there, and, although I'm a bit biased, I thought it was a wonderful meeting in a great location. Kami Kountcheva gives us some highlights from the conference, held in October 2022 in Cardiff. Read it and see what you missed out on!

Ann Johnston
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

6
news

The latest in epilepsy care

This issue: Pharmaceutical companies fined £70m over unfair price hikes, NHS launches new fibre-optic laser therapy for drug-resistant epilepsy and record numbers of nurses vote in favour of taking strike action for better pay

10
epilepsy and psychoses

Marco Mula

Dr Mula discusses our current understanding of psychoses in epilepsy and the best way to manage these in our patients

16
seizure risk in Alzheimer's disease

Melissa Barker-Haliski

Dr Barker-Haliski explains possible common mechanisms between Alzheimer's disease and epilepsy, as well as potential treatments and where future research should focus

26
highlights

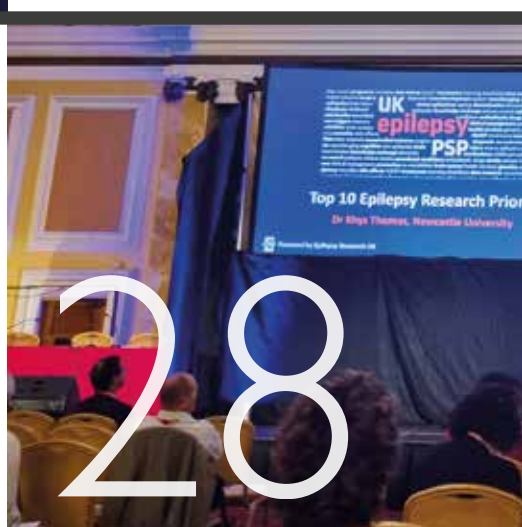
Markus Reuber

Professor Reuber highlights the key papers from the latest edition of *Seizure*. This issue: the health economic benefits of the NightWatch device and treating status epilepticus after benzodiazepines fail

28
improving care

Kami Kountcheva

Kami Kountcheva condenses down some of the excellent presentations from the latest ILAE British Branch conference, held in October 2022 in Cardiff



22 employment and epilepsy

Ramon Bautista

Prof Bautista describes problems people with epilepsy face when looking for and staying in work, and the way clinicians can support patients with this aspect of life

Research is at the foundation of so much of the work of a clinician. It gives us a better understanding of conditions, of treatments, of side effects, of population health and so much more. But research needs to be focused and – crucially – needs to answer questions people really want answered.

Part of the ILAE British Branch conference report on page 28 looks at the Priority Setting Partnership's top 10 research priorities. Dr Rhys Thomas delivered the presentation at the event, sharing that the team set out to find just that – the questions people really wanted answers to. He said now the task is to share these priorities far and wide.

But research also plays a big part in our other articles in this issue. Dr Mula discusses psychosis, a rare but serious comorbidity of epilepsy, including clinical presentations and treatments on page 10. On page 16, Dr Barker-Haliski explains the possible common mechanisms between Alzheimer's disease and epilepsy and calls for more research to understand the relationship between the conditions and define which anti-seizure medications are best used. And Dr Ramon Bautista discusses the problems faced by people with epilepsy when looking for or staying in work and the way in which clinicians can support patients. Recent research has shown that previous negative experiences can be a big deterrent for people with epilepsy. More on page 22.

With this, we wrap up another year. We would like to say a huge thank you for your continued support and we are excited to see what next year will bring. Happy holidays!

Kami Kountcheva
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Pharmaceutical companies fined £70 million over unfair price hikes

Pharmaceutical companies Pfizer and Flynn Pharma have been fined nearly £70 million after the Competition and Markets Authority (CMA) found in July that they had overcharged the NHS for an epilepsy medicine.

The CMA ruled that Pfizer and Flynn Pharma "abused their dominant positions" and charged "unfairly high prices" for the medicine phenytoin sodium over four years between 2012-16.

The companies initially came under investigation for these price hikes in 2016. At that time, the CMA issued a fine of £89 million for the two companies, after prices for the medicine went up 2600% overnight in 2012.

The companies appealed against this decision and in 2018 a tribunal overturned the decision to fine. The tribunal ruled that the CMA had not correctly applied the legal test needed to make their decision, but that there was "much in the [CMA's] decision with which we agree".

In 2020, the CMA reopened its investigation, which included additional evidence, and found that the companies had abused their dominant positions in the market by unfairly overcharging the NHS for this medicine.

Andrea Coscelli, chief executive of the CMA, stressed that phenytoin is an essential epilepsy medicine that many people rely on to manage their seizures. She added: "These firms illegally exploited their dominant positions to charge the NHS excessive prices and make more money for themselves – meaning patients and taxpayers lost out.

"Such behaviour will not be tolerated, and the companies must now face the consequences of their illegal action."

The NHS is currently in the process of a court claim for damages against the two companies.

Teva zonisamide stock levels

Zonisamide 25mg and 100mg capsules made by Teva are temporarily out of stock, Epilepsy Action has found out.

Teva have said they expect the 100mg capsules to be back in stock in February 2023 and the 25mg capsules to be back in stock in April 2023.

Until recently the 50mg capsules were also out of stock, but these came back in stock at the end of November 2022.

Grant secured for bilingual therapy services

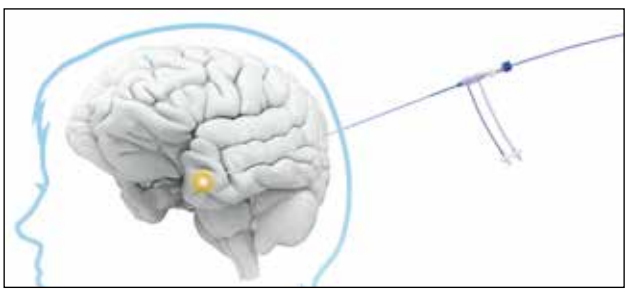
Epilepsy Action Cymru was recently awarded a £328,875 grant from the National Lottery Community Fund to provide online bilingual talking therapy in Wales.

The free Wellbeing Service will comprise one-to-one or group talking therapy sessions, available to adults with epilepsy, as well as parents and carers of people with the condition, based in Wales. They will be available in both English and Welsh, and be tailored for each individual. The organisation will be working on setting up this project in the next few months and will announce the launch of the service early next year.

Jan Paterson, manager at Epilepsy Action Cymru, said: "Epilepsy affects around 32,000 people in Wales and can have a devastating impact on people's lives and those of their families. Talking to someone can make a huge difference and help people feel less alone. This new service will provide timely access to talking therapies for people affected by epilepsy across Wales."

Other recipients of a slice of the National Lottery fund, totalling over £4million, include Solva Care, Newport and Gwent Samaritans and The Big Skill CIC.

NHS launches new laser beam brain surgery



A new fibre-optic laser therapy for people with drug-resistant focal epilepsy will be offered on the NHS, with the first of these surgeries taking place in early 2023.

This new technology allows surgeons to target the specific part of the brain causing seizures without the need for the more traditional invasive surgery.

The laser beam brain surgery will initially be available at two specialist service providers in England.

The laser treatment is carried out in an MRI scanner to help the medical team accurately navigate through the brain and avoid important structures. The treatment requires a small probe (1.5mm-wide) to be placed into the skull with the fibre optic laser at the tip of it. It works by removing the part of the brain where seizures start using heat.

People having this treatment are likely to be able to go home the next day and be back to work or usual activities within a week, according to NHS England.

The organisation said the laser beam brain surgery will benefit up to 150 people each year.

NHS national medical director Professor Sir Stephen Powis said: "This pioneering laser beam treatment for epilepsy patients is life-changing and will offer hope to hundreds of people every year who have not had success in preventing seizures with traditional drugs.

"By replacing invasive neurosurgery with a cutting-edge laser therapy, allowing clinicians to better target the parts of the brain causing the epilepsy, we not only dramatically reduce risks to these patients, but drastically reduce their recovery time both in and out of hospital."

Alison Fuller, director of Health Improvement and Influencing at Epilepsy Action, said: "This new therapy is an exciting ray of hope for the many people with epilepsy whose lives are being impacted by the harsh reality of uncontrolled seizures.

"Traditional brain surgery can be a really effective treatment, for those eligible, and we hear from many people who say it's had a positive impact on their seizures.

"But, choosing to have invasive surgery can be an incredibly difficult decision to make, given the potential risks and long recovery times involved.

"We hope that making this exciting new treatment available on the NHS gives even more people with epilepsy the chance to achieve better seizure control, which will improve outcomes and ultimately their quality of life."

NHS England says this is the latest example of the NHS delivering on the Long Term Plan commitment to ensure patients across the country have access to the latest and most effective treatments available.

Epilepsy medicine risks in pregnancy survey

Three epilepsy charities have launched a new survey to determine the level of awareness around the risks of taking certain epilepsy medicines during pregnancy.

Epilepsy Action, Young Epilepsy and Epilepsy Society have put together the Epilepsy Medicines in Pregnancy survey.

The charities said that the teratogenic risks of sodium valproate have been known for some years. However, awareness of potential risks of other epilepsy medicines may not be as widespread.

In 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) carried out a safety review of epilepsy medicines used during pregnancy. The findings showed that a number of epilepsy medicines were linked with an increased risk if taken during pregnancy, including carbamazepine, phenobarbital, phenytoin and topiramate.

The charities said they want to ensure women with epilepsy are fully aware of the risks.

Alison Fuller, director of health improvement and influencing at Epilepsy Action, said: "We are concerned that the risks of taking certain epilepsy medications during pregnancy have not been properly communicated to women and girls.

