epilepsy action

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epilepsy professional

Side-effects of AEDs

Tolerability and safety of anti-epileptic drugs

Martin Brodie

Transition clinic – Lisa Cook | Louise Douglas

NICE guidelines – Arjune Sen

Neuroimaging – Simon Keller

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VNSTherapy®
by LivaNova

Welcome to the first edition of *Epilepsy Professional* of 2018 and a belated happy new year.

The transition from paediatric to adult service can be a difficult time for patients with epilepsy. They have a chronic condition and will have built up relationships with their Child Health healthcare providers. Lisa Cook and Louise Douglas from Sheffield describe the transition service in Sheffield and how they aim to tailor their service to the needs of the young people under their care.

Good seizure control is important in epilepsy, but quality of life can be affected by side-effects to the drugs we use. Prof Martin Brodie from the Scottish Epilepsy Initiative gives an excellent review of the common side-effects of anti-epileptic drugs. This is an indispensable summary to help us in discussing these side-effects with patients.

One of the hardest aspects of having epilepsy is not knowing when the next seizure will come or if a treatment will work or not. Dr Simon Keller from Liverpool describes the role of imaging in determining prognosis in epilepsy.

Finally, Dr Arjune Sen from Oxford appraises the relevance of the current NICE epilepsy guidance to current evidence-based practice.

I hope you enjoy this issue.

Seán Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

21 highlights

Markus Reuber

Seizure editor, Prof Reuber, highlights the key papers from the latest editions. This issue: mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis and seizure detection devices

After many years of life, I heard (or rather read) the term 'decision fatigue' for the first time this year. Dr Rhys Thomas's fantastic opinion piece in this issue discusses decision-making in healthcare and the role of the healthcare system (page 33).

But decision fatigue – what a revelation! I finally understood why after spending the day deciding on phrasing, spacing, topics and images, I couldn't for the life of me pick what I wanted for dinner from the takeaway. And in terms of responsibility, my job doesn't begin to compare to that of anyone in healthcare. This issue's articles all show some of the decisions healthcare professionals have to make, and some tools to make these easier.

On page 10, paediatric epilepsy outreach nurses Lisa Cook and Louise Douglas describe the transition service from child to adult services in Sheffield. This process is full of decisions in itself, not least of all when to start transition for each individual. On page 28, Prof Martin Brodie describes some of the side-effects that epilepsy medicines can cause. Adverse effects add that extra dimension for consideration when prescribing an epilepsy medicine, alongside finding the most effective treatment.

However, there is work going into technologies and guidance to make the decision-making process a little easier on medical professionals. Dr Simon Keller describes how new imaging techniques and technology can help clinicians to predict likely seizure outcomes after surgery on page 22. On page 16, Dr Arjune Sen notes what a commodity the National Institute for Health and Care Excellence (NICE) guidelines for epilepsy are, providing evidence-based recommendations. However, he questions whether they need a revision in light of advancements in recent years.

At least we hope having a look through this issue has been an easy decision – enjoy!

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Doctor in charge of Connor Sparrowhawk's care when he died at NHS unit suspended for 12 months

The doctor in charge of Connor Sparrowhawk's care when he drowned in the bath after having a seizure, has been suspended for a year.

Dr Valerie Murphy was facing a medical practitioners tribunal to determine her fitness to continue to practise medicine. This was after it was found that she made a number of failings in Connor's care while he was at an NHS specialist unit.

On 21 February, the tribunal ruled that Dr Murphy should face a 12-month suspension from the medical register. Her case will be reviewed again when the 12 months are up.

Dr Murphy was in charge of 18-year-old Connor's care at a now closed-down Southern Health specialist unit Slade House in 2013. Connor had epilepsy, autism and a learning disability. He died a few months after becoming a resident at the facility. An independent investigation some months later found that his death was preventable.

In August, Dr Murphy admitted to 30 failings in Connor's care. A further nine failings were found proved by the tribunal. The failings included not taking a full history of Connor's epilepsy and seizures and not providing appropriate care plans. An inquest found that neglect had contributed to Connor's death.

In November, Dr Murphy's fitness to practise medicine was found to be impaired by the tribunal. It found that she had not recognised the extent of her failings and "appeared to be looking for excuses". It was also noted that Dr Murphy had shown "an absence of remorse".

After the tribunal announced its decision, Connor's mother Dr Sara Ryan said on Twitter: "'I really did 'take my eye [off] the ball' in this case. And our beautiful boy drowned. No words. #JusticeforLB"

Epilepsy Action deputy chief executive Simon Wigglesworth said: "Epilepsy Action welcomes the Medical Practitioners Tribunal Service (MPTS) decision to suspend Dr Murphy over Connor's completely avoidable death.

"The fact that Dr Murphy admitted to failing to carry out any risk assessments in relation to Connor's epilepsy shows a clear and shocking failure to deliver a basic level of care and treatment for him. This case highlights the importance of care plans in ensuring that epilepsy treatment and management is as safe and effective as possible. It is vital that professionals caring for people with epilepsy in care, support and treatment settings have been properly trained to fully understand the condition and all its implications. In fact, it is the very least that people with epilepsy deserve. It was clear in this case that Dr Murphy did not take Connor's epilepsy seriously enough which led to his tragic and needless death."

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

Focal epilepsy and mood disorders

A new US study has suggested that mood disorders and some types of epilepsy may have a shared genetic susceptibility.

In the *Epilepsia* study, Beverley Insel and colleagues looked at the prevalence of mood disorders in people with epilepsy and their families. They compared this prevalence to that of the general public.

The study looked at 192 participants – 110 with epilepsy and 82 relatives. The study looked separately at people with focal epilepsy, generalised epilepsy, both, and unclassifiable epilepsy.

The results showed that the risk of mood disorders was higher in people with focal epilepsy, but not in people with generalised epilepsy. This was true when compared with relatives without epilepsy and when compared with the general public. Prevalence of mood disorders was also found to be higher in people with epilepsy who had at least one relative with focal epilepsy.

The researchers concluded that these results support the idea that there is a shared genetic susceptibility between epilepsy and mood disorders. However, they stressed that the effect may be restricted to focal epilepsy.

Preferences regarding epilepsy medicine characteristics

A new US study has looked at the preferences of patients and neurologists when it comes to epilepsy medicines. The study identified that patients put more priority on side-effects, while neurologists prioritised efficacy.

Researchers Ettinger and colleagues wanted to find out which epilepsy medicine attributes were important to neurologists and patients. Participants were asked to complete a survey – 518 respondents were patients and 202 were neurologists. The survey asked people to choose between two hypothetical medicines, each of which had six separate characteristics. These included: level of seizure control, dose frequency, effect on coordination and balance, psychiatric issues, impact on energy level and diet restrictions.

The study found that both neurologists and patients raked seizure control as the most important characteristic and dietary restrictions as least important. However, neurologists

put more weight on seizure control than patients (45% compared with 32%). Meanwhile, patients put significantly more importance than neurologists on psychiatric adverse effects, coordination problems and impact on energy.

The study, published in *Epilepsy & Behavior* concluded understanding the difference in preferences can help clinicians and patients communicate better in the decision-making process.

Survey about rolandic epilepsy

Researchers at King's College London are looking for professionals working with children with rolandic epilepsy to take part in a survey.

Rolandic epilepsy is one of the most common types of epilepsy in children, and is almost always outgrown during puberty. It is also known as benign epilepsy with centrotemporal spikes (BECTS).

The online survey is looking for input from professionals such as paediatricians, epilepsy nurses, teachers and psychologists. It is also hoping to collect the views of parents of children with rolandic epilepsy, and children with the condition aged eight to 16 years old.

The survey will ask people to rate how important different outcomes and aspects of health are to measure when researching childhood epilepsy. This research is part of a project called CASTLE (Changing Agendas on Sleep Treatment and Learning in Childhood Epilepsy).

Anyone interested in taking part can email *castle-study@kcl.ac.uk* for more information.

Can surgery help reduce stigma in epilepsy?

A new study from India found that epilepsy surgery with good outcomes may help to reduce stigma associated with the condition in children.

Researchers Bajaj and colleagues carried out a small study to identify the effect of surgery on stigma. They analysed data, collected at a tertiary epilepsy treatment centre before and after surgery, using the child stigma scale evaluated by Austin and colleagues in 2004.

According to the study, there was a significant reduction in stigma after surgery proportional to level of seizure control. However, in nine children (30%) who had a good seizure outcome, the stigma did not reduce. The authors said this is because they had persistent neurodisability even after surgery, which also affected levels of stigma.

The researchers concluded that surgery can be helpful in reducing stigma, but better seizure control is not the only factor relevant to stigma reduction.

