epilepsy action

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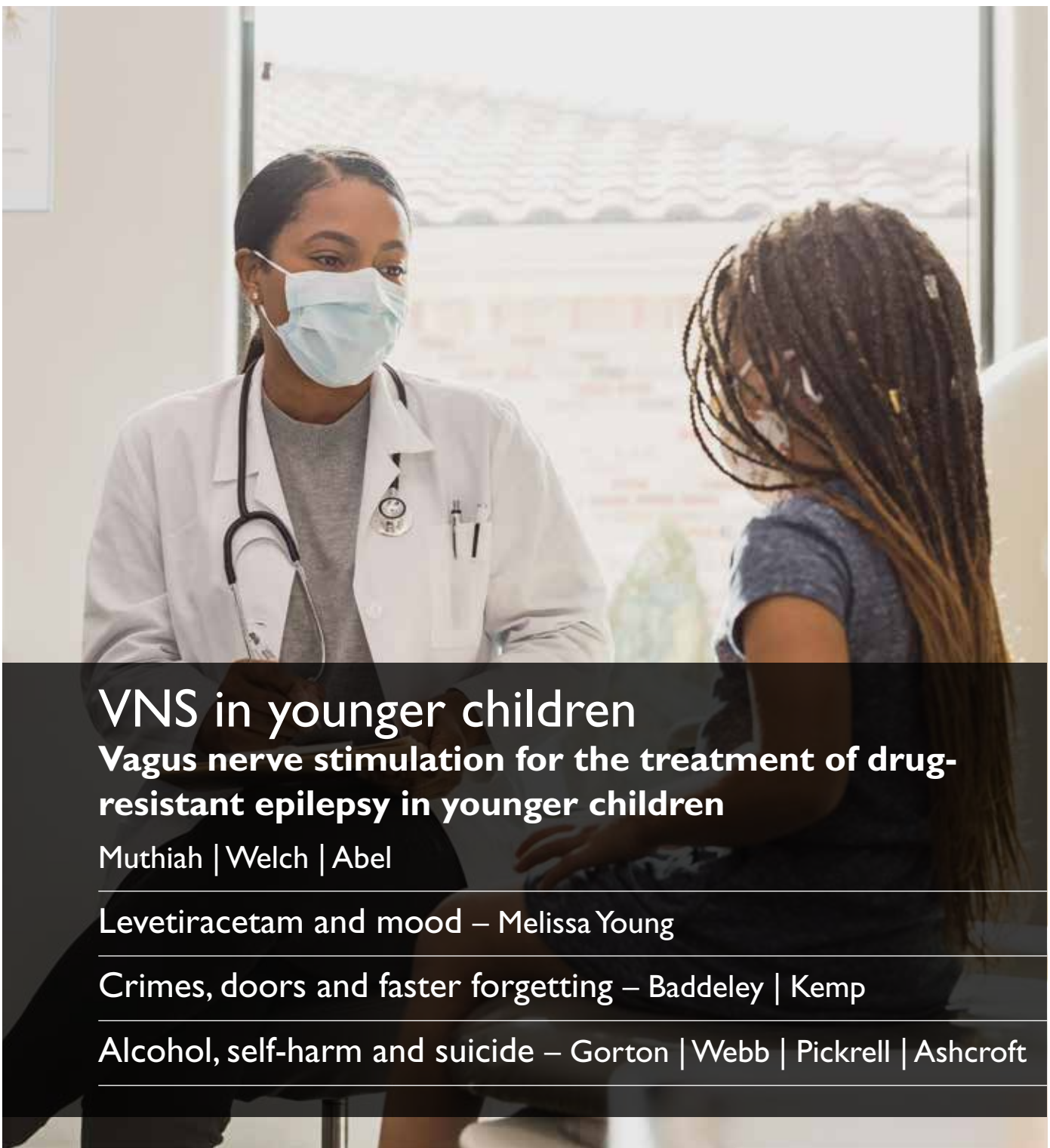

VNS in younger children

Vagus nerve stimulation for the treatment of drug-resistant epilepsy in younger children

Muthiah | Welch | Abel

Levetiracetam and mood – Melissa Young

Crimes, doors and faster forgetting – Baddeley | Kemp

Alcohol, self-harm and suicide – Gorton | Webb | Pickrell | Ashcroft

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1. Soleman et al Epilepsy & Behavior 88 (2018) 139–145 2. Orosz I et al. Epilepsia. 2014 Oct:55(10):1576-1584

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Welcome to our autumn edition of *Epilepsy Professional*. I hope readers have managed to take some time out over the summer for a bit of rest and reflection. It certainly has been a challenging time in most of our lives and already it seems the winter pressures are just starting to gain prominence.

As we return from our staycations, put the sandals away for another year and see the kids returning to school, I often feel that the new term affords us a chance to update our professional knowledge. We can learn something new, reconnect with colleagues, and attend a meeting virtually, or even, if the current climate allows, in person. I find that autumn, although it's the tail end of the year, provides a real opportunity to knuckle down and get the work done.

I think this edition of *Epilepsy Professional* does just that. I hope you enjoy the themes of mood, psychiatric illness, VNS therapy in very young children and accelerated long-term forgetting in epilepsy.

We are all aware of the alarming statistic that mortality rates in people with epilepsy are around three times higher than people of the same age without epilepsy. With this in mind, Gorton et al explore the causes of indirect death in people with epilepsy in relation to alcohol, self-harm and suicide.

In parallel, and linking almost seamlessly with Gorton's paper, Melissa Young using research from Cardiff, discusses the link between levetiracetam and mood-related side-effects. She illustrates some useful pointers for clinical practice when initiating levetiracetam, such as the risk of internal or external mood related side-effects, the relevance of sex, and a prior psychiatric history. This paper certainly is worth exploring with colleagues and patients.

We are always looking for something new, something that is a bit different and so I am sure you will read with interest Nallammai Muthiah's paper on vagus nerve stimulation in younger children. This paper explores the limited data in this area and highlights the potential benefits, complication rates and challenges in this unique population.

Finally, why not delve into Alan Baddeley and Steven Kemps fascinating paper on accelerated long-term forgetting in epilepsy? This intriguing article explores how to test for faster than usual forgetting using stories, crimes and doors testing. Overall, this discussion forms the basis for a new study in collaboration with Epilepsy Action to investigate how common more rapid forgetting is in patients with epilepsy.

I think you'll agree this selection will make interesting reading as we re-energise ourselves ready for the months ahead. I hope you enjoy this edition of *Epilepsy Professional*.

Ann Johnston
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

20 crimes, doors and faster forgetting

Baddeley | Kemp

Prof Baddeley and Prof Kemp describe creating a memory test that assesses accelerated forgetting, and they discuss the incidence of this in people with epilepsy

A place like Epilepsy Action has the profound benefit of hearing from people with epilepsy – directly and often – about their condition and their lives. And it is beyond clear that the effects of epilepsy can extend far outside seizure management. On the one hand, we can be an important resource in the clinician's toolbox, when patients want more information about things like driving, benefits and activities. On the other hand, we also need to be a mouthpiece for patients about the many other issues that come with epilepsy that the healthcare community needs to consider.

The opinion piece by Dr Rhys Thomas on page 34 perfectly encapsulates this viewpoint and the all-round theme that connects all the articles in this issue. Finding a way to treat seizures will never stop being vital, but time and again it becomes clear that care shouldn't stop there.

Our articles discuss mood-related side-effects of epilepsy medication (page 14), testing memory problems in epilepsy more accurately (page 20) and increased rates of self-harm, suicide and accidental deaths in people with epilepsy (page 28). On page 10, we also look at use of VNS in younger children. While this article looks at safety and seizure management, VNS has also been suggested to help with comorbid depression in people with epilepsy.

The Presidential Symposium at the recent International Epilepsy Congress 2021 covered the value of treating patient-reported outcomes and taking into account the patient experience. This shows how very important this is to the care of people with epilepsy. We hope you enjoy this issue.

Kami Kountcheva
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COVID-19 booster vaccine

A UK booster COVID-19 vaccine scheme is expected to go ahead and will likely start in September 2021, health secretary Sajid Javid has confirmed. This will be offered to the most vulnerable people in the UK to ensure protection continues over the winter season. The government is waiting on the final advice from the Joint Committee on Vaccination and Immunisation (JCVI) before proceeding.

The scheme is designed to help prolong protection for the most vulnerable and relieve pressure from the NHS, as winter will likely see an increase in both flu and COVID-19 cases, the Department of Health and Social Care (DHSC) explained.

Deputy chief medical officer for England, Prof Jonathan Van-Tam said: "The announcement of interim advice from JCVI is good news. It shows that the vaccine experts are thinking carefully about how best to use vaccination to protect the most vulnerable and ensure everyone's lives can remain as normal as possible for the autumn and winter."

The interim advice from the JCVI suggests a two-stage booster programme alongside the flu vaccination programme. In the first stage, a third dose COVID-19 booster vaccine would be offered to anyone over the age of 70, those living in care homes for older people and front line health and social care workers. Anyone over the age of 16 whose immune system is suppressed or who is considered clinically extremely vulnerable will also be offered the booster.

In the second stage, adults over the age of 50 and those who are household contacts of a person with a suppressed immune system would be invited for a booster. As well as this, anyone over 16 who was outlined in one of the government's at-risk groups for the flu or COVID-19 will also be invited. This includes people with epilepsy, who were included in priority group 6 during the rollout of the COVID-19 vaccination programme.

The JCVI's final advice is still awited.

The DHSC said the latest analysis from Public Health England (PHE) and the University of Cambridge suggests the vaccines so far have prevented an estimated 24 million infections and 106,000 deaths in England.

Epilepsy Action Cymru calling for another ESN role

Epilepsy Action Cymru is calling on Hywel Dda University Health Board (UHB) to appoint an extra Epilepsy Specialist Nurse (ESN).

The organisation said it has heard reports of people waiting up to 18 months to see a neurologist in areas in Wales covered by the health board. Hywel Dda UHB covers Carmarthenshire, Ceredigion and Pembrokeshire, including Bronglais, Glangwili, Prince Philip and Withybush hospitals.

