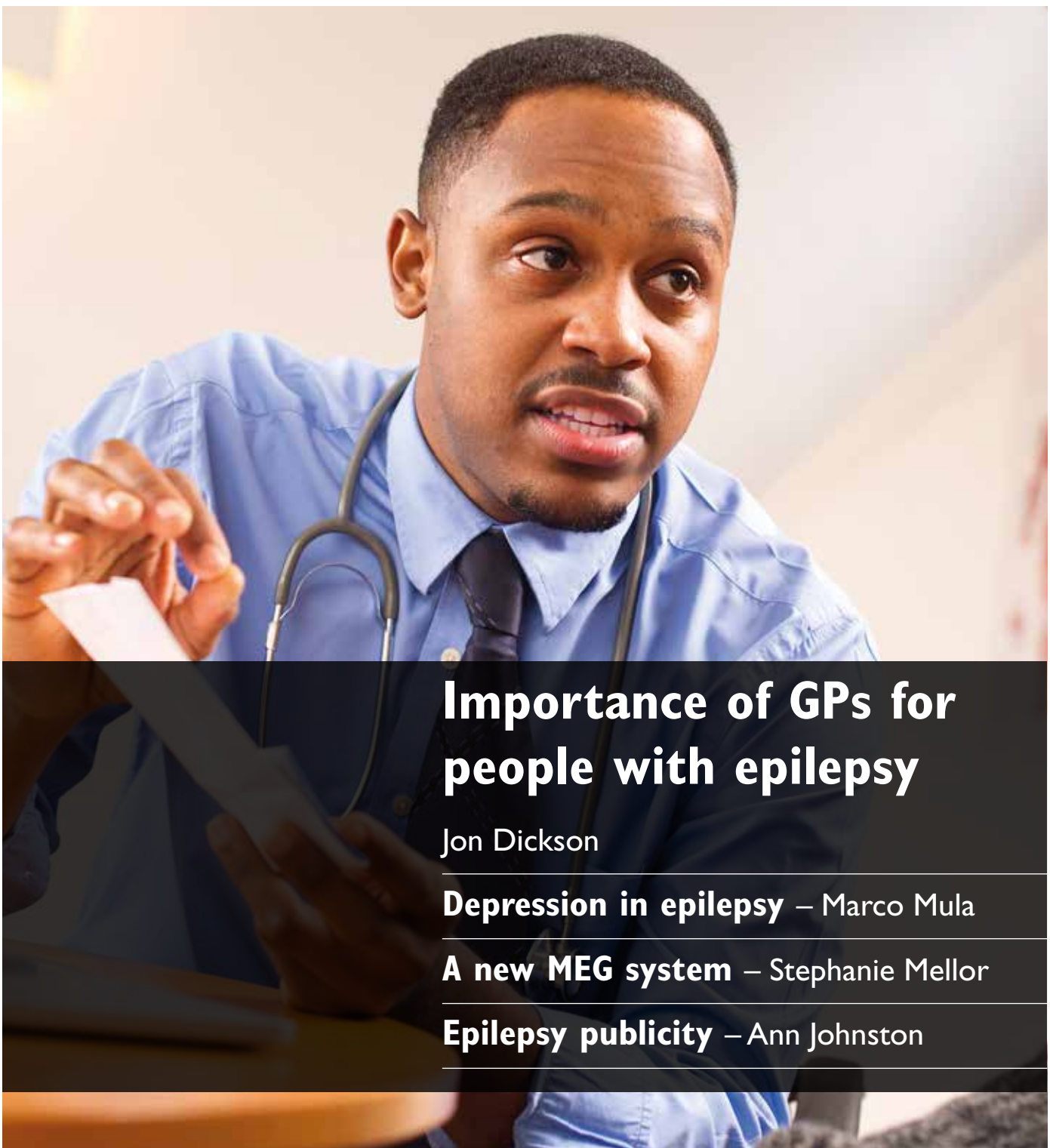
epilepsy action

issue forty-nine / Summer 2018 £3.50
(Free to Epilepsy Action professional members)

epilepsy professional



Importance of GPs for people with epilepsy

Jon Dickson

Depression in epilepsy – Marco Mula

A new MEG system – Stephanie Mellor

Epilepsy publicity – Ann Johnston

VNSTherapy®

SENTIVA®

This changes everything.

Treating patients with drug-resistant
epilepsy just got easier.

Smart Technology.
Customisable Therapy.
Built on Proven Results.

LIVANOVA BELGIUM NV
Ikaroslaan 83
1930 Zaventem
Belgium
Tel.: +32 2 720 95 93
Fax: +32 2 720 60 53

INTENDED USE / INDICATIONS:

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

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

Visit www.vnstherapy.com to learn more and view important safety information.

LivaNova
Health innovation that matters

Welcome to *Epilepsy Professional*. This edition will inspire and challenge you – but we are steering away from needless debate. *Epilepsy Professional* is a Br*xit free zone. Nowhere will you read about Scotland's devolution max, Cornwall's self-determination, or the need for an independent Dagenham and Redbridge (for any football fans). Not in these pages will you have to grit your teeth and mutter as we insist that the 'blue and black dress' in the photo that went viral on social media in 2015 is white and gold. Nor will you read an argument that Yanny is Laurel (this time an audio clip that went viral and divided opinions on what it said). We neither favour Rangers nor Celtic, Man City nor Man United, we just hope that football is the winner. In short, we are not here to argue, just advance some truths universally acknowledged.

It is in this vein that we present you three stellar articles that provide an in-depth view on three non-contentious issues. Dr Jon Dickson from Sheffield extols the virtues of a good GP for people with epilepsy. In a typical week, I may feel like I have personally seen everyone with epilepsy in the North East area. But I know that, in reality, I am sitting in a 'fortress' in a neuroscience centre, seeing just the tip of the iceberg. And GPs are needed now like never before, when it comes to implementing the new Medicines and Healthcare products Regulatory Agency (MHRA) valproate guidance.

What else cannot be argued with? Well, another thing is the fact that my patients present with a panoply of personal problems – both related to lifestyle and psychiatric factors. And I know that there is more that we can – and should – be doing. My trust has told me that I cannot be a life coach, and we cannot afford a psychologist. My business plan was rejected – but we do now have softer tissues in every clinic room, for all the good that would do... The seriousness of these lifestyle and psychiatric factors for people with epilepsy cannot be understated or underestimated, and drawing more attention to these issues is invaluable. Dr Mula unpicks the complex neurobiology behind mood disorders and epilepsy in a nuanced essay.

A final inarguable truth? Let's talk epilepsy tests for a second. To borrow from Monty Python's Life of Brian, what has EEG, that box of octopus wires, ever done for us? Except, diagnosing non-convulsive status, of course. And propping up the epilepsy surgery programme. Oh, and definitely diagnosing non-epileptic disorder. Oh and enabling syndromic classification of the epilepsies. Yes, but apart from all that, what has EEG ever done for us?

Well, obviously, a whole lot. But we do need more from our tests, and new imaging technologies are emerging – specifically MEG with optically pumped magnetometers. Without wanting to throw the humble EEG under the bus, these new imaging techniques may help add to the picture that existing techniques have given. Stephanie Mellor describes the potential new role for MEG and its superiority over EEG in certain circumstances.

And how to leave you? With something else we can all most likely agree on; that if we had our time again, none of us would train in any speciality where inspecting unwashed feet was central to our day.

Rhys Thomas
Consultant neurologist
Chief medical adviser
Epilepsy Professional

contents

26 highlights

Markus Reuber

Seizure editor, Prof Reuber, highlights the key papers from the latest editions. This issue: predicting in-hospital mortality in status epilepticus, the sociological aspects of epilepsy and best preactice in convulsive status epilepticus

When I was younger, I used to watch a cartoon called *Dastardly and Muttley in Their Flying Machines*. (Bear with me on this.) Readers may well remember the crooks of *Wacky Races*, Dick Dastardly and his dog Muttley, on their mission to stop a homing pigeon delivering messages. Each episode, they came up with a cunning plan to catch the pigeon, which would end up going awry at the last moment. As much as I enjoyed their madcap ideas, I could never understand why each time they would come up with a whole new plan instead of adapting the previous one, now that they knew how to improve it.

The authors in this issue of *Epilepsy Professional* may well agree with me on this one. In their articles, they all offer ways that we can build on the knowledge, services and technology that we already have and take it further. On page 20, Dr Jon Dickson discusses the role of GPs in managing people with epilepsy. He describes the barriers GPs face in becoming GPs with Special Interest in epilepsy, and suggests ways different health professionals can work together to improve care.

On page 12, Dr Marco Mula talks about depression in people with epilepsy. While the link between these conditions is well known, he argues that a global approach is needed to tackle stigma and communications should be opened up about difficult issues like suicide. Finally, on page 28, Stephanie Mellor describes an advancement in MEG epilepsy testing – MEG with optically pumped magnetometers. This promising technology is wearable, non-invasive and allows patients some movement during a scan.

We hope you enjoy the articles in this issue and have a great summer!

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

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

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

Publishers: Epilepsy Action (Communications department)

Advertising: contact communications manager, Sue Mitchell – 0113 210 8865 smitchell@epilepsy.org.uk

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

Higher death rates in epilepsy

According to a new study, people with epilepsy in England and Wales are at an increased risk of dying from suicide and accidents. This is compared to people without epilepsy in these areas.

Study author Dr Hayley Gorton explained that the risk of these types of deaths is still generally low in people with epilepsy (0.3-0.5%). But it is increased in comparison to people without the condition.

The study was carried out by the University of Manchester and Swansea University. It is published in the journal *JAMA Neurology*. It looked at over 900,000 people in England (44,678 with epilepsy) and nearly 300,000 people in Wales (14,051 with epilepsy).

The findings showed that people with epilepsy are twice as likely to die by suicide as people without epilepsy. They also found that people with epilepsy are three times more likely to die because of an accident.

Overdosing on medicines, either by accident or on purpose, was a major cause of death mentioned in the study. People with epilepsy were more likely to die because of overdoses than people without the condition. People most commonly overdosed on painkillers or medicines for mental health conditions, rather than epilepsy medicines.

Dr Gorton said: "Though unnatural death occurs rarely among all groups in the population, people with epilepsy are almost three times more likely to die from any unnatural cause than those without the condition. However, the direct causes of these increased mortality risks are not yet fully understood.

"Because of these risks, it's important that people with epilepsy are adequately warned so they can take measures to prevent accidents. We urge clinicians to advise their patients about unintentional injury prevention and monitor them for suicidal thoughts and behaviour."

This study follows a report from Public Health England (PHE) in March, showing that death rates in people with epilepsy have risen by 70% between 2001 and 2014. This is compared to a 6% drop in deaths overall over that period. The PHE report said that people with epilepsy living in more deprived areas may be at a three times higher risk of death than people in wealthier areas. The life expectancy for people with epilepsy was also found to be eight years less than the average.

In response to the findings in the PHE report, Epilepsy Action's chief executive Philip Lee has said that this is "shocking" and "completely unacceptable". The charity also criticised the healthcare system for often treating neurological conditions as an 'afterthought'. Speaking about the JAMA Neurology study, Mr Lee said: "This is an important study which prompts the need for more research into why people with epilepsy in particular are so at risk."

There is more information on safety and mental health on the Epilepsy Action website. People can speak to the Epilepsy Action Helpline by emailing *helpline@epilepsy.org.uk* or calling freephone 0808 800 5050. They can also contact SUDEP Action, a charity for people affected by SUDEP, by calling 01235 772 850 or through their website: *sudep.org*. The Samaritans can be reached by calling 116 123 or on their website at: *samaritans.org*.

School success linked to AED exposure

Children who are exposed to some epilepsy medicines *in utero* may do worse in school, a new study says.

The study by Lacey and colleagues looked at 440 children born to mothers with epilepsy. The researchers had access to the children's Key Stage 1 tests in maths, language and science at age seven.