Carbagen SR out of stock in UK

Carbagen SR (prolonged release carbamazepine) tablets are out of stock in all doses. Mylan, the makers of Carbagen SR, does not know when it will have these tablets back in stock.

Standard release Carbagen tablets are in stock in 200mg and 400mg doses.

UK Government launches review after three "public health scandals"

The UK government has launched a review following three "public health scandals", one of which concerns the risks around taking sodium valproate during pregnancy.

The review will look into how safety and side-effects concerns from people are handled and the processes followed by the NHS and medicine regulators. It will focus around the way three scandals were handled. One of these is around the safety concerns regarding sodium valproate.

Sodium valproate is recognised as a very effective epilepsy medicine for some people. In some women with epilepsy, sodium valproate it may be the only medicine that works. However, there is an increased risk of developmental problems and birth defects in babies born to mother taking the medicines.

Reports have said that the risks have been known since the 1970s. But many people who have had babies affected by this medicine have said they were not told about the risks. This has affected many families and has been called a "scandal" in parliament.

The review will be led by Baroness Julia Cumberlege. As part of this, two other treatment "scandals" will be looked into. One is the pregnancy test drug Primodos, which it is claimed has led to birth defects and miscarriages in women. The other is the vaginal mesh implant, which has been linked to severe and "life-changing" side-effects for women.

Prime Minister Theresa May said during Prime Minister's Questions that these issues have shown a problem with the regulatory and healthcare system.

Secretary of state for Health and Social Care Jeremy Hunt said that "the response to these issues from those in positions of authority has not always been good enough".

Epilepsy Action deputy chief executive Simon Wigglesworth said: "The announcement marks a major breakthrough for the thousands of women with epilepsy who have campaigned for change around sodium valproate.

"We urge Baroness Cumberlege to fully consider the decades of evidence provided by campaigning groups, including Epilepsy Action. This will help those families who have suffered can get some closure. It will also help women with epilepsy make fully-informed decisions about their treatment and planning a family.

"We welcome Jeremy Hunt's commitment to implementing the European Medicines Agency's recommendations around sodium valproate.

"It remains to be seen how and when these recommendations will be implemented and we are working with UK decision-makers to see how they will work in practice. Until things change, women and children will continue to be affected by something that can be potentially prevented."

Blood test for epilepsy?

Researchers in Ireland are looking to develop a blood test for epilepsy.

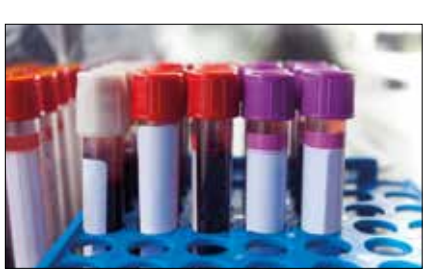
David Henshall is a professor of molecular physiology and neuroscience at the Royal College of Surgeons in Ireland (RCSI). He and his team have been studying micro RNA and its role in identifying epilepsy.

Prof Henshall leads the EpiMiRNA consortium, which aims to increase biomedical, clinical and industrial research data to improve the treatment of epilepsy. He and his team carried out research comparing the levels of micro RNA in blood samples of people with and without epilepsy. They found that one type of micro RNA was always different in the blood samples of people with epilepsy.

Prof Henshall has explained that developing a blood test for epilepsy can help simplify diagnosis process. He highlighted that healthcare professionals don't always get to witness a seizure in their patients and noted that EEGs can sometimes produce misleading results. He said a better test is needed.

Reports say that the team is now working to create a device that can detect these miRNA molecules. Their aim is to produce a simple finger-prick test and their aim is to make it available within five years.

There is more information at: *epimirna.eu*



Treatment in older people with epilepsy and intellectual disability

A new study from Ireland found that older people with epilepsy and intellectual disability (ID) were often exposed to psychotropic medicines.

The study by Dr O'Dwyer and colleagues aimed to investigate the prevalence and patterns in prescribing epilepsy medicines in older people with ID and epilepsy.

Of the 753 people with ID in the study, 205 were diagnosed with epilepsy and were receiving epilepsy medicines. About half of people (103) were on polytherapy. The researchers found that the most commonly used epilepsy medicines were valproic acid, carbamazepine and lamotrigine.

The results showed that 13.7% of people were also taking a psychotropic which should be avoided in epilepsy. They also found that 32.6% of people had a psychotropic where caution is required in epilepsy. The researchers said that 80% of these were antipsychotics with epileptogenic potential. Of the people on polytherapy, around 30% said they had been seizure free for the previous two years.

The authors concluded that the prevalence of epilepsy was high among people with ID. They found that more than half were taking more than one epilepsy medicine, but over half of people still had had seizures in the previous two years.

The authors also found that people with ID and epilepsy were often taking psychotropic medicines, which can lower seizure threshold. The study concluded that regular reviews of epilepsy medicines, and other medicines which may interact, may improve the quality of prescribing. This would require a multidisciplinary team. They also highlighted the value of improved exchange of information between specialists and primary care practitioners.

The full study is published in the *Journal of Intellectual Disability Research*.

Embrace seizure-detection device approved by FDA

The smart watch Embrace has been approved by the US Food and Drug Agency (FDA).

The watch, created by company Empatica Inc, monitors for tonic-clonic seizures and sends an alert to a chosen person.

The company explained that the device measures many indicators for a seizure. One unique feature, according to Empatica is that it measures and incorporates data from electrodermal activity. This is often used in stress research, the company said.

Embrace has already been approved in Europe as a medical device for seizure monitoring and alert, the company said.

There is more information on the Empatica website at: *empatica.com*

Call for applications for the 2019 Michael Prize

The Michael Foundation is calling for applicants for the 2019 Michael Prize.

The Michael Prize recognises the best contribution to clinical and experimental research in epilepsy among younger researchers (under 45 years old). The foundation calls this "one of the most highly regarded international awards" and the prize money is €20,000.

The 2019 prize will be awarded for research in clinical neurophysiology; neuropsychology, psychology and psychiatry; and epilepsy genetics.

Applicants can submit up to three scientific papers written in English which are published or submitted for publication at *michael-foundation.de/michaelpreis*. At least one of the papers must be from 2017/2018. Applicants must also submit a CV and indicate which of the categories their research falls in. Closing deadline is December 31, 2018.

The Michael Foundation was set up in 1962 to support scientific research into causes and treatments of epilepsy and seizures. The Michael Prize is awarded to encourage more epilepsy research.

Applications will be rated by an independent international jury and the final decision will be made by the Board of Trustees of the Michael Foundation.

Transition clinic

Moving from child to adult epilepsy services in Sheffield

Paediatric epilepsy outreach nurses Lisa Cook and Louise Douglas describe the strengths and challenges faced by the Sheffield Children's Hospital transition service

We work within the neurology department of Sheffield Children's Hospital (SCH). We are a team of five neurologists (two of whom are epileptologists) and four epilepsy nurses. We also work alongside a varied team of psychologists, psychiatrists, dieticians, occupational therapists and physiotherapists. Within the nursing team, two of us are designated to work with the families throughout the transition period. Unfortunately, it is part of a very busy role and only a proportion of our time is designated to transition. We would ideally like admin support and to spend more time improving our service. But we acknowledge that there are time and administrative constraints.

As a team, we strive to offer a seamless, safe transition into adult care. This happens at a time that is appropriate in regard to age, level of understanding and condition (which is one of the overarching principles of the National Institute for Health and Care Excellence (NICE) guidelines). We are also part of a Cross Trust Transition Steering Group, who meet on a regular basis to discuss policy and develop local guidelines.

Our caseload includes children and adolescents from South Yorkshire and Humber who have a diagnosis of epilepsy. Due to covering a wide area, we have to acknowledge that our service with regard to transition is not equitable for those living outside of the Sheffield area. That being said we still try our best to work with all professionals out of area that are involved, to ensure transition is discussed and planned for within these limitations.

Historically, our service for adolescents was called a 'counselling' service - this was not overly popular with teenagers

The adolescents we see have a variety of conditions, including some that have undergone neurosurgical intervention, vagus nerve stimulation (VNS) or are following the ketogenic diet. We also have a large number of adolescents with complex needs. They will need a more complex transition plan as they may have more than one consultant involved in their care.

Historically, our service for adolescents was called a 'counselling' service. Needless to say, this was not overly popular with teenagers and thus the uptake for appointments was poor (around 25%). The word 'counselling' appears to have negative connotations for our young adults. With the aim to improve the service, we looked at many other services and clinics within this area. We asked what we need to provide as a service. We changed the remit slightly and decided to simply change the name to an 'adolescent clinic'. Although we haven't performed a formal audit since renaming (this will hopefully be done this year) we are confident our uptake has improved. This is especially in those cases where the purpose of the appointment has been explained to the patient beforehand.

