epilepsy action

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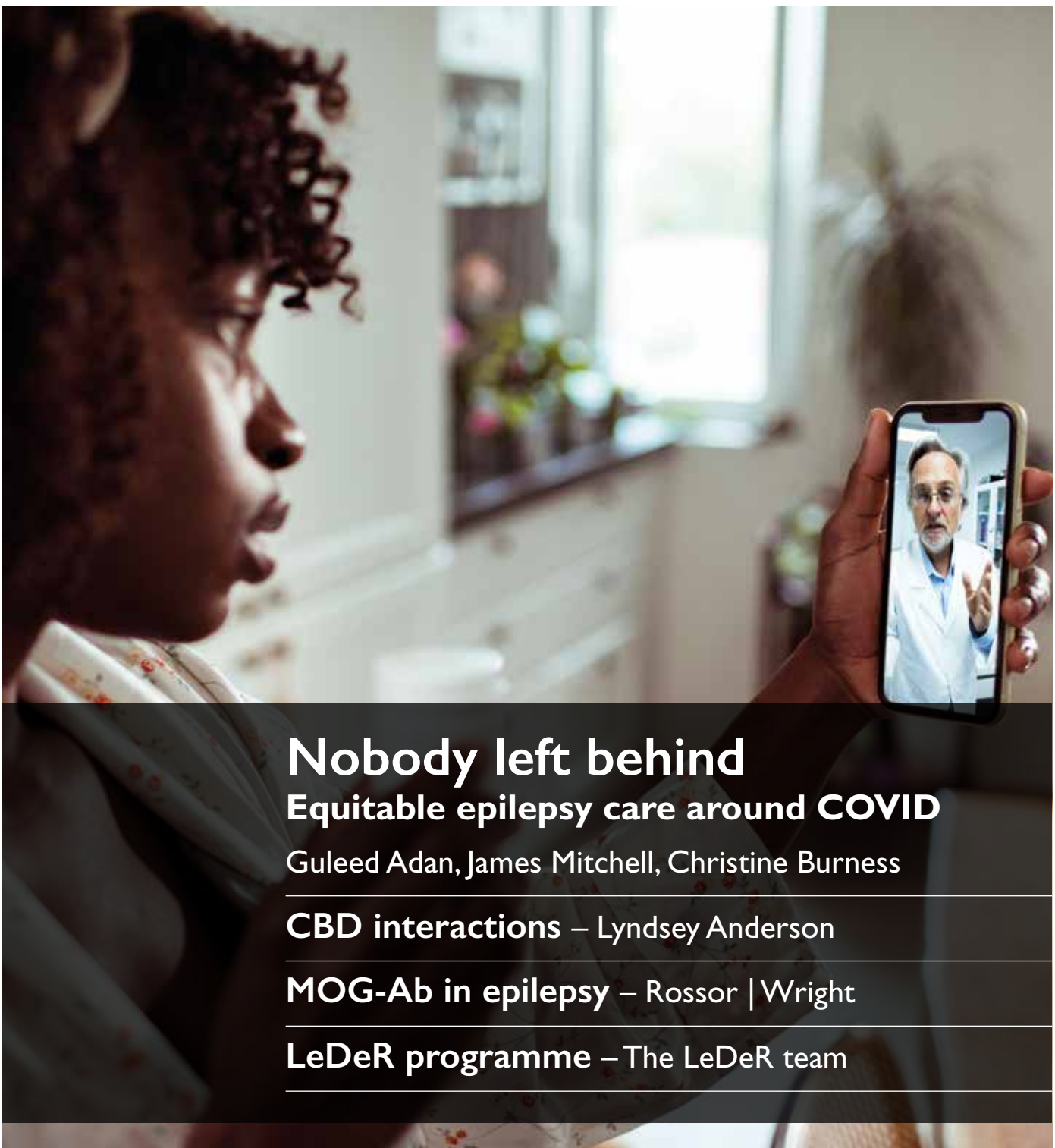

Nobody left behind
Equitable epilepsy care around COVID
Guleed Adan, James Mitchell, Christine Burness

CBD interactions – Lyndsey Anderson

MOG-Ab in epilepsy – Rossor | Wright

LeDeR programme – The LeDeR team

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LivaNova

At the turn of the year, I thought, "*2020 – that has a really positive ring to it. I think this is going to be a special year.*" How quickly that has changed. If you were playing 2020 key word Bingo, I'd expect to hear the likes of: 'bushfires', 'unprecedented', 'climate emergency', 'no deal Brexit', 'furlough', '#BlackLivesMatter', 'locust swarms', 'Prime Minister in intensive care' and 'murder hornets'. It has been quite a year and we are still only in September. With this in mind I think you will appreciate refocusing on our 'core business' – helping people with epilepsy.

Epilepsy experts are experienced in balancing risk and our greatest fear is that of a sudden death. The Learning Disabilities Mortality Review (LeDeR) process has been great at raising profile for people with intellectual disability and will undoubtedly be a valuable lever for change. There are gaps, as it is an England-only programme which focuses on inpatient death in people recognised ante-mortem to have an intellectual disability. However, there are stark findings, such as 19% of the 169 deaths from epilepsy were identified as being as a result of SUDEP. An excess was seen in males and people from a BAME background. If you are not already involved in LeDeR reviews locally at your Trust, why not consider volunteering and learn about the process?

In among service improvement, we need a little science – research can always bring hope. Here, Thomas Rossor and Sukhvir Wright discuss autoimmune causes of epilepsy and specifically anti-MOG in children's epilepsy. Myelin Oligodendrocyte Glycoprotein antibodies are better recognised and well described in cases of optic neuritis, neuromyelitis optica spectrum disorder or ADEM. You may be interested to read about their relationship with epilepsy in this review. We are always on the look-out for epilepsy syndromes that can be treated with more than anti-seizure medicines.

Not everything which is intuitive is correct. For example, are medications based on plants more natural and 'cleaner' than drugs created in a lab? When prescribing cannabidiol medication, specifically Epidyolex for seizures associated with Lennox-Gastaut and Dravet syndromes, it is beneficial to be aware of the relationships between cannabidiol and commonly prescribed anti-epileptic drugs. This is vitally important in the UK, as the cannabidiol licence insists that CBD is prescribed with clobazam – and there is a biologically relevant bi-directional interaction here. Read more from Lyndsey Anderson to see how you could make this interaction work for you and your patients.

And finally, a special article – 'Nobody left behind'. Epilepsy care in 2020 is different in light of lockdown restrictions and COVID19 fears, and we cannot ignore how much this has changed our services. Guleed Adan, James Mitchell and Christine Burness from the Walton team have captured the zeitgeist and brought together an article focussing on both the changes that have been forced upon us and the changes that we should seek to make. Providing practical advice about neglected or special groups, this is a high-class read for 2020.

My only wish? If only they also provided advice against murder hornets.

Rhys Thomas
Consultant neurologist
Chief medical adviser
Epilepsy Professional

contents

22
nobody left behind

Guleed Adan
James Mitchell
Christine Burness

Dr Adan, Dr Mitchell and Dr Burness discuss the epilepsy care provision needs of different groups of people with epilepsy and what the future of epilepsy services may look like

As we creep into September, things are starting to take the shape of some kind of normality. Families have reunited, pubs have reopened, 'staycationing' has taken off in a big way and parents have once again sent their children off for their first day at school.

Even as we tentatively stride back out into the world, everything still carries the battle scars of the COVID-19 global pandemic. We are staying at a distance, we are donning our masks and we are constantly sanitising our hands. This somewhat reflects the situation with epilepsy services in the wake of COVID. Services are starting to pick up and resume as before, all the while carrying with it the legacy of COVID in every video consultation and telephone appointment. On page 22, you will find our cover feature discussing optimising epilepsy services during and after COVID-19.

This issue, we also look at findings from the LeDeR programme around SUDEP in people with epilepsy and intellectual disability. The LeDeR team at the University of Bristol share their conclusions from their important work on page 28.

On page 10, you will find Dr Lyndsey Anderson's article describing some known interactions between CBD and other AEDs. This information becomes ever more important as patients become more and more interested in CBD treaments for epilepsy. Dr Rossor and Dr Wright also discuss the role of MOG-Ab in acute symptomatic seizures secondary to autoimmune encephalitis and in autoimmune epilepsy in their interesting article on page 16.

We hope you are doing well with the 'new normal'. Enjoy this issue!

Kami Kountcheva
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Call for urgent restart of epilepsy services

Epilepsy services need to resume as quickly and safely as possible, say leading epilepsy charities and health professionals. In a statement released in July, they have urged decision makers and clinicians to prioritise neurology, including epilepsy, as lockdown eases and services resume.

The coalition of organisations and neurologists includes the International League Against Epilepsy (ILAE), the International Bureau for Epilepsy (IBE) and the Epilepsy Nurses Association (ESNA). Epilepsy Action, SUDEP Action, Young Epilepsy and Epilepsy Scotland are also among the organisations involved, alongside a number of specialists, including consultant neurologist Dr Rhys Thomas and professor of neurology Prof Tony Marson.

The coalition says that health leaders need to act quickly to minimise additional risks for people with epilepsy, reverse reported falls in hospital attendance and prevent premature epilepsy-related deaths. It says at a minimum, people with suspected first seizures must have access to a consultation with an epilepsy expert. People should also be able to contact neurology services and receive a meaningful response.

Epilepsy Action chief executive Philip Lee said epilepsy services had understandably taken a back seat to maintain critical NHS capacity during the pandemic outbreak. However, he warned that current service provision could not be the 'new normal' for people with epilepsy.

Mr Lee said: "Health services were rightly reorganised at pace to maintain critical NHS capacity during the COVID-19 pandemic. The same pace and leadership initially shown, and subsequently demonstrated in restarting cancer and fertility services, must now be applied to restarting neurology services.

"We need to act quickly to minimise additional risks people with epilepsy continue to face. These include reduced access to services, telephone-only support, cancelled appointments and diagnosis delays."

The NHS response to the pandemic has had a negative impact on diagnosis in neurology services, the coalition warns. People with possible seizures have not been assessed with speed or had access to all the usual tests. There is a risk if people remain untreated. Every week, 21 epilepsy-related deaths are recorded in the UK, nearly half of which are thought to be avoidable.

Telephone consultations have replaced face-to-face appointments in many cases, but Mr Lee stresses that assessing the effects of a neurological condition can be very challenging over the phone. "It is not appropriate for this to be adopted as the 'norm' in the longer term unless there is solid medical evidence to support this and no likelihood of worsening health inequalities."

Epilepsy Action, Dr Thomas and Prof Marson have developed the statement with the support of the other members of the coalition. The document sets out expected service provision during the COVID-19 pandemic. It is hoped it will encourage clinicians and NHS decision makers to prioritise epilepsy services.

Families need detailed epilepsy information

Detailed epilepsy information is key for the wellbeing of families, a new study in *Epilepsy & Behavior* has found.

The authors of the review, Suzanne Nevin *et al*, sought to investigate whether parents of children with early-onset epilepsy had unmet needs for information. They also wanted to find out what people wanted to know and how they wanted the information to be delivered.

In the 11 studies included in the review, parents reported a need for "understandable, realistic and focused information". Information about comorbidities and emotional support was of particular priority. Parents said there weren't enough detailed information resources on early-onset epilepsy and said this hindered access to appropriate healthcare services. The researchers found that unmet informational needs led to more stress, poorer psychosocial outcomes and lower satisfaction levels.

The authors concluded that "healthcare professionals should be aware of the impact of a lack of epilepsy information on family wellbeing". They suggest that multipronged and tailored interventions can help give families the specific information they need.

You can find the full study at: *bit.ly/3gMpVqq*

Government apologises over 'public health scandals'

The UK government has apologised after the Independent Medicines and Medical Devices Safety Review called for a "fulsome apology" to the families affected by sodium valproate, Primodos and pelvic mesh.

This was one of nine "wide-ranging and radical" recommendations for improvements in the health system set out by the review team's report, *First Do No Harm*, published on 8 July. Other recommendations include the appointment of a Patient Safety Commissioner to advocate for patients and the establishment of schemes to meet the cost of additional care for those affected. The full list of recommendations are available at *immdsreview.org.uk*

The report follows a two-year review, chaired by Baroness Julia Cumberlege, into the "public health scandals" around the three medical interventions. The review aimed to determine what was known about the teratogenic effects of valproate by manufacturers, regulators, clinicians and policy makers. It further investigated what decisions were made and actions taken in light of this knowledge.

Baroness Cumberlege said: "I have conducted many reviews and inquiries over the years, but I have never encountered anything like this; the intensity of suffering experienced by so many families, and the fact that they have endured it for decades. Much of this suffering was entirely avoidable, caused and compounded by failings in the health system itself.

"We met with people, more often than not women, whose worlds have been turned upside down, their whole lives, and often their children's lives, shaped by the pain, anguish and guilt they feel as a result of Primodos, sodium valproate or pelvic mesh.