"The results of this new survey will help us to better understand patient awareness of the risks in taking valproate and other epilepsy medicines."

The survey is open to female epilepsy patients at: *bit.ly/3XLIoeu*

'Record numbers' of nurses to strike for better pay

'Record numbers' of nurses who are members of the Royal College of Nurses (RCN) have voted to take strike action to fight for fair pay. This is the first time RCN nurses have voted to strike in the 106 years of the RCN.

Many of the biggest hospitals across the UK will be affected by the strikes this winter. This comes at a time when NHS waiting times for routine hospital treatments have reached record highs, according to NHS England.

The strikes are expected to start before the end of this year and further plans will be announced soon.

The RCN says the strikes will be carried out legally and safely, and emergency services and other urgent care will not be affected. However, they will affect things like routine services, including planned operations, mental health services and district nursing, which will have an impact on people with epilepsy.

The RCN is asking the government to act to acknowledge the life-saving role nurses play in healthcare and to ensure nursing is an attractive job, to help fill the "tens of thousands of unfilled nursing posts".

Pat Cullen, RCN general secretary and chief executive, said: "Anger has become action – our members are saying enough is enough. Our members will no longer tolerate a financial knife-edge at home and a raw deal at work.

"Ministers must look in the mirror and ask how long they will put nursing staff through this. Across the country, politicians have the power to stop this now and at any point.

"This action will be as much for patients as it is for nurses. Standards are falling too low [through understaffing] and we have strong public backing for our campaign to raise them."

Alison Fuller, director of Health Improvement & Influencing, Epilepsy Action:

"We know the decision by nurses to take strike action has been a difficult one. Nurses are a lifeline for people with epilepsy and their families in delivering safe care and yet for too long, their workload, morale and staffing levels have been stretched to breaking point.

"We are calling on the Health Secretary to recognise the contribution nurses make to ensure they are able to do their essential work safely. In the meantime, we recognise the short-term impact the strike action will have on people with epilepsy who will be understandably concerned about their continuity of care.

"We already know patients aren't getting the best service they deserve and we anticipate that their experiences will be further impacted by the planned strike action. We will be actively seeking the views of people with epilepsy and how this is affecting their access to services and delays in their care and treatment."

The action has followed the NHS Agenda for Change pay announcements earlier in the year, which left experienced nurses worse off than a decade ago, according to the RCN. The salaries of nurses have been consistently below the rate of inflation. With the strike action, the RCN is campaigning for a pay rise that is 5% above inflation, which would be around 12%.

The RCN represents around two-thirds of nurses in the NHS.

Study launched on "revolutionary" EEG technology

A new study into "game-changing" long-term seizure-monitoring technology has launched today.

The Real World Testing and Cost-effectiveness Analysis of Subcutaneous EEG (REAL-ASE) will recruit 33 people with drug-resistant epilepsy in centres in London, Newcastle, Cardiff and Manchester, to trial the small EEG device for six months.

Through the study, the researchers are hoping to find out what it would cost for the NHS to incorporate this technology into its work, and what the benefits would be.

The new EEG technology being studied, developed by Danish company UNEEG medical, can be used to monitor brainwaves continuously for up to 15 months, while the person gets on with daily life. A small device is placed under the scalp during a 20 minute procedure under local anaesthetic.

The research team at the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) at King's College London, explained that the device can accurately monitor a person's seizures and could replace seizure diaries which can be unreliable.

The team also added that it could improve on typical EEG monitoring, which can only be done for a few days at a time, requires a hospital stay, and for which there can be long NHS waiting lists.

Alison Fuller, director of health improvement and influencing at Epilepsy Action, said: "This new technology has the advantage of overcoming some of the limitations or disruption people experience with more conventional EEGs. These often require extended hospital stays or the need for sleep deprivation which can have a knock-on negative impact on seizures.

"Having better evidence and knowledge will undoubtedly improve outcomes in safety and quality of care, which could ultimately help to reduce epilepsy-related deaths."

The study's principal investigator, Prof Mark Richardson from King's College London, said: "Clinicians treating people with epilepsy frequently make changes to therapy in the hope of improving the lives of the third of people whose seizures have not yet responded to treatment. We don't know whether a change in treatment has been helpful without a very accurate count of seizures. Unfortunately, seizure diaries are often not accurate enough to judge whether treatment has led to any improvement.

"What the use of ultra long-term EEG opens up is the possibility, in future, of very accurately judging the effect of a change in treatment. We also anticipate that ultra long-term EEG will allow us to quickly identify that someone's epilepsy is deteriorating so that we can immediately step up their care. This has the potential to be truly revolutionary for people living with a difficult illness."

The research is funded by a £1.8 million grant from the National Institute for Health & Care Research (NIHR).

Top 10 research priorities shared

The UK Epilepsy Priority Setting Partnership (PSP) announced in October the top 10 priorities for epilepsy research, developed following a nationwide project.

The team worked on the project over 18 months. They used surveys and workshops to get the input of people with epilepsy, their friends and families and health professionals to identify issues of highest priority. People with epilepsy made up the majority of the survey responders (55%).

The top 10 research priorities the team established cover themes including epilepsy-related deaths, the underlying causes of epilepsy, women's health and epilepsy, and drug-resistant epilepsy.

The research priorities were launched at the ILAE British Branch conference in Cardiff in October. There is more information about the project and the full list of the top 10 priorities on pages 28 and 29.

Milpharm levetiracetam stock

Levetiracetam 1000mg tablets made by Milpharm are temporarily out of stock. Milpharm were not able to say when they will be back in stock.

Epilepsy Action will update its drugwatch story at *bit.ly/3B1WAVS* when there is more information.

Milpharm levetiracetam 250mg and 500mg tablets are still in stock.

Figure 1. Insights into an abnormal mental state from William Shakespeare's Othello.

Epilepsy and psychoses

A rare but serious comorbidity

Dr Mula discusses our current understanding of psychoses in epilepsy and the best way to manage these in our patients.

Historical notes

Psychoses and thought disorders represent a relatively rare comorbidity of epilepsy but they can have serious consequences on patients and their families.

For centuries, the relationship between epilepsy and psychoses attracted the interest of clinicians and inspired artists, from Dostoevsky to Van Gogh.

Many authors have commented on the epileptic nature of Othello's 'trance' episodes [Emery, 1959]. However, what is remarkable in Othello is the insight of William Shakespeare into the possibility of an abnormal mental state after a seizure, anticipating the modern concept of post-ictal psychosis (*Figure 1*). This is well evidenced in the conversation between Cassio and Iago about Othello from Act IV, Scene I:

> CASSIO: What's the matter?
> IAGO: My lord is fall'n into an epilepsy.
> This is his second fit; he had one yesterday.
> CASSIO: Rub him about the temples.
> IAGO: No, forbear,
> The lethargy must have his quiet course;
> If not, he foams at mouth, and by and by
> Breaks out to savage madness.

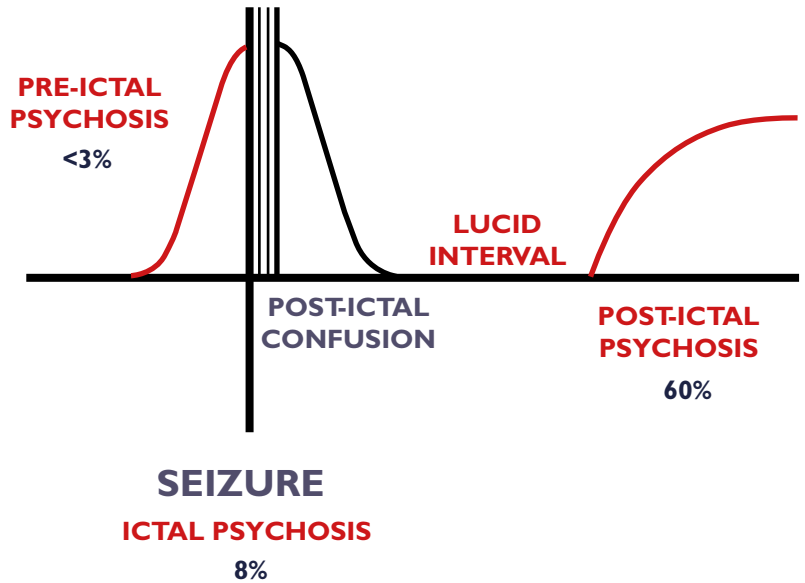
Nineteenth century clinicians were fully aware of psychoses of epilepsy. The British neurologist William Gowers, in his textbook on epilepsy, stated "occasionally, after a fit, or, more frequently, after a series of fits, an attack of mental disturbance may come on which lasts for several days. It may be simply a demented state, or there may be hallucinations with irritability and even violence" [Gowers, 1881]. The French psychiatrist Jules Falret named post-ictal psychoses "le grand male intellectuel" [de Toffol, 2016]. During the 20th Century, the relationship between epilepsy and psychoses was revitalised by the observations of Nyiro and Jablonszky who pointed out that people with psychoses and seizures had a better prognosis than those with psychoses without epilepsy. This led to the subsequent development of shock therapies for people with schizophrenia with the publications of Ladislas Meduna and Ugo Cerletti.