The children's school tests were compared to those of other children their age who were not exposed to epilepsy medicines in the womb. The results showed that fewer children exposed to sodium valproate *in utero* achieved the national average for each subject. This was also found to be true for children exposed to more than one epilepsy medicine in the womb.

However, children whose mothers had epilepsy but did not take epilepsy medicines during pregnancy were not found to do worse at school. This was also found to be the case for children who were exposed to the medicine carbamazepine in the womb.

The study concluded that exposure to some epilepsy medicines in pregnancy may affect development in children. The authors say this evidence should be balanced against the need for effective seizure control for women in pregnancy.

The study was published in March this year in the *Journal of Neurology, Neurosurgery & Psychiatry*.

NICE to update epilepsy diagnosis and management guidelines

The National Institute for Health and Care Excellence (NICE) has decided to update its Epilepsies: diagnosis and management (2012) guideline CG137.

This decision followed a surveillance report in April 2018. The report looked at Cochrane reviews and literature published between September 2013 and January 2018. It also considered ongoing research, National Institute for Health Research (NIHR) signals, and policy and guidance. Topic experts were also consulted about whether the guidelines should be updated and what updates are needed.

The decision to update the guideline was made for a number of reasons. One of these is the new warnings and regulations about the use of sodium valproate in women of childbearing age. Other reasons included new recommendations for provision of information about sudden unexpected death in epilepsy (SUDEP) and the new seizure classification from the International League Against Epilepsy (ILAE) in 2017.

The surveillance research also showed new evidence about the possible use of a number of anti-epileptic drugs (AEDs), including

perampanel, zonisamide and cannabidiol. NICE will update its guidelines for these, as well as for psychological interventions, use of vagus nerve stimulation (VNS) for focal seizures, and treatment for prolonged seizures. An update will also be made to reflect information and advice that should be given to girls and women with epilepsy about AEDs and contraception, pregnancy, breastfeeding and menopause.

The evidence found affected a significant part of the NICE guideline, so a full update of the guideline has been planned.

NICE is in the process of scheduling the update. Once this has been done, the detailed timeline will be published on the organisation's website.

The last surveillance review was done in 2014 and it was decided that an update was not needed then.

Zentiva sodium valproate discontinued in the UK

Zentiva has discontinued the following medicines in the UK:

- Sodium Valproate Zentiva 200mg gastro-resistant tablets
- Sodium Valproate Zentiva 500mg gastro-resistant tablets
- Sodium Valproate Zentiva 200 mg/5 ml liquid

Anyone taking these medicines should speak to their doctor.

Is CBT effective for depression in epilepsy?

Cognitive-behavioural therapy (CBT) for depression in people with epilepsy has limited benefit, according to a new review.

Dr Adam Noble and colleagues reviewed the symptom changes resulting from those treatments in 398 adults with epilepsy. These people were participants from five trials which fit the review criteria.

The researchers got pre- and post-treatment data from the trial authors. The treatments evaluated all included CBT and all looked to improve the effects of depression. One treatment also sought to reduce anxiety in the participants.

Altogether, it was found that the likelihood of improvement in depression symptoms was significantly higher for the people in the CBT group compared to controls. But the reviewers found that the extent of gain was low. Around two-thirds of people receiving CBT (66.9%) were 'unchanged', while 30.4 made a 'reliable improvement'. In the control group, 10.2% were found to have had improvement. The effect on anxiety was also found to be low.

Dr Noble said: "Despite all its costs, CBT resulted in only a further 20% of patients improving. A look at trials in the wider mental health literature shows we should be aspiring to get 70-80% of our patients improving and, indeed recovering, not 30%." The authors added that more, large and well-conducted trials are needed in this area. The review was published in the *Journal of Neurology, Neurosurgery & Psychiatry*.

MHRA bans sodium valproate in women without pregnancy prevention programme

The Medicines and Healthcare products Regulatory Agency (MHRA) has changed the licence for valproate medicines in the UK.

Sodium valproate must no longer be prescribed to women or girls of childbearing potential unless they are on the pregnancy prevention programme (PPP).

There is a known risk of birth defects and developmental problems in babies born to mothers taking sodium valproate during pregnancy. Other epilepsy medicines carry some risk of these complications, but the risks with sodium valproate are higher.

The changes made by the MHRA mean that healthcare professionals prescribing valproate to women or girls must make sure they are enrolled in the PPP.

As part of the PPP, the prescriber must make sure the woman or girl understands the risk if she became pregnant while taking the medicine. They must also understand the need to use effective contraception while on the medicine, and be referred to contraception services if needed. A risk acknowledgement form must also be completed and signed when the medicine is renewed, at least once a year.

The MHRA said that women and girls taking valproate at the moment should have a review of their medicine. The agency stressed that they should not stop taking their medicine without medical advice.

Further changes are expected to come in in the next few months. These include smaller pack sizes to encourage monthly prescriptions, and a warning image on the box. Computer alerts for GPs will also be put in place to help change the way they prescribe these medicines.

The European Medicines Agency (EMA) is also reviewing safety around valproate use in women of childbearing age. Stricter safety measures have been recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). Medicines regulatory body CMDh backed these measures in April. The final decision will be made by the European Commission in the next few months. This will be legally binding across the EU.

Simon Wigglesworth, deputy chief executive of Epilepsy Action, said: "We welcome the revised measures which reflect the seriousness of the risks to the unborn children of women with epilepsy during pregnancy. It is vitally important that healthcare professionals ensure that all women with epilepsy taking sodium valproate are reviewed in line with the new guidelines."

Brexit negotiators urged to put patients first

The Brexit Health Alliance has warned that people may face long delays in getting new medicines as a result of Brexit. Research cooperation and access to clinical trials may also be affected, the organisation said. The alliance is urging Brexit negotiators to prioritise patients and public health during the second phase of negotiations.

The Brexit Health Alliance includes NHS bosses, industry and medical research bodies, patients and public health organisations. It aims to protect the interests of patients, as well as safeguarding healthcare and research.

The alliance has published a briefing paper warning about how Brexit may affect people in the UK and the EU. The paper discusses the impact on patients if there is a disruption in trade between the UK and the EU. It also says a lack of cooperation in the regulation of medicines and medical devices may result. It can be accessed at: *bit.ly/2GaviyL*

Niall Dickson, co-chair of the Brexit Health Alliance, said: "It is critical that UK and EU patients do not lose out on the best treatments and medical devices as the UK leaves the EU. We want to make sure that patients continue to benefit from early access to new health technologies and cutting-edge medicines, and that includes being able to take part in international clinical trials."

Following the results of the Brexit vote, the European Medicines Agency (EMA) announced it will move its headquarters from London to Amsterdam.

Southern Health Trust fined £2m over health and safety law breaches

Southern Health NHS Foundation Trust has been fined £2m following the preventable deaths of two patients in its care.

Teresa Colvin and Connor Sparrowhawk both died at facilities run by the trust in 2012 and 2013. Connor, who was 18, drowned in the bath at Slade House in Oxford, following an epileptic seizure.

Southern Health pleaded guilty to breaching health and safety laws in September last year. The trust was sentenced on 26 March 2018 at Oxford Crown Court. Mr Justice Stuart-Smith said that the fine to be paid "marks the seriousness of the trust's offending".

In passing the sentence, the judge acknowledged that Connor's mother, Dr Sara Ryan, had faced "entirely unjustified criticism". He also called the need for the families to campaign to uncover the "serious systemic problems" within the trust "a regrettable fact".

In a statement, Connor's family said: "No one should die a preventable death in the care of the state. Learning disabled people should not die on average twenty years before their non-disabled peers. Families should not have to fight for answers and accountability."

Roger Colvin, Teresa's husband, paid tribute to his wife, saying she was "a vivacious, beautiful and loving woman".

Dr Nick Broughton, the current Chief Executive of Southern Health has said he apologises unreservedly to the families. He added: "I know that words can do little to ease the enormity of the respective families' losses and pain. But Teresa and Connor's deaths have been genuine catalysts for change, and I sincerely hope our actions to improve care as a direct result provide some comfort, however small."

The doctor in charge of Connor's care, Valerie Murphy, was suspended for 12 months by the Medical Practitioners Tribunal Service in February.

A care plan can be downloaded from the Epilepsy Action website at *epilepsy.org.uk/careplan*

US FDA approves brivaracetam medicine for children under four

The US Food and Drug Administration (FDA) approved a supplemental new drug from the pharmaceutical company UCB for children aged four years and over in May.

The company's oral brivaracetam medicine formulation, known as Briviact, can be used as monotherapy or adjunctive therapy to treat focal seizures in children in the US.

Trust recalls 2,500 patients

The Belfast Trust called in 2,500 patients for a review after an investigation into the work of a consultant neurologist in May.

Concerns were raised about Dr Michael Watt's treatment plans and diagnoses by other doctors. After this, his work was investigated by the trust and the Royal College of Physicians. This resulted in 2,500 people who received treatment from Dr Watt being asked to come in for a review. They were being treated for a number of conditions, including epilepsy and MS.

The trust has set up additional clinics and intends to see all these patients within 12 weeks of the recall. It said that everyone who needs to be reviewed in this case has been contacted.

Dr Mark Michaelson, medical chair of division, said he is truly sorry for the anxiety this may have caused people. "The recall of such a large number of patients is so that we can be confident and thorough in ensuring that patients are having the best possible care."

Simon Wigglesworth, Epilepsy Action deputy chief executive, said this situation will have a knock-on effect on waiting times. "We know waiting times in Northern Ireland are already at an all-time high of two to three years, which is unacceptable."

The trust said that Dr Watt is not treating patients at the moment, but is still an employee. An advice line has also been set up for anyone worried and needing support at 0800 980 1100.

Grey matter structure linked to epilepsy

Research from the University College London (UCL) and the Keck School of Medicine of the University of South Carolina (USC) shows that grey matter volume and thickness is reduced in MRI scans of people with epilepsy

New research published earlier this year has suggested that epilepsy is linked to thickness and volume differences in grey matter in several parts of the brain.

The study, published in the February issue of the journal *Brain*, was called the largest neuroimaging study of epilepsy to date. The research shows that grey-matter reduction is shared in epilepsy syndromes, but there are distinct patterns in this reduction between different types of epilepsy.

The research was led by University College London (UCL) and the Keck School of Medicine of the University of South Carolina (USC). Study authors Christopher Whelan et al formed the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Epilepsy Working Group – ENIGMA-Epilepsy.

The group aimed to understand factors that influence brain measures in epilepsy. They used data from 2,149 people with epilepsy and 1,727 controls from 24 research centres across Europe, North America, South America, Asia and Australia. The researchers subdivided the epilepsy group into idiopathic generalised epilepsies, left and right mesial temporal lobe epilepsies with hippocampal sclerosis (MTLE) and all other epilepsies. They then analysed and compared structural brain measures from MRI brain scans to look for differences with controls, and common patterns within the epilepsy group.

The group found that the thickness of the cortex grey matter was reduced in people with epilepsy compared to the control group. They also found that the grey matter volume was reduced in subcortical brain regions in people with epilepsy. All epilepsy groups had lower volume in the right thalamus, and lower thickness in the precentral gyri. In the MTLE groups, both had a reduction in the ipsilateral hippocampus and lower thickness in the extrahippocampal cortical regions. Each MTLE group was associated with thickness differences in various sections of the brain not found in the other MTLE group.

Lower subcortical volume and cortical thickness was associated with a longer duration of epilepsy.

We found differences in brain matter even in common epilepsies that are often considered to be benign

Some of the structural differences were even found in the group of people who had idiopathic generalised epilepsy, which is not usually associated with structural brain abnormalities.

Study author Professor Sanjay Sisodiya said: "We found differences in brain matter even in common epilepsies that are often considered to be comparatively benign. While we haven't yet assessed the impact of these differences, our findings suggest there's more to epilepsy than we realise and now we need to do more research to understand the causes of these differences."

First author Dr Whelan said: "Some of the differences we found were so subtle they could only be detected due to the large sample size that provided us with very robust, detailed data.