"We are urging the system to do what it should have done years ago, to help those who have suffered and put in place the processes that will enable it to learn from past mistakes so that we can spare other families from such anguish."

Link between gout and epilepsy

A new Taiwanese study has found that people who have gout have a higher risk of developing epilepsy.

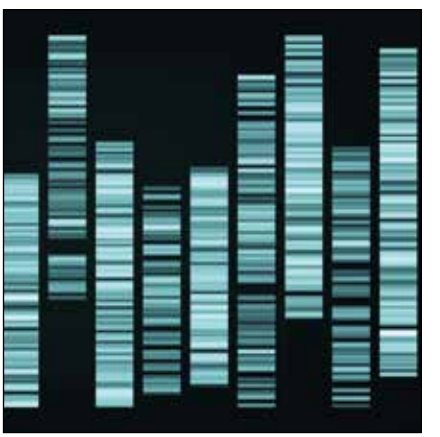
Dr Chen *et al* decided to study the link between gout and epilepsy as inflammation can be associated with both conditions.

The researchers studied 104,238 people aged over 20 years old, who were diagnosed with gout between 2000 and 2011. Compared with people without gout, who were matched for factors like age and sex, those with gout had a higher risk of developing epilepsy.

The study authors propose that either cytokines induced by the inflammation or the pain from gout itself could be the reason for this link with epilepsy. However, they say more research is needed.

The research is published in the journal *Medicine* and can be found at *bit.ly/34ItZ8S*.

Gap in genetics testing access



There is a gap in the diagnosis of genetic epilepsies in people with epilepsy and intellectual disability a new Spanish study suggests.

Published recently in the journal *Epilepsy & Behavior,* the study looked at the epilepsy units in two hospitals in Madrid. The researchers included people with idiopathic epilepsy and intellectual disability.

From the 124 people included in the study, around two-thirds (58%) had had advanced neuroimaging. Two-fifths (41%) had had prolonged video EEG and two-fifths (40%) had had a genetic test. A diagnosis of the cause was reached in less than one-fifth (18.5%) of people. The work to diagnose the cause of the condition was considered incomplete in two thirds of people (67%).

Study authors Aledo-Serrano *et al* concluded that a large proportion of patients with epilepsy and intellectual disability did not get access to modern diagnostic techniques. This was especially true for those whose seizures were controlled and those who were older.

Read the full study at *bit.ly/3hPLW9f*.

Discussions around valproate risks in pregnancy still not being had

More than two-fifths (44%) of women with epilepsy say they have not discussed the risks of taking valproate during pregnancy with their healthcare professional in the last 12 months. This is according to a new survey of 751 women published by three epilepsy charities: Epilepsy Action, Epilepsy Society and Young Epilepsy.

The survey also found that only two-fifths (41%) of respondents taking valproate said they had signed an Annual Risk Acknowledgement Form. The Medicines and Healthcare products Regulatory Agency (MHRA) says this should be completed every time a woman's treatment is reviewed by a specialist, at least annually.

The teratogenic effects of valproate medicines are well known and has been in the media over the last few years. In 2018, the MHRA changed its regulations, advising healthcare professionals that valproate medicine should not be given to women with epilepsy who can become pregnant, unless it is the only medicine that works for them. If it is, a Pregnancy Prevention Programme (PPP) must be put in place, where women are made aware of the risks and how to avoid becoming pregnant while on the medicine.

Discussions about these risks with healthcare professionals are key in helping women make informed choices about their health and that of any children they may have.

The survey showed that among women who had not received any PPP information, knowledge of the risks around valproate was much lower. One-third (34%) of these women were not aware that valproate can cause birth defects, compared to one-tenth (11%) of respondents overall. Also, over two-fifths (43%) of these women were not aware of the risks of learning and developmental problems, compared with just under one-fifth (18%) overall.

The charities behind the survey are pushing for more resources and encouragement for healthcare professionals – epilepsy specialists and others, such as GPs – to have these conversations.

Simon Wigglesworth, deputy chief executive of Epilepsy Action, said: "It's simply unacceptable that some women with epilepsy are still in the dark about the dangers of taking valproate in pregnancy.

"With a wealth of resources now available for health professionals to facilitate conversations, there is just no excuse for not explaining the risks to every woman taking valproate.

"Change needs to happen now to prevent babies being needlessly harmed and the devastating, life-long impact this has on families."

Some seizures linked to low melatonin levels

Basal melatonin levels are lower in children with epileptic seizures (ES) and electrical status epilepticus in sleep (ESES) compared to controls, a new *Epilepsy & Behavior* study shows.

Gurkan Tarcin et al wanted to investigate the relationship between melatonin levels and seizures. The study included 91 children who had melatonin level measured within half an hour of a seizure and on a seizure-free day.

Seizures were grouped based on diagnosis, semiology, aetiology, duration, EEG findings and response to treatments. The researchers looked at the melatonin levels in each group, and compared them with those of controls. Twenty-one children had ESES and their melatonin levels were compared with controls.

The study authors found that melatonin levels were lower in children with ES and ESES compared to controls. This was also true for some of the seizure sub-groups, except remote symptomatic aetiology, severe EEG findings and refractory epilepsy.

The authors say this is one of the largest studies into the link between melatonin levels and seizures. They conclude that there is a need for more research into the role of melatonin in ES and ESES, which they believe could lead to new treatments.

For the full study, visit: *bit.ly/2YSg4ZR*

Mozart's Sonata for Two Pianos in D calms epileptic activity in the brain

Listening to Mozart's Sonata for Two Pianos in D could reduce seizures in people with epilepsy by up to a third. This is according to new research from Canada, published recently in the journal *Epilepsia Open*.

Study authors Marjan Rafiee *et al* wanted to compare the effects of Mozart's sonata with that of a phase-scrambled control piece of music. They included 13 people with epilepsy in their research.

Each participant spent three months listening to the first six minutes of Mozart's sonata once a day and three months listening to the control music. Using paired t test, estimation statistics and plots, and Cohen's d, the researchers found that listening to Mozart's music once a day reduced seizures in people with epilepsy by around 35%.

The study authors acknowledged that their study was quite small. However, they said they hope it paves the way for further research looking at the mechanism behind this effect.

This study is available at *bit.ly/37UjBtT*.

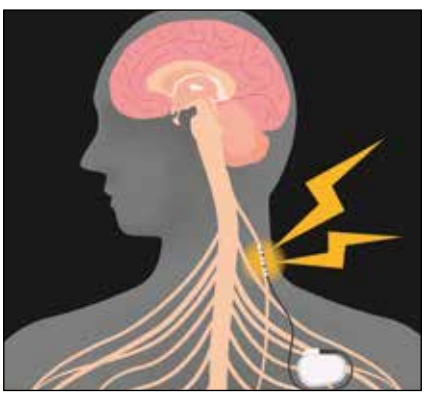
Another recent study from Thailand has looked at the effect of Mozart's sonata on interictal epileptiform discharges in children with epilepsy. The research, by Tanitnun Paprad *et al* included 32 children from birth to the age of 18.

Some of the children were in the treatment group and listened to eight minutes of Mozart's sonata while having an EEG recording. The other children were in the control group who had an EEG recording in a quiet room.

The results of this study are published in the journal *Epilepsy & Behavior*. They showed that interictal epileptiform discharges decreased in about two-thirds (67%) of the children in the treatment group. This is compared to two-fifths (42%) of the children in the control group. The study authors say the study should be replicated with more participants but that it showed the "considerable potential of music" in treating children with epilepsy.

You can find out more about this study at *bit.ly/2Z1mjtE*.

Long-term effectiveness of VNS



A new study from Turkey suggests that vagus nerve stimulation (VNS) is effective and safe for children in the long term.

Study authors Dilek Yalnizoglu *et al* investigated 58 children with drug-resistant epilepsy who had VNS put in between 1997 and 2018. The average follow-up was around six years, ranging from three months to 20 years.

The researchers found that just under half of the children had their seizures reduce by at least half, with three children becoming seizure free. The effectiveness of the VNS wasn't affected by the cause of the epilepsy, how long they had had epilepsy or what age they had the VNS put in. However, it appeared to work better in the children who had focal seizures. According to the researchers, more than half of the children also experienced an improvement in their quality of life.

The most common side-effects were voice changes and a pins-and-needles sensation. The research was published in the journal *Epilepsy & Behavior*.

Lyndsey Anderson

CBD interactions

How add-on CBD medicine interacts with AEDs

As patients become increasingly interested in cannabis-based medicines to treat epilepsy, Dr Lyndsey Anderson discusses some of the interactions observed between CBD and conventional anti-epileptic drugs. She shares more details on CBD and clobazam interactions from her recent study

Introduction

Cannabidiol (CBD) is the major chemical component in hemp varieties of cannabis. Unlike tetrahydrocannabinol (THC), CBD does not cause intoxication or euphoria. Because CBD lacks psychoactive effects, there is increasing interest in its potential to treat a wide variety of diseases, including epilepsy. A purified preparation of CBD, Epidyolex (named Epidiolex in the US), has been approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Epidyolex was first approved to treat seizures associated with the severe forms of childhood epilepsy: Dravet syndrome and Lennox-Gastaut syndrome. More recently, it has been approved in the US to treat Tuberous Sclerosis Complex. Regulatory approval for Epidyolex was granted following several Phase III randomized controlled trials (RCTs) showing that seizure frequency was significantly reduced in patients who took CBD in addition to their conventional anticonvulsants. While the RCTs show that CBD improves treatment outcomes, the mechanism of this improved efficacy is unclear. Is CBD exerting its own intrinsic anticonvulsant effect or could it be purely augmenting the anticonvulsant action of the co-administered

conventional treatments via a drug-drug interaction?

Adverse effect profile of CBD treatment

Clinical trials have shown that CBD has an acceptable safety profile with few adverse effects. A systematic review of RCT data by Chesney *et al* [2020] showed that the most common adverse effects reported for CBD have been gastrointestinal disturbances (diarrhoea and vomiting), decreased appetite, sedation and somnolence. However, when clinical trials for childhood epilepsy were excluded from the analysis, diarrhoea was the only adverse effect attributed to CBD. Serious adverse effects associated with CBD treatment were rare and included abnormal liver function tests and upper respiratory tract infections. [Dos Santos *et al*, 2020]. Again, these serious adverse effects were limited to clinical trials in intractable epilepsy patients. The greater number of adverse effects reported for CBD in RCTs for intractable epilepsy likely involves drug-drug interactions between CBD and anticonvulsants.

In the RCTs for childhood epilepsy syndromes, CBD was added to current treatment regimens, which include the simultaneous administration of multiple anticonvulsants (most often three anticonvulsants) [Devinsky *et al*, 2017; Greenwood *et al*, 2018; Thiele *et al*, 2018]. CBD was shown to cause pharmacokinetic drug-drug interactions in the RCTs.

Pharmacokinetic interactions between CBD and anticonvulsant drugs

Pharmacokinetic interactions are those where a drug can change the absorption, distribution, metabolism or excretion of another drug, changing its concentration in the body. Most of the evidence for pharmacokinetic interactions between CBD and anticonvulsants derives from studies in intractable childhood epilepsy patients. A preliminary study measured the effect of CBD on concentrations of commonly used anticonvulsants [Gaston *et al*, 2019]. While most anticonvulsant concentrations were not affected by CBD, concentrations of rufinamide, eslicarbazepine and zonisamide all increased with CBD. The numbers of patients examined in this study was relatively small, however, so potential interactions with CBD could have been overlooked. Whether CBD interacts with other commonly used anticonvulsants, such as lamotrigine, clonazepam and lacosamide, is largely unknown. More studies are needed to investigate possible pharmacokinetic interactions between CBD and commonly used anticonvulsants.

Of greatest concern are drug-drug interactions between CBD and the first-line therapies clobazam and valproic acid

Within the context of the intractable childhood epilepsies, effects of CBD on the first-line treatments clobazam and valproic acid and second-line treatments levetiracetam, topiramate and stiripentol have been well characterised. Research shows that CBD causes slight increases in plasma concentrations of both stiripentol and topiramate, although these increased concentrations remain within acceptable therapeutic ranges [Gaston *et al*, 2019; Morrison *et al*, 2019]. CBD does not appear to affect levetiracetam concentrations [Gaston *et al*, 2019].

Of greatest concern are drug-drug interactions between CBD and the first-line therapies clobazam and valproic acid. CBD does not affect plasma concentrations of valproic acid. However, a serious drug-drug interaction involving abnormal liver function tests has been observed [Dos Santos *et al*, 2020]. Thrombocytopenia (low blood platelet counts) has also been reported [McNamara *et al*, 2020]. Both of these side-effects are known consequences of valproic acid use.