The clinic

We offer four face-to-face clinics a month, each having three 45-minute appointments. We also offer two telephone clinics a month, each having three 45-minute appointments. There is also one 20-minute slot, which is designated for those who have already transitioned to adult services. We offer this appointment in order to gather feedback on the transition service and to formally discharge the child from children's services. Occasional home visits can be planned, however due to time constraints these are offered only if deemed entirely necessary.

At present, families receive a standard letter offering them an appointment. We are currently producing a letter that will accompany this to explain the purpose of the appointment and common issues that can be discussed. As previously mentioned, attendance is greater when the young person is aware of the purpose of the appointment, so we hope this will improve our attendance figures.

The issues discussed include:

- Knowledge of their condition
- Medication schedule (how to order their own)
- Safety
- Independence
- SUDEP
- Driving, exemption certificates
- School
- Exams
- Employment
- Alcohol
- Drugs
- Sleep
- Diet
- Sport
- Relationships
- Sexual health and contraception
- Friendships
- The transition process

We encourage the adolescents, when it is age appropriate, to have at least some of these appointments independently in accordance with NICE.

We currently start this process at the age of 12 years for children in mainstream schools and 14 years for children in special needs schools. The reason we choose to start later for those with special educational needs is that we are generally already heavily involved with them. Therefore, often it is not appropriate to duplicate work that is already being done (like attending annual reviews and so on). We try not to add the burden of extra appointments that may disrupt school or family life if it's not necessary.

As mentioned previously, although we would like to, we cannot offer all our adolescents exactly the same service. Our adolescents from out of the Sheffield area will generally be offered the telephone appointments, unless we can schedule them at the same time as a consultant appointment. Adolescents' appointments do not replace the contact with a consultant or an epilepsy specialist nurse (ESN). They are extra appointments with more time set aside for a more informal and relaxed discussion. When it comes to the transition process, we can only offer our Sheffield patients a combined paediatric epilepsy nurse to adult epilepsy nurse appointment at Royal Hallamshire Hospital (RHH). There is presently no consultant-led transition for epilepsy.

Attendance is greater when the young person is aware of the purpose of the appointment, so we hope [efforts towards] this will improve our attendance figures

The transition process

At the age of 12, families will receive a telephone appointment. We chose this age after looking at previous contact with families and consulting the NICE guidelines. At this age, children have transitioned into secondary education and new issues may be emerging. There may be increased anxiety from parents as a consequence of their

child's newfound independence, safety and new friendships. School work and exams may make this a more stressful time. We felt that by making contact at this age we can introduce ourselves and get to know the child and family. This way, issues can be dealt with proactively and we can build a relationship with the young person, their family and their educational setting, if necessary. We believe this helps to make the transition process smoother. If the young person is from out of the Sheffield area and already has a local ESN who has started the process of transition, we do not get involved. Again, we do not want to confuse families or duplicate work that is already being done by our colleagues. We have a very good relationship with our ESN colleagues through regular ESN meetings and contact. If the child does not have links with an ENS, we will endeavour to support families as much as we possibly can. At this age, we mention the transition process and what can generally be expected.

When seeing young people in clinic, we use a checklist to document areas that are discussed and who is involved

At 14 years, as NICE guidelines advise, we start the transition process with all families. This is often just a preliminary discussion about what they can expect. This includes information like who will be involved and when it may happen. Obviously, the age of transition varies from individual to individual. Some may be raring to go over into adult services at 16 years old, whereas some wish to stay until they are 19. The decision to commence formal transition is one that is made after consultation between the adolescent, parents, consultants, ESNs and any other health professional that may be involved. By starting this discussion at 14 years, it can take away some of the anxiety around transition.

We offer annual reviews from this point onwards. These will either be as telephone consultation or face to face in the clinic, depending on family circumstances and the area in which the young person lives.

From the age of 16 years, some young people will be ready and eager to be referred to adult service. It is our aim to ensure that everything is in place before the actual event occurs. We try to make sure the young person has been equipped with all the relevant information in order for them to make informed choices throughout their lives. For the parents and carers of young people with complex needs, where necessary, we aim to discuss some important points. They include the young person's mental capacity, any equipment they may have which may need to be transferred, financial responsibility, adult placements and residential living. We would also try to identify any social worker or external agencies who support the families. We would also refer to the complex transition team who can help with co-ordinating transition.

When seeing young people in clinic, we use a checklist to document areas that are discussed and who is involved. If issues are highlighted outside of our remit, we will make a referral to an appropriate professional, such as a psychologist or dietician. We encourage the family to build good relationships with their GP, as this is often an area that is bypassed when care has been under children's services. We can also make

arrangements to put a hospital passport in place.

If transition is to go ahead at this point, we arrange a combined nurse appointment at RHH. This clinic occurs once a month and is an opportunity for the young person to visit the adult out-patient department (OPD) and meet with our adult ESN who has responsibility for transition. At this appointment, we discuss the service and what they can expect from the adult service. This includes

information like what happens if they require emergency care or are admitted to hospital, can their parents stay, and so on.

Managing pitfalls

If the young person is not transitioning at 16 years, we discuss an emergency plan should they need to call 999. A pitfall in Sheffield is that we have two separate A&E departments – one in the adult hospital and one in the children's hospital. This has been problematic in the past, as young people who are still under the care of SCH, but are over 16 have been taken and admitted to adult services. This has proven to be traumatic for families and young people. Children with complex needs will often be provided with a consultant letter that authorises the ambulance service to bring them to SCH if it's safe to do so. We also try to highlight any young people that are more likely to require intensive care and inform the appropriate team in adult services. A specific referral pathway is available for this.

A pitfall in Sheffield is that we have two separate A&E departments – one in the adult hospital and one in the children's hospital

If they are remaining under our care post 16 years, during the annual adolescent appointment, we update transition information. We send transition leaflets provided by the Sheffield Parent Carer Forum. They are useful in explaining financial and legal aspects of transition, mental capacity, legal responsibility and advocacy. These discussions are made easier if you already have a solid relationship with the family. Families know transition has to happen at some point. But if we can achieve this at time when everybody is ready and positive, it definitely lessens the chance of complications arising.

For out of area young people, we can offer telephone adolescent appointments. When it comes to transition from a nursing point of view, we will contact the local adult epilepsy nurse on the telephone and then follow up with clinic letters. For all young people who have neurosurgery including VNS, they will be referred to RHH.

We know our service isn't perfect. A recent SCH wide Care Quality Commission inspection did highlight transition as an area that needs improvement. We are planning to audit our current service this year and hopefully respond to the findings of that. Building up relationships with young people and their family, and providing pertinent information is what we consider most important. Transition should be a process – often over the course of many years of preparation. It should be a positive experience, not something that our adolescents and their families are reluctant to face. We are passionate about improving the lives of young people in our care. We hope that in future we are able to develop a service that enables us to provide a seamless service for all adolescents in our care in line with CQC and NICE.

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Louise Douglas
Paediatric epilepsy outreach nurse
Sheffield Children's Hospital

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Professor Eric Kossoff

Professor Joerg Klepper

NICE guidelines

Is it time for a re-appraisal?

Dr Arjune Sen revisits the rough findings on NICE guideline adherence from the audience at a recent symposium at the ILAE UK Chapter meeting in 2017. He goes on to discuss some possible updates needed to help the NICE guidelines remain relevant and useful

I was privileged at medical school to be taught by the legendary Professor David Sackett, one of the three founding fathers of modern clinical epidemiology. The others are Archie Cochrane (of Cochrane Library fame) and Alvan Feinstein, previous Sterling Professor at Yale University in America. It is strange to think that a mere twenty years ago, the idea of needing robust evidence to justify your treatment decisions still met with scepticism. I remember Professor Sackett having to evangelise about the benefits of EBM (evidence based medicine) on an almost daily, sometimes even hourly, basis. It worked. Now, all modern health care systems are built on the core principles of EBM.

It also, though, soon became apparent that in public-funded health services there would need to be some consideration of cost-efficacy. Say, for example, Drug H (I choose my letter carefully) could be shown to be very effective in treating condition E. A system such as the NHS could still not advise it be prescribed if the cost was prohibitive. Although such cost efficacy is now determined by the National Institute for Health and Care Excellence (NICE), this was not its role when established. When NICE was founded in February 1999, its remit was to provide clinical guidance, harmonise care across the country and end the 'postcode lottery' [NICE, 2018]. The latter describes the situation where some patients could access healthcare not available to others purely based on where they lived. Clearly, access to Drug H should not be determined by whether you live in London, Leeds, Loughborough or Lincoln.

