epilepsy action

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# epilepsy professional

## Sodium valproate

### Valproate, women and patient empowerment

Heather Angus-Leppan

**Epilepsy misdiagnosis** – Maria Oto

**Neuropsychology** – Sallie Baxendale

**ILAE UK Chapter and ECE congresses**

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Welcome to the winter edition of Epilepsy Professional. We have a festive feast of exciting articles.

Dr Heather Angus-Leppan from The Royal Free London NHS Trust gives an excellent overview of the new MHRA regulations on the use of valproate in women of childbearing potential. She also discusses some of the pitfalls of the new regulations. We are all struggling to get to grips with these important guidelines to ensure all women with epilepsy are making the informed choices that are right for them.

When treating people with epilepsy, we are always balancing risks. Dr Maria Oto from the Scottish Epilepsy Centre, talks us through misdiagnosis in epilepsy. This is an excellent review and reminds us of the importance of always reviewing the diagnosis when things are not going as we expect.

Memory problems are a very common co-morbidity to epilepsy. Dr Sallie Baxendale from the UCL describes some reasons behind memory problems in people with epilepsy. She also gives management strategies to help reduce the nuisance caused by this common co-morbidity.

As technology moves forward, new innovations in medicine are expected and welcomed. Mustafa Sultan and Dr Rhys Thomas from Newcastle Hospitals review medical apps for people with epilepsy.

Finally, our very own editor Kami Kountcheva gives us a round-up of this year's ILAE UK Chapter meeting and the ILAE's European Congress on Epileptology.

Have a merry Christmas and may 2019 bring you health and happiness.

Seán Slaght
Consultant neurologist
Executive medical adviser
*Epilepsy Professional*

# contents

## 20 neuropsychology

**Sallie Baxendale**

Dr Baxendale looks at the reasons why patients may be complaining of memory problems and offers practical ways to help patients cope with the effects of conitive difficulties

All our lives we are told that making mistakes is a good thing. We're only human, right? That's how you learn, right? But also, we know that we shouldn't make mistakes. If I make mistakes in a job interview, I'm not going to get that job. It's a strange paradox that makes it hard to know whether to be glad for mistakes or if they should bring us out in a cold sweat.

It's hard to even imagine what it must feel like to be a medical professional and deal with the prospect and aftermath of mistakes. Especially in an overstretched and understaffed NHS. In this vein, our articles in this issue of *Epilepsy Professional* look at situations where the best course of action isn't always clear, and help unpick some of the questions.

Dr Heather Angus-Leppan takes us through the new MHRA regulations about use of sodium valproate in women of childbearing age. She suggests that there are exceptions, in which the pregnancy prevention programme – part of the regulations – may not be the most appropriate strategy (page 10). Dr Maria Oto describes the rates, causes and repercussions of misdiagnosis in epilepsy, and offers some suggestions to avoid this (page 16). Meanwhile, Dr Sallie Baxendale suggests that epilepsy or epilepsy medicines may not always be the reason why patients complain of worsening memory problems. She offers practical ways of helping people cope with the effects of cognitive difficulties (page20).

When it comes to mistakes, all we can do is do our best and share our experiences with each other. Enjoy this issue and have a fantastic festive season!

*Kami Kountcheva*
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# Child health in England and Wales poorer than other western countries

Child health in England and across the UK is falling behind other western countries, according to a report by the Royal College of Paediatrics and Child Health (RCPCH).

The report, published in October, features figures showing that death rates in one to 19-year-olds with epilepsy in England and Wales is higher than that in other western countries. The RCPCH report compared data on death rates between 2001 and 2015. It added that this trend is despite substantial falls in death rates in England and Wales in that time.

The other western countries used for comparison are the 15 countries in the EU plus Australia, Canada and Norway – known as the EU15+.

The report predicts that if current trends continue, death rates in children with epilepsy in England and Wales are likely to remain higher than those in the EU15+ countries by 2030.

President of the RCPCH and author of the report, Professor Russel Viner, said that England is at risk of falling further behind the EU15+ countries. He added that the current trends "could be turned around if key actions are taken."

The RCPCH has called on policymakers in the NHS to improve the health of children and young people as part of their long-term plan.

Epilepsy Action's chief executive, Philip Lee, said: "It is hard to believe that in 21st century Britain we are falling behind in providing quality healthcare for children with epilepsy. These figures paint a worrying picture for children and young people with the condition and these health inequalities must be addressed immediately.

"Better seizure control and more support for families to help them manage the risks associated with epilepsy would significantly improve the lives of children with the condition. This will ultimately reduce the likelihood of death associated with epilepsy. The government must act now and give children with epilepsy the attention – and future – they deserve."

The report also focuses on concerns around higher death rates in babies compared to the EU15+ countries and a predicted increase in reported mental health problems. It states that trips to A&E for children and young people could increase by 2030 and that obesity may be an increasing problem in deprived areas.

The negative effects of poverty and deprivation on the health of children across England and Wales are also highlighted.

The RCPCH report includes recommendations, such as the development of a Children and Young People's Health Strategy and a joined-up approach from the NHS to healthcare planning. They suggest more funding and better local access to mental health services, as well as better access to weight management services.

The report can be found on the RCPCH website at *bit.ly/2CiQ5R7*

The Epilepsy Action website has information on staying safe in- and outdoors (*epilepsy.org.uk/safety*) for people with epilepsy, as well as tips for caring for a child with epilepsy (*epilepsy.org.uk/children*).

# Neurological Alliance launches third patient survey

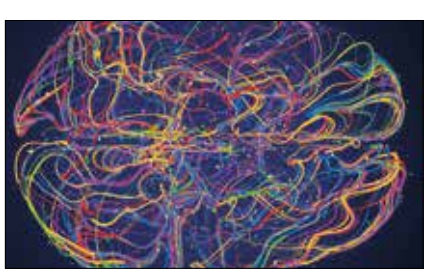
The Neurological Alliance is carrying out its third patient experience survey. The alliance is asking people with neurological conditions to share their experiences of neurology services.

The Neurological Alliance is a group of 80 organisations working together to improve services for neurological conditions in England.

The survey they carry out every two years aims to get people's views on neurology health and care services. The alliance will use the results to promote improvements. The survey is available now and closes on 17 January 2019.

The alliance said results from previous surveys have led to the creation of the National Neurosciences Advisory Group. This group was set up to drive improvement in neurological services. The surveys have also helped highlight the poor experience of people with a neurological condition and mental health problems. They have prompted work to make care planning and communication with patients more of a priority.