There is currently one ESN working for the health board, but a proposal had been made to create a post for a second ESN, which was rejected by the health board. Epilepsy Action Cymru has urged the health board to reconsider, by writing to the chief executive of Hywel Dda UHB, Steve Moore.

Epilepsy Action has stressed to the health board the vital part that ESNs play in the epilepsy healthcare team, providing support during and between appointments to patients. The letter also outlines the support ESNs offer in relieving pressure from epilepsy services, and highlights the urgent need for another ESN in the area.

Epilepsy Action is urging members and supporters in the area to also write to the chief executive to raise their concerns about the decision not to employ a second ESN. The organisation has drafted a template letter which can be downloaded from ***epilepsy.org.uk/hyweldda*** and sent by email or post.

The organisation is also campaigning more broadly for more ESNs in Wales.

Three-quarters of children who may be eligible for surgery not referred

Findings from the latest Epilepsy12 report reveal issues among children's epilepsy services in England and Wales with referrals, information provision and school care plans.

The latest Epilepsy12 report from the Royal College of Paediatrics and Child Health (RCPCH) was published in July 2021. Much of it reflects the state of children's epilepsy services during the COVID-19 pandemic as it describes the situation in November 2020.

The report showed that three-quarters (77%) of children who should have been considered for epilepsy surgery had not been referred.

The report also found gaps in the safety information given to children and their parents and carers. In one fifth of care plans, there was no evidence that water safety had been discussed, and a similar proportion showed no evidence of information on general participation and risk being discussed. Only a third (32%) of children had a school Individual Healthcare Plan.

Less than half (43%) of children and young people with epilepsy, and their families or carers, had received information around Sudden Unexpected Death in Epilepsy (SUDEP) in the first year since diagnosis. There was a significant variation in SUDEP information provided across different regions in England and Wales.

The report also identified issues around timely delivery of care, waiting times for diagnostic tests, like EEGs, and lack of referrals to paediatric neurologists or surgery services. Mental health support services for children with epilepsy were also found to be lacking, with only 15% of health boards and trusts being able to include these within epilepsy clinics.

However, the report also pointed out there was evidence that despite the challenges of the pandemic, there was a good effort to continue to provide and improve epilepsy services.

Angie Pullen, director of epilepsy services at Epilepsy Action, said: "The pandemic has understandably impacted children's epilepsy services and care for children with epilepsy has undoubtedly been negatively affected. But there have also been missed opportunities to make early epilepsy surgery referrals, along with access to timely diagnostic tests.

"The report also highlights a huge variation in the SUDEP information provided in different regions of the UK. It is unacceptable that where you live could determine the level of potentially life-saving information families receive. It is vital that children and young people, along with their families, are given all the facts about SUDEP so that they can learn the best way to manage risk and live safely."

Mental health and wellbeing should be at the centre of children's epilepsy care, according to Mark Devlin, chief executive of Young Epilepsy. He said: "The findings of this report are of particular concern, as children and young people have had to cope with the impact of the COVID-19 pandemic on their mental wellbeing, whilst still having to come to terms with their diagnosis and the challenges they might face.

"Epilepsy is not a mental health condition, yet children and young people with epilepsy are four times more likely to develop mental health problems than their peers."

The full Epilepsy12 report can be accessed at ***epilepsy.org.uk/rcpch-epilepsy12-audit***.

Fear in parents of children with epilepsy

Parents of children with epilepsy have a lot of fears for the short and long term, despite a good level of epilepsy knowledge, a new US study has shown.

Published in the *Journal of Pediatric Nursing*, the study by Fowler *et al* used the Epilepsy-related Fears in Parents Questionnaire (EFPQ) to analyse the level of fear the 40 parents in the study felt. Short-term fear levels were at an average of 28 (with possible range 8-40) and long-term fear levels were an average of 32 (ranging from 9-45).

This is despite the fact that parents got, on average, 75% correct on the knowledge questionnaire.

On average, around 80% of parents had a college education. Children ranged from infants to 18 years of age, and were most commonly first diagnosed with epilepsy before the age of three.

The study authors concluded that participating parents were knowledgeable but fearful. They said nurses need to provide verbal and written educational materials, discuss triggers and speak to parents about their fears related to epilepsy. The researchers added that nurses should identify support available to parents and help validate parents' skills in knowing what to do during a seizure.

You can read the full study at: ***epilepsy.org.uk/jpn-aug21***

NHS sends letters to women prescribed valproate

In June, the NHS sent a letter with information to 20,000 women and girls in England who have a prescription of sodium valproate.

The letters from Dr Aidan Fowler, NHS director of patient safety, were sent to women and girls aged 12-55. They offered information about actions to take if they are pregnant, trying for a baby or haven't had a recent medicine review.

This letter is part of the NHS' aim to increase patient safety after the findings of the safety review on valproate published in 2020 by Baroness Cumberlege.

Louise Cousins, director of external affairs at Epilepsy Action, said: "We welcome any further measures to ensure that women and girls are made aware of the risks of taking valproate and other medicines while pregnant. Despite recent efforts, we know there are still women who are unaware of these risks.

"This NHS letter, while rather late in the day, should help women taking sodium valproate feel more informed and empowered to prompt conversations with their doctor about their medication. It is only then that they can make truly informed decisions.

"However, GPs and health professionals need the time and resources to make sure these conversations are actually happening, and happening early. They need to make sure women are fully informed about the risks of sodium valproate before they start taking it.

"More also needs to be done to identify potential risks of taking other epilepsy medicines in pregnancy. Epilepsy Action is therefore continuing to call for all women with epilepsy to receive preconception counselling and family planning advice.

"Women should not stop taking their epilepsy medicine before talking to their doctor."

The Medicines and Healthcare products Agency (MHRA) guidance says if healthcare professionals prescribe sodium valproate, they must ensure the woman is enrolled in a pregnancy prevention programme. Epilepsy medicines should be reviewed at least yearly.

Call for DWP to halve disability employment gap

The Work and Pensions Committee has called on the government's Department for Work and Pensions (DWP) to be "bolder in its ambitions" to support disabled people to find and stay in work.

The Work and Pensions Committee released a report on 30 July entitled 'Disability employment gap' shortly after the DWP's National Disability Strategy which was published on 28 July.

The report urges the DWP to readopt its previous target of halving the disability employment gap, which remains at 30%, and to introduce a target of getting an additional 1.2 million disabled people in work by 2027.

People with epilepsy are one of the groups that are most severely affected by the disability employment gap.

The report has called for a more localised approach to providing "personalised, flexible and effective" support. It added disabled people should be involved in conversations and decision-making. The report echoed many of the recommendations made by Epilepsy Action, including for more transparency, better benefits systems and more targeted assessment processes.

The Work and Pensions Committee has also said various employment support schemes and assessments for disabled people need to be redesigned.

The full Disability employment gap report and the National Disability Strategy can be accessed at: ***epilepsy.org.uk/parliament-employment-gap***.

Epilepsy Action has recently released its Employer toolkit, available at: ***employers.epilepsy.org.uk***.

UK government rejects call for valproate redress scheme

The government has rejected the recommendation to set up redress schemes for valproate, Primodos and pelvic mesh, in its full response to the Independent Medicines and Medical Devices Safety (IMMDS) review.

The IMMDS review's report was published in July 2020 and included nine main recommendations for the government to support people affected by these medical products and safeguard the public going forward. The report also included a number of specific recommendations on valproate. The government took six months to set out its initial response to the recommendations and over a year for the full response.

In the latest response, the government rejected the recommendation to set up separate redress schemes for people affected by the three medical products the safety review focussed on. Minister of State for Patient Safety, Suicide Prevention and Mental Health, Nadine Dorries, said: "While the government is sympathetic to the experiences of those patients who gave evidence to the report, our priority is to improve the future safety of medicines and medical devices."

Daniel Jennings, Epilepsy Action's senior policy and campaigns officer, said this outcome is a devastating blow to families affected by the medical products. "We are hugely frustrated and saddened that the government has rejected the recommendation to set up a redress scheme for the many families who experienced avoidable harm and have additional needs because of valproate. The scheme would have provided much-needed and overdue help with the costs of these additional needs and enabled families to plan for the future."

The government also rejected a part of the recommendation to create specialist centres for people affected by the three products. Specialist centres for people affected by pelvic mesh have been set up, but the government has not agreed to set up any such centres for people affected by medicines used in pregnancy. Ms Dorries said the government didn't believe this was "the most effective way forward". She said the government would work on improving care for this group within the existing health services.

The latest response mentioned the sodium valproate registry, adding that a second report from it is planned for September 2021. Plans were set out to include the whole of the UK in the registry, as well as other epilepsy medicine in addition to valproate. Ms Dorries also mentioned the letter the NHS sent to women and girls in England who are prescribed sodium valproate. She said the Medicines and Healthcare products Regulatory Agency (MHRA) will work to ensure that pharmacists have to supply sodium valproate in the manufacturer's original packaging, to help make sure the patient information leaflet is always included.

However, the response does not address the report's other valproate specific recommendations, such as establishing a clear process to ensure women are able to get appropriate counselling related to their epilepsy treatment and contraceptive choices.

Mr Jennings said: "Again, the government has not responded to the specific recommendations on valproate in the Cumberlege (IMMDS) review. We wrote to the minister on the anniversary of the Cumberlege review's publication, outlining our

concerns about the lack of progress, but are still awaiting a reply."