NICE now performs assessments to determine the most appropriate treatments and also has to factor in the cost for a given treatment

NICE was originally the National Institute for Clinical Excellence before merging with the Health Development Agency in 2005 to become The National Institute of Health and Care Excellence. Presumably, there was thought given to it being The National Institute of Care and Health Excellence, but the acronym NICHE may have sent the wrong signals, so NICE it remains! NICE now performs assessments to determine the most appropriate treatments and also has to factor in the cost for a given treatment.

Naturally, these decisions are often complex, sometimes controversial. For example, if we assume that Drug H can stop seizures in all patients that have pharmacoresistant epilepsy (around 180,000 people in the UK) – that seems clearly worthwhile. However, were Drug H to cost £100 a month, the bill to the NHS would be £216 million a year if all 180,000 patients commenced Drug H. That may not seem so good at first glance. But maybe those people now no longer needed to attend A&E as they are not having seizures, there were fewer fractures and they could wean away their current medications. Then, Drug H may indeed be cost-effective after all. Moreover, if Drug H enabled more people with epilepsy to return to full time work or to education, then the positive socioeconomic impact of Drug H might justify the cost. Complex indeed!

It is to help evaluate data critically and impartially that NICE exists. As a body it has developed a formidable worldwide reputation, many looking on in envy at the clarity NICE provides. However, at home, there are those

Do you adhere to NICE guidelines:

100% of the time
12.5%

More than 75% of the time
41.7%

50-75% of the time
33.3%

Less than 50% of the time (?!)
12.5%

Figure 1. While a majority of the audience said they did as NICE recommended most of the time, 12.5% said they didn't on 50% of occasions or more

Which of the following co-morbidities does NICE not suggest patients need information about?

Risk management
12%

Psychological difficulties
6%

Social security benefits
29%

Cognitive problems ✓
35%

Road safety and driving
12%

SUDEP
6%

Status epilepticus
0%

Figure 2. Many identified that cognitive difficulties were not specifically highlighted in NICE as a co-morbidity that people with epilepsy should be made aware of. However a range of responses were elicited

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who question the applicability of NICE, particularly to nuanced decision making. Therefore, to test how well UK clinicians and interested others practised what NICE preaches, a symposium was held at the recent ILAE UK Chapter Meeting (October 2017, Leeds). Around 100 participants provided anonymous responses through keypads to a battery of questions that tried to disentangle how much NICE influenced real-life epilepsy practice. It is essential to state that this was not a scientific study of views and people may have answered in ways that do not reflect their true clinical practice. Nonetheless, the meeting seemed to generate a lot of interest and some controversy. Therefore it seemed worthwhile to at least raise the points of discussion for broader consideration.

NICE in operation

Initially the audience were asked how often they adhered to NICE guidance [NICE, 2012] and, as expected, most people applied the guidance most of the time (*Figure 1*). Of the respondents, 54.2% said they adhered to what NICE suggested more than 75% or 100% of the time. However, 12.5% of participants declared that their practice matched that in NICE guidance less than 50% of the time. Before trying to unpick this, it was important to try and determine how familiar people are with the guidance itself. Interestingly, there was uncertainty over what NICE itself stood for and a majority thought the most recent full guidance was published in 2014 (actually 2012). There was also incomplete awareness on the comorbidities that NICE referred to (*Figure 2*).

In particular, though, it seemed worthwhile to explore prescribing practice. Audience members were asked what NICE recommended as first-line treatment for focal epilepsy (*Figure 3*). The vast majority answered correctly, specifying carbamazepine and lamotrigine. However, a case was then proposed to them wherein an 82-year-old woman developed Alzheimer's disease and focal epilepsy. She also had severe osteoporosis and hypercholesterolaemia. Clearly the example is extreme, but this was deliberate to provoke discussion as to whether carbamazepine would ever be contemplated in such a patient. The reader is encouraged to consider what they would do. Should we all, perhaps, reflect on whether, with its side-effect profile, enzyme induction and adverse impact on

bone health, carbamazepine does remain a first line medication in the older population?

We then began to explore adjunctive therapy. Participants were asked to choose which anti-epileptic drugs NICE recommended as alternative first-line treatments in focal epilepsy (*Figure 4*). Carbamazepine, lamotrigine and levetiracetam were not amongst the choices. Most people correctly identified sodium valproate as being a recommended option although many also thought that topiramate was similarly recommended. The only other medication that should have been selected was oxcarbazepine, although among the audience there was a spread of responses. The audience were then asked if the first anti-epileptic drug was ineffective, would their next choice be among the following: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine or valproate. The overwhelming majority answered yes, agreeing that this would be what they did in practice.

To seed discussion, a further extreme example was then given. A young, Han Chinese woman with focal epilepsy and severe psychopathology had not been able to tolerate lamotrigine and was therefore in need of a second agent. The patient characteristics were selected to make it difficult to advocate carbamazepine [Chen et al, 2011], levetiracetam and oxcarbazepine [Tangamornsuksan et al, 2018]. However, all were also agreed, mindful of recent Medicines and Healthcare products Regulatory Agency (MHRA) guidance [MHRA, 2017], that valproate would also not be initiated in this young woman given the risk of teratogenicity. Thus, despite attesting to strong adherence to NICE guidance in prescribing, in this case at least, most would not actually implement the guidance in practice.

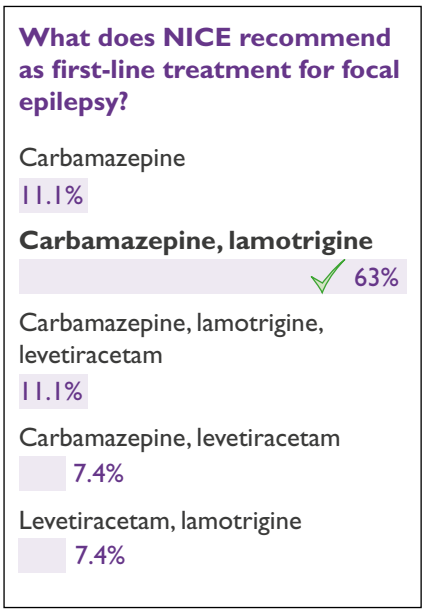

Figure 3. A clear majority were aware of the NICE recommended first-line treatments for focal epilepsy (namely carbamazepine and lamotrigine) and therefore that levetiracetam was not a NICE recommended first-line agent in this cohort of patients

Keeping NICE relevant

In the course of a relatively short symposium, it was difficult to cover the many aspects of NICE that could be discussed. Moreover, we are fortunate in epileptology that developments move quickly with new medications being licensed approximately once every two years. It would clearly be difficult for NICE to appraise efficacy and cost-effectiveness for each new anti-epileptic medication as they are licensed. However, there have been assessments of zonisamide [NICE, 2013] and perampanel [NICE, 2012] in focal epilepsy. It is also proposed that NICE assess the role of cannabidiol as adjunctive therapy for seizures in people with Dravet

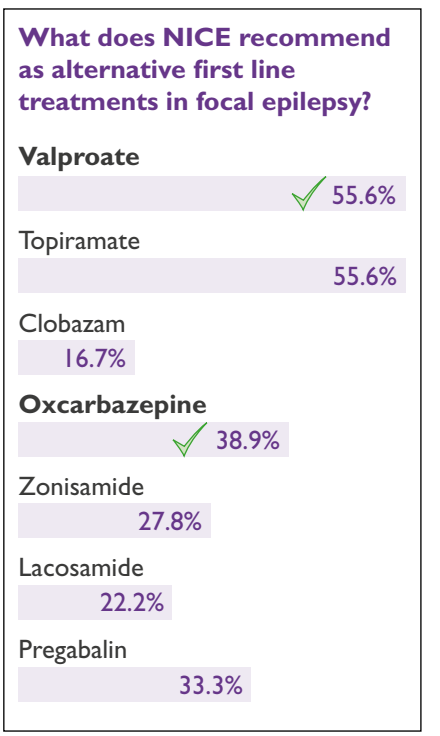

Figure 4. Participants were asked to make up to seven choices of what NICE recommended as alternative first-line agents in focal epilepsy. Most were aware that valproate was one suggested option. However, just over a third knew that oxcarbazepine was the other medication. Many more selected topiramate.

syndrome or Lennox Gastaut syndrome [NICE, 2017].

However, it has now been around six years since the definitive NICE guidance in epilepsy and a lot has happened in that interim. It is likely time for NICE guidance in epilepsy to be thoroughly reviewed. In particular, I would advocate that there be specific thought given to certain groups – notably women of childbearing potential and the elderly. NICE guidance does already refer extensively and link to MHRA guidance on sodium valproate [MHRA, 2017]. But I would suggest there now need to be separate pathways of anti-epileptic drug choice delineated for men and women. Similarly, for example, careful consideration needs to be applied to the options available for older people with epilepsy. This is an increasing demographic and one in which the incidence of epilepsy is highest and co-morbidity common.