Professionals can direct patients with neurological conditions to the survey at: *bit.ly/2DVnLWB*



# Pregabalin and gabapentin to be reclassified as class C drugs

The UK government announced last week that the medicines pregabalin and gabapentin will be reclassified as class C under the Misuse of Drugs Act 1971. The change will take place in April 2019.

The Home Office has said that these medicines will still be available for prescription after the change in law. Doctors will now have to physically sign prescriptions rather than use electronic copies. The medicines will have to be dispensed within 28 days of the prescription being written.

The Home Office said that the change means that it will be illegal for people to possess these medicines without a prescription. This is an effort towards stronger controls, accountability and a reduction in the potential for misuse of these medicines.

The government's decision to reclassify these medicines follows experts highlighting a rising number of deaths linked to their misuse. However, according to researchers from the University of Bristol, more than four in five deaths (80%) involved the misuse of these medicines alongside street drugs, such as heroin. Misuse might include people taking these without a prescription or in a way that is not prescribed by their doctor.

In 2016, the Advisory Council on the Misuse of Drugs (ACMD) raised concerns over the possibility of addiction and misuse of these medicines. It called for them to be reclassified as class C. The government consulted pharmacists, pharmaceutical companies, doctors and patients, who backed tighter controls.

Minister for Crime, Safeguarding and Vulnerability Victoria Atkins said: "Any death related to the misuse of drugs is a tragedy. We accepted expert advice and will now change the law to help prevent misuse of pregabalin and gabapentin and addiction to them. While drug misuse is lower now than it was 10 years ago, we remain committed to reducing it and the harm it causes."

This is not the first medicine used for epilepsy to be classified as a class C drug. Emergency medicines midazolam and diazepam have been listed as class C for around 30 years.

# Nurse receives British Empire Medal

Paediatric epilepsy specialist nurse (ESN) Sue Lewis has received a British Empire Medal in recognition of her work with the NHS.

Ms Lewis became the first paediatric ESN at the County Durham and Darlington NHS Foundation Trust, and has been working with children for over 30 years. Her work includes updating professional colleagues on epilepsy and running a transition clinic for young people.

# Further recall of Belfast patients

The Belfast Trust have announced that a further 1,044 patients previously seen by Dr Michael Watt, a consultant neurologist, have been offered review appointments. The review appointments will ensure that these patients are on the correct treatment.

Around 2,500 patients previously under the care of Dr Watt were recalled earlier this year.

This further recall has concentrated on specific patients taking some specialised medicines for neurological conditions including anti-epileptic drugs (AEDs), immunosuppressants and disease modifying therapies. All patients affected by this recall will be contacted by letter.

The Health and Social Care Board have clarified that past patients of Dr Watt who do not receive a letter do not need to take any action or get in touch.

The trust has warned patients not to stop or make any changes to their medication until they have been reviewed by a consultant at their appointment.

A dedicated advice line is available for anyone who may have concerns ahead of their review appointment. The Belfast Trust advice line is available on 0800 980 1100, Monday to Friday 9am-8pm.

Further information about the recall can be found on the Belfast Trust website at *bit.ly/2zvBxv1*

# Prescription guidance for cannabis-based medicines too tight

As of November 2018, UK specialist clinicians can now prescribe cannabis-based medicines to patients with "exceptional clinical need" without applying to an expert panel for a licence. However, the guidance provided for clinicians has been criticised for being too restrictive.

The UK government has rescheduled cannabis-based medicines out of Schedule 1 under the Misuse of Drugs regulations 2001. Specialist clinicians will not be limited by condition when prescribing cannabis-based medicines. However, they will need to ensure that there is clear evidence of a benefit and that all other available treatment options have been unsuccessful.

Prescription of these medicines must also be in line with the available clinical guidance. The British Paediatric Neurology Association (BPNA) published guidance ahead of the rescheduling coming into force, for use of this medicine in children with severe forms of epilepsy. This is one of three conditions that guidance will focus on. The Royal College of Physicians (RCP) has published guidance on use of cannabis-based medicines for chronic pain and nausea from chemotherapy.

Some organisations, like Epilepsy Action, are concerned over the restrictiveness of the guidance provided. The BPNA has stated that it does not recommend the prescription of non-licensed cannabis-based products for medicinal use other than Epidiolex (cannabidiol). Epidiolex represents only one type of cannabis-based medicine.

Epilepsy Action deputy chief executive, Simon Wigglesworth said: "While this change is an important step forward, the guidance we have seen so far on how it will work in practice seems extremely restrictive. It suggests that cannabis-based medicines will only be an option for a very limited number of people with epilepsy – children with Dravet or Lennox Gastaut syndromes. Though this is welcome, there are children and adults with other complex and treatment-resistant epilepsy syndromes who could potentially also benefit."

Epilepsy Action added that it recognises that good evidence of the effectiveness of cannabis-based medicines is currently limited to a few rare childhood epilepsy syndromes. However, the patient-led organisation added that adults and children with other treatment-resistant epilepsies should also be able to access these medicines. This is in cases where there is some evidence of potential effectiveness and no other treatment has worked.

"It will be down to the regulatory bodies, clinicians and commissioners to ensure that patients with a clear clinical need can access these medicines in a timely and safe manner," Epilepsy Action said.

The National Institute for health and Care Excellence (NICE) is expected to publish guidelines about cannabis-based medicines later in 2019.

# Outcomes after AED withdrawal

Researchers from China have looked at the outcome of seizure-free patients and the risk of relapse following withdrawal of anti-epileptic drugs (AEDs).

Ou et al found that prognosis of seizure-free patients is generally good and that the rate of continuing seizure freedom five years after AED withdrawal is around 57%.

The study looked at 161 patients who had been seizure-free for at least two years. They were monitored for at least three years or until their seizures relapsed following AED withdrawal. The risk factors were analysed in the patients who did and did not relapse.

The study authors found that in 72 patients (44.7%) seizures relapsed, while in 89 (55.3%) they did not. The majority of relapses happened within the first two years of AED withdrawal.

The researchers found a few factors linked to a relapse after withdrawal. These were uncontrolled seizures beyond the first six months of starting on AEDs, history of perinatal injury, multiple seizure types and patients requiring AED polytherapy. Uncontrolled seizures after the first six months of AED therapy and perinatal injury were independent risk factors of relapse.

The researchers also concluded that the seizure-free period before withdrawal of AEDs made no impact on the long-term outcome.

The study was published in the journal *Epilepsy & Behavior*.