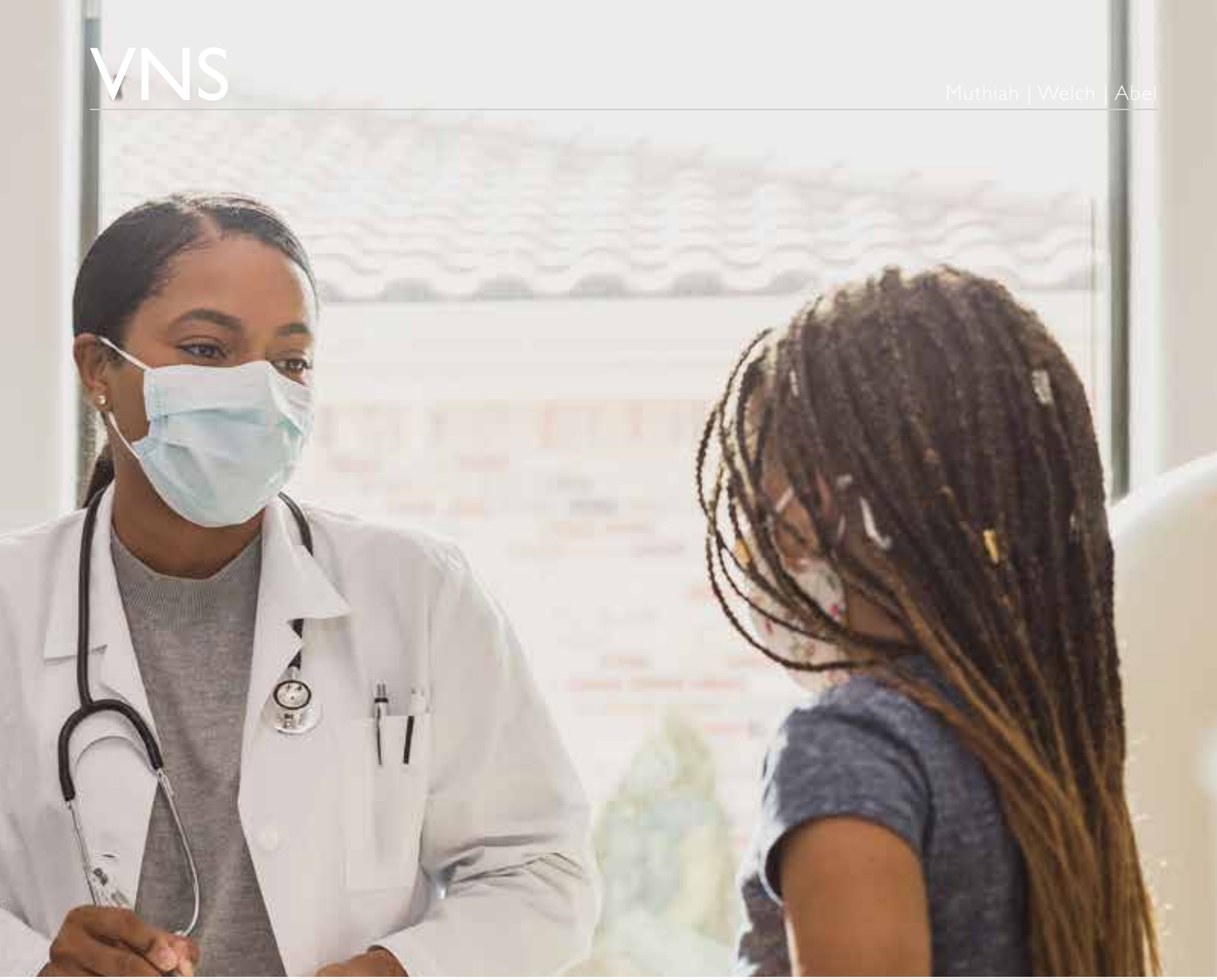
The outlined concerns include improving access to preconception counselling, identifying, diagnosing and supporting those affected by valproate exposure, improving the pregnancy prevention programme and better communication from clinicians.

"We will continue to work with MPs and others to ensure that the needs of those families harmed by valproate, and the needs of women and girls taking valproate – now and in the future – are met," he added.

The government's early response accepted a number of the recommendations, including issuing an apology, appointing a patient safety commissioner and the creation of the valproate registry. However, it did not accept a number of recommendations, including creating a redress agency for those harmed by the medical products and the creation of a task force to implement the review recommendations.

Epilepsy Action has previously criticised the government for taking six months to respond to many of the recommendations in the first place, and for a lack of response altogether to some valproate-specific recommendations.

The full government response is available at: ***epilepsy.org.uk/immds-july21***



VNS in younger children

Application of vagus nerve stimulation for the treatment of drug-resistant epilepsy in young children

Nallammai Muthiah, Dr William Welch and Dr Taylor Abel discuss recent research into the use of vagus nerve stimulation in younger children. They note the potential benefits, the possibility of a higher rate in complications and the challenges in investigating the true effect of VNS in this group.

Epilepsy is one of the most common neurological disorders in children and up to 30% of children have drug-resistant epilepsy (DRE) [Zack and Kobau, 2015]. When DRE is localised to a unitary brain focus that is safe to remove, then traditional resection-based epilepsy surgery is usually the best option and is supported by both clinical trials and observational data. However, for a large proportion of children, resective surgery is not an option because DRE is either multifocal, generalised, or involves important brain structures that cannot be removed. In these patients, vagus nerve stimulation (VNS) via an implantable pulse generator, is a widely used option that can reduce seizure frequency by ≥50% in approximately 50% of patients. An open question is whether VNS can be employed in young children and emerging data is now showing that VNS is a viable option in children younger than six [Muthiah *et al*, 2020].

While VNS has been in use longer than almost any form of neuromodulation for epilepsy, how it works to reduce seizure activity continues to be poorly understood. Seizures result from abnormal, synchronised, excessive electrical activity in the brain. It is thought that VNS has the ability to stabilise this electrical activity to prevent the onset and spread of seizures through its action of vago-thalamic afferents [Ibrahim *et al*, 2017]. Approximately 80% of the vagus nerve carries sensory input from peripheral body organs (i.e. heart, lungs and gastrointestinal tract) to the brain. The other 20% sends and outputs messages from the brain to muscles (i.e. striated muscles in the throat).

Most studies suggest that between 30% and 60% of patients with drug resistant epilepsy will achieve 50% reduction in their total seizure frequency with VNS

The vagus nerve is important for mediating coughing, swallowing, blood pressure and heart rate. When the vagus nerve is stimulated by a pulse generator, vagus nerve fibres carry this input through the brainstem into the higher processing centres of the brain. One theory for VNS mechanism of action is that this electrical signal stimulates the release of several neurotransmitters with anti-seizure effects, including serotonin, norepinephrine, glycine and GABA [Johnson and Wilson, 2018; Gonzalez *et al*, 2019]. Another theory is that electrical stimulation allows for the desynchronisation of excess brain electrical activity [Johnson and Wilson, 2018; Gonzalez *et al*, 2019]. It is also thought that VNS allows for increased blood flow to the parts of the brainstem and higher order centres [Johnson and Wilson, 2018; Gonzalez *et al*, 2019].

Most studies suggest that between 30% and 60% of patients with DRE will achieve 50% reduction in their total seizure frequency with VNS [Muthiah *et al*, 2020; Tzadok *et al*, 2019; Thijs *et al*, 2019; Krahl and Clark, 2012;

Klinkenberg *et al* 2012; Handforth *et al*, 1998; Fernandez *et al*, 2015; Englot *et al*, 2011]. It is still unclear if VNS is more beneficial for patients with specific types of epilepsy (i.e. patients with structural causes of epilepsy, genetic syndromes, idiopathic generalised epilepsy, etc.). However, most of the clinical studies describing outcomes of VNS have been in older children or adults. Additionally, newer models of VNS are now being employed that respond to changes in heart rate which is often associated with seizure activity. The rationale is that these 'closed-loop' models can stimulate the vagus nerve when they detect these changes in heart rate associated with seizures, thus preventing or shortening a seizure. The efficacy of these models compared to traditional VNS models remains unknown.

With limited clinical trial and observational data, the safety and effectiveness of VNS for DRE in young children has been a subject of debate. Recently, two studies have sought to investigate the safety and efficacy of VNS in young children. In 2015, Fernandez and colleagues described 15 patients age <3 years who underwent VNS implantation for DRE [Fernandez *et al*, 2015]. Thirty-three percent of the patients in this cohort had decreased seizure frequency at one year. Additionally, despite 40% of the cohort having a history of status epilepticus (SE), no patient had SE after VNS implantation (during the follow-up period). More recently, in 2020, Muthiah and colleagues described 99 patients age ≤6 years who underwent VNS implantation for DRE [Muthiah *et al*, 2020]. At one year of follow-up, 55% of these patients had a ≥50% reduction in seizure frequency, consistent with studies in older patients. In this cohort, the complication rate was 5.6%, consistent with the rate in older patients. However, the complication rate in the Fernandez *et al*. [2015] study was 13%, potentially reflecting a greater complication rate in the <3 years cohort, though this warrants further investigation.

A limitation of these studies is that it is challenging to measure the effects of VNS in children with epilepsy. One reason is that during development, seizures can evolve due to neurodevelopmental influence independent of any treatment (e.g. VNS). In other words, after VNS, children may either 1) stop having some seizure types or 2) develop new seizure types. Some of these changes occur independently of stimulation, but VNS may influence the evolution of a patient's epilepsy as well. It is difficult to differentiate which changes in seizure types occur due to natural brain development and which occur due to influences of VNS. Another challenge with measuring the impact of VNS is that epilepsy is usually treated with multiple modalities to optimise seizure control. Patients may have changes to their antiepileptic medications while undergoing VNS therapy, so changes in seizure frequency cannot be solely attributed to VNS.

With limited clinical trial and observational data, the safety and effectiveness of VNS for DRE in young children has been a subject of debate

One final challenge to implementing VNS in young children is the risk for complications. Children

may be more prone to the complications of VNS therapy. Minor complications including vocal changes with VNS activation, coughing, or neck pain, occur after approximately 6% of VNS surgeries. Major complications (e.g. lead wire fractures, infections, etc.) are potentially more common in young children, especially if they tend to manipulate the device or disrupt the insertion site. In our manuscript, we reported a major complication rate of 5.5% in children treated with VNS younger than age six.

In summary, VNS is a safe and viable treatment option for children with epilepsy. However, as we describe above, it must be employed carefully as it can be difficult to measure the influence of VNS therapy and certain complications may be more common. Our hope is that future research will investigate the use of VNS therapy further in younger age groups.