People with temporal lobe epilepsy have up to seven times increased risk of developing psychoses compared to the general population

The relationship between epilepsy and psychosis

Modern research provides important information about this condition. A meta-analysis of epidemiological studies shows that people with temporal lobe epilepsy have up to seven times increased risk of developing psychoses as compared to the general population [Clancy *et al*, 2014]. However, people with psychoses have also a 2-3 times increased risk of developing epilepsy [Wotton and Goldacre, 2012] with an incidence rate of seven per 1000 person-year [Chang *et al*, 2011]. Reasons for this bidirectional relationship between epilepsy and psychoses are multifaceted and probably related to neuroanatomical and neurochemical changes happening in the brain that can favour both conditions. In fact, neuroimaging studies in people with schizophrenia show abnormalities in brain networks overlapping with those involved in temporal lobe epilepsy, particularly amygdala and hippocampi [Dean *et al*, 2016]. However, epilepsy is now recognised as a network disorder rather than being due to the involvement of a single area or brain region. In this regard, a systematic review of structural and functional

Figure 2. Psychoses in epilepsy grouped according to temporal relationship to seizures.



brain alterations in people with psychoses of epilepsy points out that brain abnormalities often involve distributed brain regions and are not localised just in the mesial temporal lobe [Allebone *et al*, 2018]. In fact, people with epilepsy and psychoses can present with histological and architectural changes identified in regions distant to the seizure focus but why this happens in some patients and not in others is still unknown. It is, therefore, tempting to speculate that patients with epilepsy and psychoses represent different phenotypes and maybe even different conditions characterised by psychiatric symptoms and seizures.

Clinical presentations

Psychotic symptoms in epilepsy can present in many different clinical contexts. Historically, but also for pragmatic reasons, psychoses have been grouped according to their temporal relationship to seizures (*Figure 2*).

Pre-ictal and post-ictal psychoses are not associated with detectable changes on scalp EEG while ictal psychoses represent seizures themselves or episodes of non-convulsive status epilepticus mostly of temporal lobe origin [Trimble, 1991].

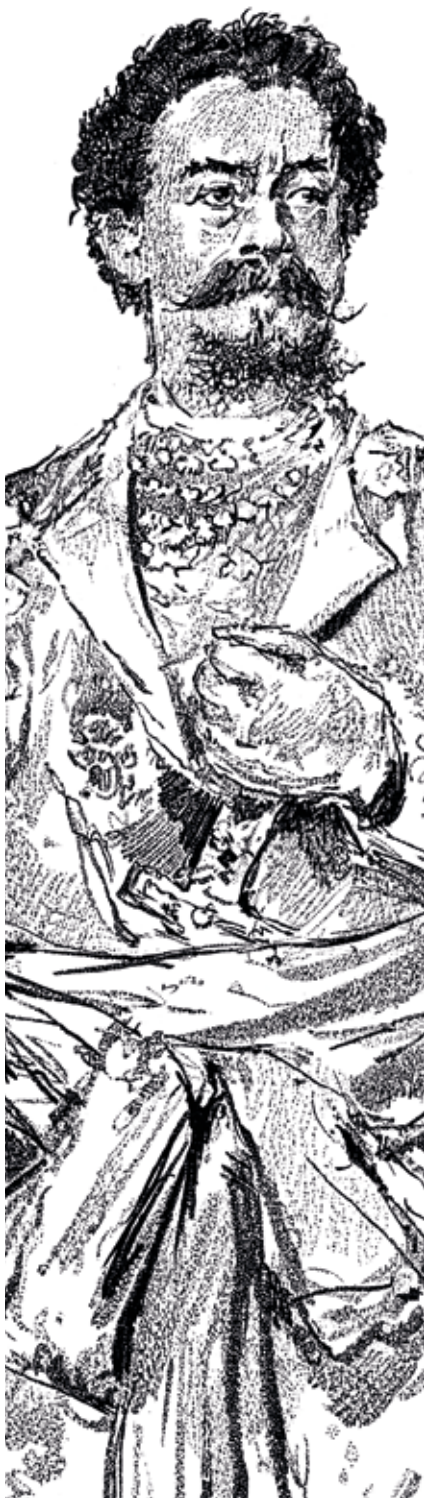
Post-ictal psychoses are the most commonly encountered peri-ictal psychoses. They tend to happen in patients with focal epilepsies, mostly temporal lobe epilepsy, and they are usually precipitated by a cluster of bilateral tonic-clonic seizures. Post-ictal psychoses are characterised by quite peculiar clinical features [Hilger *et al*, 2016]. There is a lucid interval (ie. a period of normal mental state) lasting from one to six days, but most of the time 48 hours, preceding the onset of the psychotic episode [Adachi *et al*, 2007]. The clinical presentation can be quite polymorphic but most patients present with abnormal moods (either depressed or manic) and paranoid delusion [Oshima *et al*, 2006]. Delusions of grandiosity,

mystical experiences with religious content, often associated with an elevated mood, are also reported, as well as aggressive behaviour or suicidal attempts 13[Kanemoto *et al*, 2010]. Psychotic symptoms usually remit spontaneously within days or weeks, with no need for long-term antipsychotic treatment, which is mainly prescribed to reduce mortality and morbidity. However, some patients may present multiple episodes over a short period of time and one in four patients seem to progress into a chronic interictal psychosis [Adachi *et al*, 2007]. These cases may require long-term drug treatment.

Interictal psychoses are less frequent than peri-ictal psychoses, but they tend to be chronic and sometimees last almost lifelong.

If there is no clear relationship with seizure activity, psychoses are called interictal. This type are less frequent than peri-ictal psychoses, but they tend to be chronic and sometimes last almost lifelong. They seem to occur in patients with drug-resistant temporal lobe epilepsy after many years of active epilepsy [Adachi *et al*, 2000], with structural abnormalities like bilateral hippocampal sclerosis, hamartomas or gangliogliomas. They may start after multiple episodes of post-ictal psychoses. Several authors have pointed out that interictal psychoses are different from schizophrenia [Mula *et al*, 2008; Tebartz Van Elst *et al*, 2002]. In fact, patients with interictal psychoses tend to have a better prognosis with less reported long-term institutionalisation [Ashidate, 2006; Fiseković and Burnazović, 2007]. This is probably due to a tendency of psychotic symptoms to attenuate over time and to the lack of cognitive deterioration.

Psychotic symptoms can be related to the epilepsy treatment but this is infrequent. A retrospective study in more than 2,600 people with epilepsy showed that only one in seven cases of psychotic presentations is due to antiseizure medications [Chen *et al*, 2016]. The large majority are always peri-ictal or interictal psychoses. Drug-related psychotic episodes can be due to toxic encephalopathies or, more rarely, to the so-called forced normalisation phenomenon [Chen *et al*, 2016]. This concept refers to the publications of Heinrich Landolt who reported a group of patients who had florid psychotic episodes with improvement or normalisation of the EEG. A recent systematic review of the literature shows that this phenomenon can occur in people with different epilepsy types but predominantly temporal lobe epilepsy, after many years of active epilepsy (more than 15 years) [Calle-López *et al*, 2019]. One in four patients also have some developmental delay [Calle-López *et al*, 2019]. The authors have also pointed out that this is not a drug-specific phenomenon and it can occur with Vagus Nerve Stimulation (VNS) and epilepsy surgery. In this regard, it has to be acknowledged that psychoses can be a complication of epilepsy surgery. Robust data are still limited. A prospective study shows a prevalence of de-novo psychoses of around 1% [Devinsky *et al*, 2005]. But other studies have shown higher rates. Psychoses after epilepsy surgery seem to occur mostly in the context of unsuccessful epilepsy surgery with continued seizures and/or surgical



complications [Macrodimitris *et al*, 2011]. While pre-existing psychiatric conditions, including psychotic disorders, could be a risk factor for psychiatric disorders after epilepsy surgery [Iranzo-Tatay *et al*, 2017], they should not represent a contraindication for epilepsy surgery per se. In fact, epilepsy surgery can result in improvement in other epilepsy-related symptoms such as peri-ictal psychoses and sometimes even inter-ictal psychoses [Buranee *et al*, 2016].

Management of psychoses in epilepsy

Studies on the treatment of psychotic disorders in epilepsy are almost non-existent. During the last decade, a couple of consensus papers from internal experts in the field have been published [Kerr *et al*, 2011; de Toffol *et al*, 2018] providing some guidance to clinicians. However, at present, it seems reasonable to follow internationally adopted guidelines of treatment outside epilepsy, adapting them to the individual needs of patients with epilepsy and to the specific clinical scenario [Agrawal and Mula, 2019]. Obviously, it is still unknown whether patients with epilepsy present with the same response and remission rates of people with schizophrenia or other psychoses. For all these reasons, patients with epilepsy and psychotic disorders need to be carefully monitored.

In general terms, second-generation antipsychotics like risperidone, olanzapine and quetiapine should be preferred, as they seem to be better tolerated than first generation drugs. Antiseizure medications with inducing properties on liver metabolism, such as phenytoin, carbamazepine and barbiturates, reduce the blood levels of all antipsychotics [Mula, 2016]. This interaction is particularly relevant for quetiapine that becomes almost undetectable up to 700 mg when prescribed in patients taking these antiseizure medications.

Regarding risk of seizures with antipsychotic drugs, clozapine is the one associated with the highest risk of seizures compared with placebo [Alper *et al*, 2007]. Olanzapine and quetiapine also seem to carry some risk, though to a lesser extent than clozapine, while all other antipsychotics, including risperidone, show no difference as compared to placebo [Alper *et al*, 2007]. First generation compounds, such as chlorprothixene, thioridazine and haloperidol have a slighter higher risk than second generation agents, such as risperidone and aripiprazole [Wu *et al*, 2016]. There are no studies specifically investigating depot or long-acting injectable antipsychotics in people with epilepsy and whether they are associated with an increased risk of seizure deterioration as compared to oral formulations.