There is no doubt that NICE guidance in epilepsy is an extremely valuable tool and provides an indispensable framework to shape care and try to ensure consistency of practice. It clearly stands among the best such guidance available globally and is often referred to by colleagues around the world. With this in mind, it was perhaps surprising that some among the symposium audience adhered to the guideline less than 50% of the time. Of course, as was highlighted in the meeting, guidance is exactly what it says: guidance. It is not a legal requirement to cling to each recommendation from NICE for every patient. And, as illustrated by our left-field examples, clinicians will always need to apply skill and practical judgement to do what is best for their patients. As Professor Sackett always advocated, evidence based medicine is only one component of evidence based practice. The others are clinical judgement and, importantly, patient choice. NICE guidance in epilepsy envelops and gives structure to such decision-making. We are very fortunate indeed to have such support. As a community, we should look to shape the next iteration to ensure that we can all agree that the advice provided offers optimal, holistic care to all those with epilepsy for whom we care.

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The participant response data was made at a free symposium hosted by UCB Pharma at the UK ILAE Chapter meeting in Leeds, October 2017. The author is supported by the NIHR Oxford BRC. He has received speaker honoraria and/or research funding from Bial, Eisai, GW Pharma, Livanova and UCB Pharma

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Highlights

Top picks from *Seizure*

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

Mesial temporal lobe epilepsy (mTLE) continues to be the most prevalent form of focal-onset epilepsy worldwide. A range of different pathologies can cause the condition, but one of the commonest structural abnormalities found in mTLE is hippocampal sclerosis (HS) [Wieser 2004].

Although mTLE with HS has been the focus of much research and continues to be a commonly encountered condition (especially in the developing world) some surprisingly basic questions about the condition remain unanswered. These include "what causes it?" and "why is its prevalence declining in high-income countries?"

My editor's choice from *Seizure issue 54*, a systematic review and meta-analysis by Wipfler *et al* [2018], makes a contribution to addressing these mysteries. It examines the possible link between Human Herpes Virus-6 (HHV-6) and mTLE. The primary infection with this virus usually occurs in infancy, when it causes a self-limiting fever, sometimes associated with a skin rash. While the signs of infection settle quickly, the herpes virus has a remarkable ability to persist in various body tissues including cells in the central nervous system. However, HHV-6 reactivation has been associated with a range of neurological diseases, so a link between HHV-6 infection or

reactivation and mTLE with HS would also be plausible.

Unfortunately, the HHV-6 hypothesis is proving difficult to test. Evidence of previous HHV-6 infection is found in over 90% of members of the general population, and the research studies summarised and meta-analysed in this paper are likely to have been affected by a number of biases (including the bias to publish studies with positive findings). Nevertheless, a possible association of HHV-6 and surgically treated mTLE is suggested by the analysis and HHV-6 may therefore be at least part of the answer to the questions asked above.

Seizure detection drawbacks

While significant progress in seizure detection devices has been charted in previous research, they are still associated with unacceptable error rates, both in terms of under- and over-detecting seizures.

My editor's choice from *Seizure issue 55* is a systematic review and meta-analysis of pre-ictal heart rate changes by Elisa Bruno *et al* [2018]. It focuses on a physiological parameter which currently available wearable devices are capable of measuring well and easily: the heart rate. This review, based on results from a total of 1,110 people living with epilepsy and 2,957 seizures finds that pre-ictal heart rate increases (HRI) were found in 623/2,957 (21%) seizures. The median onset time of pre-ictal HRI was 10.7 seconds prior to seizure onset (IQR 5-60). The studies which could be included in the meta-analysis yielded a pooled incidence of pre-ictal HRI of 36/100 seizures (95% CI 22-50). More fine-grained analyses suggested a higher prevalence of pre-ictal HRI in temporal lobe than other focal or generalized epilepsies, as well as a higher prevalence in adults than children. Not unexpectedly, ictal HRI were seen more commonly than pre-ictal HRI. The cumulative incidence of ictal HRI was 1,556/2,957 seizures (52.6%), with a mean increase in heart rate of 56.8% compared to baseline.

These findings suggest that seizure warning or detection systems, including sensors capable of monitoring patients' heart rate, could be useful for a fair proportion of individuals with epilepsy. However, the data also demonstrate that these could only ever provide a minority of patients with seizure warnings, and only a few seconds prior to seizure onset. Even seizure detection (rather than warning) devices based on HRI alone could only hope to pick up about half of all seizures.

This review and meta-analysis indicates that it is more likely that effective seizure warning or detection systems must also involve observations of other parameters. They will also need to be individualised to particular patients' seizure disorders.

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Neuroimaging

The prognostic value of neuroimaging for people with epilepsy

Dr Simon Keller discusses the uses of neuroimaging in epilepsy and the most promising methods that can help to predict likely seizure outcome following epilepsy surgery

Neuroimaging techniques have revolutionised clinical assessment of people with neurological, neurodegenerative and psychiatric disorders. The vast majority of people with epilepsy, and all people experiencing refractory seizures, receive at least one kind of neuroimaging investigation. The most frequently used neuroimaging method is magnetic resonance imaging (MRI), which aids the identification of brain lesions. Epileptogenic lesions can be acquired, they can develop, or they can have a presumed genetic cause. The identification of an epileptogenic lesion is often associated with medically refractory epilepsy.

A new diagnosis of epilepsy

Every day in the UK, 87 people are diagnosed with epilepsy, according to charity Epilepsy Action [Epilepsy Action, 2018]. The primary purpose of an MRI scan, which is the preferred neuroimaging investigation in epilepsy, is to determine whether seizures are caused by a brain lesion. Perhaps surprisingly, 65-75% of adults with newly diagnosed epilepsy will not have a brain lesion identifiable using conventional MRI scanning [Van Paesschen et al, 1997; Van Paesschen et al, 1998; Liu et al, 2002]. Some of these patients will have a brain lesion that evades detection using MRI and other patients will have no structural lesion at all.

The first line of treatment for people with a new diagnosis of epilepsy is anti-epileptic drug (AED) therapy. Current AED treatments control seizures in 60-70% of people with a new diagnosis of epilepsy [Kwan and Brodie, 2000]. However, it is not the case that virtually all patients with no lesion will have seizures controlled with AED treatment and all patients with a lesion will develop refractory seizures. Indeed, many patients with a brain lesion can be successfully treated with AEDs [Labate et al, 2011; Bilevicius et al, 2010], and many patients without lesions experience persistent seizures despite AED therapy [So and Ryvlin, 2015]. Therefore, an MRI scan at diagnosis of epilepsy currently has a limited ability to prospectively stratify patients according to their likely treatment outcome.

An MRI scan at diagnosis of epilepsy has a limited ability to prospectively stratify patients according to their likely treatment outcome

Refractory epilepsy and surgical evaluation

Refractory epilepsy accounts for approximately 30% of all epilepsy cases [Kwan and Brodie, 2000]. Neurosurgery is considered for many patients with refractory focal epilepsy. The evaluation of a patient's suitability for surgery is complex, and dependent on the expertise of a multi-disciplinary surgical team (MDT). This team consists of neurologists, neurosurgeons, neuroradiologists, neurophysiologists and neuropsychologists, amongst other healthcare professionals. Neuroimaging has a crucial role in evaluating patient suitability for surgery. Evidence of a focal brain lesion on MRI consistent

with the likely localisation of the seizure onset zone revealed by electroencephalogram (EEG) recordings, suggests a greater chance of a patient becoming seizure free after surgery [McIntosh et al, 2004]. Many people with refractory focal epilepsy, with no discernible lesion on MRI, undergo surgery and are rendered seizure free. However, on the whole, postoperative seizure outcome in these people tends to be slightly worse. Inter-ictal positron emission tomography (PET) and ictal single photon emission computerised tomography (SPECT) neuroimaging techniques can be helpful in patients with no MRI lesion. They can also be used when MRI and EEG findings lack agreement. In many cases, an MRI lesion is a positive prognostic factor for a successful postoperative outcome across all people with refractory epilepsy. But many people continue to experience postoperative seizures even if they present with MRI lesions (for example in hippocampal sclerosis [Bonilha and Keller, 2015]).

Postoperative seizure freedom data differs depending on the criteria used to classify it, the length of postoperative follow-up time, and the type of epilepsy, pathology and surgery. Overall, between 35-80% of people with refractory epilepsy will be rendered seizure free after surgery [Keller et al, 2017]. In the only randomised controlled trial of surgery for refractory temporal lobe epilepsy, 58% of patients were free from seizures impairing awareness one year after surgery [Wiebe et al, 2001]. The study also showed that 38% of people were free from any seizure related symptom after one year [Wiebe et al, 2001]. This was a significant improvement compared to patients who continued with AED therapy only.