When CBD is administered to patients taking clobazam, plasma concentrations of clobazam and its active metabolite, N-desmethylclobazam, significantly increase [Geffrey *et al*, 2015; Morrison *et al*, 2019]. This pharmacokinetic interaction between CBD and clobazam is believed to account for the sedation, somnolence and upper respiratory tract infection adverse effects reported in the RCTs, all recognized adverse effects of overdosing clobazam [Chesney *et al*, 2020; Dos Santos *et al*, 2020]. Because of this pharmacokinetic interaction, clobazam and N-desmethylclobazam concentrations should be monitored closely when patients commence CBD treatment and down-titration of clobazam dose may be required.

A negative connotation is often associated with drug-drug interactions because toxicity can result from pharmacokinetic interactions. However, drug-drug interactions can also be beneficial and even desired. For example, the mechanism of action of stiripentol involves a pharmacokinetic interaction with clobazam resulting in increased N-desmethylclobazam concentrations [Eschbach and Knupp 2019; Luszczki *et al*, 2010]. Since the recognised

interaction between stiripentol and clobazam is advantageous to its anticonvulsant effect, there has been speculation that the anticonvulsant effect of CBD may also simply reflect augmented clobazam exposure.

Pharmacodynamic interactions between CBD and anticonvulsants

Preclinical evidence shows that CBD has intrinsic anticonvulsant effects but an RCT in humans showing definitive anticonvulsant efficacy of CBD treatment alone has yet to be conducted. The focus on the pharmacokinetic interaction between CBD and clobazam has led most to overlook the possibility that CBD and clobazam might engender greater anticonvulsant effects through a pharmacodynamic interaction. Pharmacodynamic interactions are those where a drug alters the action of another drug without changing its concentration. In epilepsy, the effect can yield either an enhanced or an impeded anticonvulsant effect. While pharmacokinetic interactions can be easily assessed in patients by measuring drug concentrations, pharmacodynamic interactions are difficult to ascertain in humans and are usually inferred from preclinical models.

Some preclinical studies have assessed the effect of CBD on the action of anticonvulsants in animal seizure models. Collectively, CBD enhanced the anticonvulsant effects of some anticonvulsants but impeded the effects of others. In a recent study, CBD increased the potency of topiramate, oxcarbazepine, pregabalin, tiagabine and gabapentin [Socała *et al*, 2019]. However, CBD treatment interfered with the anticonvulsant action of levetiracetam. An earlier study showed that CBD increased the potency of phenytoin but, conversely, reduced the potency of clonazepam and ethosuxamide [Consroe and Wolkin 1977]. It is a challenge, even in *in vivo* preclinical studies, to dissociate pharmacodynamic interactions from pharmacokinetic interactions. In our recent study, we addressed the question of whether pharmacodynamic and pharmacokinetic interactions are involved in the combined anticonvulsant efficacy of CBD and clobazam in the treatment of Dravet syndrome.

CBD and clobazam – recent study findings

Because a pharmacokinetic interaction occurs between CBD and clobazam, many have questioned the anticonvulsant action of CBD with repeated suggestions that its efficacy is overstated. The anticonvulsant efficacy of CBD in the RCTs has been speculated to merely reflect CBD enhancing clobazam and N-desmethylclobazam concentrations. Using a variety of *in vitro* and *in vivo* approaches, including a genetic mouse model of Dravet syndrome, we aimed to address the nature of the interaction between CBD and clobazam in treating Dravet syndrome [Anderson *et al*, 2019].

Dravet syndrome is a severe childhood epilepsy syndrome characterised by seizures provoked by fever, spontaneous afebrile seizure types, cognitive deficits, behavioural disturbances and an increased risk for sudden unexpected death in epilepsy (SUDEP) [Dravet 2011]. More than 80% of Dravet syndrome patients have de novo heterozygous loss-of-function mutations in *SCN1A* [Dravet and Oguni 2013]. Heterozygous deletion of *Scn1a* (*Scn1a*+/-) in mice replicates the hallmark characteristics of Dravet syndrome. *Scn1a*+/- mice have seizures in response to an elevated body temperature, spontaneous seizures and premature death [Hawkins *et al*, 2017; Miller *et al*, 2014]. We examined how CBD and clobazam interacted against thermally-induced seizures, spontaneous seizures and mortality in Scn1a+/- mice. Additionally, we examined pharmacokinetic interactions between CBD and clobazam. We also investigated a potential pharmacodynamic interaction between CBD and clobazam at inhibitory $GABA_A$ receptors.

We found a significant drug-drug interaction between CBD and clobazam

Pharmacokinetic interaction between CBD and clobazam

Many believe that the pharmacokinetic interaction between CBD and

clobazam is the result of CBD inhibiting the cytochrome P450 (CYP) enzymes responsible for the metabolism of clobazam and N-desmethylclobazam, CYP3A4 and CYP2C19, respectively. Our research provided direct experimental evidence that CBD potently inhibited CYP3A4-mediated metabolism of clobazam and CYP2C19-mediated metabolism of N-desmethylclobazam at concentrations relevant to the therapeutic doses of CBD being administered to epilepsy patients [Anderson *et al*, 2019].

Next, we assessed the effects of CBD on the plasma and brain concentrations of clobazam and N-desmethylclobazam. We treated wildtype mice with clobazam alone or in combination with CBD. Consistent with the pharmacokinetic interaction observed in epilepsy patients, we found a significant drug-drug interaction between CBD and clobazam where CBD increased concentrations of both clobazam and N-desmethylclobazam.

Studies have highlighted pharmacokinetic and pharmacodynamic interactions between CBD and commonly used AEDs

Pharmacodynamic anticonvulsant interaction

We used the *Scn1a*+/- mouse model of Dravet syndrome to compare the anticonvulsant effects of CBD-clobazam combination therapy to the effects of each treatment alone. One surprising finding was that combination treatment with CBD and clobazam significantly improved the survival of *Scn1a*+/- mice [Anderson *et al*, 2019]. While only 44% of untreated controls survived, there was 89% survival of mice treated with both CBD and clobazam. CBD and clobazam treatments alone did not significantly affect survival.

Lastly, we investigated whether CBD could enhance the anticonvulsant effects of clobazam against hyperthermia-induced seizures, a model of febrile seizures that occur in Dravet syndrome. Both CBD and clobazam alone display anticonvulsant effects in this model. However, CBD co-treatment with clobazam displayed a significantly greater anticonvulsant effect compared to either drug administered alone. Importantly, the greater anticonvulsant effect was only observed when an anticonvulsant dose of CBD was used [Anderson *et al*, 2019]. A lower, sub-anticonvulsant dose of CBD did not promote a greater anticonvulsant effect, despite the presence of a pharmacokinetic interaction at this dose. This suggests the presence of a potential pharmacodynamic interaction between CBD and clobazam, and that the pharmacokinetic interaction alone is not sufficient to augment anticonvulsant effects.

Pharmacodynamic interaction between CBD and clobazam

The potential for a pharmacodynamic interaction begs the question of how this might occur at a molecular level. Could CBD and clobazam work cooperatively through a common molecular target in the brain? We have found previously that both clobazam and CBD enhance the activation of $GABA_A$ receptors to inhibit neuronal excitability. We next examined the combined effect of clobazam and CBD at $GABA_A$ receptors. We found evidence of a pharmacodynamic interaction as CBD and clobazam

together enhanced $GABA_A$ receptor activation to a significantly greater extent than either drug alone [Anderson *et al*, 2019].

Findings

Based on our preclinical study, the clinical efficacy of CBD in treating Dravet syndrome may not simply be explained by a pharmacokinetic interaction whereby CBD increases plasma concentrations of clobazam and N-desmethylclobazam. The pharmacokinetic interaction with clobazam, pharmacodynamic interaction at $GABA_A$ receptors and the action of CBD at complementary anticonvulsant pathways all likely contribute to CBD's efficacy in treating Dravet syndrome.

Conclusion

It is important to assess the potential for drug-drug interactions between CBD and conventional anticonvulsants as CBD is increasingly added to epilepsy treatment regimens. Clinical and preclinical studies have highlighted pharmacokinetic and pharmacodynamic interactions between CBD and commonly used anticonvulsants, with some interactions associated with increased adverse events. Because there is a propensity for drug-drug interactions with CBD co-administration, it is important to monitor anticonvulsant drug concentrations and for adverse events during CBD treatment. Despite the drug-drug interactions, research shows that CBD has intrinsic anticonvulsant activity and improves outcomes as an add-on therapy in intractable childhood epilepsies.

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Further reading

Anderson L L, Absalom N L, Abelev S V, Low I K, Doohan P T, Martin L J, Chebib M, McGregor I S, Arnold J C. Coadministered cannabidiol and clobazam: Preclinical evidence for both pharmacodynamic and pharmacokinetic interactions. *Epilepsia*. 2019;60:2224–2234.

Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, Freeman T P and McGuire P. Adverse Effects of Cannabidiol: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Neuropsychopharmacology*. 2020. 0:1-8.

Consroe P and Wolkin A. Cannabidiol - Antiepileptic Drug Comparisons and Interactions in Experimentally Induced Seizures in Rats. *Journal of Pharmacology and Experimental Therapeutics*. 1977. 201:26-32.

Devinsky O, Cross H J, Laux L, Marsh E, Miller I, Nabbout R, Scheffer I E, Thiele E A, Wright S and Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine*. 2017. 376(21):2011–20.

Dravet C. The Core Dravet Syndrome Phenotype. *Epilepsia*. 2011. 52 Suppl 2:3-9.

Dravet C and Oguni H. Dravet Syndrome (Severe Myoclonic Epilepsy in Infancy). *Handbook of clinical neurology*. 2013. 111:627–33

Eschbach K and Knupp K G. Stiripentol for the Treatment of Seizures in Dravet Syndrome. *Expert Review of Clinical Pharmacology*. 2019. 5:379-388.

Gaston T E, Bebin E M, Cutter G R, Ampah S B, Liu Y, Grayson L P and Szaflarski J P. Drug–Drug Interactions with Cannabidiol (CBD) Appear to Have No Effect on Treatment Response in an Open-Label Expanded Access Program. *Epilepsy and Behavior*. 2019. 98(Pt A):201–6.

Geffrey A L, Pollack S F, Bruno P L and Thiele E A. Drug-Drug Interaction between Clobazam and Cannabidiol in Children with Refractory Epilepsy. *Epilepsia*. 2015. 56:1246-51.

Greenwood S M, VanLandingham K E, Cross J H, Zuberi S M, Wirrell E C, Villanueva V, Checketts D, Patel A D, Roberts C, Devinsky O and Privitera M. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *New England Journal of Medicine*. 2018. 378:1888-97.

Hawkins N A, Anderson L L, Gertler T S, Laux L, George A L and Kearney J A. Screening of Conventional Anticonvulsants in a Genetic Mouse Model of Epilepsy. *Annals of Clinical and Translational Neurology*. 2017. 4:326-39.

Luszczki J J, Trojnar M K, Ratnaraj N, Patsalos P N and Czuczwar S J. Interactions of Stiripentol with Clobazam and Valproate in the Mouse Maximal Electroshock-Induced Seizure Model. *Epilepsy Research*. 2010. 90:188-98.

McNamara N A, Dang L T, Sturza J, Ziobro J M, Fedak Romanowski E M, Smith G C, Joshi S M, Leber S M, Carlson M, Robertson P and Shellhaas R A. Thrombocytopenia in Pediatric Patients on Concurrent Cannabidiol and Valproic Acid. *Epilepsia*. 2020. doi:10.1111/epi.16596.

Miller A R, Hawkins N A, Mccollom C E and Kearney J A. 2014. Mapping Genetic Modifiers of Survival in a Mouse Model of Dravet Syndrome. *Genes, Brain and Behavior*. 2014. 13:163-72.

Morrison G, Crockett J, Blakey G and Sommerville K. A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. *Clinical Pharmacology in Drug Development*. 2019. 8:1009-31.

Dos Santos R G, Guimarães F S, Crippa J A S, Hallak J E C, Rossi G N, Rocha J M and Zuardi A W. Serious Adverse Effects of Cannabidiol (CBD): A Review of Randomized Controlled Trials." *Expert Opinion on Drug Metabolism and Toxicology*. 2020. 16:517-526.

Socała K, Wyska E, Szafarz M, Nieoczym D and Wlaź P. Acute Effect of Cannabidiol on the Activity of Various Novel Antiepileptic Drugs in the Maximal Electroshock- and 6 Hz-Induced Seizures in Mice: Pharmacodynamic and Pharmacokinetic Studies. *Neuropharmacology*. 2019. 158:107733.

Thiele E A, Marsh E D, French J A, Mazurkiewicz-Beldzinska M, Benbadis S R, Joshi C, Lyons P D, Taylor A, Roberts C, Sommerville K and GWPCARE4 Study Group. Cannabidiol in Patients with Seizures Associated with Lennox-Gastaut Syndrome (GWPCARE4): A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial. *The Lancet*. 2018. 391(10125):1085–96.

epilepsy action

epilepsyspace.org.uk

The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

- Manage their epilepsy
- Feel less alone
- Increase their confidence
- Get the support they need

There's lots of epilepsy facts, tips and stories from young people sharing their experience.