Conclusion

Despite the improvements in the treatment of epilepsy, psychoses still represent a rare but serious psychiatric comorbidity. They tend to occur in people with drug-resistant temporal lobe epilepsy but clinical studies have pointed out the bidirectional relationship between these two conditions due to mechanisms only partly clarified. Full seizure control still represents the only way to minimise the occurrence of psychoses in people with epilepsy but when this is not possible, these patients need multidisciplinary management. Ideally, regional neuropsychiatric centres represent the most appropriate point of contact but when neuropsychiatry is not

available, strong partnership between neurologists and community psychiatrists is needed with clearly defined clinical pathway. Given the lack of evidence-based treatment recommendations, guidelines for the management of psychoses outside epilepsy still represent the best option. But it's important to take into account interactions with antiseizure medications and the risk of seizures with antipsychotics. Further research in this area is urgently needed in order to offer better treatments and to improve the care of our patients.

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Melissa Barker-Haliski

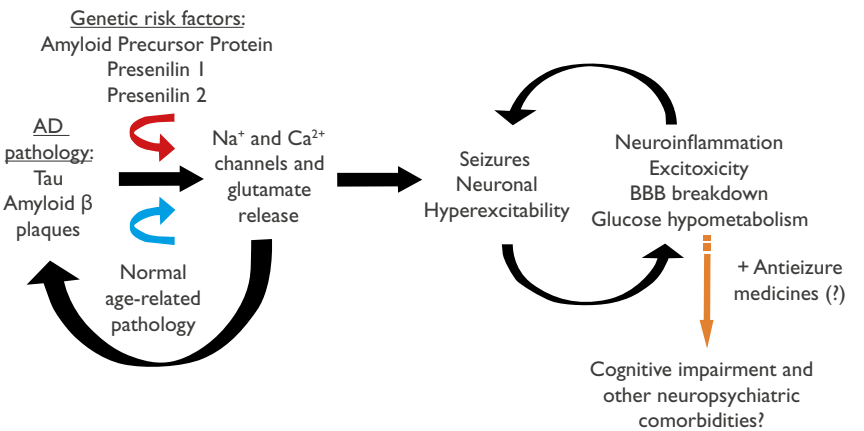
Seizure risk in Alzheimer's disease

An untapped therapeutic opportunity for epilepsy

Dr Melissa Barker-Haliski explains possible common mechanisms between Alzheimer's disease and epilepsy, as well as potential treatments and where future research should focus.

Older adults with epilepsy are the fastest-growing demographic with the diagnosis worldwide. This increase is largely driven by the progressive growth in the global prevalence of adults over 65 years old in the last half century. Seizures are also an under-recognised comorbidity of Alzheimer's disease (AD). While the incidence of seizures in adults with AD varies across studies and populations, there is generally a heightened risk of unprovoked seizures in individuals with AD. Seizure incidence is particularly high in early-onset AD (EOAD; onset prior to age 65 years) and is largely driven by specific genetic risk factors, including duplications in amyloid precursor protein (APP), and variants in the presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes [Zarea *et al*, 2016]. Seizure susceptibility inversely correlates to age of AD onset – up to 87-fold greater risk for seizures in individuals with AD onset between 50-59 years versus that of the general population [Amatniek *et al*, 2006]. Yet even late-onset AD is characterised by a greater incidence of unprovoked seizures relative to that which would be expected in similarly aged individuals (hazard ratio, 8.06; 95% confidence interval, 3.23-16.61) [Scarmeas *et al*, 2009]. Silent hippocampal (focal) seizures have been reported in AD [Lam *et al*, 2017; Lam *et al*, 2020]. The link between seizures and epileptiform activity in AD is thus an underexplored phenomenon deserving of greater clinical and basic translational research.

Figure 1. Alzheimer's disease (AD) is highly associated with seizures and neuronal hyperexcitability, which may also additively contribute to disease burden through as yet undetermined mechanisms.



Despite being clinically distinct diagnoses, epilepsy and AD share many pathophysiological similarities: temporal lobe atrophy, neuronal death, gliosis, neuritic alterations and neuroinflammation [Ackermann *et al*, 1986; Buckmaster and Dudek, 1997; Cook *et al*, 1992; Fazekas *et al*, 1989; Struble *et al*, 2010]. Both disorders are characterised by neuropsychiatric comorbidities, such as anxiety and depression, that negatively impact quality of life. If left untreated, both conditions can also evoke cognitive deficits. Seizures in individuals with AD have faster rates of cognitive decline [Vossel *et al*, 2016; Horvath *et al*, 2021; Voglein *et al*, 2020; Baker *et al*, 2019], intensifying the need to develop clinical interventions to mitigate seizures and seizure-induced cognitive impacts in AD. The disease burden of both AD and epilepsy is clearly defined by extraneous neuronal hyperexcitability. Yet, neurologists and neuroscientists are only beginning to appreciate that untreated seizures may negatively impact the trajectory of AD, and starting to spur clinical trials, mechanistic studies, and therapeutic intervention discovery. Repurposing of antiseizure medicines (ASMs) into AD is gaining increasing favour amongst clinicians with the potential to yield promising disease-modifying benefit in the future [Sen *et al*, 2021; Vossel *et al*, 2021].

The precise timing and mechanisms contributing to seizures and neuronal hyperexcitability in AD are still relatively unclear (Figure 1). In the epileptic brain, neuronal depolarisation opens voltage-gated sodium and calcium channels in the presynaptic neuron, driving release of glutamate, the predominant excitatory neurotransmitter. Excessive sodium and calcium channel opening may thus contribute not only to seizures, but also indirectly promote the excitotoxic neurodegeneration of AD through unchecked glutamate release. Neuronal depolarisation can also promote APP cleavage into pathological amyloid β (Aβ), the hallmark of AD. Synaptic activity itself promotes Aβ release [Cirrito *et al*, 2005]. Accumulated Aβ further interferes with normal glutamate clearance by impairing astrocytic excitatory amino acid transporter 2 (EAAT2/glutamate transporter-1 – Glt-1) function [Zott *et al*, 2019]. Glt-1 clears excessive glutamate in neuronal synapses, maintaining normal homeostatic levels. Left unchecked, however, excess glutamate can drive a viscous cycle resulting in extra-synaptic glutamate receptor (NMDA-type) activation and further neurodegeneration. Clearly, the neuronal hyperexcitability and seizures in AD negatively influences pathological remodeling, which additively increases seizure susceptibility, promotes excitotoxic neuronal death, and accelerates Aβ accumulation.

In addition to excitotoxic damage and neurodegeneration, neuronal hyperexcitability induces neuroinflammation characteristic of both epilepsy [Vezzani *et al*, 2013; Maroso *et al*, 2011; Kan *et al*, 2012] and AD [Heppner *et al*, 2015]. The impact of CNS inflammation depends mainly on the duration of the insult [Lach *et al*, 2022]. Persistent neuroinflammation in both AD and epilepsy can also evoke changes in the blood-brain barrier's (BBB) integrity and permeability. Effects of inflammatory mediators on BBB integrity may further reduce the threshold for spontaneous seizures, alter the sensitivity of ion channels, modify the uptake and release of neurotransmitters, and impair the ability of glia to continuously buffer ion concentrations. Thus, controlling the inflammatory response and the immediate outcomes, such as the BBB breakdown, may attenuate the impact of chronic seizures. Neuroinflammation is a therapeutic target for both epilepsy and AD, highlighting an untapped opportunity to modify disease burden.

Most of our understanding of the mechanisms of seizures in AD are derived from rodent models expressing EOAD-associated risk genes, including APP and PSEN1 [Sanchez *et al*, 2012;

Palop *et al*, 2007]. The age of clinical EOAD onset varies markedly based on the specific gene variant, but the pathology and clinical course associated with it is similar to that of sporadic AD [De Strooper *et al*, 2012], making these EOAD models suitable to study mechanisms of seizures in AD. For example, APPSwe/PSEN1dE9 mice exhibit spontaneous seizures by 4.5 months old, with cognitive deficits appearing by six months old [Janus *et al*, 2015]. The spontaneous seizures of 4- to 6-month-old APP/PS1 mice are sensitive to sodium channel-blocking ASMs [Ziyatdinova *et al*, 2011], although no study has yet assessed age-related ASM efficacy and tolerability. While spontaneous seizures are generally well-tolerated in APP/PS1 mice, roughly 10-15% of animals succumb to seizure-related mortality [Janus *et al*, 2015]. Nonetheless, these preclinical studies provide clear and unambiguous evidence that pathological Aβ accumulation is associated with excessive neuronal hyperexcitability and seizure-induced adverse outcomes. Early studies indicated that spontaneous seizures only occur after Aβ accumulation [Ziyatdinova *et al*, 2011; Sanchez *et al*, 2012; Palop *et al*, 2007]. However, more recent work is providing evidence of enhanced seizure susceptibility in early AD in the absence of accumulated Aβ [Vande Vyver *et al*, 2022]. Tau protein phosphorylation, a neuronal microtubule-associated protein that critically mediates axonal transport, is also known to increase hyperexcitability [Roberson *et al*, 2011; Putra *et al*, 2020]. Tau protein is hyperphosphorylated in AD, disrupting normal neuronal functions. Accumulation of hyperphosphorylated tau protein leads to the neurofibrillary tangles that define clinical AD [Grundke-Iqbal *et al*, 1986b; Grundke-Iqbal *et al*, 1986a]. Tau knockdown has even been proposed as a relevant therapeutic strategy in epilepsy itself [Holth *et al*, 2013], which may carry relevance to future treatment of seizures in AD.