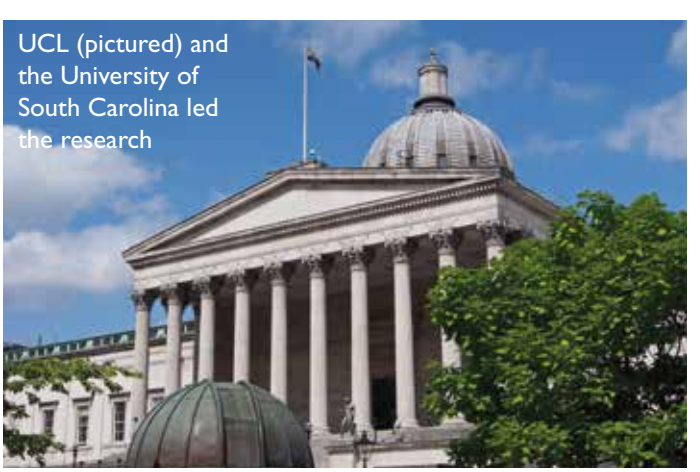
"We have identified a common neuroanatomical signature of epilepsy, across multiple epilepsy types. We found that structural changes are present in multiple brain regions, which informs our understanding of epilepsy as a network disorder."

The study concluded that the research goes to help inform current understanding of epilepsy as a network disorder. They also said it shows that some epilepsies involve more structural brain differences than first thought.

Prof Sisodiya said: "From our study, we cannot tell whether the structural brain differences are caused by seizures, or perhaps an initial insult to the brain, or other consequences of seizures. Nor do we know how this might progress over time. But by identifying these patterns, we are developing a neuroanatomical map showing which brain measures are key for further studies that could improve our understanding and treatment of the epilepsies."

The full study can be found on the *Brain* journal website at: *bit.ly/2xaQB2t*

There is more information on the ENIGMA Consortium at: *enigma.ini.usc.edu/*



UCL (pictured) and the University of South Carolina led the research

Depression in epilepsy

Some light in the darkness

Dr Mula discusses the complicated relationship between depression and epilepsy and the different ways depression may present. He suggests a global approach to reducing stigma around depression and opening up communication about important issues such as suicide

The mutual relationships between epilepsy and depression have been recognised for a long time, attracting the interest of generations of clinicians and neuroscientists [Mula, 2016]. In his famous quotation, Hippocrates stated: "melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy" [Temkin, 1994]. After more than 2,000 years, epilepsy is now recognised as a disorder of the brain characterised not only by an enduring predisposition to generate epileptic seizures. It is recognised as also characterised explicitly by the neurobiological, cognitive, psychological and social consequences of this condition [Fisher et al, 2014]. The new definition of epilepsy highlights the importance of identifying and addressing behavioural problems of patients with epilepsy as these are important parts of the disorder [Mula and Cock, 2015].

Depression is a common condition, affecting 5-10% of the general population [WHO 2017]. Epidemiological studies in people with epilepsy are showing similar prevalence rates only among seizure free patients [Jacoby et al, 1996]. The prevalence is definitely higher than that in community studies, ranging from 17-22% [Tellez-Zenteno et al, 2007]. And it is up to 55% in patients with drug-resistant epilepsy [Gilliam et al, 2004]. In general terms, these figures partially reflect the severity of the seizure disorder, not only in terms of underlying brain dysfunction, but also in terms of psychosocial difficulties. Epilepsy is still today a highly stigmatised condition, leading potentially to discrimination or marginalisation. It is a chronic disorder with significant social limitations (such as driving licence loss). The unpredictable nature of epileptic seizures and the social embarrassment potentially associated with them can lead to poor self-esteem, social withdrawal, isolation and demoralisation. Nevertheless, the relationship between epilepsy and depression has also strong neurobiological underpinnings and it is clearly more complex than a simple co-morbidity due to psychosocial issues.

Epilepsy is still today a highly stigmatised condition, leading potentially to discrimination or marginalisation

Epidemiological studies published during the last 10 years have pointed out that depression in itself can be associated with an increased risk of developing epilepsy. Data from the UK

General Practice Research Database show that the incidence-rate ratio of depression is significantly higher in the three years preceding the onset of epilepsy [Hesdorffer et al, 2012]. A population-based study in Sweden

It is now established that depression is a heterogeneous condition characterised by a wide range of different psychological, cognitive and somatic symptoms

shows that patients with depression have a two-fold increased risk of developing epilepsy [Adelow et al, 2012]. Another three population-based studies have shown very similar figures [Forsgren and Nystrom, 1990; Hesdorffer et al, 2000; Hesdorffer et al, 2006]. All these data taken together suggest two potential scenarios:

1. some patients with depression develop epilepsy as part of the 'natural course' of their depressive disorder, or
2. depression represents the premorbid phase of some epileptic syndromes

The neurobiological basis of this complex bidirectional relationship between epilepsy and depression can be found in a shared pathophysiology between these two conditions. This is in terms of anatomical structures involved, in particular limbic-prefrontal networks [Gong and He, 2015] and neurotransmitter changes [Kanner, 2012].

Is depression always the same?

Depression is one of the most frequently encountered comorbidities among patients with epilepsy. But it is still underdiagnosed and undertreated unless it is severe enough to cause major problems or disability. This is due to multiple factors. These include patients' reluctance to volunteer spontaneously mental health issues and a paucity (or total lack) of a specific training of neurologists to recognise and manage psychiatric problems. A lack of time in very busy clinics can also be a factor. However, depression is an important prognostic indicator. It is associated not only with poor quality of life [Boylan et al, 2004] but also with anti-epileptic drug (AED) resistance [Hitiris et al, 2007; Nogueira et al, 2017], increased seizure severity [Cramer et al, 2003] and increased AED side-effects [Mula et al, 2016]. It is also linked to increased risk of accidents and injuries [Gur-Ozmen et al, 2017], poor outcome after epilepsy surgery [Kanner et al, 2009] and increased mortality [Fazel et al, 2013].

Many people may still consider depression a specific and consistent disorder characterised by a fixed set of symptoms. But it is now established that depression is a heterogeneous condition characterised by a wide range of different psychological, cognitive and somatic symptoms [Goldberg, 2011]. And, in the context of a neurological condition, such as epilepsy, the phenomenology of depression can be even more complex.

People with epilepsy can develop mood disorders that are identical to those seen outside epilepsy. But an increasing number of clinicians have pointed out that mood disorders in epilepsy can be characterised by atypical features that are poorly reflected by conventional classificatory systems such as DSM-5 [Kanner, 2006]. During the 20th century, Dietrich Blumer coined the term interictal dysphoric disorder (IDD) to

refer to a subtype of somatoform-depressive disorder claimed to be typical of patients with epilepsy [Blumer et al, 2004]. According to Blumer, IDD was characterised by mood instability associated with anxiety and somatic symptoms. Modern studies pointed out that such a condition is not specific to epilepsy but can be diagnosed in up to 17% of patients with epilepsy. And it is indeed characterised by a significant component of mood instability and high comorbidity rates with anxiety

Double stigma is an established phenomenon which negatively affects both prevention and treatment

disorders (such as social phobia or generalised anxiety disorder) [Mula et al, 2008]. The presence of mood changes with dysphoria and mood swings around the ictal phase is probably typical of epilepsy [Mula et al, 2010] and is responsible for the differing features of depression in epilepsy [Mula 2013].

Depression does not affect only adults with epilepsy. Although data in children are still limited, a number of studies are now suggesting that mood and anxiety disorders are more frequent in children with epilepsy as compared to the general population [Reilly et al, 2014].

Further, it is well established outside epilepsy that 50% of adults with depression usually have a history of an anxiety disorder during childhood [Kim-Cohen et al, 2003]. For all these reasons, all health professionals dealing with people with epilepsy, both children and adults, should be aware of the problem. They should periodically screen them for mood and anxiety disorders.

A global approach to treatment

Educating patients and their doctors is the first step for a successful management of depression in epilepsy. It is important to overcome the double stigma associated with these two conditions. Double stigma is an established phenomenon which negatively affects both prevention and treatment. It creates a context in which patients are reluctant to acknowledge mental health issues and doctors are also reluctant to dig too much into it. This negative context can have deleterious psychological consequences for those who have uncontrolled epilepsy. For all these reasons, it is incredibly important to talk to our patients and increase awareness about these problems rather than ignoring them.

Mental health issues can be addressed successfully, and there are many resources available. Patients can also be directed to the many association websites, like Epilepsy

It is incredibly important to talk to our patients and increase awareness about these problems rather than ignoring them

Action, all of which have useful information on depression. Clinicians should not only inform patients about depression but also discuss stigma and discrimination in healthcare and in the wider community. This will create an environment where addressing wellbeing and mental health issues are

natural parts of the epilepsy management. There should be clear shared pathways with local psychiatric services and regional neuropsychiatry services, in order to provide access to mental health support when needed. Patients can be encouraged to get involved in a number of ways. These can include policy-making and strategic planning, formation of support groups, counselling programmes, positive living courses and inclusion in the training of mental health professionals.

In terms of treatment, during the last few years, the International League Against Epilepsy (ILAE) has issued a number of publications regarding a pragmatic approach to these problems [Kerr et al, 2011; Mula and Kanner, 2013].

Antidepressants in conjunction with cognitive behavioural therapy are considered first-line treatments for major depressive disorder and the majority of anxiety disorders. Historically, the effect of antidepressants on seizure threshold has represented a major concern for clinicians. However, this was based mainly on early anecdotal reports and EEG studies showing epileptic abnormalities during treatment with tricyclics, rather than on systematic data. Subsequent studies clarified that the supposedly increased seizure risk was real for a few specific compounds. Data from controlled trials and clinical studies show that maprotiline, high doses of tricyclics (> 200 mg daily; especially amitriptyline and clomipramine), or high doses of bupropione (> 450 mg) are associated with an increased risk of seizures [Mula, 2016a]. Meanwhile, SSRIs can be considered reasonably safe.

Subsequent studies clarified that the supposedly increased seizure risk [from antidepressants] was real for a few specific compounds

There is general agreement that 'starting low and going slow' is the best strategy. This is bearing in mind that low starting doses should not correspond to low target doses, as full remission should always be the first goal of an antidepressant treatment. AEDs with inducing properties (like carbamazepine, phenytoin, barbiturates) can reduce the blood levels of almost all antidepressants. For this reason, the antidepressant drug dose should be always adjusted according to clinical response.

Looking at the whole literature on suicide in epilepsy, 50% of indexed scientific papers have been published in the last 10 years

Suicide prevention in epilepsy

Suicide in epilepsy has represented, and probably still represents, a taboo. In fact, looking at the whole literature on suicide in epilepsy, 50% of indexed scientific papers have been published in the last 10 years, while the remaining 50% in the preceding 30-40 years [Mula, 2017]. The interest in suicide in epilepsy rapidly escalated in the last few years. The US Food and Drug Administration (FDA) alert on the increased risk of suicidal ideation and behaviour in people taking AEDs has probably contributed to that

[FDA, 2008]. Some researchers questioned the validity of FDA findings, identifying serious methodological flaws [Hesdorffer et al, 2010]. However, there is no doubt that the FDA document has finally highlighted the issue of suicide in epilepsy. An expert consensus statement developed by an ad-hoc Task Force of the ILAE pointed out the urgent need for validated screening instruments for suicide in epilepsy. The statement also noted the need for safety data for AEDs under development [Mula et al, 2013].

Prevention is the only treatment for suicide but clinical research on screening for suicide in epilepsy is still at a very early stage. The Columbia Suicide Severity Rating Scale (CSSRS) [Posner et al, 2011] is currently recommended to identify and monitor patients with epilepsy in clinical trials of AEDs [Mula et al, 2013]. But it would be unrealistic to consider the CSSRS a user-friendly clinical instrument for routine clinical practice as it is quite long, detailed and time consuming.