The content is short and interactive. It's not all reading, there's video and young people can share their own quotes, stories and videos too.

It's been created with young people and reviewed by epilepsy nurses.

Take a look at:
epilepsyspace.org.uk

Get in touch:
learning@epilepsy.org.uk

Registered charity in England and Wales (No. 234343)

Epilepsy Action
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Find out more
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MOG-Abs in epilepsy

Myelin oligodendrocyte glycoprotein antibodies in paediatric epilepsy

Dr Thomas Rossor and Dr Sukhvir Wright describe the role of MOG-Abs in acute symptomatic seizures secondary to autoimmune encephalitis and in autoimmune epilepsy

Background

A role for autoimmune disease in the pathogenesis of epilepsy was proposed over a hundred years ago [Delezenne, 1900]. This was supported by studies in the later 20th century in which seizures were induced in animals by infusion of brain-specific antibodies into the brain, and ones where the responsiveness of some pharmaco-resistant epilepsies to steroid treatment was observed [Baram *et al*, 1996]. The term 'autoimmune epilepsy' has been used to describe a wide spectrum of disease in which seizures occur in the context of autoimmune disease. But, the International League Against Epilepsy (ILAE) has recently proposed the distinction between acute symptomatic seizures secondary to autoimmune encephalitis, and autoimmune-associated epilepsy [Steriade *et al*, 2020]. The former entity recognises seizures as a symptom of an acute neuroinflammatory presentation, which may not fulfil the definition of epilepsy as an enduring predisposition to seizures. The latter encompasses the lasting predisposition to seizures that may occur for a number of reasons in the context of autoimmune brain disease.

While symptomatic seizures in the context of autoimmune encephalitis are well recognised, evidence to support isolated seizures being a manifestation of autoimmune brain disease is limited to case series and case reports [Viaccoz *et al*, 2014]. The most common presentation of seizures in the context of autoimmune disease is in adult limbic encephalitis, and, even here, the seizures are usually associated with encephalopathy or cognitive decline [Irani *et al*, 2011].

MOG-Abs were detected in a large proportion of children presenting with ADEM, revealing a distinct phenotype

Over the last few years, the role of myelin oligodendrocyte glycoprotein antibodies (MOG-Abs) in seizures and epilepsy has been explored in a number of studies and reports. MOG is a protein expressed in the outermost layer of the myelin sheath. The history of MOG-Ab demonstrates the challenges of interpreting the clinical significance of antibody assays. Initially proposed as a biomarker in multiple sclerosis, early assays detecting antibodies to the MOG protein were neither sensitive nor specific to multiple sclerosis (MS) or other neurological conditions [Ramanathan, Dale and Brilot, 2016]. This changed when cell-based assays were employed, in which only antibodies to the exposed portion of the protein in its native conformational state were detected. In a multicentre comparison of cell-based assays, an additional benefit to the positive predictive value was seen in live cell based assays over a fixed cell-based assay [Waters *et al*, 2019]. These assays were used with specific secondary antibodies to aid detection in MS and non-MS demyelinating disease patient cohorts. This led to the detection of MOG-Abs in a large proportion of children presenting with acute disseminated encephalomyelitis (ADEM), revealing a distinct phenotype of MOG-Ab associated ADEM [Baumann *et al*, 2015; Ramanathan, Dale and Brilot, 2016; Rossor *et al*, 2019]. MOG-Ab associated ADEM may be linked to a higher risk of seizures at presentation, and a higher risk of post-ADEM epilepsy [Rossor *et al*, 2019]. Nonetheless, these children would have evidence of encephalopathy by definition as part of the diagnosis.

While the role of MOG-Abs has been well recognised in a large

proportion of cases of ADEM, the recognised phenotype of MOG-Ab associated disease (MOGAD) continues to extend. It has been well described in cases of optic neuritis (ON), neuromyelitis optica spectrum disorder (NMOSD) and transverse myelitis (TM). The phenotype has expanded to also include a number of presentations with seizures in both adults and children, details of which are explored below.

Acute symptomatic seizures secondary to autoimmune encephalitis

Symptomatic seizures may be more common in disease associated with MOG-Abs compared to antibody negative disease, and disease associated with other antibodies. In a prospective study of children with both demyelinating syndromes and encephalitis, MOG-Abs were more common than all other neuronal antibodies combined [Armangue *et al*, 2020]. In twenty-two children with non-ADEM autoimmune encephalitis, 14 developed seizures.

In a retrospective study of 74 children with ADEM, 14 of the 16 children presenting with seizures were MOG-Ab positive [Rossor *et al*, 2019]. This further implicates MOG-Abs in the development of acute symptomatic seizures.

MOG-Abs can cause inflammation in the spine and optic nerves in the condition NMOSD, very similar to that caused by antibodies to Aquaporin 4 (AQP4-Ab). In a retrospective study of adult patients, five of 34 patients with MOG-Abs presented with seizures, four of those with encephalopathy. All five had abnormal MRI with cortical and subcortical changes. In contrast, only one of 100 patients with AQP4 had seizures, and it was an individual with a long-standing history of focal epilepsy [Hamid *et al*, 2018]. A normal MRI scan suggested MOG-Abs may induce a greater susceptibility to seizures.

Post-ADEM epilepsy

Seizures are well reported with the acute presentation of ADEM or autoimmune encephalitis [Hamid *et al*, 2018; Rossor *et al*, 2019], but the development of a subsequent vulnerability to unprovoked seizures may be associated with MOG-Abs. In a retrospective study of 74 children with ADEM, those with MOG-Abs were more likely to go on to develop post-ADEM epilepsy [Rossor *et al*, 2019]. The mechanisms by which post-ADEM epilepsy may occur are varied. It is possible that inflammation may result in scarring and epileptogenic foci. Equally possible is that the ongoing seizures may reflect active inflammation similar to that hypothesised in the context of isolated seizures. In the study, it was noted that the seizures in those children with post-ADEM epilepsy were relatively easily controlled, with only one child requiring dual anti-epileptic therapy. Nonetheless, the question remains as to whether, in some children with ongoing seizures after ADEM, this is a process that may be amenable to immune modulation, and be a true autoimmune epilepsy. This is a challenging clinical question, as antibody titres in children presenting with MOGAD do not predict relapse risk [Hennes *et al*, 2017]. In some studies, persistence of MOG-Ab has been associated with a relapsing disease course [Hennes *et al*, 2017]. But, recent data suggest that patients with monophasic disease may remain seropositive for many years, while patients who become seronegative may relapse and become seropositive again [Cobo-Calvo et al, 2019; Waters *et al*, 2020]. Therefore, the extent to which MOG-Abs are contributing to morbidity at any time is uncertain. Reports of recurrence of seizures following a steroid taper may add some support to the argument for a role of inflammation in epilepsy in these patients [Gutman *et al*, 2018; Ramanathan *et al*, 2018; Wong *et al*, 2018].

In a sudy of 74 children with ADEM, those with MOG-Abs were more likely to go on to develop post-ADEM epilepsy

Isolated seizures

Recently, there have been cases reported of children presenting with isolated seizures in the absence of encephalopathy, eye or spinal signs suggestive of the above disorders, in whom MOG-Ab is subsequently found to be positive [Tsuburaya *et al*, 2015; Foiadelli *et al*, 2020]. Often, this is only recognised retrospectively when a child presents, months or years after the initial seizure, with the more recognised inflammatory or demyelinating syndromes above. This raises the question as to whether MOG-Ab associated seizures may be a cause of autoimmune associated epilepsy, rather than acute symptomatic seizures secondary to autoimmune encephalitis with the expected associated encephalopathy or MRI changes.

In 2015, a Japanese case report was published in which recurrent optic neuritis was described in a seven-year-old boy with MOG-Abs [Tsuburaya *et al*, 2015]. It was noted that he had also had a single cluster of focal seizures. A brief literature review demonstrates an increasing number of children with isolated seizures being found to have MOG-Abs. The first series of four children with isolated seizures and normal MRIs were reported by Ramanathan *et al*. in 2019, all of whom went on to develop ADEM [Ramanathan *et al*, 2019]. A further two children were reported in 2020 with isolated seizures. One of them had an MRI scan of the brain consistent with ADEM at presentation and the other had a normal scan at the time of seizure but presented with ADEM one month later [Foiadelli *et al*, 2020]. As children presenting with ADEM and MOGAD may have radiological lag, it is possible that a normal scan at early presentation with seizures may miss a diagnosis of ADEM.

With growing awareness, sentinel events, often years before a presentation with demyelination, are being recognised. The question for clinical practice is whether MOGAD should be considered in the differential of a child presenting with isolated seizures. At present, the incidence of MOGAD is unknown. MOG-Ab testing in a child presenting with isolated seizures is not routine clinical practice. Where MOG-Ab has been identified, it is often in retrospect, when a child presents later with a more defined MOG-Ab associated phenotype. In those cases, serum from the first presentation may then be analysed. Data from children with MOG-Ab associated ADEM suggest that around half will relapse. If a similar proportion of children with hypothetical MOG-Ab associated isolated seizures were to have a monophasic disease course then this could represent a large number of children in whom MOG-Abs may have played a role, but this would never be identified. However, in these children, the course is likely to be benign and identification of the antibody unlikely to lead to a change in clinical management.

It is notable that those children presenting with isolated seizures associated with MOG-Abs have predominantly had focal semiology, and these occur for a discrete time period. It is likely that these events are the manifestation of a small degree of irritability, secondary to inflammation, that is undetectable on MRI, and self-limiting. More marked inflammation with more sustained seizures would therefore be more likely to result in an ADEM or cortical encephalitis type picture, and a stronger indication for MOG-Ab testing. For the self-limiting course, immune modulation would probably not be indicated. The significance of antibody titres would only be relevant at subsequent relapse when the diagnosis is more likely to be made.

Glossary

Mog-Abs – *myelin oligodendrocyte glycoprotein antibodies*
MOGAD – *MOG-Ab associated disease*
ON – *optic neuritis*
NMOSD – *neuromyelitis optica spectrum disorder*
TM – *transverse myelitis*
AQP4 – *Aquaporin 4*
ADEM – *acute disseminated encephalomyelitis*
EPC – *Epilepsia partialis continua*

Vignette

- A 12-year-old girl presents drowsy and confused to her local emergency department. In the department, she had a prolonged generalised tonic-clonic seizure requiring phenytoin to terminate

Acute symptomatic seizures secondary to autoimmune encephalitis

- She had an unremarkable past medical history, other than an admission for two focal seizures 18 months previously. She had undergone MRI brain at the time which was reported normal. CSF was acellular with negative cultures. EEG showed left fronto-temporal sharpened waves but no epileptiform discharges. She was commenced on carbamazepine after the second focal seizure with good control and had been seizure free since

Isolated seizures

- On this admission she was clinically encephalopathic. She had brisk lower limb reflexes, with no bladder or bowel involvement
- MRI brain and spine was performed which showed symmetric poorly demarcated fluffy white matter lesions. MRI spine showed subtle signal change in the cervical region. EEG showed generalised slowing. CSF showed 7 white cells /mm^3. A diagnosis of ADEM was made and she was commenced on IV methylprednisolone, followed by a tapering course of oral prednisolone. MOG-Abs were detected in the serum at a titre of 1:1280 on a live cell-based assay (Oxford Neuroimmunology; secondary antibody anti-IgG (H&L; Heavy and Light chains))
- Four months after discharge she presented again with a right-sided focal motor seizure with secondary generalisation lasting five minutes. MRI brain was repeated which showed resolution of the previous changes. CSF was acellular. Carbamazepine dose was increased and she was discharged. She has had two further seizures since and remains under follow-up with good seizure control on a single anti-epileptic drug

Autoimmune associated epilepsy

MOG-Abs and other seizure disorders

MOG-Abs have been reported in the context of other epilepsies. Epilepsia partialis continua (EPC) is a particular persistent and pharmacoresistant focal epilepsy, which has been reported in the context of MOGAD [Katsuse *et al*, 2020]. EPC is more commonly seen in Rasmussen encephalitis (RE), a progressive unilateral cerebral cortical encephalitis.

A Japanese study reported four cases in adults of unilateral cerebral cortical encephalitis with seizures, which was associated with positive MOG-Abs. The encephalitis was steroid responsive and followed a benign course [Ogawa *et al*, 2017]. This included a patient with EPC, which has also been reported in the context of MOGADs in children [Katsuse *et al*, 2020].