Glucose hypometabolism is common in both clinical [Mosconi, 2005] and preclinical [Mosconi *et al*, 2008] AD, as is the compensatory shift to alternative fuel sources, such as ketone bodies [Ding *et al*, 2013; Klosinski *et al*, 2015; Yao *et al*, 2009]. Reduced hippocampal glucose utilisation correlates to cognitive deficits over time in normal aged individuals and can also predict those individuals who go on to develop mild

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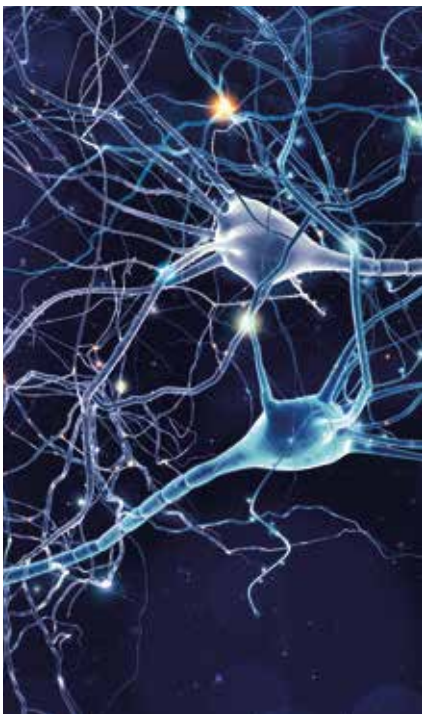
Until strategically identified and developed therapies for seizures in AD can be approved, focal seizures in AD may be beneficially controlled by repurposing ASMs. This may carry the added benefit to indirectly slow disease progression and reduce the severity of neuropsychiatric comorbidities. Indeed, a randomised prospective study of 95 AD patients aged 60–90 years old with reported seizures compared the anticonvulsant efficacy of levetiracetam (n = 38), phenobarbital (n = 28) and lamotrigine (n = 29). There were no detectable differences in the 12-month change in seizure freedom and responder rate [Cumbo and Ligori, 2010]. However, that study also assessed the cognitive impact of ASM administration to AD patients stratified



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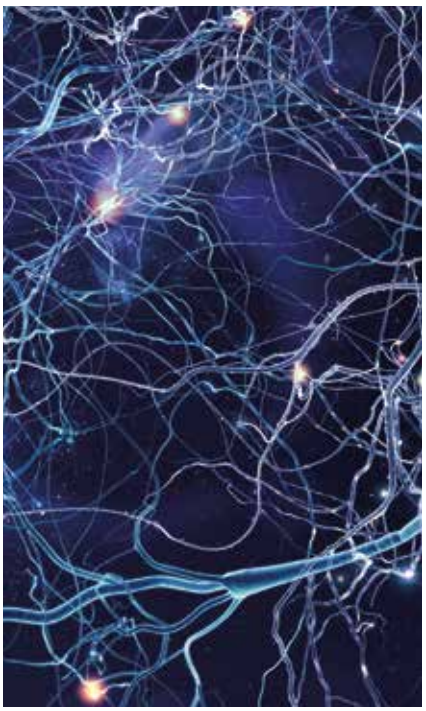

by seizure history, finding that phenobarbital evoked negative cognitive effects, levetiracetam improved attention, short-term memory and oral fluency, and lamotrigine conferred better moods [Cumbo and Ligori, 2010]. Limited clinical evidence would suggest that ASMs may improve cognitive function in mild cognitive impairment [Bakker *et al*, 2012], however the rigorously conducted randomised controlled trials in AD patients are in short supply [Lehmann *et al*, 2021]. Vossel and colleagues assessed the efficacy of low-dose levetiracetam (125 mg/kg, b.i.d. for four weeks) versus placebo in a phase 2a study in 55 age-matched individuals with AD. They reported improvements in cognitive function exclusively in patients with epileptiform activity who received levetiracetam [Vossel *et al*, 2021]. Whether other ASMs are similarly beneficial in AD patients with epileptiform activity or documented seizures is clearly an area in need of further rigorous clinical study. Administration of appropriately selected ASMs to individuals with AD (eg. lamotrigine for neuropsychiatric deficits vs levetiracetam for cognition) could possibly improve quality of life and prolong the period of independent function [Lehmann *et al*, 2021].

Discovery of ASMs exclusively for seizures in AD, including the rational selection of precisely targeted agents for seizures in this population, is an untapped opportunity to shift the disease course. Yet greater effort is needed to address how causes of late-life seizures may influence functional decline in AD and epilepsy. Epilepsy research is increasingly relying on

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preclinical models of paediatric developmental epileptic encephalopathies, including Scn1a+/- [Kaplan *et al*, 2017] and KCNQ 2/3 [Leppert and Singh, 1999] models to identify novel therapeutic agents for these indications [Bialer *et al*, 2020b]. While the concept that an AD model could represent an ASM discovery platform is at first counterintuitive, our studies in tandem with the clinical and preclinical work of other groups reveals a chance to similarly prioritise ASM discovery specifically for seizures in AD. Our studies [Beckman *et al*, 2020;Vande Vyver *et al*, 2022] have uncovered Aβ-dependent and -independent contributions underlying seizure risk and ASM efficacy in AD-associated preclinical models. Critically, we are the first to demonstrate that loss of normal PSEN2 function is associated with age-related changes in seizure susceptibility which may carry critical implications for future ASM discovery and mechanistic studies in seizures in AD. Pharmacological studies in PSEN2 null [Beckman *et al*, 2020] and APP overexpressing mouse models [Vande Vyver *et al*, 2022; Ziyatdinova *et al*, 2016; Ziyatdinova *et al*, 2015; Ziyatdinova *et al*, 2011; Sanchez *et al*, 2012] indicate that ASMs are effective against hyperexcitability in preclinical AD models. Altogether, these studies may also translate to improved treatments for people with epilepsy, more broadly.

Ultimately, seizures may be a manageable feature of AD [Lam *et al*, 2017; Cretin *et al*, 2016; Vossel *et al*, 2013] as seizures in older adults are generally not drug-resistant [Hernandez-Ronquillo *et al*, 2018]. Many ASMs currently exist that are safe and well-tolerated in older adults with epilepsy [Piccenna *et al*, 2022]. However, further clinical trials to define which ASMs are most useful and well-tolerated, as well as translational studies to understand the biological basis of seizures in AD, are still needed to address this medical need. Critically, the intersection between seizures and AD remains relatively underexplored but represents an intriguing new frontier to uncover novel drivers of seizures and therapeutic targets for drug discovery for disease modification.

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Ramon Bautista

Employment and epilepsy

Considerations for the 21st century

Prof Ramon Bautista discusses problems people with epilepsy face when looking for and staying in work, and the way clinicians can support patients with this aspect of life.

The opportunity to work and become gainfully employed opens immense opportunity for all individuals, resulting in financial independence, self-determination, and the ability to make a positive contribution to society.

Over the past century, individuals with epilepsy have gained more acceptance into the workforce – a consequence of increased societal acceptance and improved seizure control. In the past, all individuals with seizures were thought to have an incurable neuropsychiatric condition, necessitating involuntary and lifelong confinements into asylums [Letchworth, 1900], and being deprived of the ability to work.

Societal acceptance of epilepsy has improved to the extent that stigma,

while not totally eradicated, has been lowered, especially in more developed countries. Because of this, patients with epilepsy now have more opportunities to participate more fully in society.

Treatment options for people with epilepsy have also got better, both in terms of seizure control, as well as decreased adverse effects. Given the current number of anti-seizure medications (ASM), as well as the options for epilepsy surgery and neuromodulation, the lives of many patients with refractory epilepsy have improved.

Because of this, for an ever-increasing number of individuals with epilepsy, participating in the workforce is a very reasonable aspiration. Some evidence has shown that in the UK, the employment rate for individuals whose seizures are controlled is similar to the general population [Jacoby, 1995]. However, a more recent systematic review has also shown that employment rates of people with controlled and uncontrolled seizures were similar [Wo *et al*, 2015]. This disputing evidence shows that as well as seizure control, more support is also needed in other areas. It should be emphasised that for individuals with less than complete seizure control, as well as those with seizure control, there should be opportunities for gainful employment.

Despite all of the advancement in societal acceptance and medicine, there is still evidence of higher rates of un- and under-employment in people with epilepsy than in the general population [de Souza *et al*, 2018]. More remains to be done if we are to maximise employment opportunities for individuals with epilepsy. Aside from optimising seizure control, several initiatives ought to be undertaken to assist epilepsy patients in their quest to become employed.

First, and in this author's opinion, probably most importantly, there is a need to develop educational/vocational programmes that cater to the unique needs and circumstances of individuals with epilepsy [Fraser *et al*, 1984; Jacoby, 2012]. Aside from poor seizure control, the lack of adequate education and training remains a major cause of decreased employment among individuals with epilepsy. Unfortunately, many individuals with epilepsy begin to have seizures during their formative years, causing them to miss out on much of their education. Many established educational systems can be typically poorly equipped to support individuals who are unable to fully participate during their early years, making it difficult for many to catch up despite improved seizure control later in life. This can result in people with epilepsy receiving a lower education level and lower qualifications [de Souza *et al*, 2018]. An educational programme that caters to the circumstances of individuals with epilepsy, and preferably affiliated with companies via training and internship programmes, will go a long way in successfully transitioning many individuals with epilepsy into the workforce.

There is also a need to pay attention to the adverse effects of treatment, particularly as it affects our patients' ability to work

There is also a need to pay attention to the adverse effects of treatment, particularly as it affects our patients' ability to work. This should be easier now given the greater arsenal of ASMs to choose from. It is important to realise that ASMs that may be more convenient to prescribe, such as levetiracetam, may not necessarily be the preferred drug if a patient wishes to be gainfully employed, as one common adverse effect is that of heightened irritability and mood issues. Despite their patients' achieving seizure freedom, providers should not hesitate to modify the treatment regimen and even prescribe another ASM if current medications adversely affect their patients' ability to work. These decisions are usually made on a case-by-case basis, thus the need to individualise therapy.