Although there is always a risk of complications with any kind of major surgery, epilepsy surgery is relatively safe. Few patients experience minor or major complications resulting from surgery [Hader et al, 2013]. It would be helpful for patients and clinicians alike if reliable prognostic markers of postoperative seizure outcome were available to assist clinical decision-making and guide patient expectations.

The International League Against Epilepsy acknowledges the importance of abnormal brain networks for the generation of seizures

Preoperative neuroimaging offers the potential to provide non-invasive prognostic markers of postoperative outcome. There has been an exponential rise in the publication of research articles that have applied increasingly sophisticated neuroimaging – typically, MRI – techniques to predict postoperative outcome in refractory epilepsy. These approaches are the focus of the remainder of this article.

New developments in neuroimaging: significance for epilepsy

Most people with epilepsy, and all with refractory epilepsy, receive MRI in the context of clinical evaluation. Therefore, it would be convenient if reliable prognostic markers of treatment outcome could be determined using this method of investigation. As mentioned, gross lesions on preoperative MRI provide limited prognostic information for individual patients. This is why quantitative analysis of specialised MRI scans has been increasingly applied in

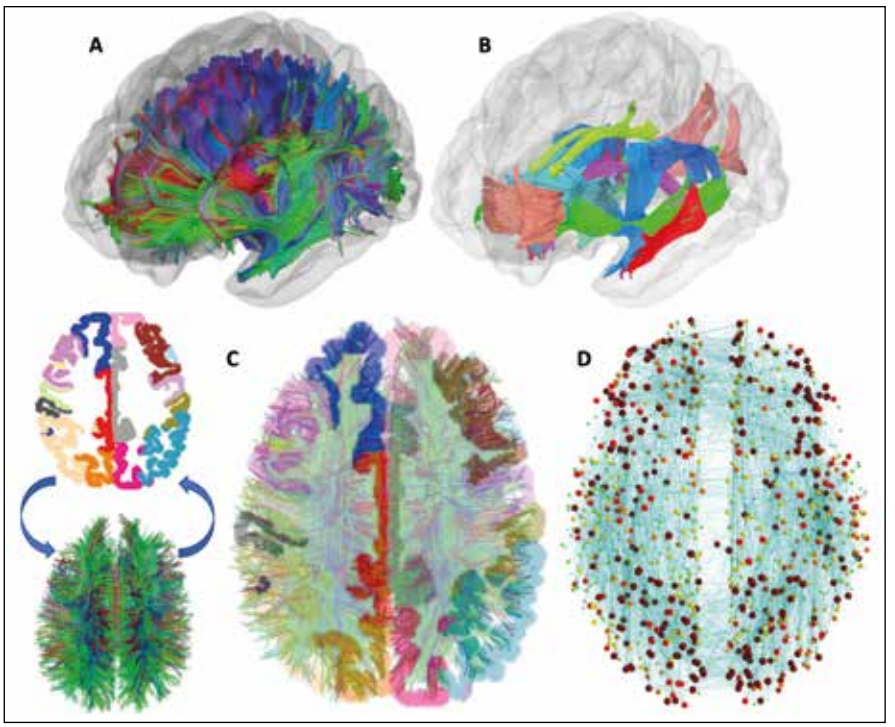

Figure 1. Resolving structural connectivity with DTI. A. Reconstruction of the principal directionality of white matter fibres (green = fibres running front to back/back to front; blue = fibres running top to bottom/bottom to top; red = fibres running left to right /right to left). B. From (A), the major white matter tract bundles can be delineated and changes in architecture measured. C. Merging parcellated structural MRI scans (top) with DTI data (bottom) permits the analysis of regional structural connectivity across the entire brain. D. From (C), whole-brain structural networks can be derived that contain information on the topology and degree of connections between brain regions. Measures of white matter tract architecture and network configurations are increasingly being applied to study human epilepsy.

research studies. One developing area of imaging research in epilepsy is analysis of brain connectivity and networks. Neuroimaging brain connectivity and networks is particularly important in epilepsy because of the nature of the condition. The International League Against Epilepsy (ILAE) acknowledges the importance of abnormal brain networks for the generation of seizures [Fisher et al, 2017].

Brain connectivity and networks can be modelled using many approaches. Most commonly, structural connectivity and networks are modelled using diffusion tensor MRI (DTI) approaches. Using sophisticated image analysis algorithms, DTI allows researchers to quantify various measures of impaired structural connectivity. It does this through assessment of white matter tract architecture or through the configuration of whole-brain structural networks (*Figure 1*).

Functional brain connectivity and networks may be investigated using resting-state functional MRI (rsfMRI). rsfMRI permits evaluation of interactions in activity between different areas of the brain when a person is not performing an explicit task. Functional connectivity can be modelled using temporal correlations of activity between discrete brain regions. If resting functional activity is correlated between regions they are considered connected and part of a network. Given that functional networks govern cognitive and sensory processes, these methods are particularly important in the identification of the neural correlates of cognitive and psychiatric co-morbidities in epilepsy.

At the present time (February 2018), a PubMed search for 'epilepsy' and 'MRI' and 'connectivity' yields 233 studies. Existing research studies indicate reproducible patterns of abnormal connectivity in the more

common epilepsies. For example, refractory temporal lobe epilepsy has been associated with abnormal structural and functional connectivity within the limbic system. Idiopathic generalised (genetic) epilepsy has been associated with thalamocortical connectivity impairments. There have been MRI brain connectivity applications in many other chronic epilepsy disorders, including Lennox-Gastaut syndrome, frontal lobe epilepsy, and malformations of cortical development including focal cortical dysplasia. There have also been applications in epilepsy disorders that may naturally enter remission, such as benign childhood epilepsy with centrotemporal spikes (BECTS). To determine whether imaging brain connectivity can provide insights into the development of epileptic disorders and treatment outcome is a crucial research endeavour.

DTI and rsfMRI are not included in clinical evaluation of people with epilepsy. This is due to a number of factors, most notably because the clinical utility of these approaches for individual patients has not yet been demonstrated. Furthermore, these approaches typically require computation of abnormal connectivity and networks in patients compared to a cohort of healthy controls. Connectivity patterns in controls serve as prior knowledge of normal brain structure and function, and deviations from these patterns are considered as abnormal in patients. The acquisition of advanced MRI data in healthy controls is typically considered research practice, which further complicates the integration of these approaches into clinical practice.

Neuroimaging biomarkers: new insights

With respect to human epilepsy, there are three main kinds of neuroimaging biomarkers that can be evaluated. They include the prediction of:

1. The development of epilepsy from an asymptomatic state or after a first seizure
2. Seizure remission after AED therapy
3. Seizure freedom after neurosurgical intervention

There have been virtually no sophisticated neuroimaging investigations into (1) and (2). This remains an important future research direction. There have been an increasing number of studies that have used sophisticated preoperative neuroimaging techniques to predict

To determine whether imaging brain connectivity can provide insights into the development of epileptic disorders and treatment outcome is a crucial research endeavour

postoperative seizure outcome in people with refractory epilepsy. They have most typically been looking into temporal lobe epilepsy. Although a detailed review of these studies is beyond the scope of this article, 'connectivity' seems to be the key word. For example, structural and functional MRI studies have looked into patients who go on to experience postoperative seizures after temporal lobe surgery. The studies report that the patients had preoperative abnormalities in thalamotemporal and thalamocortical networks, relative to patients who are rendered seizure free [Keller et al, 2015a; Keller et al, 2015b; He et al, 2017]. We have recently reported that localised architectural alterations of white matter tracts

located within thalamotemporal networks enable the prediction of seizure outcome after temporal lobe surgery in patients with hippocampal sclerosis. This was shown with 84% sensitivity and 89% specificity [Keller et al., 2017], which is currently higher than clinical predictions.

So called 'connectome' imaging approaches have increasingly been applied to preoperative DTI and rsfMRI. They are used to determine aspects of network disruption that are associated with persistent postoperative seizures. These studies are providing new insights. However, there are some issues that need to be considered with these studies. Firstly, there appears to be – at present – a lack of reproducibility of findings across studies. In preoperative connectome studies of seizure outcome after temporal lobe surgery, rarely do studies report the same topological correlates of persistent seizures. Secondly, most studies are cohort-based applications; using an individual's connectome to predict their likely postoperative outcome has not yet been rigorously tested. Nevertheless, some connectome studies have identified preoperative thalamotemporal network alterations underlying persistent postoperative seizures [Bonilha et al, 2015], similar to other measures of brain connectivity [Keller et al, 2015a; Keller et al, 2015b; He et al, 2017; Keller et al, 2017].