# Promising results from new sleep seizure device

A new study from the Netherlands has looked at the effectiveness of a new sleep seizure detection device. The device – Nightwatch – is a bracelet worn on the arm. It uses heart rate and movement to sense what the authors called 'major' seizures.

For their study, the researchers considered 'major seizures' to be those that were clinically urgent. They included tonic-clonic, long generalised tonic and intense motor seizures which they call hyperkinetic seizures. They also included other major seizures which were not typical, such as clusters of myoclonic or tonic seizures.

The study was carried out between 2015-17 on 28 people with epilepsy and a learning disability who had more than one sleep seizure in a month. People taking part were residents in epilepsy centres and were studied for two to three months. They were also filmed during this time, so researchers could see when the device did and did not sense major seizures.

The study covered 1,826 nights and 809 major seizures. The device could sense over four-fifths (85%) of major seizures in each participant. This was compared to a bed sensor, which recognised around one-fifth (21%) of these seizures.

The developer of the device, Livassured BV, said this device has a much better sensitivity than other technology currently available.

The researchers found that 51% of the Nightwatch alerts were a false positive, which the researchers called 'reasonable'. The device very rarely gave a false negative result.

Study authors Dr Johan Arends and colleagues highlighted that uncontrolled seizures are a risk factor for sudden unexpected death in epilepsy (SUDEP). As cases of SUDEP tend to happen overnight and be unwitnessed, the researchers suggest that this sensor could help in preventing SUDEP.

However, there are still concerns that night-time monitoring systems won't help people who live alone or don't have a carer.

To get the Nighwatch in the UK, the cost is £1,130 including shipping. Livassured also offers a money back guarantee. The research was published in the journal *Neurology*.

# Reporting side-effects

In November, the Medicines and Healthcare products Regulatory Agency (MHRA) ran its third campaign to raise awareness of its Yellow Card Scheme. This allows members of the public and health professionals to report suspected side-effects of medicines. The MHRA said this helps recognise issues which may not have been previously known. Side-effects can be reported on the Yellow Card Scheme website at *yellowcard.mhra.gov.uk*

# LITT treatment outcomes

A new US study has looked at the seizure outcomes of laser interstitial thermal therapy (LITT) in patients with mesial temporal lobe epilepsy (MTLE).

The *Epilepsy & Behavior* study by Le et al prospectively tracked cases of patients with MTLE between 2014-17. The study used Engel classification and reduction in baseline seizure frequency as the primary outcomes. They also analysed complications resulting from the treatment.

Thirty patients underwent amygdalohippocampotomy using LITT and were followed up for 6-44 months. A more than 50% reduction in seizure frequency was seen in 28/29 (97%) of people. In 22/29 people (76%) there was a more than 90% reduction in seizure frequency. Using the Engel classification, 18/29 people (62%) were free of disabling seizures (Class I) and 9/29 (31%) were completely seizure free. In 6/26 people (21%) disabling seizures were rare (Class II) and in 5/29 people (17%) there was a worthwhile improvement (Class III).

The researchers explained that complications to the LITT treatment included perioperative seizures in 10/29 people (34%) and non-seizure complaints in 6/29 people (21%). Three people experienced neurological deficits. Complications were largely temporary except in one case, the study authors explained. They concluded that this was a well-tolerated treatment with a marked seizure reduction outcome for the majority of patients.

# Sodium valproate

## Valproate, women and patient empowerment

Dr Angus-Leppan describes the new MHRA regulations around use of sodium valproate in women and girls of childbearing age and discusses some possible exceptions

The new Medicines and Healthcare products Regulatory Agency (MHRA) regulations on valproate [MHRA, 2018] affect patient safety, empowerment and choice. This article discusses exceptional circumstances related to the regulations. It summarises our professional responsibilities in providing resources to guide patients in their decision-making. There are government initiatives that could improve the current guidance. These would enable collection of crucial data which would increase future choice. This article is restricted to valproate use in epilepsy, focusing on the United Kingdom. Valproate use for other indications, particularly in bipolar disease and migraine is common and discussed elsewhere [Angus-Leppan and Liu, 2018].

## What are the MHRA regulations on valproate use in women of childbearing potential?

These are summarised in *Box 1*. There is international agreement that valproate is a significant teratogen. The effects on the unborn child may be permanent and severely disabling. This has a life-long impact on the family and the community as well as the child [Angus-Leppan and Liu, 2018]. Specialist review is needed in all women of childbearing potential considering valproate. Alternatives should be offered where possible and safe. However, for some, valproate will be the only effective medication to prevent seizures [Sanjay et al, 2018].

## Are there exceptions to the regulations?

The MHRA regulations now require an annual signed form confirming adherence to the Pregnancy Prevention Programme in women of childbearing potential taking valproate. They include that for some women with epilepsy, there may be no suitable alternatives to valproate. In some patients "who are already pregnant switching antiepileptic medicines may not be feasible" [MHRA, 2018]. Frequent convulsions or status epilepticus affect both mother and child. The Association of British Neurologists suggests "there are likely to be some women who, even after informed consultation, choose to carry a pregnancy while taking valproate" [Angus-Leppan and Liu, 2018; Sisodiya et al, 2018; Wright, 2018].

**The MHRA include that for some women with epilepsy there may be no suitable alternatives to valproate**

We have outlined exceptional circumstances in which for a child or woman of childbearing potential, a

*Box 1. MHRA regulations on valproate use in women of childbearing potential*

**MHRA legislation 2018 (summary)**

In girls and women of childbearing potential –

- Valproate must be initiated and supervised by a specialist
- Should not be used unless other treatments are ineffective or not tolerated
- Highly effective* contraception should be arranged before the first prescription is issued

*Highly effective contraception = user independent methods (intrauterine device, progestogen only implant and female sterilisation)

See MHRA 2018 for full details [MHRA, 2018].

*Box 2. Exceptional circumstances guidance*

**Valproate post MHRA use: suggested guidance on exceptional circumstances [Angus-Leppan et al, 2018; Watkins et al, 2018].**

The MHRA has issued new regulations regarding the use of valproate [MHRA, 2018].

Its use will be banned in women and girls of child bearing potential unless they adhere to the Pregnancy Prevention Programme, to prevent the development of foetal abnormalities. There is international consensus that valproate is a significant teratogen, that alternatives should be offered where possible and safe, and that all women in whom it is considered need specialist review.