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Further reading

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Melissa Young

Levetiracetam and mood

Factors associated with levetiracetam mood-related adverse effects: a retrospective case note review

Melissa Young discusses the link between levetiracetam and mood-related side-effects

One of the most popular anti-seizure medicines (ASMs) currently in use is levetiracetam (LEV), which was first licensed in 2000 and is now widely prescribed. However, as with all drugs, it comes with a risk of adverse reactions. The British National Formulary (BNF) lists some of LEV's most common side-effects as dizziness, drowsiness, headache, nausea and insomnia [NICE BNF, 2021]. Negative mood-related adverse effects (NMRAE), such as depression, irritability and aggression, used to be considered rarer side-effects until around 2005 when awareness began to grow and these issues became more noticeable. Most individuals experience only mild mood disturbance, however more severe side-effects have also been recorded. Evidently, we must do everything we can to avoid potentially inducing such serious negative side-effects in people. However, at the same time, LEV is a very effective ASM and offers a large number of people great seizure control with minimal problems. So the ideal solution is to be able to predict who might experience NMRAEs with LEV, and explore other treatment options for them. A step towards this solution is to uncover factors that correlate with experiencing NMRAE on LEV, a goal which many researchers have been attempting to tackle for years.

Negative mood-related adverse effects, such as depression, irritability and aggression, used to be considered rarer side-effects of levetiracetam until around 2005

One of the earliest studies into this area found that in a sample of 517 patients on LEV, 10.1% developed psychological adverse effects [Mula *et al*, 2003]. The presence of these effects was found to significantly correlate with history of febrile convulsions, status epilepticus and previous psychiatric history. They also found that lamotrigine (LTG) co-therapy was protective against adverse effects. However, it is important to note that these patients had only been taking LEV for a relatively short period of time due to its recent licensing, and therefore may not yet have developed any adverse effects. A more recent study with a similar design but larger sample of 4,085 patients with epilepsy, 1,890 of which were on LEV, also looked into this. It found that psychiatric history, secondarily generalised seizures, absence seizures and intractable epilepsy were all significantly associated with psychological and behavioural side-effects [Chen *et al*, 2017].

The majority of the research in this area is in the form of case reports, focusing on specific examples of patients who suffered adverse mood effects on LEV. These reports, while hard to generalise or statistically analyse due to the focus on qualitative data, can be very useful in uncovering factors that could predict these effects. One such case report

Table 1. Percentage of patients who were experiencing each category of seizure frequency.

Frequency	Total	Group S	Group C
>1 per day	**13%**	24%	2%
>1 per week	**31%**	34%	28%
>1 per month	**27%**	20%	34%
>1 per year	**23%**	18%	28%
<1 per year	**6%**	4%	8%

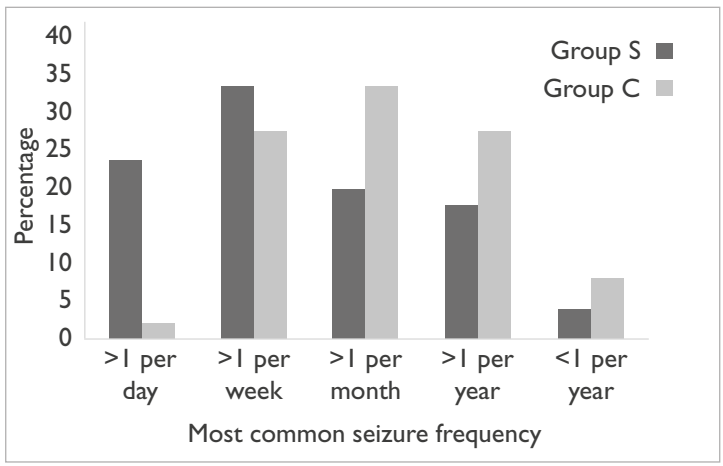

Figure 1. A graph to show the percentage of patients experiencing each seizure frequency, separated by group (=p<0.05).*

investigated a 66-year-old man who had been seizure free for five years on 1000mg of LEV. He ran out of medication and subsequently suffered two breakthrough seizures, so his dose was increased to 2000mg. Within one month he was experiencing suicidal ideation, a major depressive episode, and had attempted an overdose. The only noted psychiatric history was alcohol dependence, however no official psychiatric assessment was undertaken. Also, there was no follow up after he discontinued the drug [Kaufman *et al*, 2013]. Another case report investigated a 79-year-old male who began showing homicidal ideation three months after starting LEV. After six months, he threatened to kill his wife and himself. On admission to a psychiatric facility he denied any delusions, and anti-psychotics had no effect. Only a week after discontinuing the LEV did the suicidal and homicidal threats abate. This is an unusual case, as homicidal behaviour is very rarely seen in cases of LEV mood disturbance. It was possible that other factors were at play other than purely drug side-effects. Nonetheless, it does seem likely that introduction of LEV exacerbated the problem [Aikoye and Rangwani, 2018].

Studies have shown that there is unlikely to ever be a clear-cut solution to the problem of NMRAEs associated with LEV. However, the more we learn about patients who have experienced this, the closer we can get to preventing it. The following study is a retrospective case note review of 100 epilepsy patients who had taken LEV. The aim was to collect information on as many factors as possible, using clinic letters rather than face-to-face consultations, as this allowed for a larger sample size. The data would then be analysed to find any correlations between the group and the factors.

Study method

All patients under Cardiff and Vale University Health Board (CAV UHB) who had been on LEV at any point during their treatment were eligible for inclusion. Patients also needed to have had an MRI scan, a diagnosis of epilepsy and recent clinic letters containing all the necessary information. For patients

Table 2. Percentage of patients in Group S who experienced internal change compared to external change.

	NMRAEs included	Total	Group S	Group C
Internal change	Low mood, depressed, mood swings, suicide attempt, anxious, suicidal thoughts, tearful, withdrawn, emotional, hallucinations, psychosis, self-harm, isolated, paranoid, confused, frustrated, miserable.	**63%**	50%	75%
External change	Irritable, aggressive, angry, short-tempered, edgy, difficult, abrupt, agitated, behavioural problems, nasty.	**37%**	50%	25%

who had discontinued LEV, reasons for stopping needed to have included some mention of NMRAE. This was defined as any change from normal in the patient's mood, behaviour or personality, and must have been explicitly stated somewhere in the patient's record, either by the patient or someone who knows them.

A total sample of 100 patients was obtained, with 50 patients who stopped LEV (from now on referred to as Group S) and 50 patients who continued LEV (now referred to as Group C). Sex was balanced for 1:1 ratio in each group. The mean age in both groups was 43 (Group S σ = 14.74, Group C σ = 16.66).

Significant findings

i. Seizure frequency

This was taken as the frequency most commonly experienced by the patient, across all available clinic letters. For simplicity, this was categorised into one of five frequencies, as shown in *Table 1*. As shown in *Figure 1*, the largest difference was seen in patients experiencing >1 seizure a day. In Group S, 24% of patients were most commonly experiencing more than one seizure a day, while in Group C this was just 2% of patients. It is true that a higher seizure burden is usually accompanied by a higher medication dose and therefore it was considered that this could be a third factor mediating the association between seizure frequency and incidence of NMRAEs. However, upon investigation no correlation between seizure frequency and LEV dose was found.

ii. Nature of NMRAE

Note that this category applies to Group S only, and was intended to investigate if the type of NMRAE experienced by the patients who stopped LEV correlated with any other factors. Given this was a subjective judgement of mood by the patient or people who attended clinic with them, the descriptors were categorised for ease of comparison. This was done by 'direction of change'; internal changes were those affecting how the patient felt in themselves, while external changes were those affecting how the patient behaved towards others. Some examples of how descriptors were categorised can be seen in *Table 2*. On average, internal NMRAEs were more common than external. However, when separated by sex, a noticeable pattern emerged whereby internal changes became more common in women and less common in men, with the opposite effect seen for external changes, as shown in *Figure 2*.

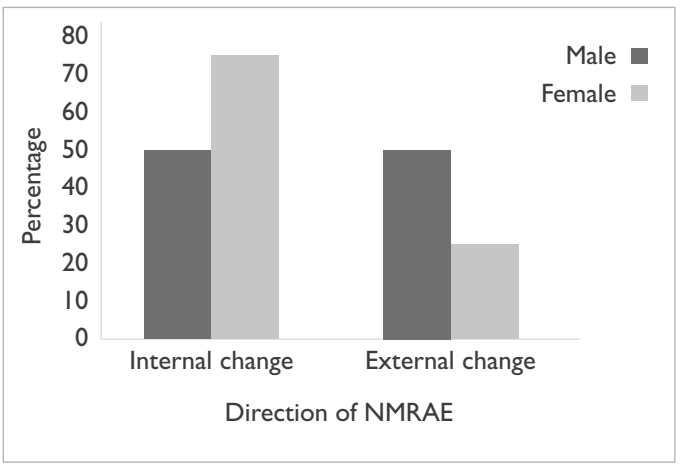

Figure 2. A graph to show the percentage of patients experiencing an internal vs external NMRAE separated by sex (=p<0.05).*

Table 3. Percentage of patients who had known previous psychiatric history of each severity, and percentage of total patients with no or unknown psychiatric history.