The future

Neuroradiological practice has remained fairly stable over the past 20 years for the evaluation of epilepsy. Specialised MRI techniques, such as DTI and rsfMRI, have been put to good use in research, but have failed to materialise as routine clinical evaluation tools. This is particularly due to the lack of evidenced clinical utility of these approaches. Clearly, prospective studies that aim to demonstrate their clinical utility and prognostic value are an important future direction. The application of neuroimaging techniques to study brain connectivity and networks in epilepsy is intuitive, and likely to be revealing. These techniques have the potential to be important for stratified medicine in epilepsy.

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Side-effects of AEDs

Tolerability and safety of anti-epileptic drugs (AEDs)

Prof Martin Brodie describes some of the side-effects associated with different AEDs and discusses what people with epilepsy and their families need to know from their prescriber

If a person with epilepsy has two seizures a month, this equates to maybe two or three bad days that month. However, if their anti-epileptic drug (AED) treatment causes side-effects, every day may be a bad one. Adverse effects too carry a high economic burden for the patient and the healthcare system [De Kinderen et al, 2014]. Doctors tend to focus on the efficacy of AED therapy, whereas people with epilepsy and their caregivers are often more concerned about their tolerability and safety.

No drug is free from adverse effects, but there are a range of different clinical scenarios relevant to short and long-term treatment with AEDs. Understanding these and communicating the risk-benefit ratio accurately and sensitively is an essential component of the healthcare professional's duty to their patient. The situation is often complicated by psychiatric and other medical comorbidities, for which drug treatment may also be being prescribed. The more severe the epilepsy, the greater the likelihood of these complicating issues affecting the brain [Brodie et al, 2016].

An AED may have been taken without problem for a number of years. But often, it can be blamed for a new set of symptoms and signs in a person with epilepsy by a doctor working in a different speciality. If the innocent AED is withdrawn, the patient can add recurrent seizures to their healthcare burden. This scenario is often complicated by the long list of potential side-effects. This is supplied to the patient with their prescription by the pharmacist, and often contributes to a patient's anxiety. In this short review, I will discuss the range of adverse effects that can arise with commonly used AEDs and touch on how to communicate these appropriately to the patient and their caregivers.

Definition and classification

The World Health Organisation (WHO) defines an adverse drug effect as: "a response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for modification of physiological function" [Edwards and Aronson, 2000]. They can be classified into a number of separate types {Perucca and Gilliam, 2012]. The longer a new drug has been prescribed in everyday clinical practice, the better identified will be its side-effect profile. Regulatory drug trials are artificial in design. They are carried out largely in patients with refractory epilepsy already taking one, two or three other AEDs. All this means they do not provide an honest assessment of the risk to benefit ratio [Brodie et al, 2017].

Prof Martin Brodie

Type A

Type A effects can be attributed to the drug's mechanism of action and are usually dose-dependent. Common problems include dizziness, drowsiness, double vision, nausea, vomiting, fatigue, sedation and ataxia. These effects are particularly likely to occur in patients with difficult to control epilepsy taking more than one AED. These side-effects can usually be decreased by dosage reduction. Concomitant treatment for other disorders often contribute to these problems. The older AEDs such as phenobarbital, phenytoin,

carbamazepine, ethosuximide and the benzodiazepines are often implicated in producing these symptoms at higher doses [Kennedy and Lhatoo, 2008]. Nevertheless, most AEDs can cause these problems in susceptible patients.

People with epilepsy should be made aware that a small reduction in dosage may reduce these troublesome symptoms without worsening seizure control. I build this advice into my discussion with every patient when introducing a new AED. Sodium valproate commonly causes hair loss, gastrointestinal disturbance and dose dependent tremor. Lamotrigine uniquely produces insomnia. Perampanel unusually precipitates falls.

Any adverse consequences should be dealt with by dosage reduction or replacement of the offending agent with an alternative AED

Many people with epilepsy also have comorbid psychiatric disorders, including depression, anxiety, psychosis, bipolar disorder and autism [Lin et al, 2012]. Symptoms of these existing problems can be uncovered or worsened by some AEDs, such as topiramate, zonisamide, levetiracetam and perampanel [Brodie et al, 2016]. Increased irritability, impulsiveness and aggression are particularly associated with low-dose levetiracetam and high-dose perampanel. In addition, topiramate and possibly also zonisamide may cause cognitive impairment, including word finding difficulties [Javed et al, 2015]. These problems should be sought early. Any adverse consequences should be dealt with by dosage reduction or replacement of the offending agent with an alternative AED. When the dose of any drug is increased, discussion of potential problems that could arise should be undertaken on a routine basis together with the solution. This often means returning to the previous dose of the offending AED. Sometimes adjusting the dosage interval or the number of times that the AED is taken every day may be sufficient to solve the problem.

Type B

Type B reactions are uncommon and are usually related to individual immunological or genetic vulnerability [Zaccara et al, 2007]. They can consist of rashes, which can be mild and maculopapular. However, they could also be severe and life-threatening, particularly when they are associated with systemic symptoms, such as fever, muscle aches and pains and headache. These cover a range of rare conditions including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug related rash with eosinophilia and systemic symptoms (DRESS).

More rarely, aplastic anaemia (affecting the bone marrow), agranulocytosis (lowered white blood cell count), systemic lupus erythematosus or hepatotoxicity (chemical-driven liver damage) can develop. These can be life-threatening if the AED is not rapidly withdrawn [Perucca and Gilliam, 2012]. Routine blood tests will often uncover these systemic problems. The most commonly implicated drugs include phenobarbital, phenytoin, carbamazepine, ethosuximide, lamotrigine and oxcarbazepine [Brodie, 2017]. Sodium valproate can cause dose-dependent thrombocytopenia (low platelet levels), pancreatitis and hepatotoxicity.

All of the above are complications that usually arise within a few weeks or months of starting treatment and so can – and must – be recognised early.

This is more likely to occur if the patient and family have continued access to the epilepsy team. Any new and alarming symptoms arising a month or two after starting an AED should be rapidly reported by the patient to their family doctor or epilepsy specialist. But equally, if such a problem arises some years after the AED has been started, this is not an idiosyncratic reaction, but another disease state. Thus, the doctor should not be tempted to withdraw AED treatment, thereby worsening the situation by exacerbating the epilepsy without improving the new symptoms and signs.

Type C

Type C reactions are chronic effects that result from cumulative drug use [Perucca and Gilliam, 2012]. They progress slowly and require long-term exposure to the offending agent, often over many years. The chronic use of hepatic enzyme-inducing AEDs, particularly phenobarbital, primidone, phenytoin and carbamazepine can have a negative effect. It can increase the turnover of vitamin D and sex hormones, causing osteoporosis or osteomalacia and sexual dysfunction in both men and women. These AEDs also raise the serum cholesterol, thereby increasing the likelihood of the subsequent development of coronary artery disease and stroke [Brodie et al, 2013].

Type B reactions are uncommon and are usually related to individual immunological or genetic vulnerability

Other long-term problems with phenytoin include gum hyperplasia, acne, and facial coarsening. Dupuytren's contracture and frozen shoulder are unusual chronic side-effects associated with phenobarbital and phenytoin administration. Changes in body habitus can include weight gain with sodium valproate, vigabatrin and pregabalin, and weight loss with topiramate and zonisamide [Ben-Menachem, 2007]. Reduction in sweating and hyperthermia in hot countries can be an unusual consequence of treatment with topiramate and sometimes zonisamide and rarely will be life-threatening [Gaitatzis and Sander, 2013]. These two AEDs are also implicated in the production of renal stones.

Dose-dependent chronic hyponatraemia (abnormally low sodium blood levels) is a common dose-related problem with carbamazepine, oxcarbazepine and eslicarbazepine acetate, particularly in elderly people established on diuretics [Brodie et al, 2009]. Vigabatrin, uniquely, causes concentric visual field defects, which are often irreversible [Maguire et al, 2010]. Blue-grey discolouration of the skin, lips, nails and mucous membranes resulted in the recent withdrawal of retigabine (exogabine) from clinical usage [Brodie, 2015].

Type D

Type D issues relate to delayed and irreversible problems including teratogenic and carcinogenic effects [Perucca and Gilliam, 2012]. Adverse effects of AEDs on the foetus can present as foetal loss, intrauterine growth retardation, impaired postnatal development and behavioural problems in childhood [Tomson and Battino, 2012]. The major culprits are topiramate, phenobarbital and, particularly, sodium valproate, although other AEDs have been implicated particularly at high dosage and as polypharmacy. These defects include facial clefts, congenital

heart disease and spina bifida. Exposure to sodium valproate in daily doses exceeding 1000 mg has been associated with reduced IQ [Meador et al, 2013] and an increased risk of subsequent development of autistic spectrum disorders [Christensen et al, 2012]. Accordingly, the Medicines and Healthcare Products Regulatory Agency (MHRA) in Europe issued a detailed statement on 21st January 2015 to the effect that: "Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women, unless other treatments are ineffective or not tolerated." These issues should be discussed with all women with treated epilepsy planning a pregnancy. I also like to include the partner in these, often sensitive, discussions. There is no hard evidence associating any AED with the production of carcinogenesis [Perucca and Gilliam, 2012].