The MHRA recognises that in some women with epilepsy, valproate cannot be stopped during pregnancy without major risk to the person and the unborn child. Both frequent convulsions and convulsive status epilepticus are potentially dangerous to both mother and child. We outline the situations in which a child or woman or her authorised representative may decide that she will continue valproate even though she might be, or may become, pregnant. We also consider when the pregnancy prevention programme is not appropriate, although a risk acknowledgement form would still be required.

**1. Emergency situations**

- Status epilepticus or serial seizures in a female of childbearing potential when valproate is considered by her medical specialists to be the most effective medication to control her seizures
- In this situation discussion with the patient is usually not possible so treatment is given on a best-interest basis under mental capacity legislation. Informed discussions about continuation of valproate and the associated risks would be undertaken on recovery with her, or with her advocates where capacity is impaired. Consent would be sought at a later date from the patient

**2. Epilepsy in a female of childbearing potential in whom valproate is the most effective medication and the fully informed woman decides it is the best option for her. This refers to cases where the Pregnancy Prevention Programme is not appropriate**

- This may follow unsuccessful trials of other medications
- It may be in women who are currently seizure free on valproate

Pregnancy Prevention Programme is not chosen (*Box 2*). Completion of the MHRA risk acknowledgment form with annotation is still required. The exceptional situations include emergencies, those making a fully informed decision and whose treating professionals agree pregnancy prevention is not appropriate, and those with impaired capacity. A best-interest process supporting the continuation of valproate is needed for this group, which includes some people with intellectual disability. This guidance is signed by >70 epilepsy clinicians working in tertiary, secondary and community care supporting people with epilepsy. It is endorsed by the Royal College of Psychiatrists Intellectual Disability Section and the United Kingdom Learning Disability Professional Senate. This guidance has been received by the MHRA as an open letter.

**Understanding diversity of viewpoints, lifestyles, situations, sexuality, needs and aspirations is essential**

Charities and patient groups help us to listen to patient concerns. The public hearing on valproate provided a platform for charities, individuals,

as first line monotherapy, and who, after fully informed discussion, do not wish to change to another medication because of the risks to their personal safety of switching to an alternative
- Women who are not able to become pregnant for health-related or physical reasons
- Women who, after fully informed discussion, do not wish to use the forms of contraception recommended by the MHRA for personal, religious or health reasons

**3. In those who may lack capacity, such as some women with intellectual disability, an individual assessment of abilities to make informed choices on epilepsy management and medication issues is needed**
- In some women with moderate to profound intellectual disability, consent to sexual intercourse may be unlikely, so pregnancy is not likely to occur. In these women, pregnancy would raise significant concerns of abuse, sexual exploitation or rape
- Pregnancy prevention may be part of the care plan to manage psychological distress arising from menstruation in women with moderate to profound intellectual disability lacking mental capacity to understand the natural physiological changes
- Those with mild intellectual disability should be managed as other women are. But they will need particular care to support their decisions in this area and may require augmented communication to enable them to make informed decisions on using medication. There may need to be involvement of special parenting services in addition to other key stakeholders such as social care

professionals and organisations to speak about valproate and its dangers when used during pregnancy [EMA, 2017]. Patient empowerment should also reach those patients who do not have a public voice.

Lack of resources (professional time) is the biggest barrier to patient empowerment and truly informed consent. Generic guidelines alone or 'information dumping' without patient involvement in what matters to them are not enough. Understanding diversity of viewpoints, lifestyles, situations, sexuality, needs and aspirations is essential. There is no universal 'woman's view' (or man's view) of the world. Listening to the patients' situations and concerns takes expertise and time. Health professionals also need education and reminders to ensure we don't slip into maternalistic advice. We aim to be evidence-based in our practice. At the same time, we have the job of helping patients to navigate their journey and make individual decisions. The weight of each part of the evidence will mean different things to each person. The case vignettes illustrate this (*Box 3*).

## What are our responsibilities here and now?

The first step is to identify women of childbearing potential taking valproate. Surveys by Epilepsy Action and others show that many women taking valproate are still not aware of the potential dangers during pregnancy [Epilepsy Action, 2017].

Heather Angus-Leppan

*Box 3. Example cases*

**Case vignettes (reproduced in anonymised form with patient or carer permission)**

***S*** has a male partner and wishes to start a family. She has genetic generalised epilepsy. In the past, she has had fractures and facial injuries during seizures. She continues on two anti-epileptic drugs at maximum dose, with one to two major seizures each year. She is aware that she could die during a seizure. She decides to avoid valproate until she has completed her family.

***J*** has three healthy children. As a child, she was seizure free on valproate. She felt suicidal on levetiracetam. She switched to lamotrigine at high dose after her first pregnancy. She had two major seizures in the first six months after her second and third babies. She knows about the risks of valproate but she wants to take it. She does not want any further major seizures. She does not want to try other medications. She is planning a fourth child.

***C*** has no children. She would like some, but not yet. She is seizure free on valproate and does not want to change as she had a friend who died during a seizure. She does not accept the forms of contraception suggested by MHRA guidelines for personal and religious reasons.

***A*** has moderate intellectual disability. She lives in a residence and comes home to her parents for weekends. She has had no major seizures on valproate for five years, and her parents and carers agree she does not have the mental capacity to make decisions about sex or medications. Her mother was upset that it was suggested ***A*** must go onto contraception. Her mother says that ***A*** could not consent to sex, so if she got pregnant it would be rape. She says that it is not fair that ***A*** should have to have contraceptive injections or have a procedure.

***B*** has well controlled epilepsy on valproate. She occasionally has sex with men and uses condoms. She is approaching menopause. She comes to see her specialist. The visit is because she was told she must go onto contraception. She does not want to as her mother had breast cancer, and she does not want an IUD as she does not want to have a procedure she thinks is unnecessary.

***L*** is in a same sex relationship and seizure free on valproate for epilepsy. She also has bipolar disorder. She was told by a health professional that she has to start contraception. She refuses this. She wants to continue valproate and has read and discussed this in detail.

Information needs to be tailored to patient need – for most people this will be an individualised discussion [Friedrich et al, 2018] and this is in line with MHRA recommendations. Prompt discussions with a specialist about the benefits and risks of valproate and alternatives are the gold standard of care.

We also have a duty to inform patients about the risks of changing medications, of avoiding valproate or not taking any anti-epileptics. These include risks of major seizures, including the small but real risk of dying during a seizure, impact on driving and other activities. Surveys estimate the majority of people with epilepsy are still not informed about the risks of sudden unexpected death in epilepsy (SUDEP) [Keddie et al, 2016]. The risk of major seizures and the small risk of death is material information for all patients [Fryar, 2015]. It must be weighed up in their decision-making about medications.