Severity	Psychiatric history included	Total	Group S	Group C
Mild	Depression, anxiety, stress, behavioural issues.	**55%**	48%	65%
Moderate	Learning difficulties, panic attackes, ADHD.	**13%**	9%	17%
High	Suicide attempt, suicidal thoughts, self-harm, substance abuse, eating disorder, aggression, violence, psychosis	**32%**	42%	17%
None	N/A	**3%**	2%	4%
Unknown	N/A	**61%**	56%	66%

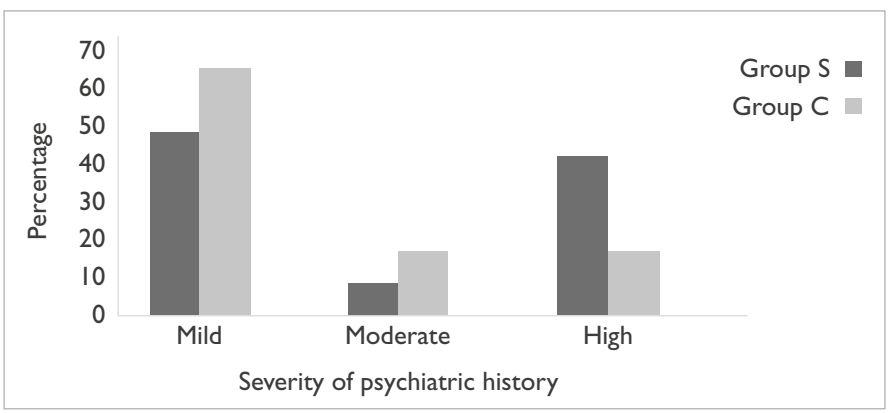

Figure 3. A graph to show the percentage of patients who had confirmed psychiatric history of varying severity, separated by group (=p<0.05).*

iii. Psychiatric history

This was the category where the largest difference was expected, based on findings in previous research. Patients were categorised as 'Yes' if there was confirmation of any psychiatric history, 'No' if there was confirmation of no psychiatric history, and 'Unknown' if it was not mentioned. Results showed that psychiatric history was present for 42% of Group S and 30% of Group C. This initially suggests only a slight difference in presence of psychiatric history between the two groups. Therefore, to investigate further, the psychiatric history was categorised according to severity as either mild, moderate or high. Some examples of how various psychiatric illnesses were categorised can be found in *Table 3*. Following this, it became clear that there was a higher incidence of severe psychiatric history in Group S than Group C, as shown in *Figure 3*.

Discussion

This research has demonstrated that there are very few factors which reliably correlate with experience of NMRAEs during LEV therapy. However, the significant findings are able to propose some previously unresearched associations which may be of interest.

Firstly, NMRAEs appear to be significantly more prevalent in patients with a high seizure frequency. The mechanism, and indeed the direction, of this effect is unclear but does suggest considering an alternative ASM in patients with a high seizure burden.

Secondly, the nature of the NMRAE experienced seems to vary by sex in terms of its direction. Females were found to be significantly more likely to experience internal NMRAEs, such as low mood and depression. Males were equally likely to experience external NMRAEs, such as aggression and irritability, as internal. This echoes previous findings on the nature of mental illness in males and females [Rozenfield and Mouzon, 2012], suggesting that LEV may increase an

individual's propensity to develop psychiatric problems. While this finding does not help in choosing who to prescribe LEV to, it does help us predict the nature of the NMRAE a patient may experience on the drug. This can allow us to fully inform individual patients of the side-effects they are most at risk of, so that any disturbance can be picked up more quickly.

Thirdly, the presence of severe psychiatric illness in a patient's history seems to be predictive of experiencing NMRAEs. Previous research had suggested that any psychiatric history increased the risk of NMRAEs when taking LEV, which may have led to the drug not being considered in patients with a mild or moderate psychiatric history. However, the findings of this research demonstrate the risk is relatively low in these patients, and it may be more beneficial to consider an alternative ASM only in patients with severe psychiatric history.

However, perhaps the most striking finding of this study is that in 61% of the sample there was no mention of psychiatric history in the patient's notes. This is a pertinent issue, as even without considering the effects of LEV, epilepsy patients are at considerably higher risk of mental health issues. Research has found a 33% prevalence of depression [Viguera *et al*, 2017] and a 40% prevalence of anxiety [Pham *et al*, 2017] in patients with epilepsy. This demonstrates that it is crucial to make sure that psychiatric wellbeing is discussed regularly in clinic. However, due to the pressures on the NHS and the limited time allotted for appointments, most of which is used to discuss seizure control and medication, it is very difficult for clinicians to create time for discussion of mood. Hence there exists a need for resources that support a more formal evaluation of mood in epilepsy clinics. This is not just to monitor any NMRAEs that arise as a result of medication, but also to provide more holistic patient care in general.

This research was carried out under the supervision of Dr Khalid Hamandi at the Cardiff and Vale University Health Board

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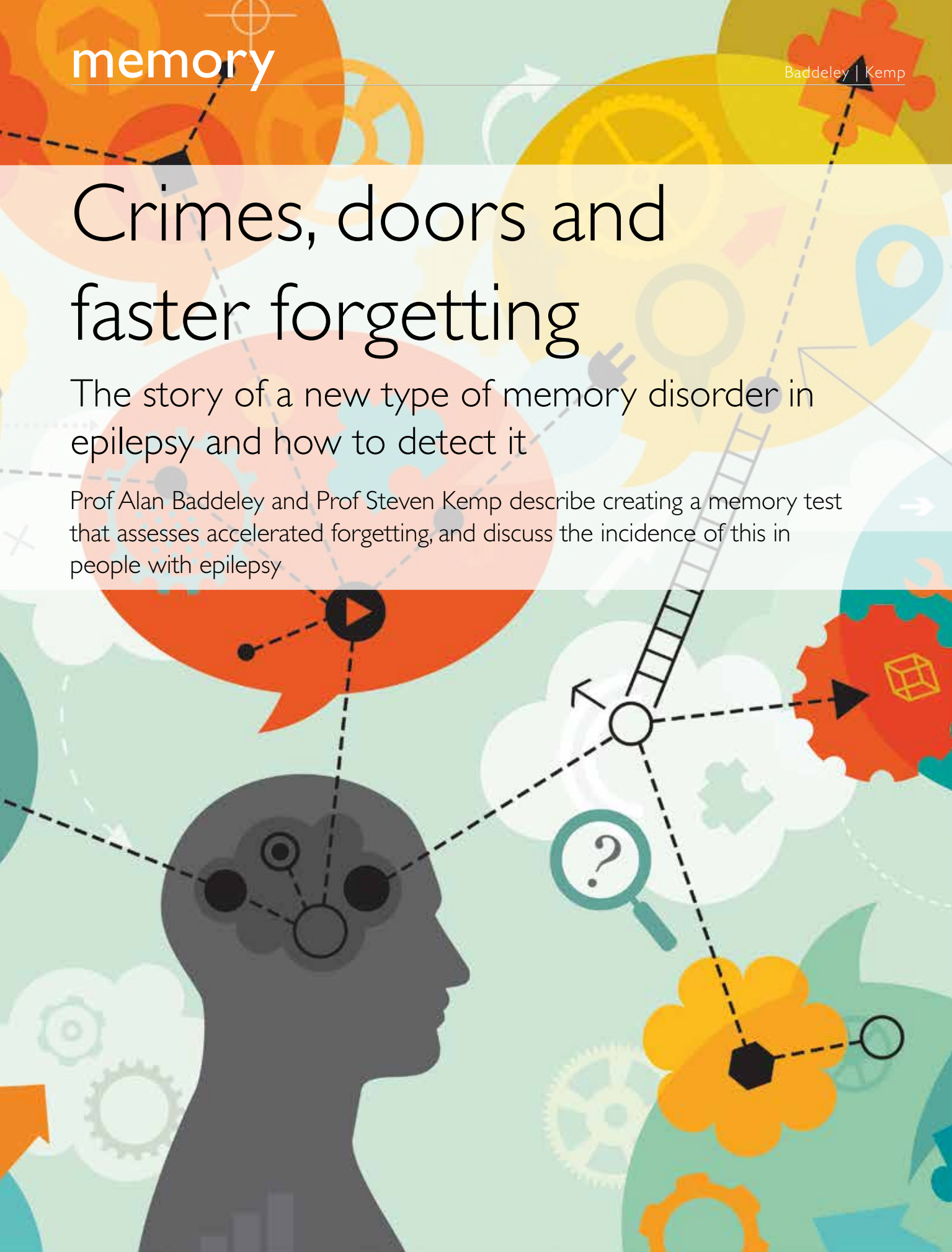
Crimes, doors and faster forgetting

The story of a new type of memory disorder in epilepsy and how to detect it

Prof Alan Baddeley and Prof Steven Kemp describe creating a memory test that assesses accelerated forgetting, and discuss the incidence of this in people with epilepsy



We all are inclined to complain about our memories, but, in fact, memory is a remarkably effective system or rather an alliance of systems. Psychologists tend to distinguish between **working memory**, the capacity to hold things in mind while thinking about them, **semantic memory**, our library of knowledge of the world and **episodic memory**, our capacity to remember specific events and episodes. This allows us to distinguish one event, for example meeting a friend last week, from all the other occasions of meeting them. This ability to remember individual experiences, is crucially important for our capacity to live independently, but is also the most vulnerable type of memory with problems ranging from those we all experience as we grow older to the dense amnesia that accompanies the later stages of Alzheimer's Disease. It can occur in epilepsy and can be an unwanted side-effect of epilepsy surgery, but is by no means universal.

However, while clinical deficits in episodic memory are widespread, rate of forgetting is surprisingly consistent. Even very densely amnesic patients who have great difficulty in acquiring new memories do not forget them any faster than people without dense amnesia. This is convenient for the psychologist assessing a person's memory, as they can assume that whatever is remembered after half an hour or so, accurately reflects the patient's memory with no need to call them back for later testing.

We clearly needed better ways of detecting a condition that has become known as Accelerated Long-term Forgetting (ALF)

But over recent years it has become increasingly clear that this may not always be the case. It was already understood that objective neuropsychological test scores and patients' subjective memory reports do not always match. Some patients that do well on formal cognitive tests report poor memory, and vice versa. This dissociation was generally attributed to psychological factors such as anxiety or depression. However, reports began to appear of people who performed well on standard memory tests, then later showed quite dramatic forgetting. This unusual pattern was found to occur particularly in people with epilepsy [Zeman *et al*, 2013]. Such people will, of course, complain of memory problems. But, unfortunately, we are not very good at assessing our own memories, and given apparently good performance over the typical test session they are likely to be discounted. We clearly needed better ways of detecting a condition that has become known as Accelerated Long-term Forgetting (ALF). The problem at the time was that standard neuropsychological memory tests assessed memory over delays typically of 45-60 minutes, which fits in well with clinic appointments. Clinicians did not have tests to detect faster than usual rate of forgetting occurring over hours, days or weeks. There was a clear need to develop more specialist long-term memory tests to improve

our understanding of the impact of epilepsy on memory and develop memory rehabilitation approaches for epilepsy patients. Consequently, an interested group of neurologists, neuropsychiatrists and clinical and academic neuropsychologists was formed in the UK. This group aimed to tackle this problem and iron out various methodological challenges in developing new formal tests of long-term memory.