Conclusion

MOG-Abs are associated with a broad spectrum of clinical presentations, some of which include seizures. When seizures are present, this is frequently in the context of significant clinical manifestations of encephalopathy, radiological evidence of inflammation or demyelination, and other biomarkers suggestive of an autoinflammatory condition that may provoke investigation for antibodies. The spectrum of MOGAD is wide and continues to expand as availability of testing increases along with clinician awareness.

While recognition of the MOGAD spectrum has increased dramatically in the last decade, the pathogenicity and mechanism by which MOG-Abs may be epileptogenic remains uncertain. There is an urgent need for further studies in this area.

The long-term outcomes for children with MOGAD also remain uncertain. There appears to be a higher risk of epilepsy following ADEM associated with MOG-Abs, and it may be appropriate to counsel families accordingly. Nonetheless, the majority of children with ADEM do not develop epilepsy, and caution must be exercised interpreting the results of the retrospective studies to date.

While studies evaluating crude measures of disability have encouraged a cautiously positive prognosis for many children with MOG-Abs, there is evidence of a far greater cognitive burden for children with autoimmune brain disease as compared to adults [Wright and Wood, 2020]. Future prospective studies must include detailed neuropsychological testing as an outcome.

The possibility of MOG-Abs being a factor in the presentation of isolated seizures opens the possibility of an epilepsy in which the underlying cause may be treatable. It is, as yet, unclear the extent to which otherwise asymptomatic MOGAD contributes to the presentation of

children with epilepsy. Of the reports, it appears that most children presenting like this will be unusual in that seizures are predominantly focal, MRI abnormalities relatively common, and many will present with a subsequent event making the diagnosis clearer. In the context of such a presentation, testing for MOG-Abs may be of benefit. In contrast, the yield is likely to be low in a child presenting in the manner of a generalised epilepsy of unknown cause.

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Further reading

Armangue T. *et al.* (2020) Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. *The Lancet Neurology*, 19(3), pp. 234–246.

Baram T Z. *et al.* (1996) High-dose corticotropin (ACTH) versus prednisone for infantile spasms: A prospective, randomized, blinded study. Pediatrics. NIH Public Access, 97(3), pp. 375–379. [online]Available at: */pmc/articles/PMC3100715/?report=abstract* (Accessed: 17 July 2020).

Baumann M. *et al.* (2015) Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. *Journal of Neurology, Neurosurgery and Psychiatry*. 86(3), pp. 265–272.

Cobo-Calvo A. *et al.* (2019) Usefulness of MOG-antibody titres at first episode to predict the future clinical course in adults. *Journal of Neurology*. 266(4), pp. 806–815.

Delezenne, C. (1900) Sérums néurotoxiques. *Ann Inst Pasteur*. 14, pp. 686–704.

Foiadelli, T. *et al.* (2020) Seizures and myelin oligodendrocyte glycoprotein (MOG) antibodies: Two paradigmatic cases and a review of the literature. *Multiple Sclerosis and Related Disorders*.

Gutman J M. *et al.* (2018) Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in patients with optic neuritis and seizures. *Journal of the Neurological Sciences*. 387, pp. 170–173.

Hamid S H M. *et al.* (2018) Seizures and encephalitis in myelin oligodendrocyte glycoprotein IgG disease vs aquaporin 4 IgG disease. *JAMA Neurology. American Medical Association*. 75(1), pp. 65–71.

Hennes E M. *et al.* (2017) Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. *Neurology*. 89(9), pp. 900–908. doi: 10.1212/WNL.0000000000004312.

Irani S R. *et al.* (2011) Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Annals of Neurology*. 69(5), pp. 892–900.

Katsuse K. *et al.* (2020) Epilepsia Partialis Continua as an Early Sign of Anti-Myelin Oligodendrocyte Glycoprotein Antibody-positive Encephalitis. *Internal medicine (Tokyo, Japan)*. 59(11), pp. 1445–1449.

Ogawa R. *et al.* (2017) MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. *Neurology: Neuroimmunology and NeuroInflammation*. 4(2).

Ramanathan S. *et al.* (2018) Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *Journal of Neurology, Neurosurgery and Psychiatry*. 89(2), pp. 127–137.

Ramanathan S. *et al.* (2019) Isolated seizures during the first episode of relapsing myelin oligodendrocyte glycoprotein antibody-associated demyelination in children. *Developmental Medicine and Child Neurology*. 61(5), pp. 610–614.

Ramanathan S. *et al.* (2016) Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. *Autoimmunity Reviews*. pp. 307–324.

Rossor T. *et al.* (2019) Early predictors of epilepsy and subsequent relapse in children with acute disseminated encephalomyelitis. *Multiple Sclerosis Journal*.

Steriade C. *et al.* (2020) Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia*. p. epi.16571.

Tsuburaya R S. *et al.* (2015) Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in a Japanese boy with recurrent optic neuritis. *Brain and Development*. 37(1), pp. 145–148.

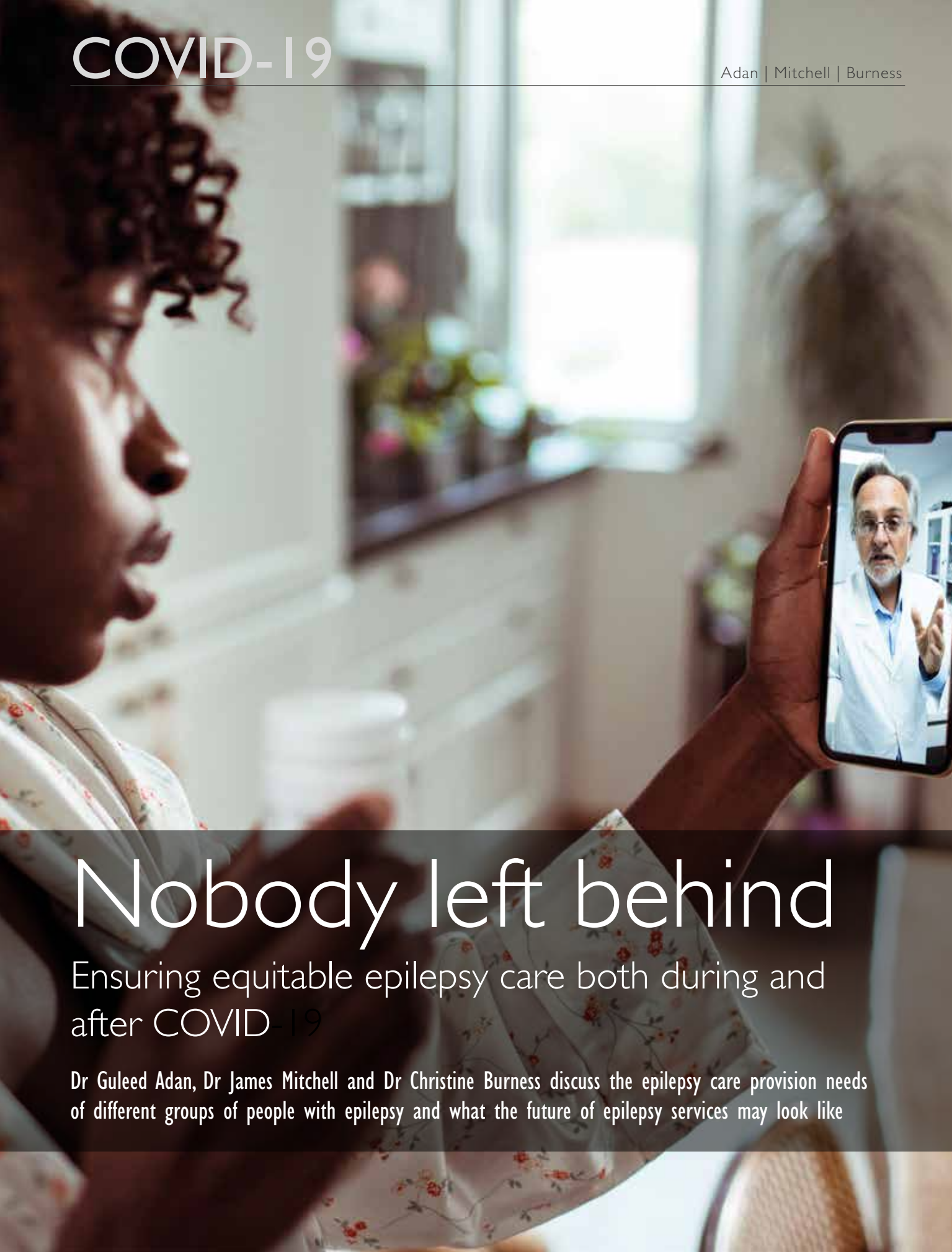
Viaccoz A. *et al.* (2014) Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology*. 82(7), pp. 556–563.

Waters P. *et al.* (2020) Serial Anti-Myelin Oligodendrocyte Glycoprotein Antibody Analyses and Outcomes in Children with Demyelinating Syndromes. *JAMA Neurology*. 77(1), pp. 82–93.

Waters P. J. *et al.* (2019) A multicenter comparison of MOG-IgG cell-based assays. *Neurology*. 92(11), pp. E1250–E1255.

Wong Y Y M. *et al.* (2018) Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. *European Journal of Neurology*. 25(5), pp. 782–786.

Wright S K and Wood A G. (2020) Neurodevelopmental outcomes in paediatric immune-mediated and autoimmune epileptic encephalopathy. *European Journal of Paediatric Neurology*, 24, pp. 53–57.



Nobody left behind

Ensuring equitable epilepsy care both during and after COVID-19

Dr Guleed Adan, Dr James Mitchell and Dr Christine Burness discuss the epilepsy care provision needs of different groups of people with epilepsy and what the future of epilepsy services may look like

The COVID-19 pandemic has led to considerable changes in how we deliver epilepsy care in centres all over the world [Adan, Mitchell and Marson, 2020; French *et al*, 2020]. It is likely that many of these changes will persist, ensuring healthcare services adapt to the legacy of the pandemic to continue providing optimal care for people with epilepsy. In the acute phase of the response, all non-urgent clinical activity was either cancelled or postponed. This included, but was not limited to, routine epilepsy follow-up, inpatient video telemetry and epilepsy surgery. These changes were essential to continue a safe service. This was because many neurologists and specialist nurses were redeployed to less familiar areas, such as the intensive care units to support their colleagues providing acute clinical care. As the initial wave of the pandemic subsided, we saw the cautious reintroduction of most epilepsy services as specialists were eventually released from their secondment to these unfamiliar roles. The acute reaction from neurology services under both local and national guidance from the Association of British Neurologists [Mummery and Kipps, 2020] to the pandemic should be commended, as it was both swift and robust. However, as we enter the next phase of the NHS response to COVID-19, all chief executives of NHS Trusts have recently been instructed to "accelerate the return of non-COVID health services" [NHS England, 2020]. Even prior to this mandate from NHS England, we have once again seen the successful and safe delivery of epilepsy care return to specialist centres across the country. This is largely thanks to the successful lobbying from several epilepsy bodies and eminent UK based epileptologists [Epilepsy Action, Marson and Thomas, 2020].

This model of healthcare is unlikely to be universally accessible or appropriate for all people with epilepsy

Much of this reintroduction of services has been facilitated by the rapid adoption of remote clinical models of delivery where possible, particularly the use of telemedicine [Brigo *et al*, 2020]. Specialised digital audio-visual technology is able to facilitate remote clinical consultations with both new and follow-up epilepsy patients. This reduces the risk of coronavirus exposure to both patients and healthcare staff that would come with face-to-face consultations. Telemedicine is by no means a novel concept in epilepsy care, with longstanding successful use of telephone clinical encounters by physicians and nurse specialists in particular [Smith, 2016]. The key difference between remote clinical service provision prior to COVID and present practice is that telemedicine has been promoted from being an adjunctive part of clinical care for people with epilepsy to the dominant means of care delivery. It is important that this is highlighted, as it is possible that this model of healthcare is unlikely to be universally accessible or appropriate for all people with epilepsy. We will highlight the groups of people with epilepsy that may require some additional consideration in the way we deliver epilepsy care during the pandemic and as we move into a post COVID-19 era.

Pregnancy and pre-conception counselling

Pregnant women with epilepsy are a particularly high-risk group, in whom the benefit of a face-to-face consultation, if timed correctly, may outweigh the risk of exposure to the virus. For example, an epilepsy review conducted on a day when these women are already attending the hospital for planned essential antenatal care would minimise additional exposure and travel. There is established consensus for coordinated multidisciplinary care between

epilepsy clinicians and obstetricians to improve outcomes in these patients [Bhatia, Adcock and Mackillop, 2017]. During this pandemic it is arguably of even greater significance to embrace collaborative working, and an accurate shared database of pregnant women with epilepsy between epilepsy and obstetric services is imperative. This cohort is also more likely to require plasma anti-epileptic drug (AED) levels compared to other people with epilepsy, due to the altered pharmacokinetics of AEDs during pregnancy [Tomson, Landmark and Battino, 2013]. As such, provisions for safe venepuncture should be in place where clinically indicated. The provision of epilepsy services for these women needs to be balanced with their increased risk of COVID-19, reflected in the placing of all pregnant women in the 'vulnerable group' by the UK's chief medical officer on 16 March 2020 [Public Health England, 2020*b*]. Clearly, the shape of the service should be tailored to the individual risk profile of the mother. Those from black and minority ethnic (BAME) groups and those in their third trimesters are at greatest risk of both contracting COVID-19 and having severe forms of the disease. Decisions surrounding how care should be delivered in this circumstance should be made in partnership with pregnant women and their epilepsy and obstetric clinicians.