The Neurological Disorders Depression Inventory for Epilepsy (NDDIE) was developed for the rapid and objective detection of a major depressive episode in patients with epilepsy [Gilliam et al, 2006]. It has shown to be very practical and user-friendly. The NDDIE is now available in a number of languages and many clinicians around the world are becoming increasingly familiar with this screening tool in their clinical practice. The NDDIE has been also validated as a suicidality screening instrument, showing good psychometric properties [Mula et al, 2016].

The NDDIE has been also validated as a suicidality screening instrument, showing good psychometric properties

Suicide may still be considered an unmentionable issue by many

Further reading

Adelow, C., Andersson, T., Ahlbom, A., Tomson, T., 2012. Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy. *Neurology* 78, 396–401.

Blumer, D., Montouris, G., Davies, K., 2004. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. *Epilepsy Behav* 5, 826–40.

Boylan, L.S., Flint, L.A., Labovitz, D.L., Jackson, S.C., Starner, K., Devinsky, O., 2004. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 62, 258–61.

Cramer, J.A., Blum, D., Reed, M., Fanning, K., 2003. The influence of comorbid depression on seizure severity. *Epilepsia* 44, 1578–84.

Fazel, S., Wolf, A., Långström, N., Newton, C.R., Lichtenstein, P., 2013. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet Lond. Engl.* 382, 1646–1654.

Food and Drug Administration (FDA) US, 2008. Antiepileptic drugs and suicidality *http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf*

Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel, J., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M., Wiebe, S., 2014. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* 55, 475–482.

Forsgren, L., Nystrom, L., 1990. An incident case-referent study of epileptic seizures in adults. *Epilepsy Res* 6, 66–81.

Gilliam, F.G., Barry, J.J., Hermann, B.P., Meador, K.J., Vahle, V., Kanner, A.M., 2006. Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 5, 399–405.

Gilliam, F.G., Santos, J., Vahle, V., Carter, J., Brown, K., Hecimovic, H., 2004. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia* 45 Suppl 2, 28–33.

Goldberg, D., 2011. The heterogeneity of "major depression." World Psychiatry 10, 226–228.

Gong, Q., He, Y., 2015. Depression, neuroimaging and connectomics: a selective overview. *Biol. Psychiatry* 77, 223–235.

Gur-Ozmen, S., Mula, M., Agrawal, N., Cock, H.R., Lozsadi, D., von Oertzen, T.J., 2017. The effect of depression and side effects of antiepileptic drugs on injuries in patients with epilepsy. *Eur. J. Neurol.* 24, 1135–1139.

→

neurologists, as they may feel uncomfortable in asking the patient directly. The use of the NDDIE as a rapid suicidality-screening instrument represents a simple way to introduce the issue of suicide in a busy epilepsy clinic. It will also stimulate epilepsy centres to develop shared care pathways and suicide prevention programmes with liaison psychiatric services and regional neuropsychiatry services. In May 2013, the 66th World Health Assembly adopted the first-ever Mental Health Action Plan of the World Health Organization (WHO) with the goal of reducing the rate of suicide by 10% by 2020 [WHO, 2014].

The epilepsy community should not miss this opportunity. We should support the dialogue between neurology and psychiatry services in the development of effective suicide-prevention strategies in order to reduce premature mortality in people with epilepsy.

During the last two years, Dr Mula has received consultancy fees from UCB Pharma, Eisai, Bial and Elsevier and has intellectual property rights with Springer.

Dr Marco Mula
Consultant in neurology and epileptology
St George's University Hospitals
Reader in neurology
St George's University of London

Hesdorffer, D.C., Allen Hauser, W., Olafsson, E., Ludvigsson, P., Kjartansson, O., 2006. Depression and suicide attempt as risk factors for incident unprovoked seizures. *Ann. Neurol.* 59, 35–41.
Hesdorffer, D.C., Berg, A.T., Kanner, A.M., 2010. An update on antiepileptic drugs and suicide: are there definitive answers yet? *Epilepsy Curr* 10, 137–145.
Hesdorffer, D.C., Hauser, W.A., Annegers, J.F., Cascino, G., 2000. Major depression is a risk factor for seizures in older adults. *Ann. Neurol.* 47, 246–9.
Hesdorffer, D.C., Ishihara, L., Mynepalli, L., Webb, D.J., Weil, J., Hauser, W.A., 2012. Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. *Ann. Neurol.* 72, 184–191.
Hitiris, N., Mohanraj, R., Norrie, J., Sills, G.J., Brodie, M.J., 2007. Predictors of pharmacoresistant epilepsy. *Epilepsy Res.* 75, 192–196.
Jacoby, A., Baker, G.A., Steen, N., Potts, P., Chadwick, D.W., 1996. The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study. *Epilepsia* 37, 148–161.
Kanner, A.M., 2006. Depression and Epilepsy: A New Perspective on Two Closely Related Disorders. *Epilepsy Curr.* 6, 141–146.
Kanner, A.M., 2012. Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders? *Lancet Neurol.* 11, 1093–1102.
Kanner, A.M., Byrne, R., Chicharro, A., Wuu, J., Frey, M., 2009. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. *Neurology* 72, 793–799.
Kerr, M.P., Mensah, S., Besag, F., de Toffol, B., Ettinger, A., Kanemoto, K., Kanner, A., Kemp, S., Krishnamoorthy, E., LaFrance, W.C., Jr, Mula, M., Schmitz, B., van Elst, L.T., Trollor, J., Wilson, S.J., 2011. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 52, 2133–2138.
Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch. Gen. Psychiatry* 60, 709–717.
Mula M., 2013. The interictal dysphoric disorder of epilepsy: a still open debate. *Curr Neurol Neurosci Rep.* 13, 355.
Mula, M., 2016. Neuropsychiatric symptoms of epilepsy. Springer, London.
Mula, M., 2016a. The pharmacological management of psychiatric comorbidities in patients with epilepsy. *Pharmacol. Res.* 107, 147–153.
Mula, M., 2017. Depression in epilepsy. *Curr Opin Neurol.* 30,180-186
Mula, M., Cock, H.R., 2015. More than seizures: improving the lives of people with refractory epilepsy. *Eur. J. Neurol.* 22, 24–30.
Mula, M., Jauch, R., Cavanna, A., Collimedaglia, L., Barbagli, D., Gaus, V., Kretz, R., Viana, M., Tota, G., Israel, H., Reuter, U., Martus, P., Cantello, R., Monaco, F., Schmitz, B., 2008. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. *Epilepsia* 49, 650–656.
Mula, M., Jauch, R., Cavanna, A., Gaus, V., Kretz, R., Collimedaglia, L., Barbagli, D., Cantello, R., Monaco, F., Schmitz, B., 2010. Interictal dysphoric disorder and periictal dysphoric symptoms in patients with epilepsy. *Epilepsia* 51, 1139–1145.
Mula, M., Kanner, A.M., 2013. Introduction--Treatment of psychiatric disorders in adults with epilepsy: what every epileptologist should know. *Epilepsia* 54 Suppl 1, 1–2.
Mula, M., Kanner, A.M., Schmitz, B., Schachter, S., 2013. Antiepileptic drugs and suicidality: an expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. *Epilepsia* 54, 199–203.
Mula, M., McGonigal, A., Micoulaud-Franchi, J.A., May, T.W., Labudda, K., Brandt, C., 2016. Validation of rapid suicidality screening in epilepsy using the NDDIE. *Epilepsia* 57, 949–955.
Mula, M., von Oertzen, T.J., Cock, H.R., Lozsadi, D.A., Agrawal, N., 2016. Clinical correlates of memory complaints during AED treatment. *Acta Neurol. Scand.* 134, 368–373.
Nogueira, M.H., Yasuda, C.L., Coan, A.C., Kanner, A.M., Cendes, F., 2017. Concurrent mood and anxiety disorders are associated with pharmacoresistant seizures in patients with MTLE. *Epilepsia* 58, 1268–1276.
Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am. J. Psychiatry* 168, 1266–1277.
Reilly, C., Atkinson, P., Das, K.B., Chin, R.F.M.C., Aylett, S.E., Burch, V., Gillberg, C., Scott, R.C., Neville, B.G.R., 2014. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics* 133, e1586–1593.
Tellez-Zenteno, J.F., Patten, S.B., Jetté, N., Williams, J., Wiebe, S., 2007. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 48, 2336–2344.
Temkin, O., 1994. The Falling Sickness. The Johns Hopkins University Press, Baltimore.
World Health Organization (WHO), 2014. Preventing suicide: a global imperative. WHO Document Production Services, Geneva, Switzerland
World Health Organization (WHO), 2017. Depression and Other common mental disorders. Global Health Estimates. WHO Document Production Services, Geneva, Switzerland

Treat them like family!

Improve patient wellbeing with VNS Therapy®

- ✔ Fewer Seizures
- ✔ Shorter Seizures
- ✔ Faster Recovery
- ✔ Decreased Seizure Severity

- ✔ Fewer Medications
- ✔ Improved Alertness, Mood and Memory
- ✔ Improved Quality of Life

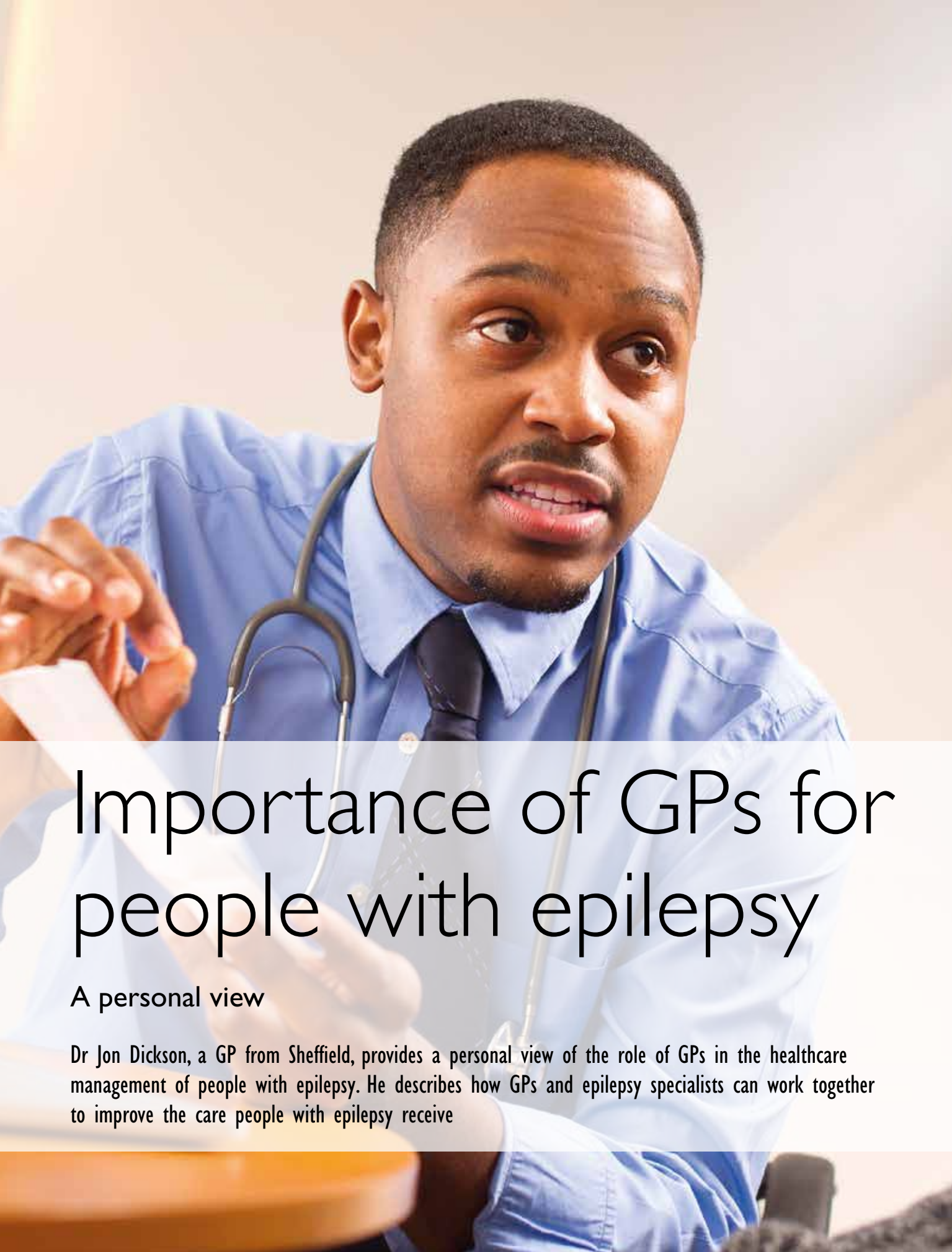
VNS THERAPY EUROPEAN INDICATION FOR USE VNS Therapy is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to seizure medications. The Model 106 AspireSR® (Seizure Response) features the Automatic Stimulation Mode, which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.
CONTRAINDICATIONS: The VNS Therapy system cannot be used in patients after a bilateral or left cervical vagotomy. Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with the VNS Therapy system. Diagnostic ultrasound is not included in this contraindication. Cardiac arrhythmia (Model 106 only)—The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias or who are using treatments that interfere with normal intrinsic heart rate responses.
WARNINGS: Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy Physician Manuals, including information that VNS Therapy may not be a cure for epilepsy. Since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, or in strenuous sports that could harm them or others. A malfunction of the VNS Therapy system could cause painful or direct current stimulation, which could result in nerve damage. Removal or replacement of the VNS Therapy system requires an additional surgical procedure. Patients who have pre-existing swallowing, cardiac, or respiratory difficulties (including, but not limited to, obstructive sleep apnea and chronic pulmonary disease) should discuss with their physicians whether VNS Therapy is appropriate for them since there is the possibility that stimulation might worsen their condition. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. MRI can be safely performed; however, special equipment and procedures must be used.
ADVERSE EVENTS: The most commonly reported side effects from stimulation include hoarseness (voice alteration), paresthesia (prickling feeling in the skin), dyspnea (shortness of breath), sore throat and increased coughing. The most commonly reported side effect from the implant procedure is infection.