The problem initially seemed to be a simple one. The psychology of memory started in the 19th century with the study of forgetting, surely we must know enough to develop a suitable test by now! There was, however, a serious problem, that of testing the same person on the same material several times over days weeks or months. Each time the memory is tested, the material recalled tends to be strengthened, a form of rehearsal that could mask important forgetting. Indeed, a recent development in the educational field has been to emphasise that testing knowledge may be a more effective way of establishing it than presenting the material again. But as each test involves relearning, the many patients who have problems of learning but not of forgetting may gain less from each test and hence appear to be forgetting faster.

One way of avoiding this is to test only part of what has been learned at each delay, for example presenting four stories and testing one immediately, one after 20 minutes, one after 24 hours and one after a week. Four separate stories does, however, place a very heavy initial learning load, a particular problem for patients who may have a learning deficit as well as faster forgetting. For this reason, each story has to be relatively short with the number of questions asked limited to six or seven facts at each delay, making it a very blunt instrument for detecting rate of forgetting.

A possible way around this problem was offered by a task devised many years before to test the effects of cold on memory in trainee divers [Baddeley *et al*, 1975]. We suspected they would not be greatly interested in the material from most

There was a clear need to develop more specialist long-term memory tests to improve our understanding of the impact of epilepsy on memory and develop memory rehabilitation for epilepsy patients

neuropsychological tests leading us to develop the Wrecks Test. This interested the divers and also allowed a large number of questions to be generated from a small set of readily imageable descriptions of sunken wrecks. There were four distinctive types of wreck (liner, fishing boat etc) all having a distinctive name (Lucky Lucy, Northern Star etc), resting at a distinctive depth on a particular type of sea bottom surrounded by different underwater vegetation. Recall involved asking a series of specific questions, for example "How deep was the Lucky Lucy?" The material proved easy to learn and allowed a large number of test questions that were easily scored.

It seemed a promising way ahead, but since we could not assume an enthusiasm for wrecks in our population, we transferred the test to a description of four minor crimes in a small seaside town. (TV schedules suggest that most people are

interested in crime!) Each crime had a victim whose age, sex and nationality needed to be remembered, as well as a criminal, their age and sex, the crime and the location. For example: "The elderly Russian lady had her handbag snatched outside the cathedral by a young girl who ran away". Three other crimes were included and memory was tested by probing one associated feature, for example "What crime was committed against the Russian person?" allowing these to be asked in either order (e.g., who had their handbag snatched?). This yielded a total of 80 questions, which allowed 20 to be tested immediately and 20 at each of three delays (which ranged from 20-minutes to 1-month later). Each delay included a different sample of questions from all four crimes and with no questions repeated [Baddeley *et al*, 2014].

Preliminary testing using the Crimes Test in York comparing young and older participants was encouraging. This led to the inclusion of the Crimes Test in a doctoral thesis concerned with epilepsy in Oxford. This produced very encouraging results with substantial forgetting in the patients, compared to very little in the control group of people without epilepsy [Drane, 2012].

At this point we decided that there was a need to develop a visual equivalent of the Crimes Test as the memory of people with epilepsy can differ depending on the location of the epileptic focus

However, the controls had learned more than the patients and were, in fact, virtually perfect on the initial test and showed very little later forgetting. This raised two problems: one, was the test too easy? If so, the memory traces could be weakening, but still strong enough to allow perfect performance. And two, if this was not the case, why did the comparison group show so little forgetting?

Meanwhile back in Leeds, a series of studies were examining the Crimes Test in more detail, asking questions such as whether the test was too easy and whether it made a difference whether people were tested by telephone or face to face. Happily, these and other studies suggested that the Oxford sample was not typical and testing by telephone or face to face gave the same results. This meant that patients could be retested at each delay without the need to return to the clinic each time. At this point we decided that there was a need to develop a visual equivalent of the Crimes Test, as the memory of people with epilepsy can differ depending on the location of the epileptic focus (i.e. the left or right temporal lobe).

For the visual test (The Doors Test) we selected four door scenes, a church, a factory, domestic house and a gate. In each case, memory for the colour of the door, its surroundings, an object above the door and a creature in front of it was required, again allowing a total of 80 questions. We found the task of remembering these four apparently simple door scenes surprisingly difficult. We had to present each for a total of 10 seconds and check immediately afterwards that the relevant features had been learned before going on to test memory.

The next stage was to run the Crimes Test and Doors Tests side by side with a group of young people without epilepsy. We needed to ensure

that performance was not too high and that roughly comparable amounts of forgetting of the verbal Crimes and the visual Doors Test were found over delays up to one month. These studies were run in York and Leeds with the help of volunteer psychology student testers, who each recruited four friends who were willing to be tested over a one-month period. All seemed to be going well; the tasks were roughly equivalent, not too hard nor too easy on first test, but still gave a reasonable score after a one-month delay [Baddeley *et al*, 2018]. There was, however, much less forgetting than we expected. Could it be that although no question was tested twice, that testing one feature, for example the bag being snatched from the Russian person, might evoke the whole incident? Was this serving as a reminder that would then slow down forgetting? We went on to test this by comparing performance after a month between two groups, one who had the intervening tests at one day and one week and another who were only tested after a month. There was a clear difference. Forgetting after a month's unfilled delay was much greater [Baddeley *et al*, 2021]. This suggested that probing one feature was, in fact, doing just that – serving as a reminder and hence slowing forgetting. Did that mean that anyone who had a learning problem would also have difficulty benefiting from the intervening test and thus appear to have faster forgetting? Had we failed?

There was a ray of hope. This depended on the way in which the intervening tests had prevented forgetting. It is known that even densely amnesic patients can benefit relatively normally from "priming". Priming occurs when an existing memory is reactivated, but does not necessarily mean that memory is relearned. If this were the case, then amnesic patients with normal forgetting, but impaired learning, should benefit from intervening testing of other features in the same way as controls. We were fortunate at this point in collaborations with the University of Edinburgh where a number of PhD students were focusing on more theoretical aspects of forgetting. One of these, Andrea Stamate, was testing a large sample of patients with Alzheimer's disease using a method very similar to that used in the Crimes Test, comparing the patients to age matched controls.

The crucial question was whether the patients would gain the same benefit from intermediate testing as the controls, suggesting that our effect reflected re-activating the existing memory trace?

The crucial question was whether the patients would gain the same benefit from intermediate testing as the controls, suggesting that our effect reflected re-activating the existing memory trace? If they showed no effect of the intervening tests, this would suggest a relearning account that would rule out our test. Happily, across two separate studies, despite their learning impairment, the patients did derive the same benefit as the control group from the intervening tests. This suggested that our test was not a relearning, but rather a priming effect in which the original memory trace is reactivated [Stamate *et al*, 2020]. That means that we are indeed measuring forgetting and indicated that the

Oxford study was reflecting faster forgetting in people with epilepsy.

This left the final acid test of what would happen if both tests were given to patients with temporal lobe epilepsy? Once again a doctoral thesis came to the rescue, in which Tom Laverick tested a group of people with epilepsy and a matched control group on both the Crimes and Doors Tests. He studied forgetting on both tests after 20 minutes, 24 hours and a week [Laverick *et al*, 2021]. The patients clearly forget substantially more than the controls. This replicates the earlier Oxford study and suggests that the problem for the patients lies in the activation of what appear to be vulnerable memory traces. This showed a clear deficit even after a week's delay, an effect that seems likely to become more marked after longer delays. Almost all of the patients showed some degree of faster forgetting, even though they were not selected on this basis.

This suggests that faster forgetting may be more common in epilepsy than had previously been realised. Why should that be the case? Much of the earlier work was concerned with demonstrating that forgetting could not be attributed to poor initial learning and hence focused on those cases whose initial learning was well within the normal range. There is, however, no reason not to expect that faster forgetting also occurs in people who also have poorer initial memory. This was indeed the case for our own patients who required twice as much practice to bring them up to a normal level of learning.

So how common is more rapid forgetting in people with epilepsy? We simply do not know. We are, however, currently trying to find out in collaboration with Epilepsy Action, using a new version of both the Crimes and Doors Tests that can be delivered via Zoom. We invited people with epilepsy and their partners (who would be their case matched controls) to take part in a trial and are delighted with an excellent response. This work is ongoing and will, we hope, lead on to a more substantial and well funded study. This would allow us to establish the extent to which faster forgetting occurs in people with epilepsy. This will also allow us to continue to refine our ALF tests (verbal and non-verbal) for both research and clinical use, and, in due course, help ameliorate the impact of ALF on quality of life and daily functioning.

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Markus Reuber

Highlights

Top picks from *Seizure*

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

I retain vague memories of a period in my pre-clinical studies when pharmacology seemed relatively straightforward. Anticonvulsants were used to treat seizures, antidepressant drugs for depression, antihypertensives to control high blood pressure and statin therapy to reduce the levels of cholesterol. Lowering levels of cholesterol made good sense because of its contribution to atherosclerosis and the risk of myocardial infarction or stroke. This period of relative bliss was initially challenged when I found out about 'good' (HDL) and 'bad' (LDL) cholesterol and the importance of the HDL:LDL ratio. However, since then, it has become clear that the effects of statins extend well beyond the regulation of cholesterol metabolism. In fact, their benefits in the primary and secondary prevention of complications of vascular disease are not exclusively mediated by cholesterol levels or ratios. They also offer benefits by decreasing oxidative stress and inflammation, and by antithrombotic actions [Liao and Laufs, 2005].