The 2015 MBRRACE-UK report highlighted that 86% of women with epilepsy who died of sudden unexpected death in epilepsy (SUDEP) had not received pre-conception counselling [Knight *et al*, 2009]. In light of this, pre-conception counselling for all women with epilepsy is now seen as part of good clinical practice and is associated with improved epilepsy and non-epilepsy related outcomes for both mother and baby [Winterbottom *et al*, 2014; Shepley, 2016]. It is essential that these critical conversations continue to take place to ensure standards for women with epilepsy do not regress.

On a related topic, it is also important to highlight that the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued temporary guidance for specialists to support females of childbearing potential taking sodium valproate during the COVID-19 pandemic [MHRA, 2020]. In particular, this temporary guidance has been published by the MHRA to support adherence to the Pregnancy Prevention Programme (PPP) requirements for "girls (of any age) and women of childbearing potential taking valproate during the pandemic, particularly patients who are shielding due to other health conditions". The temporary guidance encourages that annual valproate reviews are not delayed because of COVID-19 and that valproate initiation should be via face-to-face consultation only, except where patients are shielding. It also says provisions should be made for home pregnancy testing where necessary and that all adverse drug reactions should continue to be reported using the Yellow Card Scheme. This is all the more pertinent in light of the significant recommendations regarding valproate made in the recently published report of The Independent Medicines and Medical Devices Safety Review [Cumberlege, 2020].

The pandemic has laid bare many of the health and wider inequalities that persist in our society

Epilepsy surgery and vagus nerve stimulators

There will undoubtedly have been a number of planned epilepsy surgeries that have been postponed. Surgery may be curative for a proportion of patients with drug resistant focal onset epilepsy [Jobst and Cascino, 2015]. For some, ongoing seizures due to delayed epilepsy surgery may result in significant morbidity and increased mortality, given the elevated risk of SUDEP in those with intractable seizures [Engel, 1999; Benbadis *et al*, 2003]. If the COVID-19 pandemic continues to delay 'elective' surgery, a pragmatic approach may need to be taken, whereby patients with a high risk of coming to harm without surgery may need to be prioritised. This is particularly the case in paediatric epilepsy surgery, where delays can lead to significant harm in children having multiple life-threatening seizures [Romanowski and McNamara, 2020].

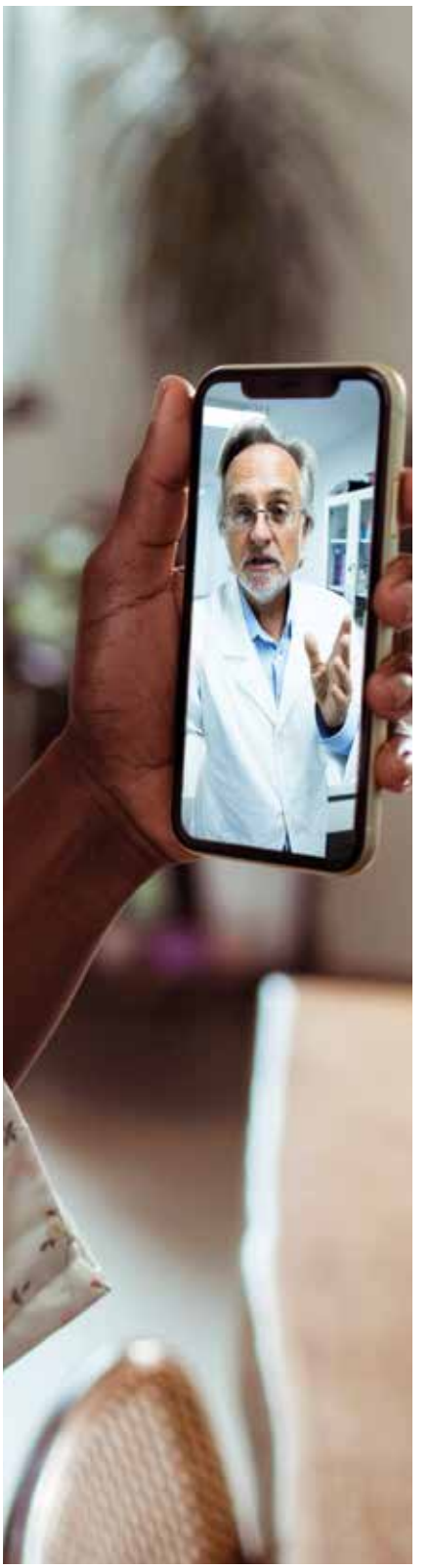
A similarly pragmatic approach may need to be applied in the case of patients with vagus nerve stimulators (VNS) in situ. Patients should be prioritised for timely replacement of the generator in those approaching end of battery life, given that battery depletion has been reported to be associated with an increase in seizures in a proportion of patients [Osorio *et al*, 2007; Cukiert *et al*, 2015]. Some patients who experience a worsening of seizure control when their VNS battery runs down never attain the same level of seizure control from the delayed replacement [Casazza *et al*, 2006]. VNS reviews should continue remotely by telemedicine and those with highest risk should be invited for face-to-face visits for alterations to stimulation settings.

Learning disabilities

Another group that have had a particularly difficult time during this period have been people with epilepsy and concomitant learning disabilities. The isolation during the height of lockdown, and the loss of many integral services to these patients and their families, will have been devastating. Data has not yet been released from the UK regarding the extent of the problem. However, early results from a survey performed in Milan of 409 families showed that families struggled and were particularly distressed by the worsening or occurrence of behavioural disorders [Granata *et al*, 2020]. They found that the interruption of regular routines in addition to rules imposed by the lockdown caused loss of acquired skills and autonomy, regressive behaviour, severe hyperactivity, and explosions of anger in patients with intellectual disabilities and psychiatric comorbidity. This has been compounded by the inability to attend regular group facilities. They not only provide an essential social environment for wellbeing but serves as a temporary respite for family members with caring responsibilities. This adds to the burden on family members in what is already a challenging time. Although psychological support remains available remotely, it may not always be sufficient to meet the complex needs of these patients and their family members. A more tailored approach that fully takes into account the needs of people with learning disability and epilepsy, as well as their carers, should be built into future epilepsy care models.

Black, Asian and Minority Ethnic (BAME) groups

The National Institute of Health and Care Excellence [NICE, 2012] recognises that adults with epilepsy from black and minority ethnic groups may have specific cultural and communication needs and these should be considered during both diagnosis and management. COVID-19 has had an undeniably significant and disproportionate impact on black and



minority ethnic communities in the UK, with higher incidence, morbidity and mortality [PHE, 2020]. The pandemic has laid bare many of the health and wider inequalities that persist in our society, and, in many communities, this has resulted in a mistrust and scepticism of healthcare services [Dodds and Fakoya, 2020]. Specific consideration should therefore be given to how we communicate with people with epilepsy from this demographic. Otherwise, there is a genuine danger that a significant number of patients may become disconnected and disengaged from epilepsy services due to fears surrounding COVID-19. There could also be a wider loss of confidence in the healthcare system. The disparities in healthcare outcomes for people from BAME communities during the pandemic, coupled with a number of recent high profile instances of racial and societal injustice, led the American Epilepsy Society to make a powerful condemnation of all forms of inequality [AES, 2020]. It is clear that as epilepsy professionals, we have both an opportunity and obligation to ensure we provide high-quality, equitable care to people with epilepsy regardless of their background.

Mental health

The negative impact of the pandemic on the mental wellbeing of people with epilepsy cannot be underestimated. This has been a particularly stressful and uncertain time for those with epilepsy and their carers. Early data from China highlighted and quantified the significant toll on the mental health of people with epilepsy during the pandemic [Hao *et al*, 2020]. There are a number of theories about why the pandemic has been particularly difficult for people with epilepsy. They include isolation, anxiety surrounding the disease itself, concerns regarding economic security and fears surrounding availability of critical anti-epileptic medication [Kuroda, 2020].

Fortunately, epilepsy charities and voluntary sector organisations have played a critical role in supplementing

Further reading

Adan G H, Mitchell J W and Marson T. (2020) Epilepsy care in the COVID-19 era. *Clinical medicine (London, England)*. 20(4):e104–e106.
Baroness Cumberlege on behalf of the Independent Medicines and Medical Devices and Safety Review (2020) First Do No Harm [online] Available at: *https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf* (Accessed: 11 August 2020).
Benbadis S R, Heriaud L, Tatum IV W O and Vale F L. (2003) Epilepsy surgery, delays and referral patterns - Are all your epilepsy patients controlled? *Seizure*. 12(3):167-170
Bhatia M, Adcock J E and Mackillop L. (2017) The management of pregnant women with epilepsy: a multidisciplinary collaborative approach to care. *The Obstetrician & Gynaecologist*. 19(4):279-288
Brigo F, Bonavita S, Leocani L, Tedeschi G, Lavorgna L and Digital Technologies, Web and Social Media Study Group of the Italian Society of Neurology. (2020) Telemedicine and the challenge of epilepsy management at the time of COVID-19 pandemic, *Epilepsy and Behavior*. 110:107164.
Cukiert A, Cukiert C M, Burattini J A and de Moura Lima A. (2015) Seizure Outcome after Battery Depletion in Epileptic Patients Submitted to Deep Brain Stimulation. *Neuromodulation*. 18(6):439-441
Dodds C, and Fakoya I. (2020) Covid-19: ensuring equality of access to testing for ethnic minorities. *BMJ (Clinical research ed.)*. 369:m2122.
Engel J. (1999) The timing of surgical intervention for mesial temporal lobe epilepsy: A plan for a randomized clinical trial. *Archives of Neurology*. 56(11):1338-1341
Epilepsy Action, Marson T and Thomas R H. (2020) Optimising healthcare for people with epilepsy during the COVID-19 pandemic-July 2020.
French J A, Brodie M J, Caraballo R, Devinsky O, Ding D, Jehi L, Jette N, Kanner A, Modi A C, Newton C R, Patel A A, Pennell P B, Perucca E, Sander J W, Scheffer I E, Singh GWilliams E, Wilmshurst J and Cross J H. (2020) Keeping people with epilepsy safe during the COVID-19 pandemic, in *Neurology*. Published online ahead of print.
Granata T, Bisulli F, Arzimanoglou A and Rocamora R. (2020) Did the COVID-19 pandemic silence the needs of people with epilepsy? *Epileptic Disord*. 22(4):1–4.
Jobst B C and Cascino G D. (2015) Resective epilepsy surgery for drug-resistant focal epilepsy: A review. *JAMA - Journal of the American Medical Association*. 313(3):285-293.
Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S and Kurinczuk J J. (2009) Saving Lives, Improving Mothers' Care Maternal, Newborn and Infant Clinical Outcome Review Programme.
MHRA (2020) Valproate Pregnancy

the psychological support available to people with epilepsy and their families during this difficult time [Epilepsy Action, 2020]. These crucial interventions, which aim to alleviate the stress and anxieties of people with epilepsy during this pandemic, may well have a positive impact on optimising their seizure control [Huang *et al*, 2020]. COVID-19 will likely continue to shape the way we all live, work, socialise and access healthcare services for the foreseeable future. Therefore, we must ensure that the psychological support afforded to people with epilepsy during this time remains accessible, robust and fit for purpose.

Conclusion

As the pandemic progresses, and we approach a 'new normal', it is increasingly clear that there are a number of people with epilepsy for whom remote clinical service delivery is not enough. There will need to be careful consideration about how we choose to deliver epilepsy care to these patients moving forward, to ensure that it remains truly equitable and accessible for all. A one-size-fits-all approach is unlikely to lead to satisfactory outcomes for every patient with epilepsy. Although telemedicine, in particular, has led to an evolution in epilepsy care, it is by no means a panacea. Although this has been a difficult and uncertain time for our patients and their families, it has also brought with it an opportunity to change both how and where healthcare is delivered. Patient-centred qualitative research is essential to fully inform how we plan, deliver and fund epilepsy services in the future. It must include a rich, representative and varied sample of people with epilepsy, inclusive of as many different patient groups as possible. We must consider the needs of all of our patients to ensure that no one is left behind as our epilepsy care model is optimised and rebuilt to address the legacy of COVID-19.