**Information needs to be tailored to patient need - for most people this will be an individualised discussion and this is in line with MHRA recommendations**

We have a duty to signpost the potential risks of the MHRA recommended contraception, if it is being considered. For most epilepsy specialists, this is beyond our expertise and requires joint working across other specialties.

## What are the government's responsibilities?

Women who are seizure free on valproate may not be seeing a specialist [Craig, 2018] It may be difficult to make contact with some of them. The onus of this should not fall solely on the prescriber in primary care, an additional responsibility in an already over-stretched system.

The important and potentially life-changing discussions about

valproate includes understanding the individual's life situation, aspirations and their epilepsy. This includes their desire or otherwise to have children. These discussions touch on very personal issues. They are time-consuming if this is more than a tick-box exercise. There are no extra resources made available to do this. They are needed.

Some crucial information is missing from the MHRA booklet. It quantifies the risks of valproate. It does not quantify or signpost the risks of alternatives, in terms of adverse effects and relative ability to control seizures. It does not quantify the risks of not taking any anti-epileptic drugs. The potential risks of the contraception mandated by the MHRA are not mentioned. It is not practical to cover these issues in any detail in the booklet. In line with the principles of informed decision-making, they should be mentioned and references signposted [Fryar, 2015].

The current MHRA acknowledgement form could be improved. There is no space for an NHS number or identifier on the form. There is no space for annotations (for example if there are exceptions) or user feedback. We are expected to give a paper copy to the patient and GP, and ensure it gets into the (usually electronic) patient record. The potential for mislaying forms could be overcome by an electronic form.

**Some crucial information is missing from the MHRA booklet – it does not quantify or signpost the risks of alternatives (to valproate)**

We are missing important opportunities and responsibilities to monitor the effects of the new MHRA legislation. There is no system in place to record the potential adverse effects of the MHRA advice. The impact of the new regulations on cognitive development of young women avoiding valproate (Angus-Leppan and Liu, 2018), on seizure control and complications of seizures (including death) are unknown. There have been seizure-related injuries and death in women stopping valproate. We do not know how many. Making the MHRA forms electronic, coupled with data collection and linked to data registry, would go some way towards better understanding. There is also a need to capture data on those women who avoid valproate and their outcomes. We have the technology to do this. It would cost money, but this information is material to decisions of all patients, now and in the future.

*Heather Angus-Leppan has been an Association of British Neurologists representative on one of the MHRA Valproate Stakeholders' Network meeting (2018) and UK representative on the Sanofi European Valproate educational programme Advisory Board (2018).*

*She holds Eisai Investigator initiated non-pharmaceutical grants (2017) and has received Honoraria for non-promotional lectures from Eisai (2017) and UCB (2016).*

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# Epilepsy misdiagnosis

## Raising awareness and maintaining vigilance

Dr Maria Oto describes the rates, causes and repercussions of misdiagnosis in epilepsy. She offers some suggestions to minimise this occurrence

The misdiagnosis of epilepsy is not uncommon and the consequences for affected individuals can be devastating. Patients wrongly diagnosed as having epilepsy find that many aspects of their lives are restricted. They are often exposed to powerful as well as teratogenic drugs and overall may be profoundly disadvantaged by a condition they don't have. An example is a 40-year-old woman with dissociative seizures misdiagnosed as epilepsy over 10 years ago. She is now on multiple anticonvulsants and had a recent admission to ITU for presumed status epilepticus. Unfortunately, this is not unfamiliar.

## The size of the problem

Studies investigating misdiagnosis rates of epilepsy are heterogeneous and difficult to compare. However, overall, the rate of a false positive diagnosis of epilepsy in unselected patients may be in the region of 20% [Xu et al, 2016]. The rate is even higher in children and people with learning disabilities, partly due to the presence of a large number of non-epileptic events that can potentially be misdiagnosed as epilepsy [Xu et al, 2016; Stroink et al, 2003; Chapman et al, 2011].

Due to diagnostic complexities, as well as misdiagnosing other paroxysmal disorders such as syncope as epilepsy, the diagnosis of epilepsy could also be missed. Although the consequences of missing the diagnosis are not negligible, in general, the risks of missing the diagnosis of epilepsy are overestimated. This may potentially contribute to a rushed and incorrect diagnosis of epilepsy.

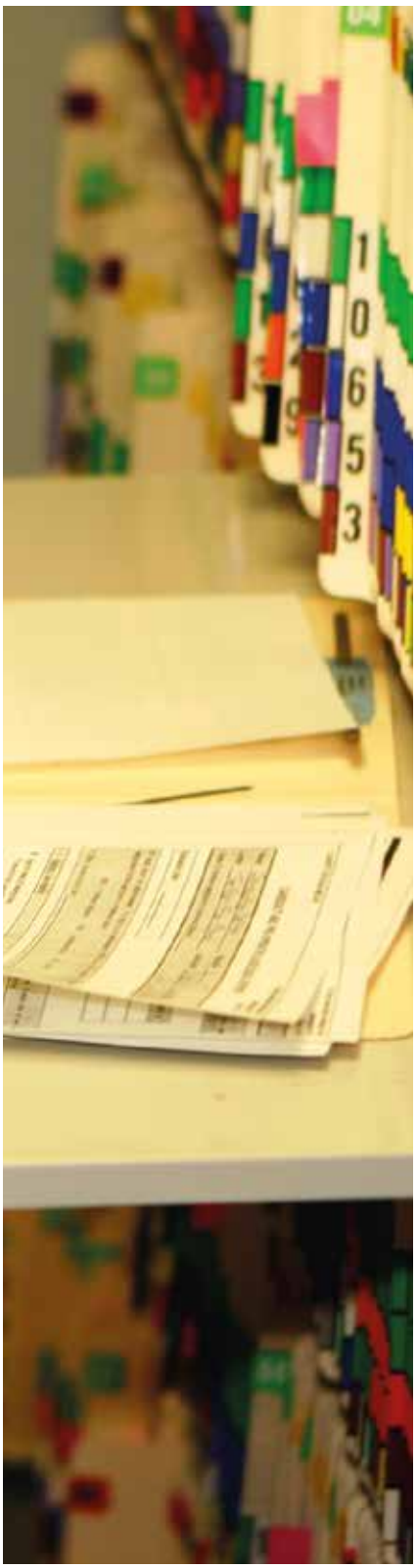
**Many individual features of epileptic seizures are shared by other types of paroxysmal attack and the differential diagnosis is wide**

## Why does misdiagnosis of epilepsy continue to be a significant issue?

In the first place is the fact that the diagnosis of epilepsy is mostly clinical and therefore dependent on the skill of the clinician to obtain an accurate and thorough history. Additionally, there is no clinical test specific or sensitive enough to confirm or reject the clinical opinion definitively.
To complicate matters, epileptic seizures are heterogeneous and can manifest in many forms. There is no unique clinical feature that unequivocally supports a diagnosis of epilepsy. Many individual features of epileptic seizures are shared by other types of paroxysmal attack and the differential diagnosis is wide. Ideally diagnosing clinicians would have knowledge and experience of the full range of psychological, cardiological and neurological conditions that imitate , but this is rare in practice.