Statins exert their beneficial effects on cholesterol metabolism by inhibiting the rate-limiting enzyme of the L-mevalonate pathway, the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This pharmacological effect reduces inflammation through effects on downstream metabolites of the same pathway. These metabolites play critical roles in different steps of the body's immune response including immune cell activation, migration, cytokine production, immune metabolism and cell survival [Zeiser, 2018].

Importantly, a number of studies suggest that these effects are not only pharmacologically demonstrable but also of clinical significance. The clinical benefits of statin therapy may include anti-seizure and anti-epileptogenic effects, especially in the context of post stroke epilepsy [Etminan *et al*, 2010; Guo *et al*, 2015]. My editor's choice from issue 88 of *Seizure*, an observational study of 1,033 patients followed up after experiencing stroke by Yanmei Zhu *et al,* adds to this evidence [2021]. In this study, the incidence of post stroke epilepsy was 0.4% among the 245 patients who received double dose statin therapy and 2.5% in the 788 patients treated with a standard dose. These findings strengthen the rationale for large prospective studies of intensive statin therapy in patients with stroke and in older individuals with probable cerebrovascular disease presenting with a first seizure.

Long COVID

Unfortunately, for many people, the medical triumph which the COVID-19 vaccines represent may only mark the end of the beginning rather than the beginning of the end of the pandemic. A recent study of 4,182 incident cases of COVID-19 in the UK, who logged their symptoms prospectively in the COVID Symptom Study app, looked at 'long COVID'. The study reported that 13.3% had symptoms lasting >28 days, 4.5% for >8 weeks and 2.3% for >12 weeks [Sudre *et al*, 2021]. The prevalence of long COVID suggested by these figures would not be much of a societal problem if the infection was a rare disorder. But, if more than 10 or 20% of the population are infected [Wells *et al*, 2020], and 2.3% continue to have symptoms after four months, the number of those with ongoing difficulties will be very large indeed.

While the vaccines have proven a remarkably effective tool to deal with the wave(s) of acute COVID-19 infection, the search for the most effective ways of dealing with long COVID is still on. Several of the symptoms of this new disease entity – fatigue, headache, anosmia – point to a possible cause in the central nervous system (CNS), but what are the disease mechanisms?

My editor's choice from issue 89 of *Seizure*, a review article by Elizabeth Carroll *et al,* makes a small contribution to this search [2021]. Although COVID-19 infections sometimes involve acute symptomatic seizures or status epilepticus, evidence of direct SARS-Co-V-2 infection is only found in a minority of cases. This conclusion is based on their investigation of the results of cerebrospinal fluid (CSF) analyses in a total of 69 patients whose CSF findings have been published in previous case series and reports. Evidence of a positive CSF SARS-CoV-2 Polymerase Chain Reaction (PCR) was only found in 13% of the patients in whom this test was carried out.

Evidence of viral invasion of the CNS only being found in a relatively small proportion of cases suggests that long COVID may be a syndrome with a different cause in most people. Or it may have different causes in different people. Latent CNS infection is unlikely to make a major contribution if the virus does not tend to invade CNS in the acute phase of the illness. The effects of abnormal clotting in the context of the acute illness or prolonged immune activation may be relevant in some cases. Others may be suffering from a syndrome more akin to ME or functional neurological disorder. We may well have occasion to learn much more about long COVID over the next few years.

Subjective epilepsy experiences

It is well known that dogs rely much more strongly on their sense of smell than their sense of vision and that acute hearing is more important for bats than their eyes. Humans tend to recognise far less well to what extent their sense of vision drowns out other sensory inputs. We like to see things with our own eyes before we believe them. We are strangely suspicious of our other senses, even if what they tell us is objectively right and the predominance of visual processing leads us to get things wrong. Those wanting to experience this for themselves should look up videos of the McGurk effect on YouTube: they will 'see' that what they 'hear' may not be what has been said. And to 'hear' correctly, they will need to close their eyes.

Issue 90 of *Seizure* is a Special Issue, celebrating 15 years of the Latin American Summer School of Epilepsy (LASSE). This made the task of identifying a single contribution as my editor's choice particularly difficult. The choice I ultimately made was in part influenced by the fact that Peter Wolf, the author of the manuscript, has been one of the most active and popular contributors to the LASSE project. But also I was drawn by the fundamental significance of its topic: the importance of subjectivity in the understanding and treatment of epilepsy [Wolf, 2021]. In his essay, Peter Wolf describes how video-EEG and the increasing availability of home video recordings of seizures have greatly advanced our understanding of the visible manifestations of epilepsy. However, he also discusses how these developments are at risk of drowning out the patient's voice and the information clinicians could obtain by creating the conversational space. This allows patients to share their subjective experiences. The relative dearth of research into subjective seizure descriptions is all the more surprising as the interpretation of the patient's history continues to be the most important diagnostic tool in the seizure clinic [Plug and Reuber, 2009]. Peter Wolf also reminds us that, as the expert on their own seizure experiences, the patient is worth listening to. This is still the case even if the patient's expertise will need to be combined with that of the medical specialist to gain a fuller understanding of the patients' accounts.

Perhaps the suspicion of non-visible information is justified in view of how the human brain has evolved. However, this is no excuse not to be aware of our habit to favour 'objectivity' – including sensory perceptions which we can reasonably expect to share with others. It's important to try to counteract our tendency to pay less attention to our patients' efforts to communicate subjective experiences which cannot really be shared. If we don't access our patient's 'inside knowledge' we cannot hope to understand epilepsy – or to treat it.

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Alcohol, self-harm and suicide

What should clinicians know about how these affect people with epilepsy?

Dr Gorton, Prof Webb, Dr Pickrell and Prof Ashcroft discuss findings from their research into alcohol use, self-harm, suicide and unnatural deaths in people with epilepsy and what clinicians should look out for

Introduction

People with epilepsy have mortality rates which are around three times higher than people of the same age without epilepsy [Nevalainen *et al*, 2013]. In 2016, Devinksy *et al* highlighted the urgent need for accurately classifying deaths that are directly or indirectly attributed to epilepsy, and for accurately estimating the magnitudes of risk for these causes of death. At the same time, we conducted a series of epidemiological studies that could go some way toward answering these questions. Our focus was specifically on indirect causes of death, including suicides, accidents and alcohol-related death [Gorton *et al*, 2018a; Gorton *et al*, 2021]. We had a particular interest in suicide and extended this to consider non-fatal self-harm [Gorton *et al*, 2018b] and the potential contribution of anti-seizure medication (ASM) to suicide and self-harm [Gorton *et al*, 2016; Gorton *et al*, 2018c]. We will briefly summarise the findings from these studies and highlight how they might inform your practice.

We conducted epidemiological studies in two population-based datasets that were based on general practice data. These were the Clinical Practice Research Datalink (CPRD) in England and the Secure Anonymised Information Linkage (SAIL) Databank in Wales. Both datasets were linked to Office for National Statistics (ONS) mortality data and to hospital admission records.

We had a particular interest in suicide and extended this to consider non-fatal self-harm and the potential contribution of anti-seizure medication (ASM) to suidice and self-harm

Accidental death

In our matched cohort study comparing people with epilepsy to those without epilepsy in the CPRD (44,678 vs. 891,429) and SAIL databank (14,051 vs. 279,365), we found that people with epilepsy were at three-fold increased risk of accidental death (deprivation-adjusted pooled HR: 2.97, 95% CI 2.54-3.48) [Gorton *et al*, 2018a]. In our study, the majority of deaths were classified as 'other accidental', making it difficult to draw clear conclusions on the types of accidents taking place. Future research should look at types of accidental deaths in epilepsy to try to establish effective preventative measures.

Fatal poisoning

In the same study [Gorton *et al*, 2018a], a five-fold elevation in risk

was evident for accidental poisoning with medication (deprivation-adjusted HR: 4.99, 95%CI 3.22-7.74). We estimated a three-fold increased risk of suicide by medication poisoning (deprivation-adjusted HR: 3.55, 95%CI 1.01-12.53). This estimate was imprecise due to the small number of deaths recorded against this cause. Nonetheless, both findings highlight the need for vigilance as regards fatal poisoning in people with epilepsy. Some of this might be influenced by the accessibility of medicines to people with epilepsy. Indeed, having access to means, in this case medication, increases risk of suicide [Hawton and Van Heeringen, 2009].

However, ASMs were rarely involved in poisonings, mentioned in approximately a tenth of fatal poisonings in people with epilepsy and 2.5% of poisonings in those without epilepsy. This corroborates with reports to the USA National Violent Death reporting system, where just 6% of suicide poisonings in people with epilepsy involved ASMs [Tian *et al*, 2016]. Despite people with epilepsy having access to ASMs, they are not commonly featured in poisoning reports. It is possible that some under-reporting has occurred. In our study [Gorton *et al*, 2018a] we were limited to the ONS reporting categories to extract medication data, which has limited granularity. Alternatively, it might be a reflection of improved safety profiles of the most commonly prescribed ASMs compared to historic use of phenobarbital, for example, which commonly featured in poisoning [Mackay, 1979]. Similar to the general population [ONS, 2020], opioids were the most commonly implicated medicines in poisoning in our epilepsy (56.5%, 95% CI 43.3, 69.0%) and comparison (47.3%, 95% CI 41.4, 53.3%) cohorts [Gorton *et al*, 2018a]. This is a useful reminder of the need to consider medications that patients may have direct access to via prescription.

The use of medicines other than ASMs in poisonings is indicative of people having access to other medicines that are prescribed for comorbid conditions. Half of adults with epilepsy are known to have a least one comorbidity [Keezer *et al*, 2016]. Given this, it is important to consider the risks of accidental death and suicide associated with these concomitant physical health and mental health conditions. People with epilepsy are two to five times more likely to have a mental health problem than those without [Mula *et al*, 2021]. The risk of suicide in people with mental health problems is between five and 18 times that of those without [Singhal *et al*, 2014] and accidental death is two to seven times more common [Crump *et al*, 2013]. The contribution of comorbid health problems to the risk of suicide in people with epilepsy should be considered. In our study, we observed a doubling of risk of suicide in people with epilepsy versus those without the condition [Gorton *et al*, 2018a]. Others have reported that the suicide risk in people with epilepsy and comorbid psychiatric disorder is higher than among individuals with epilepsy alone [Fazel *et al*, 2013].