As we approach a 'new normal', it is increasingly clear that there are a number of people with epilepsy for whom remote clinical service delivery is not enough

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Prevention Programme: temporary advice for management during coronavirus (COVID-19) - GOV.UK. [online] Available at: *https://www.gov.uk/drug-safety-update/valproate-pregnancy-prevention-programme-temporary-advice-for-management-during-coronavirus-covid-19* (Accessed: 13 August 2020).

Mummery C J and Kipps C M. (2020) UK neurology response to the COVID-19 crisis. *Clinical Medicine, Journal of the Royal College of Physicians of London*. 20(3):266–269.

NHS England (2020) Third Phase of NHS Response to COVID19. [online] Available at: *https://www.england.nhs.uk/coronavirus/publication/third-phase-response/* (Accessed 20 August 2020)

NICE (2012) '1 Guidance | Epilepsies: diagnosis and management | Guidance | NICE'. NICE. [online] Available at: *https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance* (Accessed 20 August 2020)

Osorio I, Overman J, Giftakis J and Wilkinson S B. (2007) High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia*. 28(8):1561-71

Public Health England (2020a) Beyond the Data: Understanding the Impact of COVID-19 on BAME groups. [online] Available at: *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892376/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf* (Accessed: 20 August 2020)

Public Health England (2020b) Staying alert and safe (social distancing) - GOV.UK. [online] Available at: *https://www.gov.uk/government/publications/staying-alert-and-safe-social-distancing/staying-alert-and-safe-social-distancing-after-4-july* (Accessed: 13 August 2020).

Romanowski E and McNamara N. (2020) Invited Commentary: Is pediatric epilepsy surgery 'elective'? Considerations in the era of COVID-19. Neurology Blogs. [online] Available at: *https://blogs.neurology.org/covid-19-coronavirus/invited-commentary-is-pediatric-epilepsy-surgery-elective-considerations-in-the-era-of-covid-19/* (Accessed: 11 August 2020).

Shepley S A. (2016) Preconception to postpartum care: the need to maximise the safety of women with epilepsy. *British Journal of Neuroscience Nursing*. 12(3):118–123.

Smith P. (2016) Telephone review for people with epilepsy. *Practical neurology*. 16(6):475–477.

Tomson T, Landmark C J and Battino D. (2013) Antiepileptic drug treatment in pregnancy: Changes in drug disposition and their clinical implications. *Epilepsia*. 54(3):405-14 d

Winterbottom J B, Smyth R M D, Jacoby A and Baker G. (2014) Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome. *Cochrane Database of Systematic Reviews*.

LeDeR programme

Learning Disability Mortality Review programme findings on SUDEP

The LeDeR team at the University of Bristol discusses the findings from the LeDeR reviews around sudden unexpected death in epilepsy (SUDEP) in people with intellectual disability

The prevalence of epilepsy amongst people with intellectual disability (ID) is 18-22 per 100 people, with the likelihood of having epilepsy rising with the level of ID [Robertson *et al*, 2015; Carey *et al*, 2016]. Despite this, the experiences of people with ID remain under-represented in epilepsy research [Shankar, 2018] and a greater understanding is important in order to reduce health inequalities [Robertson *et al*, 2015; Young *et al*, 2015].

People with epilepsy are at risk of SUDEP, which is defined as:

> *Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥30 min or seizures without recovery in between), in which post-mortem examination does not reveal a cause of death [Nashef et al, 2011]*

It is important to note that there is no specific international classification of diseases (ICD-10) code used for SUDEP in a medical certificate of cause of death (MCCD). This means it is possible that mortality estimates are conservative

or vary according to local coding conventions. Most instances of SUDEP are coded as 'epilepsy' or 'seizure disorder'.

Annually, 1 in 1,000 people with epilepsy in the UK (approximately 600 people each year) are thought to die as a result of SUDEP [Young *et al*, 2015]. Risk factors for SUDEP are understood to include [Shankar *et al*, 2019; Sveinson *et al*, 2018]:

- ID
- Early onset of epilepsy
- Increased severity and prevalence of seizures in the six months prior to death (especially generalized tonic-clonic seizures)
- Absence of treatment or changes to drugs
- Polypharmacy
- Being aged 20-40 years
- Male gender
- Sleeping in the prone position
- Problematic use of alcohol
- Receiving treatment for depression or anxiety

Many of the risk factors are amenable to medical advice or the implementation of risk management strategies [Kiani *et al*, 2014; Liebenthal *et al*, 2015; Carey *et al*, 2016; National Institute for Health and Care Excellence, 2012; Shankar *et al*, 2018; Sveinson *et al*, 2018].

SUDEP Action's Epilepsy Death Register (SAEDR) [see Colwell *et al*, 2015] and the North American SUDEP Registry (NASR) [Verducci *et al*, 2019] are large scale current and ongoing research initiatives into SUDEP. These programmes actively collect information volunteered by families or carers of those who have died; NASR additionally reviews medical records. SAEDR reported gaps in service provision for those at risk and gaps in knowledge about SUDEP amongst families and health care professionals. NASR confirmed established risk factors and the need to discuss risks and preventative strategies with the individual, their families and those who care for them.

While ID is increasingly recognised within research, "very few studies explore ID as a risk factor and fewer still analyze its impact" [Young *et al*, 2015]. Existing research indicates that people with ID who have epilepsy are more likely to die as a result of SUDEP than the general population of people who have epilepsy [Tellez-Zenteno *et al*, 2005; Kiani *et al*, 2014]. Tellez-Zenteno *et al* estimated this to be 3.4 times more likely.

Thematic analysis indicated three core themes in relation to the deaths from SUDEP: the use of assistive technologies, changes in seizure activity prior to death, and epilepsy related care

Method

The LeDeR programme is the first national programme of its kind in the world. It aims to support improvements in the quality of health and social care service delivery for people with ID, and to help reduce premature mortality and health inequalities for this population. Deaths of people with ID in England aged four years and over are notified to the programme and each death is reviewed locally. A description of the review process is available online [University of Bristol]. Completed reviews are collated and analysed, with findings reported in the programme's annual reports which can be accessed online at *bit.ly/2EV9IBX*.

From 1 July 2016 to 31 December 2019, 7,145 deaths were notified to the LeDeR programme. Reviews were completed for 45% of these at the end of this period, 169 of which reported epilepsy as the cause of death in Part 1 of the MCCD.

We word-searched these 169 reviews using the terms 'sudden unexpected death in epilepsy' and 'SUDEP'. Selected reviews were then thematically analysed in order to make recommendations to improve care and reduce the risk of SUDEP.

Findings

Thirty-two (19%) of the 169 deaths from epilepsy were identified as being as a result of SUDEP.

There was a disproportionate number of males, people from Black, Asian and Minority Ethnic (BAME) groups, and people of a younger age. Twenty-three of the 32 deaths (72%) were of males, nine (28%) were from BAME groups, and 17 (53%) were under 35 years of age. The median age was 30.5 years (range 11 – 67 years).

Almost two-thirds (n=20, 63%) of the 32 people who died from SUDEP lived in a residential care home, supported living or supported housing. Twelve (37%) lived with their family or alone.

The majority (n = 27, 84%,) died in their usual place of residence. In most cases (n=22, 69%), the person was alone when they died; usually (n = 20) when thought to be sleeping.

Thematic analysis indicated three core themes in relation to the deaths from SUDEP: the use of assistive technologies, changes in seizure activity prior to death, and epilepsy related care.

Assistive technologies

Assistive technologies used by people with epilepsy include devices that alert others that the person is having a seizure. In 14 of the 32 reviews, such

technologies were said to have been present or had been recommended but were not in use at the time of a person's death. Reasons for this included that the equipment was faulty or that the individual or their family had declined its use. Discussing a lack of maintenance, one reviewer wrote:

'Ian* had a seizure mat. The mat was broken. It had originally been funded by [name of organisation] but there was no contract with the provider to fix or replace it. Had this been working it may have alerted the sleeping carer…'

There were also occasions where a personalised approach to the provision of technology appeared to be lacking. In the following example the person did not wish to have a sensor fitted in their home but would have considered another type of device, were it have been more easily available:

'Leah was offered a sensor to be installed in her property that would sound an alarm if she were to have a seizure, but stated that she did not feel that this was necessary…Leah had not purchased an epilepsy watch…as she feels that they are too expensive.'

Findings indicate a need for a greater understanding of SUDEP, and actions to minimise risk of SUDEP by all involved in caring and supporting people with ID who have epilepsy

Changes in seizure activity or general health prior to death

The joint-second most common theme in relation to the deaths from SUDEP was of changes in seizure activity and general health prior to the person's death. Eleven of the 32 reviews (34%) reported that the individual had experienced an increase in their usual seizure activity in the days prior to death:

'In the September before his death in January, the care home informed the GP that he had not been seen by neurology for six years and some of his seizures were causing concern…'

Eleven of the 32 reviews also noted general health-related changes in the person during the days or weeks prior to their death, including infection, a deterioration in health, being unusually tired or feeling dizzy:

'He did not fully recover from the virus and continued to deteriorate in health until his sudden death.'

Problems with epilepsy-related care

The other joint-second most common theme in relation to the deaths from SUDEP was of problems with epilepsy-related care. Eleven of the 32 reviews (34%) noted this. The problems were largely related to medication, including medication not being given on time, a refusal by the person to take medication, and medication not being at a therapeutic level:

'The toxicology tests revealed he had 13mg per litre of sodium valproate (his epilepsy drug Epilim) in his blood, the toxicologist noted this is lower than the evidenced therapeutic [level] of 50-100mg per litre.'

'…he did not take the doses regularly…a clear Care Plan was needed around refusal to take medication.'

The other key problem with epilepsy-related care was in relation to communication between services:

'…a clinical decision was made to increase…anti-epileptic medication. However, there was [a] 2-week delay

for the clinic to send this information in a letter to her GP and therefore the dose was not increased...'

Conclusion

Findings from the 32 LeDeR reviews of deaths of people with ID from SUDEP support the already established risk factors for SUDEP. These are being 20-40, male gender, having an increase in seizures in the six months prior to death, and an absence of treatment or insufficient adjustments to treatments in the face of changes in seizure patterns. Many died during the night when they were alone and were found in the prone position. The reviews also highlighted issues around the provision, use and maintenance of assistive technologies, as well as instances of apparent health deterioration prior to SUDEP. Finally, they show missed opportunities to improve epilepsy related care, particularly in relation to medication. These can be read together as indicating a need for a greater understanding of SUDEP, and actions to minimise risk of SUDEP by all involved in caring and supporting people with ID who have epilepsy. Epilepsy is the second most frequently reported potentially treatable cause of death in people with learning disabilities [University of Bristol, 2020]. The key message for epilepsy professionals is to ensure all those involved in the care and support of people with ID who have epilepsy understand what SUDEP is and the crucial role they and others have in reducing these risks. Our findings suggest a need to return to basic safety measures, including the provision of training about epilepsy, up-to-date care plans and assessments, and access to an epilepsy nurse between appointments if required.

While we recognise that a small number of people are included in this analysis, it is important to also recognise the value of these individual experiences, particularly because of the currently small pool of research that this contributes to. Importantly, our findings can be updated when we receive further LeDeR reviews of deaths of people from SUDEP.

** All names have been changed to protect confidentiality*

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Further reading

Carey I, Shah S M, Hosing F J, DeWilde S, Harris T, Beighton C and Coo D G. (2016) Health characteristics and consultation patterns of people with intellectual disability: a cross-sectional database study in English general practice, British Journal of General Practice, 66(645):264-270.

Colwell B, Hanna J, Osland K and Smithson W H. (2015) Findings from the SUDEP Action Epilepsy Deaths Register (EDR) 2013-2015. [online] Available at: https://epilepsydeathsregister.org/sites/default/files/edr_-_ilae_poster_sept_2015.pdf (Accessed: 20 August 2020)

Kiani R, Tyrer F, Jesu A, Bhaumi S, Gangavati S, Walker G, Kazmi S and Barrett M. (2014) Mortality from sudden unexpected death in epilepsy (SUDEP) in a cohort of adults with intellectual disability. Journal of Intellectual Disability Research, 58(6):508-520.

Liebenthal JA, Wu S, Rose S, Ebersole J S, Tao J X. (2015) Association of prone position with sudden unexpected death in epilepsy, Neurology, 84:703-709.

Nashef L, So E L, Ryvlin P and Tomson T. (2011) Unifying the definitions of sudden unexpected death in epilepsy, Epilepsia, 53(2):227-233.

National Institute for Health and Care Excellence (2012). [updated 2020] Epilepsies: diagnosis and management. [online] Available at: https://www.nice.org.uk/guidance/cg137 (Accessed: 20 August 2020)

Robertson J, Hatton C, Emerson E and Baines S. (2015) Prevalence of epilepsy among people with intellectual disabilities: A systematic review, Seizure, 29: 46-62.

Shankar R, Rowe C, Van Hoorn A, Henley W, Laugharne R, Cox D, *et al*. (2018). Under representation of people with epilepsy and intellectual disability in research, PLoS ONE, 13, 6.