*The information contained here represents partial excerpts of important prescribing information from the product labeling. Patients should discuss the risks and benefits of VNS Therapy with their healthcare provider. Visit www.VNSTherapy.com for more information.

ECEAdvert16E1

LIVANOVA BELGIUM NV
Ikaroslaan 83
1930 Zaventem
Belgium
Tel: +32.2.720.95.93
Fax: +32.2.720.60.53
www.VNSTherapy.com

VNS Therapy®
by LivaNova



Importance of GPs for people with epilepsy

A personal view

Dr Jon Dickson, a GP from Sheffield, provides a personal view of the role of GPs in the healthcare management of people with epilepsy. He describes how GPs and epilepsy specialists can work together to improve the care people with epilepsy receive

General practice is the largest medical speciality in the UK. There are 37,000 general practitioners (GPs) (full-time equivalents) and 7,875 general practices in the National Health Service (NHS) in England [Powell and Parkin, 2016; The Kind's Fund, 2016]. The majority of medical consultations in the NHS take place in general practice and nearly everybody in the UK is registered with their local NHS GP. General practice is an essential part of good quality care for people with epilepsy but its role in their care is ambiguous. Epilepsy is complex and there are very few educational materials or training courses for GPs. Many GPs do not feel confident or competent in managing many aspects of epilepsy care. This adversely affects people with epilepsy who may find that their GP is unable to provide the care that they need and that epilepsy services are difficult to access [Dickson et al, 2012].

General practice (also known as family practice internationally) is difficult to define precisely. It means different things in different contexts (nationally and internationally). General practice has been at the heart of the NHS in the UK since its inception in 1948. General practices are not NHS organisations but they are independent contractors to the NHS. The traditional NHS general practice was led by one or more GP partners who owned the premises and ran the business. This is still the *modus operandi* for most general practice but the team of people delivering medical care within the practice has grown especially over the last 10 years. It now includes managers, nurses, pharmacists, paramedics, midwives and physiotherapists. Other recent changes include the number of GPs who are salaried members of staff in a practice rather than partners. They also include the number of GPs working outside traditional general practice in diverse settings such as primary or urgent care centres, hospitals and ambulance services.

The traditional NHS general practice was led by one or more GP partners who owned the premises and ran the business

GPs are expert medical generalists [Reeve and Byng, 2017; RCGP, 2012]. The specialism of general practice is not defined by detailed knowledge of, for example, neurology or dermatology, but by focus on the individual patient – the person. The relationship between the individual patient and the doctor is at the heart of general practice and it is based on trust. The commitment of the GP to the individual is maintained regardless of the disease(s) they are affected by. General practice is characterised by proximity to the patients' home, accessibility (available when required without delay) and continuity (provided over many years, often a lifetime). It also places emphasis on context (housing, relationships, employment) and on the wider determinants of health such as smoking, exercise, alcohol and air pollution. It encourages self-care, autonomy, healthy living and primary prevention (immunisation, screening and drug treatment).

Jon Dickson

"Generalist knowledge is characterised by a perspective on the whole rather than the parts, on relationships and processes rather than components and facts; and on judicious, context-specific decisions on how and at what level (individual, family, system) to consider a problem"

Greenhalgh, in McWhinney's Textbook of Family Medicine, 2016, [Freeman, 2016]

GPs use their expertise in assessment, investigation and treatment but they also rely on the expertise of other healthcare professionals (nurses, specialist nurses, consultants etc). They coordinate care from multiple healthcare professionals into a single, coherent and comprehensive package. General practice is the primary point of contact for most healthcare needs for most of most people's lives. General practice is highly valued by patients [Appleby and Robertson, 2016] and it is highly effective [Starfield, 2011; Kringos, 2012]. International evidence shows that national health systems with strong primary care systems are the most effective and the most cost-effective. It also shows that the NHS is one of the best healthcare systems in the world [Davis et al, 2014].

Medicines and multi-morbidity

Most anti-epileptic drugs (AEDs) are initiated by consultants but the responsibility for ongoing prescribing usually rests with GPs. AEDs are complex medicines with diverse and potentially serious side-effects and they have important interactions with other drugs. Adherence to AED regimes is often poor which results in significant loss of efficacy. AEDs are known to have important implications for women of childbearing age, as many interact with contraceptive medications and many can increase the risk of teratogenic effects. Most women go to their GPs for contraceptive advice and for prescribing and fitting of contraceptives such as pills, coils and implants. GPs are often asked to provide pre-conception advice and to assess couples with difficulty conceiving. General practice is also where most community antenatal care is based (led by community midwives).

Ongoing prescribing of AEDs requires an understanding of the indication of the drug, how to assess its effectiveness and side-effects, and how to take appropriate action if the regimen is suboptimal. The British National Formulary (BNF), the resource that most GPs use to guide prescribing, can be unhelpful for AEDs. Dose and titration schedules are often poorly described and do not reflect the standard practice of epilepsy specialists. The BNF describes blood test monitoring for some drugs that is not considered necessary by most specialists. The process of titration of AEDs is time-consuming and titration led by GPs is arguably unfeasible given current workload pressures [The King's Fund, 2016]. Many Clinical Commissioning Groups (CCGs) have traffic light systems to guide GPs as to which drugs are suitable for independent GP prescribing and which require specialist input [The Sheffield Area Prescribing Group, 2018]. Many areas also have shared care protocols (SCP) (care shared between GPs and hospital specialist) to support GPs in this role and to clarify responsibilities between the GP and the specialist. But

Most AEDs are initiated by consultants but the responsibility for ongoing prescribing usually rests with GPs

these documents are often long, contain detailed and complex information and are difficult to access during busy clinical sessions. A working knowledge of over 25 commonly used AEDs is a challenge for GPs. This leaves them with clinical, ethical and financial concerns (including the cost of medical indemnity) about taking responsibility for AEDs. In practice, there is concern that many long-term prescriptions of AEDs are infrequently reviewed and under-supervised.

Multi-morbidity refers to the presence of more than one long-term health condition. As the population ages and treatments for previously life-shortening conditions improve, multi-morbidity is becoming increasingly common [Barnett et al, 2012]. The most common long-term conditions are cardio-metabolic disorders (hypertension, diabetes, obesity, ischaemic heart disease), mental illness (most commonly anxiety and depression) and chronic pain [Wallace et al, 2015]. Many people with epilepsy have multiple long-term conditions and many are taking multiple medications which may interact and may have cumulative side-effects.

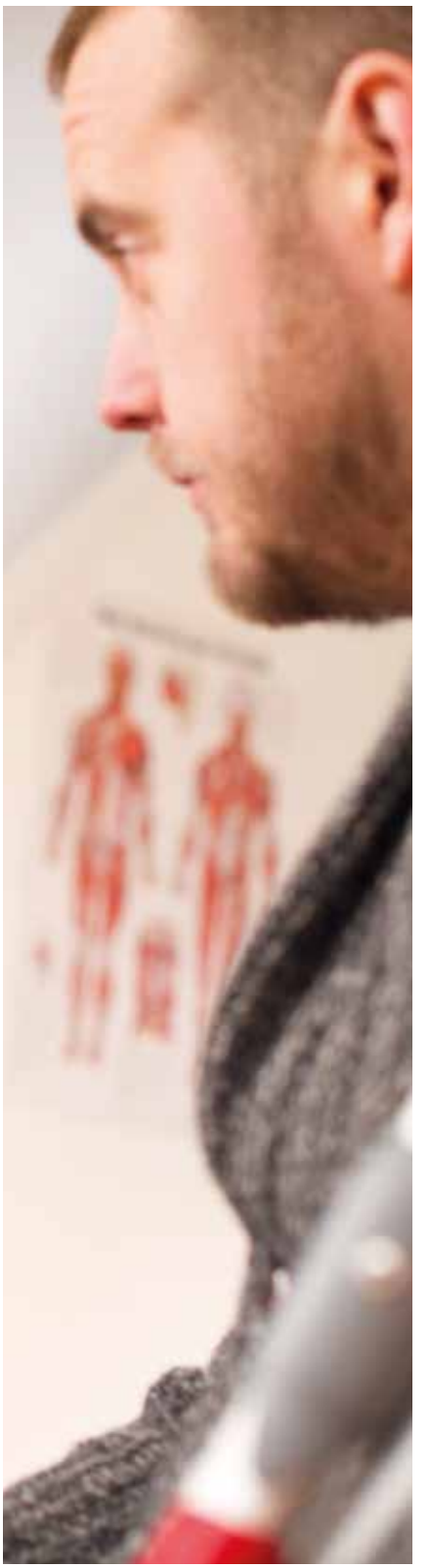
The impact of care from specialists who focus their interventions on a single body system is limited and the role of the medical generalist comes to the fore

Multi-morbidity affects the majority of elderly patients, many of whom are frail and have conditions which span multiple specialities. Much of the evidence-base underpinning national clinical guidelines comes from populations who are not representative of patients with multi-morbidity. The guidelines, therefore, have limited and often unknown applicability for these patients. The impact of care from specialists who focus their interventions on a single body system is limited and the role of the medical generalist comes to the fore. It includes synthesising multiple health problems into a single formulation, deviating from clinical guidelines in the best interest of the individual and focussing on care of the person not the disease. Providing responsive care close to home, including within the patients' homes, is of special importance in people who are elderly and frail, disabled or socially isolated.

Mental illness is one of the most common long-term conditions and it is a common comorbidity among people with epilepsy. Mental illness requires a holistic approach to treatment, including regular follow-ups, an intimate knowledge of the patient, and a combination of psychological and medical treatment. GPs manage the majority of mental illness in the NHS, especially depression and anxiety. They therefore have a crucial role in the treatment of patients with epilepsy who have these conditions.

Quality Outcomes Framework

The Quality Outcomes Framework (QOF) was introduced in general practice in the NHS in England in 2004 at the same time as the new GMS (General Medical Services) contract. It remains the key framework for providing standards and remuneration for the assessment and management of chronic diseases in general practice. NICE has been responsible for advising NHS employers on QOF since 2009. In 2004, epilepsy was one of the diseases included in QOF.