As already mentioned, the diagnosis of epilepsy is mostly based upon a detailed history and is dependent upon a witness description. Seizures, however, are not always observed and even when a first-hand witness description is available it may not be accurate or reliable [Van Donselaar et al, 2006].

Because of all of the above challenges, the diagnosing clinician must have the skill and perseverance to take a complete and detailed history. However, they must also have the ability to recognise when the information gathered is not sufficient to make a definite diagnosis of epilepsy. Relying on a poor or



incomplete history is one of the main factors contributing to misdiagnosis [Smith et al, 1999].

## Common epilepsy imitators

Although the differential diagnosis of epilepsy is extensive, the most commonly misdiagnosed attack disorders are syncope, followed by psychogenic non-epileptic seizures (PNES).

Syncope is a transient and self-limiting loss of consciousness which usually leads to a collapse. The most common form, reflex or vasovagal syncope, is generally a benign condition that rarely requires treatment. Up to 40 % of people will experience a faint at some point during their life. There is, however, another subgroup of patients who have an underlying cardiac cause and for whom the consequences can be fatal if the correct diagnosis is missed [Zaidi et al, 2000].

A significant number of patients with syncope are misdiagnosed as having epilepsy because of the misconception that convulsive movements, myoclonic jerks, vocalisation or incontinence are exclusive features of epilepsy. In fact, they are also frequently associated with syncope.

PNES is the second most common disorder misdiagnosed as epilepsy and represents up to 20% of patients presenting with seizures to a specialist clinic. Since most patients with PNES are presumed to have refractory epilepsy, they are at high risk of iatrogenic harm. This might be through exposure to anti-epileptic drugs (AEDs) and inappropriate intensive care admission when prolonged episodes are mistakenly identified as status epilepticus. In addition, failure to recognise the underlying psychological cause means that appropriate treatment is not implemented [Oto and Reuber, 2014].

## Absence of reliable diagnostic tests

Routine electroencephalogram (EEG) is often used inappropriately, mostly due to a poor understanding of its limitations. The sensitivity of an interictal EEG for detecting epilepsy is low and, more importantly, the presence of epileptiform abnormalities in the EEG does not always support a diagnosis of epilepsy. Interictal epileptiform discharges can be found in 10-30% of patients with the diagnosis of PNES only, in patients who are prescribed psychotropic drugs or who have cerebral pathology. It is therefore important to be aware that an abnormal EEG should not be viewed as confirmation of epilepsy. Overreliance upon and misinterpretation of routine EEG results often contributes to the misdiagnosis of epilepsy [Smith et al, 1999; Benbadis and Tatum, 2003].

**When faced with legitimate diagnostic doubt, the most adequate step should be watchful waiting rather than committing to a premature and poorly sustained diagnosis of epilepsy**

Video EEG is frequently referred to as the gold standard diagnostic test for epilepsy but it is only useful if the patient has a typical seizure during the test. In practical terms, it is often very difficult to capture seizures during a limited period of video EEG recording. Even if a typical epileptic event is recorded, it will not always be associated with EEG epileptiform discharges, as for example in frontal lobe seizures.

Neuroimaging is not a diagnostic test although it has an important role in the investigation of the underlying causes of the epilepsy. As in the case of the EEG, neuroimaging can contribute to a misdiagnosis if not used appropriately. As MRI has become more powerful, incidental findings may mislead clinicians who eventually diagnose epilepsy despite a doubtful clinical history.

## Ways of improving diagnostic accuracy

The level of expertise of clinicians is an important factor and there is evidence that the rates of misdiagnosis are lower among epilepsy specialists. National Guidelines already recommend that the diagnosis should be made by a specialist with expertise in epilepsy. Investing in training, expanding services and facilitating access to specialist clinics are all measures that could reduce the misdiagnosis rates [SIGN, 2015; NICE, 2012].

Another way to minimise misdiagnosis is by recognising that at times, a confident diagnosis of epilepsy is not possible and that even specialists on occasion can get the diagnosis wrong.

When faced with legitimate diagnostic doubt, the most adequate step should be watchful waiting rather than committing to a premature and poorly sustained diagnosis of epilepsy [Beach and Reading, 2005; Chowdhury et al, 2008]. Once given the label of epilepsy it is difficult to challenge, as is clear from the long diagnostic delay in patients with PNES [Oto and Reuber, 2014].

Statistically and practically, all individuals involved in the care of patients with epilepsy will encounter, wittingly or not, misdiagnosed epilepsy in their routine clinical work. This is largely given the imperfect reliability of the diagnostic process. It is therefore our responsibility to acknowledge this and take steps to manage this issue by routinely reviewing or questioning the diagnosis of epilepsy. This is particularly when patients fail to respond to standard treatment.

## Conclusion

An accurate diagnosis of epilepsy is essential for a successful treatment, it is therefore fundamental to get the diagnosis right. The diagnosis of epilepsy, however, can be challenging for a range of reasons. Some can be addressed by improving access to specialist services, but others depend on accepting that diagnostic doubt is not always avoidable.

Recognising when we don't have enough information and readiness to question and review diagnosis are two of the potentially effective ways to minimise diagnostic errors.

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# Neuropsychology

## Why now? A critical question in the evaluation of memory complaints in people with epilepsy

Dr Sallie Baxendale looks at the reasons why patients may be complaining of memory problems and practical ways to help patients cope with the effects of cognitive difficulties

Epilepsy is an unusual entity in neurology in that the primary diagnosis is determined by the presence of a symptom of brain dysfunction – a seizure. This is rather than a diagnosis being made in reference to the underlying process causing the dysfunction, as is the case in most other neurological diseases. A poor memory is often cited as one of the most frequent comorbidities of epilepsy in the neuropsychological literature. In reality, both seizures and a poor memory often represent different manifestations of the same underlying brain pathology.