People with epilepsy are two to five times more likely to have a mental health problem than those without and the risk of suicide in people with mental health problems is between five and 18 times that of those without

Factors contributing to self-harm

While we did not see frequent use of ASM in fatal self-poisonings, ASMs have been reported to be often involved in non-fatal self-harm poisoning in people with epilepsy [Meyer *et al*, 2014]. It is important to continuously monitor the involvement of ASMs in self-harm, suicide and accidental poisoning. This is particularly considering the recent rise in the frequency with which gabapentin and pregabalin are involved in drug-related deaths [ONS, 2020] and self-harm [Daly *et al*, 2018]. This is a problem wider than the epilepsy community as, although traditionally ASMs, these medicines have generally been repurposed by clinicians for other conditions [Montastruc *et al*, 2018].

We used the CPRD to investigate self-harm in people with epilepsy [Gorton *et al*, 2018b]. Firstly, we estimated that self-harm risk was elevated fivefold in the year following epilepsy diagnosis (aHR 5.31, 95% CI 4.08, 6.89), with a threefold (aHR 3.31, 95% CI 2.85, 3.84) increased risk persisting into subsequent years. Secondly, we identified factors that might increase risk of self-harm in people with epilepsy. Having a mental health problem increased risk, as did having multiple GP consultations [Gorton *et al*, 2018b]. The two could be interlinked, with people seeking help for their mental health problems, or they could be independent. That point of contact could, however, provide an opportunity for discussion with these patients about self-harm, should the clinician deem that appropriate. This corroborates the World Health Organization (WHO) recommendations that generalist healthcare providers should ask people about self-harm if they are aged over 10, have epilepsy and present with distress or pain [WHO, 2015]. For epilepsy specialists, an awareness of such potential consultations and associated records might be useful. Means to facilitate collaboration with, and access to, mental health teams could also be beneficial.

We estimated an elevated risk of self-harm for people not prescribed an ASM in the 90 days prior to report of self-harm; those taking two ASMs rather than monotherapy; and for those who had recently augmented treatment

We observed patterns in ASM usage associated with self-harm. We estimated an elevated risk of self-harm for people not prescribed an ASM in the 90 days prior to report of self-harm (OR 1.47, 95% CI 1.01-2.12); those taking two ASMs rather than monotherapy (OR 1.84, 95% CI 1.33, 2.55); and for those who had recently augmented treatment (OR 2.12, 95% CI 1.38, 3.26) [Gorton *et al*, 2018b]. This is likely to be a reflection of the severity or underlying control of epilepsy, rather than the ASMs per se. It is plausible that non-adherence to, lack of tolerance or lack of efficacy of ASMs contribute to this increased risk. When considering treatment changes, it is therefore important for clinicians to actively explore mental health issues in addition to changes in seizure frequency.

Role of anti-seizure medication

In addition to considering the role of ASMs in poisoning, whether ASMs themselves might influence suicide or self-harm has been explored through

epidemiological studies. However, the evidence-base generated to date is inconclusive [Ferrer *et al*, 2014; Gorton *et al*, 2016]. In 2008, the USA Food and Drug Administration (FDA) associated an increased risk of suicidality with ASM use versus placebo [FDA, 2008]. The interpretation and understanding of risk was confounded by the underlying risk of epilepsy or other conditions being treated. The comparison to placebo is largely an unrealistic comparison for most people with epilepsy, where treatment with ASMs is a necessity. Well-designed and robust studies using epidemiological data, to predict rare outcomes, such as suicide, are challenging. Compared to valproate, we reported no difference in risk of self-harm in people with epilepsy who were new-users of carbamazepine (HR 1.53, 95% CI 0.89, 2.64) or lamotrigine (HR 1.35, 95% CI 0.79, 2.29) [Gorton *et al*, 2018c]. However, with just 91 reported self-harm events across the cohorts, this was a small study and requires replication in other datasets. Studies that compare risks of self-harm or suicide with individual ASMs versus a reference ASM would be useful. They can help to understand if any particular ASM should be avoided or preferred, once other prescribing factors have been considered.

Alcohol-specific death

In our studies focusing on unnatural mortality and self-harm, we noted that people with epilepsy had higher prevalence of alcohol misuse than the comparison cohorts [Gorton *et al*, 2018a; Gorton *et al*, 2018b]. As well as reflecting epilepsy caused by alcohol related issues, this could reflect the increased risk of mental health issues. This highlighted the need to better understand alcohol-specific death in epilepsy [Gorton *et al*, 2021]. We compared people with incident epilepsy to a matched cohort and estimated a fivefold increase in risk of alcohol-specific death (deprivation-adjusted HR 4.85, 95% CI 3.46, 6.79) in those with epilepsy. Notwithstanding the potential bi-directionality of alcohol misuse and epilepsy, there is a need for awareness among clinicians of the risk of alcohol-specific death in this group.

Implications for practice

By bringing together our series of studies, we hope to highlight and contextualise to epilepsy professionals, some of the specific risks of dying by suicide, accident or an alcohol-specific cause; and of non-fatal self-harm. Much of this relates to raised awareness and vigilance among epilepsy healthcare providers. Where appropriate, this might underpin education and intervention amongst specific patient groups [Devinsky *et al*, 2016]. It is imperative that we step back and continue to see the patient as the whole person that they are. This will help to understand any additional factors that might influence a person's risk of any of these outcomes, beyond that contributed by epilepsy specifically.

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What is your risk appetite?

I don't play the stock market and I am not a cryptocurrency investor. However, I know that if you are seeking professional help with regards to investments, your personal advisor will attempt to gauge your risk appetite. The simple adage is not to gamble more than you can afford to lose – however, not all risks are financial.

Some medical students earn a little pocket money as 'healthy' volunteers for first in man clinical trials. Here, they are definitely risking something which they could scant afford to lose: their health. However, the chances of this happening are so low, and the remuneration so handsome, that a week's work may allow them to take the rest of the summer off, or to travel. These are predominantly foolhardy young men, intelligent but not wise. (And this is why medical training must take so many years, as it allows these callow students to mature. There is simply no discernible need to teach the Krebs cycle or the clotting cascade beyond padding out the curriculum, for fear of otherwise producing an army of 21-year-old doctors). ***Reader, I know, for I too was once an impetuous tyro.***

As a clinician, how do you gauge the risk appetite of the person with epilepsy that you are treating? There are people on our books that an algorithm would identify as having missed their chance at epilepsy surgery, or that they have remained on medication for too long. Are we perfectly aligned with the people we care for and careful not to shove them towards an unwelcome treatment choice? Or is it too easy to do too little? I have said this before and I am certain I will say this again – it is very easy to do epilepsy badly. By this I mean, it is possible to be a low ambition, low impact, low energy, low risk clinician. It is possible to not raise expectations, not look for or treat epilepsy beyond seizure diaries, and not be proactive about identifying future epilepsy or medication issues. I am sure there will be people who can hear a consultation about sleep, weight or mood concerns and think their only responsibility is to push or pull a large (metaphorical) lever marked more or less carbamazepine.

I'm not sure that everyone reading this would be happy to be retooled as an epilepsy life coach. But if you adopted a role of guide or guru, could you lead people with epilepsy towards what they should be expecting? '***For you seizure freedom is the goal.***' Do we tell people that they should be aiming for driving and that anything less is a failure? '***In your case, I think we can keep the same seizure control, but swap meds for some with more tolerable side-effects***.' How do you negotiate the transition of ambition from seizure control, to the containment of medication effects?

I see epilepsy clinicians, like psychiatrists, as the great masters of risk. It would take a paradigm leap to allow us to move from advising from a position of experience, towards shared decision making based around risk. This brings me back to another familiar tune. We have a desperate need for investment in clinical epilepsy and epilepsy research to achieve something like this. How can I adequately counsel a woman, unexpectedly pregnant and taking valproate, when I have population risks and not individualised risks to hand? What do I suggest when I have around 30 epilepsy medicines to prescribe, but safety data in pregnancy for only a handful as monotherapy, and a paucity of particulars for drugs in combination? And why is still the case, when some of these drugs have been treating people with epilepsy longer than I have?

So, this is my 'don't have nightmares, do sleep well' moment: are we risk masters for a collection of diseases, with no coherent way to measure true seizure control or response to therapy, and meagre data for us to advise on life changing decisions? How do we know we are getting this right? What is your appetite for risk?

Dates for the diary

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

2021

23-24 September
ILAE British Branch Virtual Annual Scientific Meeting
Virtual congress
www.ilaebritishconference.org.uk/

23-26 September
15th World Congress on Controversies in Neurology (CONy)
Virtual congress
cony.comtecmed.com

19-22 October
7th Global symposium on medical ketogenic dietary therapies
Brighton, UK
globalketo.com

28-30 October
3rd International Congress on Mobile Devices and Seizure Detection in Epilepsy
Copenhagen, Denmark
na.eventscloud.com/ehome/index.php?eventid=574764&

2022

5-6 March
ILAE British Branch Virtual 18th Specialist Registrar Epilepsy Teaching Weekend
Virtual event
epilepsyteachingweekend.com

20-25 March
3rd International Training Course on Neuropsychology in Epilepsy
Bordeaux, France
bit.ly/3fae9rL

28 April - 2 May
14th European Paediatric Neurology Society Congress (EPNS)
Glasgow, UK
epns-congress.com/

9-13 July
14th European Epilepsy Congress
Geneva, Switzerland
epilepsycongress.org/eec

Next issue:

Dr Andrew Schomer

Dr Schomer discusses depth of sleep, postictal heart rate and SUDEP

Dr Helbig, Dr Lewis-Smith and Dr Thomas

Dr Helbig, Dr Lewis-Smith and Dr Thomas discuss the role of big data in supporting research and clinical care in epilepsy

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