It is well-established that individuals with epilepsy may present with a variety of neuropsychological profiles, due to differences in disease pathophysiology and seizure location [Aldenkamp and Arends, 2004]. Because of this, it may become necessary that patients undergo detailed neuropsychological testing in order to determine their cognitive strengths and weaknesses. This can help point them to better profession options.

It is also well-known that a significant number of individuals with epilepsy suffer from psychiatric co-morbidities [Barry *et al*, 2007; Mula *et al*, 2021]. Physicians should play an active role in managing these conditions, particularly in situations and locales where there is a dearth of mental health providers. Even now, psychiatric conditions remain underdiagnosed among individuals with epilepsy [Mula *et al*, 2021], and many neurologists still hesitate when it comes to prescribing antidepressants and other psychotropic medications to their patients [Kanner and Palac, 2000]. Effectively managing psychiatric comorbidities among epilepsy patients will greatly increase their potential to

Ramon Bautista

thrive in the workplace.

Careful thought should go into assessing the work status and limitations of patients with epilepsy. It is this author's experience that there can be a tendency of employers to lump all individuals with epilepsy into a 'no-work' category, especially if they are less than completely seizure free. However, work limitations should differ among all individuals, for example those who experience only nocturnal seizures from those who have them during the daytime. Likewise, there is likely to be a different set of challenges for patients who experience only auras from those who have convulsions. Women with anticipated catamenial seizures should have a different set of work considerations from those whose seizures occur unpredictably. In general, many individuals with epilepsy who are not seizure free are still able to work as long as the job does not require driving, operating heavy or power machines, consistent climbing ladders, or lifting heavy objects overhead.

Transportation constraints have been the bane of many an epilepsy patient when it comes to working [Sillanpas and Shinnar, 2005]. This is especially true in regions where public transportation facilities are lacking. For many, this concern has been somewhat averted by the shift to work from home and telework for many companies. When possible, individuals with epilepsy can and should be able to make use of these work modalities.

There has also been a recent surge in the number of ASMs that may stop seizures outside the emergency room and hospital environment, such as intranasal and intramuscular benzodiazepines [Gidal and Detyniecki, 2002; Gaínza-Lein *et al*, 2017]. For many individuals with epilepsy who are employed, especially for those who have cluster seizures, medications such as these should be readily available if they were to have seizures in the workplace, and co-workers should be instructed on how to administer them. This would lessen the need for emergency room visits and hospitalisations. It's important to stress that training and instructions are key for anyone administering rescue medication, and this may currently be lacking, as Gaínza-Lein *et al* have found.

And just as having individuals in the workplace who are knowledgeable of CPR has become commonplace, it should also become standard practice to educate workers on how to care for a colleague who may experience a seizure in their presence. This would lessen the occurrence of potentially harmful interventions, such as putting a foreign object into an individual's mouth during a seizure. Epilepsy education for the lay public may help decrease stigma by enhancing understanding of the condition [Harden *et al*, 2004]. As well as that, epilepsy training for key figures, such as teachers and counsellors can have a demonstrable positive effect on the experience of people with epilepsy in different settings [Khaled *et al*, 2020].

It has been shown that, for some individuals with epilepsy, a lack of personal motivation prevents them from seeking employment

Lastly, for some individuals with epilepsy, there is a need to have a discussion about work and employment, especially if they have relatively controlled seizures. It has

been shown that, for some individuals with epilepsy, a lack of personal motivation prevents them from seeking employment [Bautista and Wludyka, 2007]. The reason for this varies and encompasses personal, family, and societal disincentives, including previous negative experiences of employment [Francis *et al*, 2019]. Physicians should encourage their patients to develop a positive attitude towards work.

Overall, the horizon appears bright for individuals with epilepsy who would like to work. There are currently devices in development that may someday enable patients to predict when their seizures may occur well in advance, and this can help them plan their work situation. Even more than their non-epilepsy colleagues, our patients should pay attention to issues such as work-life balance in order to optimise work productivity while minimising the associated stressors. In the years and decades to come, I hope that becoming employed and staying in employment becomes a more easily attainable goal for many of our patients. There is both an individual and a societal good that arises whenever we encourage an individual with epilepsy to work.

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Markus Reuber

Highlights

Top picks from *Seizure*

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

I predict that a large step change is afoot in the provision of ongoing care to patients who have been diagnosed with epilepsy. This step change will involve a switch from the reliance on self-reported seizure frequencies to the use of objective tools capable of capturing data about the frequency and severity of recent seizures. It is very clear that self-reported seizure frequencies – even when based on diaries – are highly unreliable. This is true especially in patients with focal impaired awareness and absence seizures, but also in those who have seizures during sleep but without a bed partner. In one study, the group medians of individual documentation accuracies for overall seizures, simple partial seizures, complex partial seizures and bilateral tonic-clonic seizures were 33.3%, 66.7%, 0%, and 83.3%, respectively [Hoppe *et al*, 2007]. Even patients who are highly motivated to record their seizures (like those undergoing inpatient video-EEG monitoring for diagnostic purposes) often fail to record their seizures. This is most likely because the seizure has reduced their ability to remember or to record it in the postictal state. Self-report of seizure frequencies is of even more limited value in young children or some people with learning disabilities.

My Editor's Choice from *Seizure* issue 101 is a prospective study evaluating the health economic benefits of NightWatch, one particular objective seizure monitoring and recording system, by Anouk Engelgeer *et al* [2022]. While this system is of limited value in the detection of seizures with minor motor components, it has previously been shown to pick up bilateral tonic-clonic seizures with a high level of accuracy and with an acceptably low number of false alarms [Arends *et al*, 2018]. Accurate information about the level of control of seizures – especially of tonic-clonic seizures from sleep – may be more important for the prevention of SUDEP than the ability of others to provide immediate postictal assistance.

In the context of the study by Engelgeer *et al*, the benefits of using this objective seizure monitoring system in children with uncontrolled epilepsy were more immediately measurable. Societal care provision costs fell significantly from the pre-monitoring baseline to the intervention period. Most of the cost difference was explained by child and caregiver healthcare costs, and 10% by productivity changes. Univariate sensitivity analyses on the perspective and imputation method demonstrated the robustness of the findings.

The demonstration of cost effectiveness is likely to contribute to an increase in the use of seizure monitoring systems such as NightWatch by allowing more clinicians to prescribe such systems for their patients. While further refinement of monitoring technology and improvements in monitoring data analysis and transmission to specialist services is still needed, this development will be another important step towards embedding objective seizure monitoring in routine epilepsy care.

Treating status epilepticus after benzodiazepines fail

Supported by well-established business models, the development of new drug treatments for the ambulatory care of patients with epilepsy continues at a rapid pace. Apart from the novel substances themselves, the research underpinning their development provides insights into ictogenic and epileptogenic mechanisms. While our ability to predict what will work for whom continues to be limited, we gain at

least some understanding of modes of action, efficacy and side-effect profiles of new treatments for different types of epilepsy from premarketing studies.

This situation contrasts strongly with the development of new treatments for status epilepticus. Although pretty much every drug ever licenced for the chronic treatment of epilepsy has been tried in this setting, most status epilepticus treatment studies have been carried out independently of the drug development process. The financial rewards of developing new treatments for status epilepticus are much less certain than those that can be hoped for in relation to new drugs likely to be prescribed for months or years. Never mind the fact that there is an evident need for the development of better treatments for an epileptological emergency which continues to be associated with substantial mortality or secondary morbidity.

Most status epilepticus treatment studies have been carried out independently of the drug development process

We are still waiting for genuinely new treatments for status epilepticus to become available. However, several recent, fully powered, publicly funded trials have at least informed us how we should use some of the medications already available to us in the 40% or so of patients in whom first line treatment with benzodiazepines fail [Kapur *et al*, 2019; Appleton *et al*, 2020; Dalziel *et al*, 2019]. These head-to-head randomised studies were much needed, but, by virtue of their design, they had to focus on a limited number of drug options. What's more, they included levetiracetam (a drug not included on the WHO list of essential medications and therefore unavailable in many countries) but they did not include phenobarbitone (given that it's use has receded in many developed countries because of its potential to cause respiratory suppression).

While we continue to wait for new and better treatments for status epilepticus, my Editor's Choice from Seizure issue 102 aims to fill some of the knowledge gaps about the choices available for the treatment of status epilepticus when benzodiazepine treatment has failed. The systematic review, conventional and network meta-analysis by Puneet Jain *et al* [2022] based on 17 RCTs considered outcomes including seizure cessation within 60 minutes, seizure freedom for 24 hours, death, respiratory depression warranting intubation and cardiovascular instability. Phenobarbital and high-dose levetiracetam emerged as significantly superior to phenytoin with respect to seizure cessation within 60 minutes. Network ranking placed phenobarbital, high-dose levetiracetam and high-dose valproate on places one to three in terms of status cessation. In pairwise comparisons, phenobarbital was associated with a higher risk of need for intubation and cardiovascular instability while levetiracetam had a better safety profile than fosphenytoin. The fact that levetiracetam emerged as the "safest best" medication overall may provide an additional argument for the inclusion of this drug in the WHO list of essential medications. In the meantime, those clinicians only having access to phenobarbitone may console themselves with the fact that, with careful use, this oldest of the anti-seizure medications still in widespread use remains unsurpassed in terms of controlling status after benzodiazepines have failed.