Shankar R, Ashby S, McLean B and Newman C. (2019) Bridging the gap of risk communication and management using the SUDEP and Seizure Safety Checklist, Epilepsy & Behaviour, 103.

Sveinsson O, Andersson T, Carlsson S and Tomson T. (2018) Circumstances of SUDEP: A nationwide population-based case series, Epilepsia, 59:1074-1082.

Téllez-Zenteno J F, Ronquillo L H and Wiebe S. (2005) Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors, Epilepsy Research, 65:101-115.

University of Bristol (2020). The Learning Disabilities Mortality Review (LeDeR) Annual Report 2019. [online] Available at: http://www.bristol.ac.uk/sps/leder/resources/annual-reports/ (Accessed: 20 August 2020)

University of Bristol. Detailed process of reviewing deaths. [online] Available at: http://www.bristol.ac.uk/sps/leder/about/detailed-review-process/ (Accessed: 20 August 2020)

Verducci C, Hussain F, Donner E, Moseley B D, Buchhalter J, Hesdorffer D, Friedman D and Devinsky O. (2019) SUDEP in the North American SUDEP Registry: The full spectrum of epilepsies. Neurology, 93:227-236.

Young C, Shankar R, Palmer J, Craig J, Hargreaves C, McLean B, Cox D and Hillier R. (2015) Does intellectual disability increase sudden unexpected death in epilepsy (SUDEP) risk?, Seizure, 25:112-116.

Markus Reuber

Highlights

Top picks from *Seizure*

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

I am not sure that I can recall a single consultation in which risks were not considered, and not many in which they were not explicitly discussed. When a seizure disorder is first diagnosed, patients and clinicians need to think about risks related to activities such as cooking, bathing, childcare, work, recreation and driving. As the focus moves to treatment, they will consider the risk of further seizures versus those of idiosyncratic or dose-related adverse effects, teratogenicity and interactions with other medications or medical conditions. Risks become a particularly prominent concern when patients are pregnant or planning pregnancy, or are considering surgical procedures for epilepsy.

Risk assessments play a prominent role in routine epileptological practice. This makes the first finding of the systematic review by Cordet Anne Smart *et al* [2020], my Editor's Choice from issue 78 of *Seizure*, rather surprising: the literature about risk discussions is actually very limited. Although quantitative and qualitative studies were within the scope of this review, the authors were only able to identify 17 relevant studies. They were largely limited to the discussion of sudden unexpected death in epilepsy (SUDEP). What we learn from these studies is that patients would like an early, face-to-face discussion of SUDEP,

with timings individually adjusted and additional written materials provided. We also find that that clinicians may be more anxious of discussing this subject than patients and patients may benefit from an explanation provided by a more senior and experienced clinician. Checklists to guide the conversation exist but the effects of their use have not been well studied.

Unfortunately, we need to know much more about this topic. As Roy Beran [2020] points out, it makes a lot of sense to discuss the risk of SUDEP in the context of the many other risks, which patients need to consider as they learn to live with a seizure disorder. The heterogeneity of epileptic seizure disorders and the individuals who experience them mean much more work will be needed to provide truly 'evidence-based' practice recommendation for different communication scenarios. It is clear, though, that the discussion of risks has to be individualised if it is going to be meaningful for specific patients. It would also be important to extend the range of methodologies to improve communication. Questionnaires and surveys cannot tell us much about what exactly clinicians say, and how patients and accompanying individuals make sense of this, during clinical encounters. Previous studies have used Conversation Analysis in epileptological settings. The discussion of risk would be an ideal focus for future studies using this or similar methodologies.

COVID-19

In the countries which were initially ravaged by the COVID-19 pandemic, people are now emerging again from the lockdown imposed by their governments. The attention is shifting from the emergency provision of extra hospital beds and ventilators to the development of new ways of working. The aim is now to reduce the infection risk to patients and clinicians through measures like telephone or video-phone consultations. Routine surgical procedures are rescheduled, often after complex preparations including testing for COVID-19 infection and quarantine procedures. While life is still far from 'normal', people are experimenting with a new kind of normality that may be sustainable for months, and possibly longer.

Studies suggest that the likelihood of seizure occurrence often follows a steady pattern

My Editor's Choice from issue 79 of *Seizure* is a review by Ali Asadi-Pooya [2020]. One thing clinicians specialising in the treatment of seizure disorders will learn from this review is that their services may occasionally be called upon to treat patients with COVID. This is what previous experience with other corona viruses (such as SARS or MERS) suggests. These, and other corona viruses, do not only affect the respiratory organs through which they enter the body. They are also capable of causing encephalitides, which may be

associated with seizures [Li *et al*, 2016; Saad *et al*, 2014].

Similarly, COVID-19 can cause neurological symptoms. In one case series based on observations among 219 patients admitted to hospital with serious COVID-19 infections in China, 36.4% had neurologic manifestations. The commonest symptoms were dizziness (17%) and headache (13.1%). Impairment of taste (6%) and smell (5%) were also quite common. Depending on whether the cases were categorised as 'severe' or 'non severe', stroke, brain haemorrhage or TIAs were seen in 6% vs 1%, impaired consciousness in 15% vs 3%, and skeletal muscle injury in 19% vs 5% [Mao *et al*, 2020].

Reports of seizures or status epilepticus in the context of COVID-19 infections so far have been only sporadic. However, it would be surprising if the many haematological, immunological and metabolic complications attributed to this virus or – or their treatments – were never associated with epileptological complications. One possible complication is non-convulsive status epilepticus. This may well be missed in settings where neurologists are not involved in providing front-line care, and access to EEG is limited because of resource limitation or because of infection control measures.

Improving treatment responsiveness

For many people with epilepsy, the unpredictability of their seizures is a particularly disabling aspect of the condition. It is primarily because of this unpredictability that activities have to be restricted, certain jobs become impossible or people may not be allowed to drive. However, several recent studies have demonstrated that – surprisingly often – epileptic seizures are not an entirely random occurrence. Leaving aside those who are able to identify (and avoid) particular seizure triggers, these studies suggest that the likelihood of seizure occurrence often follows a steady pattern. This raises the possibility that the risk of seizures could be forecast, similarly to the risk of rain. While the majority of epilepsies have been shown to be subject to some degree of diurnal variation [Quigg, 2000], seizures stick very closely to a predictable pattern in 10-20% of patients (who have often not noticed this) [Karoly *et al*, 2018].

My Editor's Choice paper from issue 80 of *Seizure* is an article by Assaf Potruch, Salim T. Khoury and Yaron Ilan [2020]. In their wide-ranging narrative review, Potruch *et al*. initially consider the currently recognised mechanisms for the pharmacoresistance of epilepsies. They then explore how natural body rhythms could be harnessed to improve the responsiveness to treatments – including the anti-epileptic drugs already at our disposal today. Similarly to repurposing existing drug treatments for other disorders, they propose using interventions we already have in our arsenal, but using them in a much more targeted way. They suggest observing and taking account of the natural brain and body rhythms and avoiding potential iatrogenic effects of regular drug dosing, potentially including the loss of effectiveness. Potruch *et al*. argue that our existing antiseizure treatments could be much more effective if they were delivered in a more targeted fashion, especially at precisely the time they are needed. Given that epilepsy is a highly heterogenous condition, an ideal chronobiologically informed treatment would take account of a broad range of specifics characterising a person's epilepsy and also monitor their brain and body rhythms. Some of these ideas are not new. But the closed-loop deep brain stimulation systems now used routinely in some countries contain the technology that makes the detection of the rhythms, which co-determine the timing of seizures, much more feasible. Perhaps this technology could be repurposed to administer individually optimised pharmacological treatments in the future.

Further reading

Asadi-Pooya A. Seizures associated with coronavirus infections. *Seizure* 2020; 79: 49-52

Beran R. Discussing the risks related to epilepsy – an holistic approach. *Seizure* 2020, 78:134-135.

Karoly PJ, Goldenholz DM, Freestone DR, *et al*. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. *Lancet Neurol* 2018;17:977-85.

Li Y, Li H, Fan R, Wen B, Zhang J, Cao X, *et al*. Coronavirus Infections in the Central Nervous System and Respiratory Tract Show Distinct Features in Hospitalized Children. *Intervirology* 2016; 59: 163-169.

Mao L, Jin H, Wang M, *et al*. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690

Potruch A, Khoury ST, Ilan Y. The role of chronobiology in drug-resistance epilepsy: The potential use of a variability and chronotherapy-based individualized platform for improving the response to antiseizure drugs. *Seizure* 2020; 80: 201-211

Quigg M. Circadian rhythms: interactions with seizures and epilepsy. *Epilepsy Res* 2000;42:43-55

Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, *et al*. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014; 29: 301-306.

Smart CA, Page G, Shankar R and Newman C. Keep Safe: The when, why and how of epilepsy risk communication. *Seizure* 2020; 78, 136-149.

Anti-social media?

The last six months during the COVID-19 pandemic have been challenging for everyone. We've been through society lockdown, working from home, furlough, travel bans, less access to healthcare and allied services, and limited social contact with family and friends. Despite these restrictions on our freedom, we have seen many acts of kindness and of people going the extra mile. For example, carers in nursing and residential homes have been 'living in' to restrict viral transmission, or previously unknown neighbours who have been dropping off shopping, prescriptions, running errands and making phone calls for shielding or vulnerable people. These true acts of kindness, an appreciation and understanding that we are all in this together, has reminded me of the good that we can see in humanity. Yet, it is so saddening that even in the worst of times, a minority of people still used the lockdown and the social isolation to cause harm and exploit the most vulnerable.

The internet has been a lifeline to many during this pandemic, especially those with epilepsy and others with chronic disease. Connectivity through social media platforms such as Facebook, Instagram and Twitter provide social contact, support and educational information. Conferencing tools such as Zoom, Microsoft Teams and Skype have also enabled people to work from home and to connect with their loved ones. Although not a new phenomenon, it's distressing that during the pandemic these support and connectivity tools have used as a mechanism for cyber bullying, trolling and hate crimes directed at people with epilepsy.

It's been well reported in the media that these platforms have been used for a variety of malicious and distressing online attacks, ranging from videos of people mocking and imitating seizures, to flashing GIFs aimed at inducing seizures. The potential harm from such attacks is huge. A seizure can cause physical injuries, psychological distress, could risk someone's driving eligibility, current or future employment and endanger life. As an epilepsy clinician, I cannot understand the mindset of the minority of people who deliberately set out to cause harm. I cannot believe it is just lockdown boredom or ignorance.

It is encouraging to see some social media companies beginning to take these attacks seriously by banning certain search terms such as epileptic, seizure/seizures, photosensitive/photosensivity. But is this really enough? Will organisations ever be able to stamp out such abuse? We have seen similar trends in mental health disorders, such as anorexia and bulimia, in which the internet tools have been abused and caused more harm to already vulnerable individuals.

It's been well reported in the media that these social media platforms have been used for a variety of malicious and distressing online attacks

Given the nature of such attacks, the insensitivity, the distress and the abuse caused, we should push for further responsibility and accountability.

Sadly, even in 2020, it is another reminder that we, as a group of epilepsy professionals, still have a lot of work to do in dispelling myths and misconceptions around epilepsy and seizures. This media coverage has once again raised the profile of epilepsy in our society, and we must harness this for good. We must use it as a platform to aid understanding of epilepsy, to educate people and to lobby local and national governments.

So, as we move towards autumn, the times remain uncertain, we don't know what next week will bring, but let's continue to look after each other.

Dates for the diary

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

2020

5-9 July
14th European Congress on Epileptology (ECE)
POSTPONED TO 2022
Geneva, Switzerland
epilepsycongress.org/ece

20-26 September
7th Residential International Course on Drug Resistant Epilepsies
Tagliacozzo, Italy
ilae.org/congresses

2-5 October
14th World Congress on Controversies in Neurology
London, UK
emedevents.com

8-10 October
4th ILAE British Branch Epilepsy Neuroimaging Course
Chalfont St Peter, UK
https://ilaebritish.org.uk/events/

6 November
Irish Epilepsy League Annual Meeting
Dublin, Ireland
ilae.org/congresses

12-13 November
4th Dianalund International Conference on Epilepsy:
Comwell, Korsør, Denmark
ilae.org/congresses

2021

3-5 March
Fetal and Neonatal Neurology Congress
Paris, France
mcascientificevents.eu

1-5 June
14th European Paediatric Neurology Society Congress
Glasgow, UK

28 August – 1 September
34th International Epilepsy Congress
Paris, France
epilepsycongress.org/iec/

Next issue:

Mark Atherton

Case study: biotinidase deficiency in infancy.

David Henshall

Potential new targets for epilepsy medicine development.

If you are interested in submitting a research paper for inclusion in *Epilepsy Professional,* please contact the Editor: *kkountcheva@epilepsy.org.uk*

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