While the underlying abnormality may result in seizures, any associated cognitive difficulties are often apparent on a daily basis. These can sometimes have a more devastating impact on someone's quality of life and opportunities than their seizures which may be infrequent. To make matters worse, the most common treatments aimed at controlling the propensity to have seizures (antiepileptic medications and surgery) tend to exacerbate the cognitive difficulties associated with the condition. It is therefore no surprise that memory problems are among the most frequent complaints in the epilepsy clinic. For those fortunate enough to have a local neuropsychology service, these complaints often result in a referral for a formal assessment. One of the first questions a neuropsychologist will ask is: 'Why now?'

## Why now?

The timing of a referral often provides important diagnostic information itself. The answer to the 'why now?' question often lies not in the suspected epilepsy concerns that prompted the referral, but in more benign processes and interactions.

While cognitive development is most marked in childhood, cognitive functions are dynamic and develop and decline in a systematic way across the adult lifespan. Standardised psychometric tests are carefully designed to ensure 'stable' function over the course of someone's lifetime. They essentially measure where someone's ability lies in relation to a healthy peer group. This means that someone who obtains an IQ of 105 at the age of five (indicating function at or around the 63rd percentile), should obtain a score within a small margin of this point at any subsequent assessment throughout their lifetime. Any subsequent measurement significantly below this level indicates a deviation from the normal, expected trajectory of change. This deviation can reflect neurological or psychological factors and often represents a combination of both. A standardised cognitive score doesn't represent function in a given domain in any absolute sense. It simply represents how someone is functioning on a task relative to the function of healthy peers of the same age. On one level, this is obvious – an average five-year-old can't do what an average 35-year-old can do, and an average 85-year-old will be different again. Figure 1 represents the normal trajectory of change in absolute ability over the adult lifespan (adapted from Baxendale, 2011)

**The answer to the 'why now' question often lies not in the suspected epilepsy concerns that prompted the referral, but in more benign processes and interactions**

As can been seen from *Figure 1*, verbal comprehension increases throughout adulthood, peaking in the fifth decade as experience adds to vocabulary and reasoning skills. Meanwhile, processing speed and perceptual reasoning plateau in very early adulthood and have begun to deteriorate by the age of 35. Even more marked deteriorations in memory function are evident over the adult lifespan, particularly in the visual domain. See *Figure 2*.

Longitudinal studies have demonstrated similar developmental

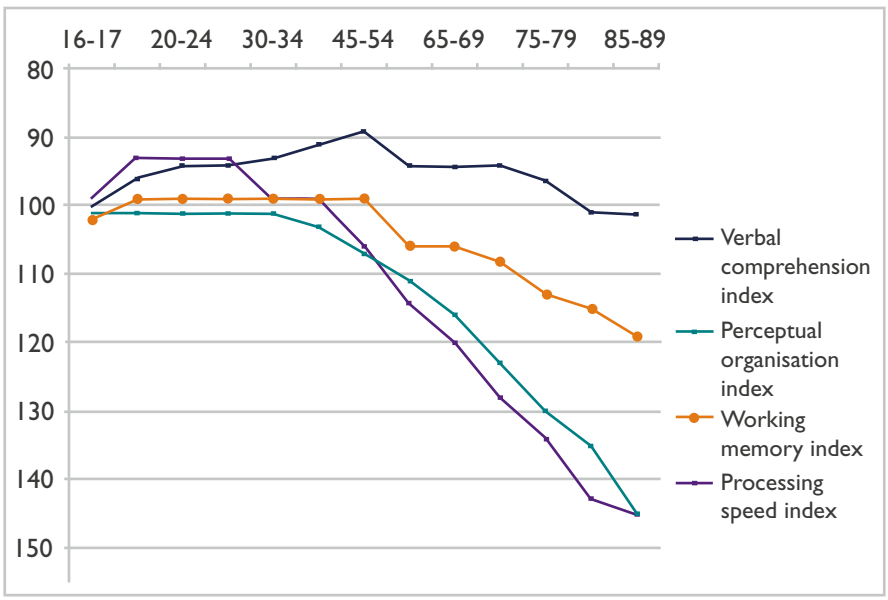


*Figure 1: Developmental trajectory of change in intellectual function over the adult lifespan (adapted from Baxendale, 2011). The impact of age on the calculations of IQ indexes using an identical raw score profile. The scale has been reversed on the IQ axis so that the orientation of graph lines reflects the development (up) and decline (down) in ability across the age ranges in an intuitive way*

and decline trajectories for people with epilepsy [Helmstaedter and Elger, 2009]. However, those who develop epilepsy in childhood exhibit a developmental hindrance in memory function, demonstrating a slower progression of function in childhood. They also begin to plateau earlier. While they deteriorate at a similar gradient to normal controls, they hit a level of functional impairment sooner because they started from a lower level.

It is therefore unsurprising that a substantial number of people with epilepsy really begin to suffer with cognitive difficulties in middle age and beyond. This doesn't necessarily represent an accelerated deterioration in function. However, they hit the level at which impairment has an impact on everyday life sooner than their peers.

The results of a formal neuropsychological assessment showing 'stable' function (ie they have maintained their function in relation to that of their peers) can be very frustrating for people. They may be keenly aware that they cannot do what they used to be able to do and their cognitive difficulties are really beginning to interfere with their everyday activities. It is vital to reassure someone who has undergone a formal assessment that scores indicating 'stable' function don't negate their subjective complaints. Their difficulties are real. The 'normal' results can reassure the patient and clinician alike that a sinister progression is unlikely to be present, but they do not mean that there isn't a problem to be addressed.

The first stage in 'treating' these difficulties is to explain the normal cognitive aging process and to show how this may be responsible for the increase in difficulties someone may be experiencing. Just this knowledge can have a very significant impact in reducing the anxiety and hypervigilance. This may have grown around their cognitive difficulties, significantly exacerbating the problems in doing so.