Type E effects represent adverse drug interactions, which are common with some of the older AEDs, but will not be discussed further in this paper [Zaccara and Perucca, 2014].

Conclusion

Successful long-term treatment of a chronic disorder like epilepsy requires well-tolerated AEDs that do not produce acute or chronic adverse effects. These problems can be dose-related or idiosyncratic. Potential adverse effects should be discussed in detail with the patient and often partner or family, particularly in a younger or older person, when a new AED is prescribed. That way, any problems can be recognised early and treated as quickly as possible. All such side-effects are the clear province of the prescribing clinician, who regularly and rightly gets the blame when these symptoms are overlooked or ignored. This is because reducing or stopping the drug is the only way to solve the problem, which can on occasion be life-threatening. Accordingly, it is essential that everybody involved in the pharmacological management of people with epilepsy keeps up to date with all the potential adverse effects that can arise with each prescribed medication. Reducing side-effects has also, not surprisingly, been shown in a number of studies to improve quality of life [Luoni et al, 2011]. We must never forget the sage advice of Hippocrates: "make a habit of two things: to help or at least to do no harm".

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Director, Epilepsy Unit
Scottish Epilepsy Initiative

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Decisions, decisions

The 'butterfly effect' is another name for the chaos theory. It describes the theory of unintended consequences, where one or many seemingly inconsequential decisions may provoke a multitude of larger – perhaps disastrous – outcomes.

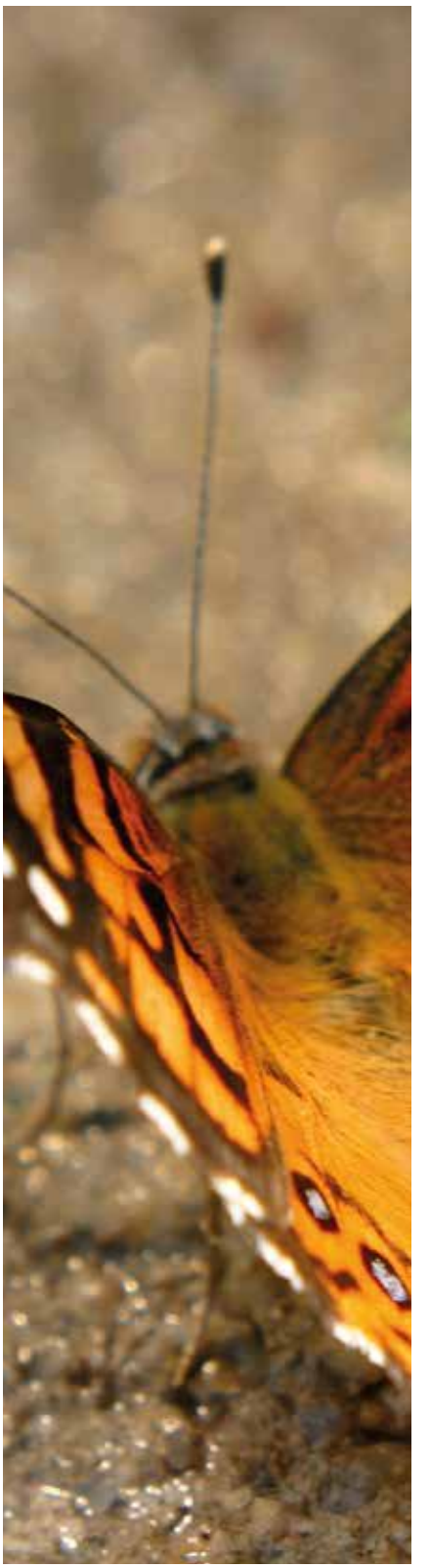
We are all at risk of this – but mostly so within our professional lives. Not only are we state-sponsored decision makers, but we work within a labyrinthine interconnected network. We commit to a cornucopia of conscious and unconscious decisions.

But even when we make decisions all day every day, there are many circumstances that can impair decision-making. I know that when I am feeling anxious about a new social situation, for example, I can obsess about what to wear. This, regrettably, has led me to overthinking the situation and making more mistakes rather than fewer. Misunderstanding 'lounge suit' as meaning 'the poshest thing you own' had me in black-tie at one of my first epilepsy events. And, consequently, I was mistaken for a waiter all night. But I am thankful that the barriers within which I can fail are so narrow, being, unmistakably, a white, middle-class male. And I know this isn't true for everyone.

I had previously scoffed at impresarios such as Mark Zuckerberg going on about the perils of 'decision fatigue'. This is the death by a thousand cuts to your psyche of making micro decisions all day long. He famously helps reduce the effects of this by wearing the same style of clothes every day – and you could argue this is Homer Simpson's motivation too. (Who am I to say that Homer Simpson is not a similar paragon of high-level cognitive wizardry?) But I do believe that the burden of making decision after decision can lead to mistakes of all sizes.

And this is why one of the huge benefits of the NHS is the inefficiency. (Bear with me.) Where there is a flimsy join in our work, there is a weakness. I think of this as my 'centre-court theory'. When a ball is hit down the centre of the court in a doubles match, and each player is on either side, the ball is likely to be missed ('Your ball!'). But it's actually in the reach of both players.

But, there is strength in the crossover of responsibilities and we can often be saved by the overlapping areas of control. This way, any mistake invariably crosses the eye line of a few of us and is more likely to be caught. A complex, Kafka-esque clockwork construction like the NHS is often all joins – but with each of these creases comes an opportunity to work with a



colleague. Shared-care, team-working, The Medical Firm, second-opinions, handovers – these are all chances to gain something from a talented colleague. Much of this happens in a 'multi-disciplinary team', and is more often than not inefficient for the individual clinicians, but there is abundant net gain. All hail the inefficiencies of the NHS!

But when there isn't this care crossover, or when financial strain leads to a shortage of resource in a system, decision-making can become compromised. Which leads me on to think of blame. How do individuals make mistakes? How do mistakes get attached to an individual? With the impact of the butterfly effect, a mis-prescription from me, for example, could end one of two ways. It could be saved by the multi-tiered inefficiency of being checked by my secretary, my registrar, the pharmacist or the patient. Or it could snowball into an emergency admission with status epilepticus and worse.

Centre-court errors could happen every day. For instance, I might email the nurse specialists asking for help – both of them. Do they both follow up my request? Does neither of them? Is their workload too steep for them to stop and check (and then remind me that I should be more accurate in my requests)?

The system, of course, is not a spontaneously occurring self-aware meta-being. But it is a framework in which we work that we have some degree of control over and we should take responsibility for its deficiencies.

There can sometimes be exceptional outcomes – the extreme negative outcomes that are always potentially around the corner when working in healthcare. Do they need a human target for blame? When the creaky, leaking and dysfunctional system has let the patient and their family down, do we blame the last link in the chain (invariably a clinician)? Or do we need an exceptional case with an exceptional level of evidence to prove individual blame? Maybe this is how we protect the public from the exceptional cases where medics have been reckless?

Maybe I am to blame – but it may not be for the last poor decision which may result in harm. It may be for passively tolerating the critical faults in the structure. It may be for failing to recognise that when there are exceptional absences from colleagues and, say, the IT system goes down, this is a set-up for failure. Maybe I am to blame for not appreciating that individuals working under these circumstances are at an intolerable risk of making a state-sponsored mistake.

Dates for the diary

March 2018

22-24
2018 ILAE British Chapter Epilepsy Neuroimaging Course
London, UK
bit.ly/2AZGASZ

April 2018

4-7
EEG in the First Two Years of Life
Cambridge, UK
bit.ly/2opF9s5

15-20
2nd International Training Course on Neuropsychology in Epilepsy
Provence, France
bit.ly/2GzYgXW

May 2018

2-5
4th International Congress on Epilepsy, Brain & Mind
Brno, Czech Republic
www.epilepsy-brain-mind2018.eu/

12-13
Young Epilepsy Section: YES Kick off Workshop
London, UK
bit.ly/2HAMYUC

13-16
14th EILAT Conference on New Antiepileptic Drugs and Devices
Madrid, Spain
www.eilatxiv.com

August 2018

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

September 2018

20-22
ISSET 2018
Rome, Italy
bit.ly/2EZlmdi

Epilepsy and depression

Dr Marco Mula describes spotting, diagnosing and treating depression in patients with epilepsy, as well as preventing suicide.

Primary care support

Dr Jon Dickson discusses the role of GPs in treatment and management of people with epilepsy.

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