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Improving care

Presentations from the ILAE British Branch conference

Kami Kountcheva condenses down some of the excellent presentations from the latest ILAE British Branch conference, held in October 2022 in Cardiff.

This year, one thing was for certain – everyone was thrilled to be meeting again in person at the ILAE British Branch conference. Taking place in Cardiff's City Hall, the meeting saw medical professionals from around the country gather to exchange thoughts, opinions, knowledge and expertise.

We share a summary of some of the fantastic talks at the meeting, looking at improving and advancing care.

Research

Research priorities

Dr Rhys Thomas, honorary consultant neurologist at Newcastle Hospitals NHS Foundation Trust, was first up to present during the session called, 'Are we at a tipping point for research into epilepsy?' Dr Thomas presented on the UK Priority Setting Partnership's (PSP) Top Ten research priorities launch.

Dr Thomas started off highlighting that epilepsy is a common condition, but is the subject of inequalities in research funding, with other conditions being allocated more funding than epilepsy.

The PSP went out to identify the top 10 priorities for research in epilepsy to help focus the funding requests and opportunities. The year-long project included all aspects of epilepsy, including causes, prevention, diagnosis, treatments, clinical management and SUDEP. The group left out dissociative seizures and anything not relevant in the UK.

The team carried out a survey of over 2,000 people to get the questions that people want answered. They returned around 5,500 research priorities, which the team summarised into 110 research questions and later reduced down to 57. The team put these out in another survey, which returned nearly 2,800 responses. This helped narrow the questions down to 25. The team then held a workshop to get these down to the 10 top priorities for research.

The top 10 priorities include SUDEP, personalised medicine, drug-resistant epilepsy and the impact of hormonal changes in women

The top 10 priorities include SUDEP, personalised medicine, drug-resistant epilepsy and the impact of hormonal changes in epilepsy in women.

Dr Thomas said it's not enough that the results are published in medical journals, but they need to be disseminated far and wide. Dr Thomas said we need new energy, new task forces and new bodies of work to answer these questions.

Opportunities for improvement

Prof Arjune Sen, consultant neurologist at The John Radcliffe Hospital, presented next on The National Institute for Health and Care Excellence (NICE) and the intersectoral global action plan (IGAP) on epilepsy and other neurological disorders 2022-2031.

Prof Sen explained that NICE is designed to level out disparity and eliminate the postcode lottery. He said inequity is even more evident as you move around the world. As an example, Prof Sen explained that Zimbabwe only has one neurologist in the country. They only have the older generation anti-seizure medicines ASMs available and their guidelines are based on NICE.

Prof Sen explained that he applied to be a part of NICE and found that it comprises a large team, which is well supported and diligent. The guidelines are split over two committees and take 75 committee meetings to update.

Their common purpose is to improve the care of people with epilepsy everywhere. Prof Sen stressed that guidelines are guidelines – they are recommendations to improve care throughout the national health service. They should allow optimal clinical judgement and they should be **aspirational**.

Prof Sen acknowledged that some of the guidelines may be unrealistic.

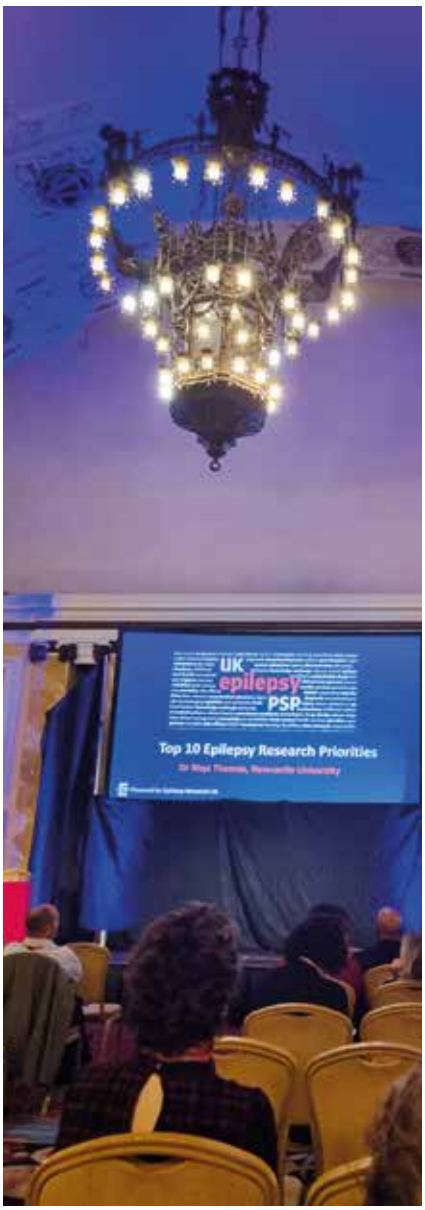

Figure 1. The PSP's top 10 research priorities.

The top 10

10 How can big data analysis, though artificial intelligence and machine learning, aid the diagnosis and management of epilepsy?

9 What causes drug-resistant epilepsy and how can it be best treated?

8 How can quality of life be improved for people with epilepsy, their families and carers, including those bereaved by epilepsy?

7 How do hormonal changes in women throughout the lifespan (eg puberty, pregnancy, menopause) impact epilepsy, and how can this impact be addressed?

6 How can tools, devices and biological markers be used to accurately predict and prevent seizures and the onset of epilepsy?

5 How can targeted, personalised medicine, such as gene therapy, be used to treat and/or prevent epilepsy?

4 How does epilepsy and epilepsy treatment impact neurodevelopment, and can this be managed or prevented?

3 What impact do epilepsy, seizures and anti-seizure medications have on brain health – including cognition, memory, learning, behaviour and mental health?

2 What underlying mechanisms cause epilepsy in children and in adults?

1 What are the causes and contributing factors of epilepsy-related deaths, including sudden inexpected death in epilepsy, and how can these deaths be prevented?

For example, the guidelines say referral should happen within two weeks after a first seizure or after a period of remission, EEG should be done within 72 hours, or MRI within six weeks. While this is unrealistic due to pressures on the health system, it's something to strive for, he said.

Prof Sen explained the guidelines can be used to leverage and demand the services you need in order to deliver that kind of care. He added that it's beholden on the clinicians to make these requests.

For areas that NICE doesn't include, Prof Sen said what is needed is high quality evidence and for this evidence to be published. He said future work should focus on inequalities in specialist care for people with epilepsy in the UK, with research on hard-to-reach or marginalised groups. With trials and publications, this can help inform future guidelines.

The World Health Organisation (WHO) has a vision and goal to make epilepsy more of a priority, with a global target of 75% of countries updating or adapting their priorities, strategies, plans of framework by 2031. Prof Sen added that epilepsy is used as an example by WHO to show how improvements can be done in other neurological conditions as well.

Collaborative research

Last up in the session, Prof Tony Marson, consultant neurologist and epileptologist at The Walton Centre, discussed a national research collaborative - #Every1EndingEpilepsy. This project aims to radically advance research into epilepsy through investment, collaboration and action.

Prof Marson started by saying that, currently, epilepsy care in the UK costs around £2bn. Prof Marson said this includes, for example, lots of hospital admissions and he highlighted that it's clear that there is a massive efficiency problem. He said we should be able to reduce the costs to the NHS, as we are currently wasting money in the way we deliver epilepsy care.

Research funding is currently unbalanced, with a lot of underinvestment in epilepsy. Prof

Marson said that people with epilepsy represent a huge population, and yet epilepsy has much less funding than other conditions, like Parkinson's disease and dementia, proportional to the population. But he added that we can't just say we need more money for research.

Instead, Prof Marson said that we're at the early stages of a journey to try to increase the funding for epilepsy research – a one-off "moon shot" for £60m from institutional funders.

The #Every1EndingEpilepsy project is initially looking to the strengths, knowledge and experience of epilepsy experts across the country in order to find the challenges and gaps currently in the way of increasing the capacity for fast-track epilepsy research.

Prof Marson said the project is in the process of stakeholder engagement and putting together a steering group. Their aim is to bring the community together across the pipeline from basic science through to implementation. They want to develop programmes of work and a roadmap to enable the project to move forward.

You can get involved in the project and find out more at epilepsyresearch.org.uk/every1endingepilepsy or by contacting angie.pullen@eruk.org.uk

Prof Sen explained that the guidelines can be used to leverage and demand the services you need in order to provide that kind of care

Non-convulsive status epilepticus

The Salzburg Consensus Criteria

Professor Sandor Beniczky, neurologist and clinical neurophysiologist at the Danish Epilepsy Centre (Dianalund), delivered the keynote talk of the conference in which he discussed the Salzburg Consensus Criteria for non-convulsive status epilepticus (NCSE) and its application in practice.

Prof Beniczky began by saying that the ILAE Task Force classifies status epilepticus (SE) along four axes – age, aetiology, EEG and semiology (detailed seizure description). He said that the semiology can help differentiate convulsive status epilepticus (CSE) from NCSE, depending on whether there are prominent motor symptoms or not. He added that CSE can be diagnosed without EEG but that NCSE nearly always needs an EEG to make or confirm the diagnosis.

The Salzburg Consensus Criteria aim to increase the diagnostic accuracy of NCSE. With these criteria, NCSE can be diagnosed if it is clinically suspected and the EEG shows epileptiform (spike, spike and wave or sharp wave) discharges with a frequency of more than 25 in 10 seconds ('fast' EEG changes) or epileptiform discharges with a frequency of less than 25 in 10 seconds in association with other clinical or EEG features.