Jon Dickson

"If general practice fails, the whole NHS fails"

Roland and Everington, 2016, BMJ

Practices were expected to focus on four epilepsy 'indicators':

1. Maintain a register of patients with epilepsy
2. Review their seizure frequency
3. Record seizure freedom (yes/no)
4. Provide conception, contraception and pregnancy advice to all women of childbearing age

No comprehensive studies were ever conducted on the effect of the epilepsy QOF indicators on patient care. There is evidence that rates of annual review for people with epilepsy increased from less than 20% to over 90%, which seems positive. But there was scepticism among GPs that they had the time, knowledge and skills to make the required reviews meaningful [Minshall and Neligan, 2014]. Epilepsy was removed from QOF (except the requirement to keep a disease register for epilepsy) in 2014. Without a national strategy to replace it, this seems to signal relegation of epilepsy in the priorities of the NHS which has caused concern among people with epilepsy and their advocates.

Garekeepers

General practice is a high-capacity speciality. Small changes in the proportion of general practice consultations which result in referral to secondary or tertiary care can quickly overwhelm the lower capacity secondary or tertiary specialities. The role of GPs as 'gatekeepers' to secondary and tertiary care is therefore very important for the effectiveness and efficiency of the NHS. The majority of new referrals to specialised epilepsy clinics come from GPs but this is the tip of the iceberg. Most healthcare needs of people with epilepsy are optimally managed exclusively in general practice. When problems arise that cannot be managed in general practice the input of specialists is required. Traditionally, this has been through out-patient appointments but arguably these appointment systems are inflexible and focussed on hospital processes rather than the needs of patients. Telephone advice by way of a single short phone call may be all that is required. But this is often not available and an appointment in an out-patient clinic weeks or months away is the only option.

This seems to signal relegation of epilepsy in the priorities of the NHS which has caused concern among people with epilepsy and their advocates

Syncope with brief convulsions is a common reason for referrals from general practice to neurology and epilepsy clinics. NICE provides clear guidance on the assessment of transient loss of consciousness (TLOC). It states that specialist input is not usually required for '…people with a firm diagnosis… of uncomplicated faint, situational syncope, orthostatic hypotension.' But within the constraints of a 10-minute GP appointment, with limited training and expertise and without access to telephone advice, GPs often feel the need for referral to specialist clinics.

In contrast to many chronic diseases such as asthma, COPD and diabetes, very few general practices have a GP with a Special Interest (GPwSI) in epilepsy. The British Chapter of the ILAE has a GP Society which meets regularly but there are less than 30 members who regularly attend. There are specific challenges for GPs who may be inclined to developing epilepsy as a special interest:

- Epilepsy has a lower prevalence than most of the chronic diseases which GPs tend to focus on (which are often part of QOF)
- The lack of an objective biomarker for active epilepsy and seizures is problematic
- Key investigations such as MRI and EEG have traditionally not been available to GPs

None of these are insurmountable but to develop a significant workforce of GPwSIs in epilepsy would require a multi-faceted approach involving multiple organisations. A competency framework for GPwSIs in epilepsy has been published [Epilepsy GPwSI Stakeholder Group, 2007]. But, in contrast to GPwSIs in dermatology, this was never followed-up with measures to support GPs developing epilepsy as a special interest. These could include

To develop a significant workforce of GPwSIs in epilepsy would require a multi-faceted approach involving multiple organisations

an accredited training programme, the opportunity for GP supervision or mentoring by epilepsy specialists, and endorsement or investment in the role by commissioners and other stakeholders.

Conclusions

Over many decades, multiple reports by clinicians, politicians and charities have highlighted variability in the quality of care for people with epilepsy and significant deficiencies in many geographical regions in the UK [Dickson et al, 2015]. Unfortunately, many of the problems highlighted over 30 years ago still persist today. Among epilepsy specialists, one detects a frustration about the perceived disengagement of GPs. In general practice, one feels that there is a fatalism about lack of access to specialist services, long waits for appointments, and sub-optimal outcomes for people with epilepsy. None of the problems are insoluble but the solutions require closer working between general practice and epilepsy services. This will require sustained effort and the support of politicians, local healthcare leaders and third sector organisations.

Thanks to Dr Richard Grünewald and Dr Richard Oliver for kindly providing feedback on the manuscript.

Dr Jon M Dickson
Senior Clinical Lecturer
The University of Sheffield

j.m.dickson@sheffield.ac.uk
@Dr_J_M_Dickson

"Knowing is not enough; we must apply. Wishing is not enough; we must do."

Johann Von Goethe

Epilepsy Action offers a training course for primary care nurses. For more information, visit: *epilepsy.org.uk/training/primary-care-nurses*

Further reading

Appleby J and Robertson R, Public satisfaction with the NHS in 2015 Results and trends from the British Social Attitudes survey, 2016.
Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, and Guthrie B, Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study., Lancet (London, England), vol. 380, no. 9836, pp. 37–43, Jul. 2012.
Davis K, Stremikis K, Squires D, and Schoen C, Mirror, Mirror on the Wall, The Commonwealth Fund, 2014.
Dickson JM, Scott PA, and Reuber M, Epilepsy service provision in the National Health Service in England in 2012, Seizure, vol. 30, pp. 26–31, 2015.
Epilepsy GPwSI Stakeholder Group, Guidance and Competencies for the Provision of Services Using Practitioners with Special Interests (PwSI) - Epilepsy , 2007.
Freeman TR, McWhinney's Textbook of Family Medicine. Oxford University Press, 2016.
Kringos DS, The strength of primary care in Europe. Nivel, 2012.
Minshall I and Neligan A, Have the New GP Contract and NICE guidelines improved the clinical care of people with epilepsy?, Seizure, vol. 23, no. 10, pp. 874–877, 2014.
Powell T and Parkin E, General practice in England. Briefing paper. House of Commons Library., 2016.
Reeve J and Byng R, Realising the full potential of primary care: uniting the 'two faces' of generalism., Br. J. Gen. Pract., vol. 67, no. 660, pp. 292–293, Jul. 2017.
Royal College of General Practitioners, Medical Generalism, 2012.
Starfield B, Politics, primary healthcare and health: was Virchow right?, J. Epidemiol. Community Health, vol. 65, no. 8, pp. 653–5, Aug. 2011.
The King's Fund, Understanding pressures in general practice, 2016.
The Sheffield Area Prescribing Group, Traffic Light Drugs List, 2018.
Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, and Smith SM, Managing patients with multimorbidity in primary care., BMJ, vol. 350, p. h176, Jan. 2015.

Markus Reuber

Highlights

Top picks from *Seizure*

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

Today, in most circumstances [Toerien et al, 2013], there is an expectation that patients should participate in a collaborative process when important decisions are made about their treatment. Having said that, there are some clinical scenarios when it is difficult or impossible to take patients' own views into account. Decisions about the treatment of patients in refractory status epilepticus fall into this category. Doctors may have to decide what is in the patient's best interest without their input. Sometimes they will need to be mindful of the available resources. They may have to balance the chances of one patient's survival against those of another, when only one patient can benefit from the single available intensive care bed.

In these difficult situations, one doctor may well arrive at a different conclusion from another. This is especially when they base their impression on gut instinct alone (or worse: the last similar patient they have seen). For these situations, evidence-based guidance is crucial.

My editor's choice from *issue 56* of *Seizure* by Caroline Reindl et al is a very welcome addition to the evidence, which can support this decision-making process [Reindl et al, 2018]. Reindl et al compare the accuracy of four clinical scores designed to predict in-hospital mortality. Negative predictive value levels of 90%+ demonstrate that all four scores are likely to identify probable survivors of status epilepticus with a high level of accuracy. However, given that the positive predictive values of all scores were less than 20%, this study also demonstrates that these clinical scores should not be used in isolation to make decisions about treatment escalation. Nevertheless, these scores are likely to be much more accurate predictors of survival after status epilepticus than nonspecific prognostications.

Sociological aspects of epilepsy

More commonly than not, the medical care for patients with epilepsy strongly focuses on the seizures. Detailed enquiry about possible medication side-effects or mental health symptoms may fall by the wayside when patients are seen in time-pressured circumstances. Scant attention is paid to the discussion of 'lifestyle' issues, such as work or study, partnership, family planning or parenthood. And never mind patients' experience of epilepsy-associated stigma.

My editor's choice from *Seizure issue 57* is a review by Katharine Bailey and Nancie Im-Bolter [2018]. It examines epilepsy from a sociological point of view and reminds us that

seizures are only one modest aspect of the lived experience of epilepsy. In my experience, paediatricians and paediatric neurologist tend to have a better grasp of the effects of medical conditions on domains such as family life, education, personal and social development. This is compared to clinicians providing care for adults. So, it is perhaps no surprise that this review focuses on the (more substantial) paediatric literature. However, the approach taken – the application of Bronfenbrenner's ecological model of development [Bronfenbrenner, 1977] – and the findings, are just as relevant in adult neurology.

The most important lesson from the broad understanding of epilepsy implicit in the review by Bailey and Im-Bolter is that seizures are not the only treatable manifestation of the disorder. There is much scope for reducing disability and distress by paying attention to smaller and larger social structures. These may be things contributing to patients' understanding of epilepsy, their ability to cope with the disorder and their risk of psychiatric comorbidities.

Best practice in convulsive status epilepticus

There are many unanswered medical questions and serious conditions which we lack effective treatment for. And this can be hard to take. But there is another scenario which can be even harder for patients and health professionals alike. This is when we know what to do, when highly effective treatments are available, but are simply not administered in an appropriate or timely fashion.

Status epilepticus is an example of such a scenario. Benzodiazepines can control convulsive status epilepticus (CSE) successfully in over two thirds of cases. Second line drugs achieve acute seizure control in a further 10-20%. Earlier control of CSE is associated with better outcomes in terms of survival, recovery time and cognitive function. It has been known for many years that 'time is brain' in CSE and that the responsiveness to benzodiazepines diminishes significantly after 20 minutes. Despite this, CSE is often treated poorly. Medications are given too late or in inadequate doses. Another common error is the repeated administration of insufficient doses of benzodiazepines until clinicians lose sight of how much medication they have given. Although protocols and guidelines exist in many treatment centres, deviations from the protocols are almost the rule rather than the exception.

I have chosen two editor's choice papers from *Seizure issue 58*. The systematic review by Preena Uppal et al is the first paper. This summarises the findings of studies comparing outcomes of CSE treatments in which clinicians adhered or deviated from treatment protocols. It clearly demonstrates the dangers of a non-methodical approach. The commonest problem was the administration of excessive doses of benzodiazepines. This was associated with an almost six-fold increase in the risk of respiratory depression, need for intubation or intensive care admission.

The second paper is a narrative review by Coral Stredny et al. This focuses especially on the gap between what is known about best and common practice in the treatment of paediatric CSE. Thirty years ago, the acute treatment of myocardial infarction was revolutionised by the introduction of clear treatment algorithms. Over the last 10 years, the emergency treatment of patients presenting with strokes has benefited from the same approach. These are good models to follow if we want to achieve a similar revolution in the outcome of CSE.

Further reading

Bailey K and Im-Boulter, N. Social context as a risk factor for psychopathology in children with epilepsy. *Seizure* 2018;57:14-21.