The criteria also provide diagnostic information in those patients in whom there is a clinical suspicion of NCSE but without any epileptiform discharges. This is when the patient's EEG shows continuous rhythmic delta-theta activity with a frequency of more than 5 cycles in 10 seconds ('slow' EEG changes) and at least one of the three following features:

- Clinical and EEG improvement following the use of intravenous anti-seizure medications (ASMs)
- Subtle clinical features
- Typical spatiotemporal evolution

The criteria also define a final group, labelled as 'possible NCSE'. This is defined as patients with clinical fluctuation without evolution or EEG improvement without clinical improvement.

The team undertook a validation study to determine the diagnostic accuracy of the EEG criteria for NCSE. They studied 120 patients. Fifty

Further reading

Epilepsy Research UK. #Every1EndingEpilepsy. [online] Available at: https://epilepsyresearch.org.uk/every1-ending-epilepsy/ Accessed 18/11/22.

Goselink RJM, van Dillen JJ, Aerts M, *et al*. The difficulty of diagnosing NCSE in clinical practice; external validation of the Salzburg criteria. Epilepsia. 2019;60(8):e88-e92

Krogstad MH, Høgenhaven H, Beier CP, Krøigård T. Nonconvulsive status epilepticus: validating the Salzburg criteria against an expert EEG examiner. J Clin Neurophysiol. 2019;36:141-5.

Leitinger M, Beniczky S, Rohracher A, *et al*. Salzburg consensus criteria for non-convulsive status epilepticus—approach to clinical application. Epilepsy Behav. 2015; 49:158-63.

Monsson OS, Roberg LE, Gesche J, Beier CP, Krøigårdab T. Salzburg consensus criteria are associated with long-term outcome after non-convulsive status epilepticus. Seizure. 2022;99:28-35.

fulfilled the Salzburg Consensus Criteria and, of these, 42 had NCSE. Seventy did not fulfil the criteria and only one of them had NCSE. The criteria gave only one false negative and eight false positives. Prof Beniczky stated that this indicated a sensitivity of 97.7%, a specificity of 89.6% and the overall accuracy of 92.5%.

Prof Beniczky stated that their validation study indicated a sensitivity of 97.7%, a specificity of 89.6% and the overall accuracy of 92.5%.

Prof Beniczky also shared some results from external validation studies, which showed slightly different findings from his team's results. A retrospective study undertaken in Denmark [Krogstad *et al*, 2019] found a high agreement between the Salzburg Consensus Criteria and the reference standard. Another study from 2019 from the Netherlands [Goselink *et al*, 2019] investigated 191 patients. Only 12 had NCSE according to the Dutch team's own 'gold standard' criteria, and the group found a much lower sensitivity than that of Prof Beniczky's study, 67%, and a specificity of 89%. Prof Beniczky explained that this difference reflected the fact that the Dutch group had used a modified version of the Salzburg Consensus Criteria and that the statistical models used were not appropriate.

Prof Beniczky shared findings from a recent study published in Seizure [Monsson *et al*, 2022]. This showed that the 'fast', rather than the 'slow' electroencephalographic criterion for NCSE was statistically significantly associated with a better survival after two years of follow-up. In addition, patients classified as 'possible NCSE' had a better prognosis compared to patients fulfilling the Salzburg Consensus Criteria with either 'fast' or 'slow' EEG changes. The data presented by Monsson *et al*, are interesting and clearly have implications for the management of NCSE and require confirmation from further research. It must also be noted that there are numerous causes of NCSE and this is likely to influence whether patients fall into the 'fast' or 'slow' group.

Prof Beniczky concluded by stating that there is also a future for using neuroimaging as an additional prognostic factor in NCSE.

Presenters

Dr Rhys Thomas
Honorary consultant neurologist
Newcastle Hospitals NHS Foundation Trust

Prof Arjune Sen
Consultant neurologist
The John Radcliffe Hospital

Prof Tony Marson
Consultant neurologist and epileptologist
The Walton Centre

Prof Sandor Beniczky
Neurologist and clinical neuropsychologist
Danish Epilepsy Centre

Words by

Kami Kountcheva
Editor
Epilepsy Professional

Research update

Epilepsy Action health improvement and research manager, Tom Shillito shares updates from Epilepsy Action's research work

Epilepsy Action supports research and quality improvement projects in many different ways. We can provide information and advice, organise workshops and focus groups, provide Patient and Public Involvement (PPI) representatives, advertise projects to new participants, and disseminate results. Our PPI representatives come from our dedicated team of Experts by Experience, a group of volunteers who have epilepsy or care for someone with epilepsy, and are trained in research and quality improvement skills. We also recruit to research studies, focus groups and workshops from our members who have expressed interest in research.

We have recently run two focus groups for a video monitoring technology project. From a pool of over 200 interested volunteers, we selected twenty individuals who had experience of epilepsy healthcare and video telemetry. We held two groups, one for people with epilepsy and one for carers. At both groups we discussed their experiences of epilepsy care, any testing they'd experienced, how they feel about video telemetry, and their impressions of the new technology. The conversations were rich and insightful, and the feedback gathered will both help to shape the technology itself, and guide the way it may be implemented within the NHS.

We are also running a focus group alongside the South East Genomic Medicine Service Alliance, investigating experiences of genetic testing for people with epilepsy and their carers. This work is part of the National Nursing and Midwifery Genomics Transformation Programme: Epilepsy workstream. We will be discussing participants' experiences of genomic testing, what they have been offered and how they felt about it, if they understood the testing they underwent, the support they received, and how they feel the service could be improved. This will help to shape the future of genetic testing for people with epilepsy within NHS England.

Our Expert by Experience volunteers are currently giving feedback on some interview schedules investigating how NHS patients feel about Patient Reported Outcome Measures (PROMs). The aim of the project is to see how PROMs impact healthcare outcomes and value for money in healthcare, and these interviews will gather data about how patients and carers in the epilepsy service feel about PROMs, what they know about them, and if they feel they have an impact on healthcare. Our Experts by Experience are reviewing the interview schedules to make sure the topics and questions will make sense to people with epilepsy and their carers, that the questions will prompt useful answers, that they are relevant to people with epilepsy, and how they would feel if asked the questions. This will ensure the interviews conducted are as successful for the researchers, and enjoyable for the participants, as possible.

We also promote research projects to our members and encourage participation. We have been supporting a project that is investigating whether cognitive behavioural therapy delivered through an app can improve mental health outcomes in people with epilepsy. Recruitment has recently closed, with over 180 participants registering for the app. Of those, more than 120 were recruited directly through Epilepsy Action, either via our website or emails to members. Our recruitment success led to the researchers recruiting more than their target number of participants.

If you're interested in learning more about our research, and seeing how we can support you, please visit our website ***epilepsy.org.uk/professional/support-for-researchers***

Fighting for better

Life just doesn't seem to stop getting harder. We seem to have had 12 years of austerity, Brexit, COVID, war in Europe and now a cost-of-living crisis. Through this all, we work to try and do our best for our patients. But it takes its toll. In the NHS, we work for our patients. They have the expectation of care, free at the point of need and we do the best we can to deliver that with the resources we have.

But those resources have been stretched. They are stretched so far it often feels as if they are at the point of breaking.

This makes our jobs harder. It is hard enough in itself to be a healthcare professional. We are there to navigate people through some of the hardest parts of their lives. We make diagnoses that are devastating and disabling to people, and we want to do that compassionately, with the time and in a timeframe that the patients need to help them to adjust and come to terms with their new reality.

But budget cuts mean that those pathways are stretched. Job roles are left vacant. Waiting times go up. Patients wait longer and are understandably disgruntled about this. The time to respond to enquiries is longer. Many of us end up working late to get questions answered, we do more than we are paid for, we get home late. We do what we can, but our jobs get increasingly difficult. I am sad to say that I know more than a few epilepsy professionals who have left their profession with burnout.

Very few people come into the health professions just to make money, but we have a reasonable expectation to be able to live with some comfort. The Royal Collage of Nursing (RCN) estimate that nurses pay has fallen in real terms by 20% in the last 10 years and that there are nearly 50,000 unfilled registered nursing positions in England alone. That extent of a real term pay cut cannot be made up for by clapping on doorsteps.

It is, therefore, not surprising that the vote for strike action by the RCN has been successful. Unless the government changes its stance, the RCN members will be going on strike, and this will include many of our epilepsy specialist nurse colleagues.

In the short term, it is easy to argue that by striking, our colleagues will be endangering patients. But I think the opposite is true. The pay and conditions of all NHS workers have been degraded in the name of austerity and the services we are part of are held together by our good will. But good will only goes so far when you need to pay your mortgage and feed your children.

I support our colleagues in their strike. Without fighting for better pay and conditions for nurses and all those who work in health and social care, we will never get to a point where we are able to retain staff and build the responsive, compassionate services our patients with epilepsy need. Services that are also fair and compassionate to those who work within them.

Dates for the diary

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

2023

16-20 January
12th EPODES Advanced Course
Brno, Czech Republic
bit.ly/3UipCqX

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)
Madrid, Spain
bit.ly/3FIlgdw

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

8-13 October
10th Eilat Educational Course: Pharmacological treatment of epilepsy
Jerusalem, Israel
eilatedu.com

2024

3-8 March
4th International Training Course on Neuropsychology in Epilepsy
Lyon, France
bit.ly/3gLFWD4

5-8 May
Seventeenth Eilat Conference on new Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3u7Mzm6

Next issues:

Prof Patrick Kwan

Prof Kwan discusses self discontinuation of anti-seizure medications and managing this in patients.

Dr Joseph Anderson

Dr Anderson describes the use and importance of population level health monitoring in epilepsy.

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

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