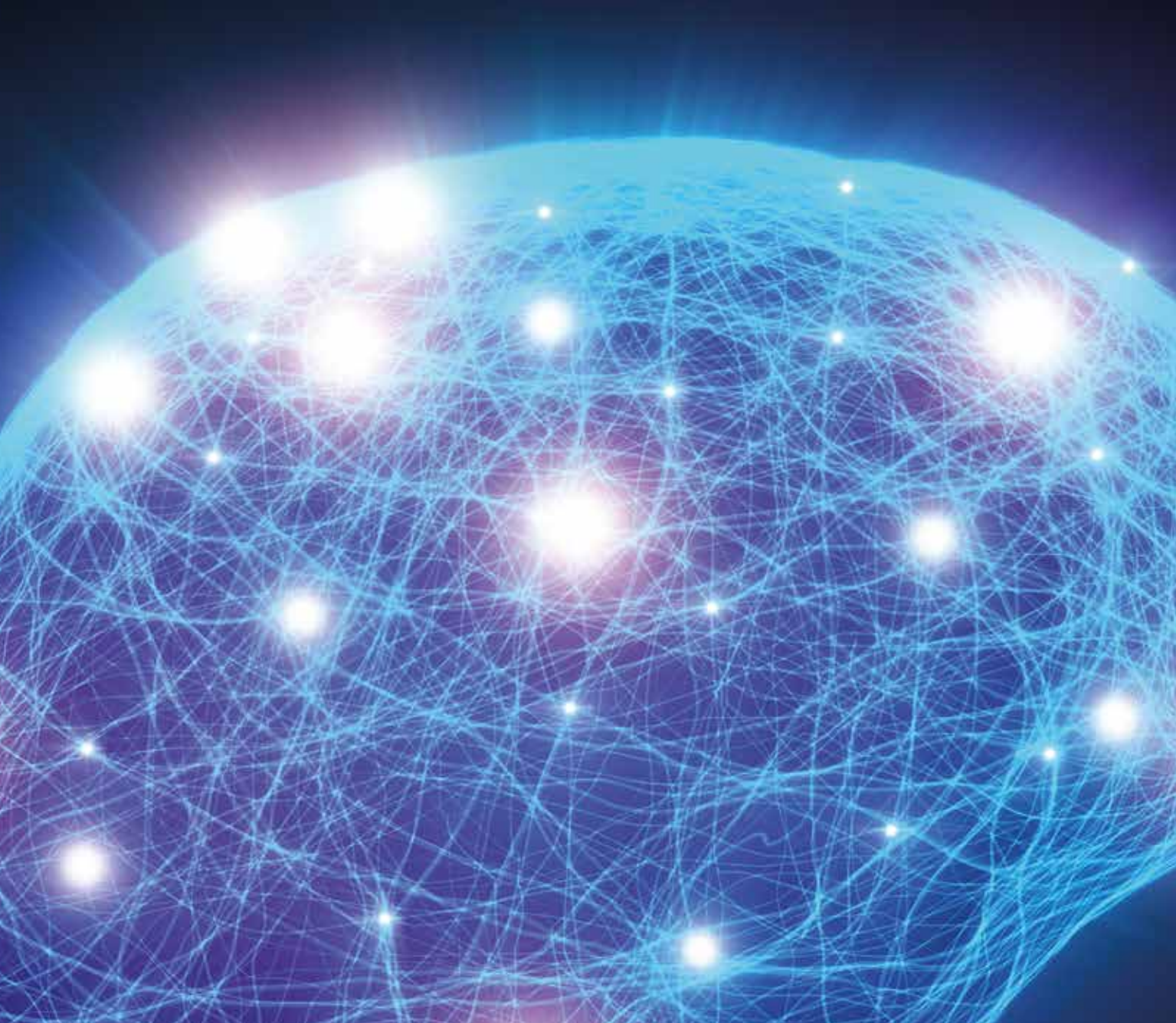
Bronfenbrenner U. Toward an experimental ecology of human development. *Am Psychol*;1977:513-531.

Reindl C, Knappe RU, Sprul˙gel M, Sembill J, Mueller TM, Hamer H, Huttner H, Madzar D. Comparison of scoring tools for the prediction of in-hospital mortality in status epilepticus. *Seizure* 2018, please add bibliographic details.

Stredny C, Abend N, Loddenkemper T. Towards acute pediatric status epilepticus intervention teams: Do we need "Seizure Codes"? *Seizure* 2018.

Toerien, M., Shaw, R., Reuber, M. Initiating decision-making in neurology consultations: 'recommending' versus 'option-listing' and the implications for medical authority. *Sociology of Health & Illness* 2013;35,873-90.

Uppal P, Cardamone M, Lawson J. Outcomes of deviation from treatment guidelines in status epilepticus: A systematic review. *Seizure* 2018.



A new MEG system

MEG with optically pumped magnetometers: possible use in epilepsy

Stephanie Mellor describes the new MEG technology developed by the University of Nottingham and University College London and discusses its potential use in people with epilepsy

Neuroimaging is increasingly important in diagnosing and treating epilepsy. For patients with drug resistant epilepsy, surgical removal of the portion of the brain causing their seizures may be the best treatment available. Accurate identification of this area is therefore crucial. Magnetoencephalography (MEG) is one technology for doing just that. Small magnetic fields produced by neural activity are measured non-invasively so that the site of the activity can be reconstructed.

MEG is unique in neuroimaging in having both good spatial and temporal resolution. However, it is traditionally expensive, stationary and prone to motion artefacts. A new MEG system being developed at the University of Nottingham and UCL promises to change that by using a new type of magnetic sensor. This is known as an optically pumped magnetometer (OPM).

Principles of MEG

Electroencephalography (EEG) is the most common functional imaging technique used in epilepsy evaluations. It has excellent temporal resolution and measures neuronal activity more directly than techniques dependent on cerebral blood flow, such as fMRI. However, if it is recorded non-invasively, it is difficult to pinpoint the active brain region as the skull and scalp blur electric fields. One solution is to perform EEG intracranially (iEEG), but naturally this is highly invasive.

MEG works on a similar principle to EEG, except that the magnetic field induced by neural currents is measured rather than the electric field. Magnetic fields are not affected by tissue and so MEG boasts both good temporal and spatial resolution, despite being measured outside of the head. It is therefore non-invasive and is being increasingly used clinically.

MEG boasts both good temporal and spatial resolution despite being measured outside of the head

Presurgical planning for refractory epilepsy is, by far, the most common clinical use of MEG [Stufflebeam, Tanaka and Ahlfors, 2009]. For patients with focal epilepsy, removal of the epileptogenic focus may be curative. For approximately one third of surgical candidates, this location is unclear from structural MRI images [Stufflebeam, Tanaka and Ahlfors, 2009]. In these cases, MEG may be used to help identify the focus.

For EEG or MEG, interictal spikes are generally used to localise the epileptogenic focus. Activity between seizures is used rather than ictal activity because MEG recordings are sensitive to motion. Movement of only 5mm can prevent data from being used [Gross et al, 2013]. Naturally, a patient cannot be expected to remain still during a seizure.

In addition to mapping the epileptogenic focus, MEG is used to localise the eloquent cortex (the areas of the brain which control critical functions, such as motor skills, language processing and vision). Identifying these areas pre-surgery helps the surgeon to avoid them. Unlike spontaneous interictal discharges, these areas must be stimulated to be active in an MEG scan, so the patient is set a task during the scan. fMRI could be used to map the eloquent cortex but MEG is sometimes preferred

because the epileptogenic focus can be found simultaneously.

The clinical value of using MEG to localise the epileptogenic focus when other neuroimaging techniques have been unsuccessful is generally well acknowledged. MEG can provide information not observed in EEG for approximately one third of surgical candidates [Sutherling et al, 2008]. When the two techniques are combined, the sensitivity and specificity of the overall system is better than either modality alone [Duez et al, 2016]. Use of MEG has also been linked to seizure-freedom after surgery. It has been shown that if the epileptogenic focus found with MEG falls within the surgically resected region, the probability of seizure-freedom is significantly higher than if the two are not concordant [Englot et al, 2015; Stefan and Trinka, 2017]. Further research is required to better quantify this connection, but overall it is clear that MEG is clinically useful in certain circumstances.

However, detecting the magnetic fields from neural current flow is non-trivial. They are exceptionally small, of the order of 10^{-15} Tesla at the scalp surface. The Earth's magnetic field is of the order of 10^{-5} Tesla, so MEG must be performed in a shielded room to reduce this and other background fields as far as possible. Additionally, extremely sensitive magnetometers are required. Until recently, superconducting quantum interference devices or SQUIDs have almost exclusively been used for this task. The temperature of these superconducting sensors must be kept close to absolute zero for them to operate. A standard MEG system is a bit like a large thermos flask with a helmet-shaped space for the subject's head. Around the sides of this helmet there is an array of around 300 SQUIDs immersed in liquid helium. The sensor positions are fixed to accommodate the helium and cannot be placed directly on the scalp. The advantage of this is that there is very little preparation required for a MEG scan, as the patient need only sit in the scanner. However, it comes with many disadvantages.

This has traditionally limited MEG to patient groups who can remain relatively still and prevented use of ictal activity in clinical evaluations

Firstly, the sensors are generally far from the scalp surface; the signal to noise ratio (SNR) of MEG could be dramatically improved if the magnetometers were nearer to the neural current sources. The one-size-fits-all helmet means that this is particularly true for people with smaller heads. Secondly, as mentioned above, the data is significantly affected by a patient moving within the helmet. This has traditionally limited MEG to patient groups who can remain relatively still and prevented use of ictal activity in clinical evaluations [Medvedovsky, 2015].

OPM-MEG

To overcome many of these issues, a group at the University of Nottingham and University College London have developed a new, wearable MEG system [Boto et al, 2018]. This uses OPMs to detect neuromagnetic fields, rather than SQUIDs. An OPM is a state of the art magnetometer. It has a sensitivity comparable with that of a SQUID but, unlike SQUIDs, OPMs do not have to be cryogenically cooled. This opens up the possibility of cheaper MEG and removes the need for the position of MEG channels to be fixed.

The overall design of an OPM is, perhaps surprisingly, not that new. The first magnetometers which relied on atomic interactions were developed in the 1950s [Bell and Bloom, 1957]. However, they have only recently become sensitive, small and light enough to be used in MEG [Shah and Wakai, 2013]. Today, OPMs are approximately the size of a packet of mints. Externally, they are approximately body temperature, so the sensors can be placed directly onto the head. Each one contains three key components; a laser, a small cell of Rubidium vapour and a photodiode. The details of OPM operation can be found in [Sander et al, 2012].

Previously, OPMs have been shown to be able to measure neuromagnetic fields with a sensitivity comparable to SQUIDs [Sander et al, 2012; Boto et al, 2017; Johnson, Schwindt and Weisend, 2010; Kim et al, 2014]. The novelty of the new system is that it is wearable: an array of OPMs are held directly onto the scalp with a 3D-printed headcast. This has benefits for the SNR and motion sensitivity of the overall system.

When the OPMs are directly on the scalp surface, the sensitive element of each one is around 6mm from the scalp [Boto et al, 2018]. This is around 3cm closer to the neural magnetic field source than SQUIDs in traditional MEG. For adults, this means that the SNR of an ideal OPM-MEG system could be three to four times that of traditional MEG [Boto et al, 2016]. For children, due to their smaller head size, the increase in SNR should be considerable.

Multiple studies have shown that increasing the SNR of MEG improves its sensitivity to neural current flow and spatial resolution [Boto et al, 2017; Boto et al, 2016; Goldenholz et al, 2009]. With traditional MEG, it is common for too few interictal spikes to be observed during a recording to localise the epileptogenic focus accurately [Stefan et al, 2011]. Because of its higher sensitivity to neural currents, OPM-MEG is expected to sometimes be able to observe interictal spikes which are missed in traditional MEG. This means that the information from a MEG scan may be useful for a higher proportion of surgical candidates. It should be noted that this is yet to be tested for epilepsy patients, so the true impact is unknown.

The patient can move naturally while OPM-MEG is recorded, without significant degradation of the signal, as demonstrated by Boto et al [2018]

OPMs are designed to operate in zero magnetic field and have a relatively small dynamic range (±1.5nT). If the total magnetic field surpasses around 2.5nT, the sensors saturate and cannot be used. This is a problem – the remnant magnetic field from the Earth in a standard magnetically shielded room is approximately 25nT. However, a set of nulling coils have been designed and made at the University of Nottingham to reduce this field to almost zero. These are electromagnetic coils placed either side of the patient, which generate fields equal and opposite to the background magnetic field, cancelling it out. Within a shielded room, they have been shown to keep the magnetic field approximately uniform within a 40 x 40 x 40cm^3 volume [Boto et al, 2018].

The nulling coils allow the OPMs to stay operational for movements within this 40 x 40 x 40cm^3 region. In the wearable system, the position of each OPM is fixed relative to the patient's head so the only significant change in recorded magnetic field should be because of a change in neural current. Therefore, the patient can move naturally while OPM-MEG is recorded, without significant degradation of the signal, as demonstrated by Boto et al [2018]. It is hoped that in a future iteration, the system will be robust to more significant movements and OPM-MEG will allow the recording of ictal activity.

For children or other patient groups who have difficulty remaining still, this is a game changer. Across imaging modalities, young children struggle to keep still in the often-unstimulating scan conditions [Centeno et al, 2016]. For a traditional MEG scan, measures have to be taken to reduce the motion artefacts in the data. Typically either the child's head position is tracked during a scan, computationally demanding algorithms are used to reduce motion artefacts in recorded data, or a child is sedated for the duration of the scan [Wehner et al, 2008; Ettl et al, 2013]. None of these options are ideal, either compromising on time or the patient's comfort. A system which is resilient to natural

movements reduces the need for any such considerations.

Conclusion

MEG can be a powerful tool for epilepsy treatment. Currently, it is used in presurgical planning both to identify the epileptogenic focus and the eloquent cortex. Agreement between MRI and MEG source localisation is a strong predictor of seizure freedom after surgery [Englot et al, 2015], suggesting that the information from an MEG scan is non-redundant. However, traditional MEG is limited by cost, sensitivity and motion artefacts.

Boto et al [2018] recently demonstrated a new OPM-MEG system which overcomes many of these issues. They showed conclusively that electrophysiology can be measured with OPM-MEG equally well as with traditional MEG, even when the subject is moving significantly. Previous simulations suggest that OPM-MEG could deliver higher SNR than existing MEG systems [Boto et al, 2016], indicating that the information it provides may be more clinically useful than traditional MEG. However, further testing of this system is required before it is used outside of a research environment; currently experiments have only been performed with healthy participants.

Nevertheless, the theoretical potential of OPM-MEG is huge. OPM-MEG is cheaper, less maintenance intensive, has better SNR and is less sensitive to motion than traditional MEG. Children and other patient groups with uncontrollable movements, who previously had to be sedated, could be scanned awake. Ideally, having a scanning mechanism which is motion insensitive and which can detect interictal epileptic spikes will reduce the need for intracranial EEG, avoiding invasive procedures for some patients. All in all, OPM-MEG could transform the way severe, drug-resistant epilepsy is evaluated and treated.

The OPM-MEG work is funded by a Wellcome award which involves a collaboration agreement with QuSpin, the company who build the OPMs. The author does not benefit financially from QuSpin or any other aspect of the project.

Stephanie Mellor
Research Student
Wellcome Centre for Human Neuroimaging
UCL Institute of Neurology

Further reading

Bell, W. E. and Bloom, A. L. (1957) 'Optical Detection of Magnetic Resonance in Alkali Metal Vapor', Physical Review. *American Physical Society*, 107(6), pp. 1559–1565.
Boto, E. et al. (2016) 'On the potential of a new generation of magnetometers for MEG: A beamformer simulation study', *PLoS ONE*, 11(8), pp. 1–24.
Boto, E. et al. (2017) 'A new generation of magnetoencephalography: Room temperature measurements using optically-pumped magnetometers', *NeuroImage*, 149(January), pp. 404–414.
Boto, E. et al. (2018) 'Moving magnetoencephalography towards real-world applications with a wearable system', *Nature*. Nature Publishing Group, 555(7698), pp. 657–661.
Centeno, M. et al. (2016) 'Optimising EEG-fMRI for Localisation of Focal Epilepsy in Children', *PLOS ONE*. Edited by D. Yao. Public Library of Science, 11(2), p. e0149048.
Duez, L. et al. (2016) 'Added diagnostic value of magnetoencephalography (MEG) in patients suspected for epilepsy, where previous, extensive EEG workup was unrevealing', *Clinical Neurophysiology*. Elsevier, 127(10), pp. 3301–3305.
Englot, D. J. et al. (2015) 'Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery', *Epilepsia*, 56(6), pp. 949–958.
Ettl, S. et al. (2013) 'Management of head motion during MEG recordings with Flying Triangulation', DGaO Proceedings, pp. 287–2013. Available at: *http://www.dgao-proceedings.de/download/114/114_a13.pdf* (Accessed: 22 May 2018).
Goldenholz, D. M. et al. (2009) 'Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography.', Human brain mapping. *NIH Public Access*, 30(4), pp. 1077–86.
Gross, J. et al. (2013) 'Good practice for conducting and reporting MEG research', *NeuroImage*. Academic Press, 65, pp. 349–363.
Johnson, C., Schwindt, P. D. D. and Weisend, M. (2010) 'Magnetoencephalography with a two-color pump-probe, fiber-coupled atomic magnetometer', *Applied Physics Letters*. American Institute of Physics, 97(24), p. 243703.
Kim, K. et al. (2014) 'Multi-channel atomic magnetometer for magnetoencephalography: A configuration study', *NeuroImage*. Academic Press, 89, pp. 143–151.
Medvedovsky, M. (2015). Methodological and clinical aspects of ictal and interictal MEG. University of Helsinki. Retrieved from *https://helda.helsinki.fi/bitstream/handle/10138/156438/methodol.pdf?sequence=3*
Mégevand, P. and Seeck, M. (2018) 'Electroencephalography, magnetoencephalography and source localization', *Current Opinion in Neurology*, p. 1.
Sander, T. H. et al. (2012) 'Magnetoencephalography with a chip-scale atomic magnetometer', Biomedical Optics Express. *Optical Society of America,* 3(5), p. 981.
Shah, V. K. and Wakai, R. T. (2013) 'A compact, high performance atomic magnetometer for biomedical applications', *Physics in Medicine and Biology,* 58(22), pp. 8153–8161.
Stefan, H. et al. (2011) 'MEG in frontal lobe epilepsies: Localization and postoperative outcome', *Epilepsia*. Wiley/Blackwell (10.1111), 52(12), pp. 2233–2238.
Stefan, H. and Trinka, E. (2017) 'Magnetoencephalography (MEG): Past, current and future perspectives for improved differentiation and treatment of epilepsies', *Seizure*. W.B. Saunders, 44, pp. 121–124.
Stufflebeam, S. M., Tanaka, N. and Ahlfors, S. P. (2009) 'Clinical Applications of Magnetoencephalography', *Human Brain Mapping*, 30, pp. 1813–1823.
Sutherling, W. W. et al. (2008) 'Influence of magnetic source imaging for planning intracranial EEG in epilepsy.', *Neurology*. American Academy of Neurology, 71(13), pp. 990–6.
Wehner, D. T. et al. (2008) 'Head movements of children in MEG: quantification, effects on source estimation, and compensation.', *NeuroImage*. NIH Public Access, 40(2), pp. 541–550.

Epilepsy publicity

Although I probably didn't really want to, how could I not write about valproate? Surely it has all been said – is there really another opinion?

But consider this: has there ever been a time – albeit mainly in light of the valproate story – when epilepsy has had such publicity? To me it seems that the time is now, and that presently, a unique opportunity is in the offing, to keep people talking about epilepsy.

Interested and engaged epilepsy clinicians have been well versed in valproate probably for the best part of 20 years. They have been acknowledging its superior efficacy in treating generalised epilepsy yet increasingly in the knowledge of its teratogenic effects and devastating neurodevelopmental consequences for children exposed *in utero*. In April 2018, the Medicines and Healthcare products Regulatory Agency (MHRA), after prolonged pressure from many, including patient groups, changed the licence for valproate. This has big implications for women of childbearing age with generalised epilepsy and for epilepsy practice across all spheres of care.

Patient groups, the media and epilepsy professionals might wonder why such restrictions on valproate have taken so long when the research demonstrating neurodevelopmental delay has been so overwhelming. Arguably, epilepsy clinicians are familiar with valproate's indications, dosing, side-effects and even the colour of the tablets. So, for engaged clinicians, the change in practice might be small, although I suspect the administrative burden less so. But for some people with epilepsy, there are certain challenges ahead. Some worthy of mention include the learning disability population and those with a historical diagnosis of epilepsy, now seizure free, who may no longer identify with the condition. Others for whom there may be implications are those living rurally and those whose care is delivered from psychiatry, maybe even requiring valproate for dual purpose.

It strikes me that valproate is now emerging as a specialist only drug, with a new licence akin to other drugs with adverse risk profiles. An example is isotretinoin (Roaccutane), used with a special licence in dermatology for acne, of which this editor has distant memory. Although the licence restrictions on isotretinoin and valproate are now similar, the real-life differences are huge, reflecting the risk profiles of the two conditions. Epilepsy is one of the commonest neurological disorders, carrying significant

morbidity and mortality. It is often a lifelong condition, requiring lifelong treatment and often has significant restrictive implications on employment and driving to name but a few.

So, despite the good and the bad with regard to valproate, can we turn these challenges and unanswered questions into opportunities? It could be a chance for all to deliver and, where needed, to develop the best care for everyone with epilepsy.

As clinicians, can we view this as an opportunity to deliver the best care? Could it mean improved patient safety, risk management, shared decision-making, consent and ultimately a facilitator for informed patient choice? Can we, by building on current resources and maybe with investment, reach out and be a proactive service rather than one which historically – at best – has been simply reactive?

This also is a unique chance to get your managers talking about epilepsy. I see this as a real opening in which to develop services in order to deliver the best care. The MHRA mandates annual reviews for women on valproate. To my mind, this consolidates the need for more epilepsy nurse specialists in existing departments and the development of new posts in deficit geographical areas. The valproate story is also a chance for a revolution and investment in information technology resources in epilepsy care. I see a pressing need for intelligent databases and smartphone apps to inform clinical services, with the potential for contract and prescribing reminders for patients, clinicians and pharmacists.

And finally, can there be a renewed incentive among neuroscientists and the pharmaceutical industry to develop new treatments? Can there be an incentive to couple the best science, clinical data and patient outcomes to develop an epilepsy drug as efficacious as valproate yet as safe as houses?

So, in light of the change in valproate's licence, can we harness these questions and challenges with a renewed momentum to keep people talking about epilepsy? There is a chance for us to do this by keeping valproate on the lips of clinicians, managers, scientists and politicians.

Dates for the diary

July 2018

19
Epilepsy study day for learning disability nurses
Abergele, UK
epilepsy.org.uk/walesprof-abergele

August 2018

25
YES ECE Meeting
Vienna, Austria
www.ilae.org/congresses/yes-ece-meeting

26-30
13th European Congress on Epileptology
Vienna, Austria
www.epilepsyvienna2018.org/

September 2018

20-22
19th International Symposium on Severe Infantile Epilepsies: Old and New Treatments (ISSET) 2018
Vatican City in Rome, Italy
bit.ly/2EZlmdi

26-28
ILAE British Chapter Annual Scientific Meeting
Birmingham, UK
www.ilaebritishconference.org.uk/

28
Irish Chapter of the ILAE 8th Annual Expert Day
Dublin, Ireland
www.ilae.org/files/dmfile/Ireland-Expert-Day-Programme-Sept2018.pdf

October 2018

5-9
6th Global Symposium on Ketogenic Therapies for Neurological Disorders
Seogwipo, Korea
keto2018jeju.org/

November 2018

1-3
Video-EEG in Paediatric Epilepsies: From seizures to syndromes
Madrid, Spain
bit.ly/2LiOBrP

Care for people with epilepsy and learning disability

Dr Lance Watkins discusses potential issues with care provision to people with epilepsy and learning disabilities and possible improvements in this area.

CBD update

Dr Hannah Cock provides an update on the latest research on cannabidiol and what the future for this potential new medicine looks like.

Epilepsy Professional's advisory panel

optima

XLTEK

Diagnostic EEG

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

natus neurology

To find out more call 020 3058 0850

www.optimamedical.com