The second stage involves developing some degree of acceptance. Again, a psycho-educational approach should be employed. This can help ensure that someone understands that these problems are an integral part of their condition and that there is no silver bullet that will resolve them. However, there are some strategies that can be employed to reduce the nuisance of these difficulties on everyday function. These can be loosely termed under the acronym SOS (strategies, outsourcing, social support). Strategies might include describing actions out loud to ensure that you are attending to your actions and properly encoding them. For example, this could be

saying 'it is Tuesday morning and I am switching off the iron'. If someone says this while they are carrying out the action, they are far less likely to start worrying about whether they turned off the iron later in the day. They will recall saying it out loud. Outsourcing memory functions to phone apps, diaries, post-it notes and whiteboards ensures that someone doesn't have to recall many items, just one (eg check the phone or whiteboard list). Smartphones can be programmed to prompt actions, thereby further reducing the burden of memory to recall things automatically. Social support can be used to harness the support of others to shore up a poor memory. Those around someone with a poor memory can ensure that they impart important information. They can do this in a way that allows for the best chance of recall by repetition and additional prompting where necessary. All of these methods can be combined in a bespoke package to practically address the difficulties that someone's cognitive problems pose in everyday life. This phase of treatment is very pragmatic. The goal isn't to 'improve' someone's cognition but to find ways around the problems it is causing.

## Lifestyle factors

For many years, the development of acceptance and the application of SOS techniques have been the mainstay of neuropsychological rehabilitation. However, obesity is increasingly being recognised as a significant contributory factor in accelerated cognitive aging in the general population. Although research in the epilepsy population is in its infancy, evidence is beginning to emerge that obesity also confers significant neuropsychological morbidity in this group. This appears to be at least equal to that associated with anxiety and low mood [Baxendale et al, 2015]. In the general population accelerated aging has been halted and in some cases reversed following lifestyle changes which address obesity. It remains to be seen whether similar benefits are present in people with epilepsy, but in the meantime, healthy lifestyle advice is unlikely to do any harm.

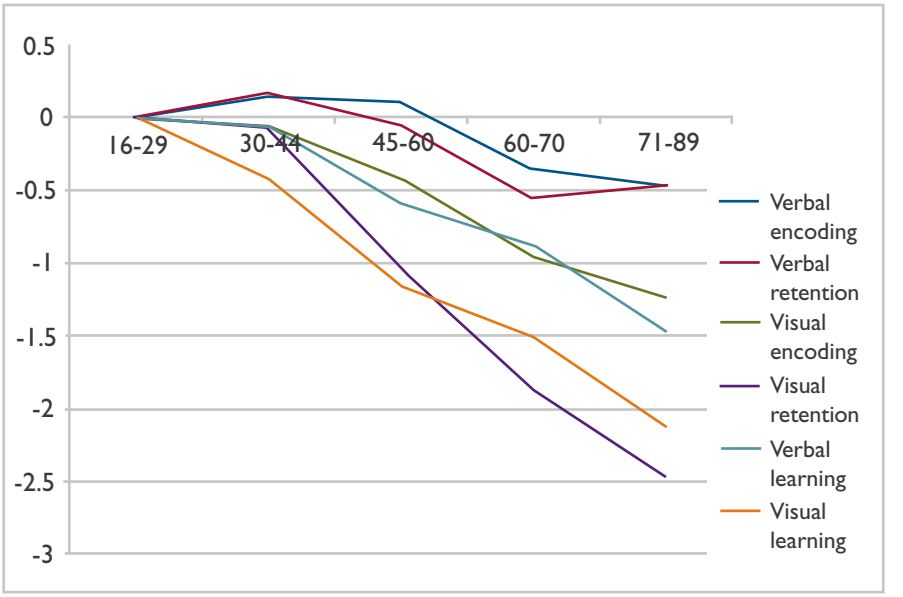


*Figure 2: Developmental trajectory of change in memory functions over the adult lifespan. The impact of age on the calculations of z scores using an identical raw score profile. The scale has been reversed on the z score axis so that the orientation of graph lines reflects the development (up) and decline (down) in ability across the age ranges in an intuitive way*

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## Additional resources

Sallie Baxendale's book Coping with memory problems [2014] has specifically been written for people with subjective memory complaints. It explains how memory works, why it begins to fail as we age and gives tips and strategies for reducing the nuisance this causes. It has been selected for the Reading Well 'Books on Prescription' scheme, meaning a copy is available in every library in England. It is currently being translated into Welsh and will be available in Welsh Libraries as part of the scheme in 2019.

# Highlights

## Top picks from *Seizure*

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

Transient loss of consciousness (TLOC) is one of the most common neurological reasons why patients attend emergency departments [Dickson et al, 2016]. Over 90% of presentations are due to epileptic seizures (ES), syncope or psychogenic non-epileptic seizures (PNES) [Malmgren et al, 2012]. The accurate and rapid distinction between these different causes of TLOC is key to patients accessing appropriate diagnostic and treatment pathways. Unfortunately, initial post-event investigations have low sensitivity and limited specificity and are often carried out in primary care or emergency departments by generalists. Not surprisingly, misdiagnosis rates for the causes of TLOC of 20-30% have been reported [Malmgren et al, 2012].

In my editor's choice article from *Seizure volume 61*, Alistair Wardrope et al [2018] explores simple decision rules – for instance based on demographic, clinical or semiological features. They ask if these could predict the most likely cause of TLOC and enable non-experts to investigate and treat patients with this presentation more effectively. Sixteen publications met the inclusion criteria for this review. All reported that combinations of different criteria can support the differential diagnosis to some extent. However, no individual criterion differentiated between the diagnoses with high sensitivity and specificity. What is more, none of the diagnostic questionnaires investigated have been validated prospectively against gold-standard diagnostic criteria.

More and more clinical decision-making processes are driven by evidence-based scores or flow charts. But the highly important diagnostic distinction between the common causes of TLOC will still need to be made on the basis of informal judgements of clinicians.

### Long-term surgery outcomes

My editor's choice from *Seizure issue 62* makes an important contribution to our understanding of temporal lobe surgery [Helmstaedter et al, 2018].

The main neurological concern in relation to this form of epilepsy surgery is damage to brain structures supporting memory functions. Previous cross-sectional and short-term longitudinal investigations raised the possibility that temporal lobe epilepsy may be associated with an acceleration of 'normal' age-related memory decline [Helmstaedter et al, 2002; 2003]. The new longitudinal study describes cognitive outcomes a mean of eight years (5-22) after epilepsy surgery [Helmstaedter et al, 2018].

The major immediate losses of memory functions with temporal lobe epilepsy surgery were confirmed. But memory functions did not continue to decline at the speed of 'normal' age-related decline. Over the longer term, memory functions in patients with temporal lobe epilepsy (TLE) who had undergone surgery did not differ from those treated with medication alone. Successful epilepsy surgery was not found to be associated with a group-level improvement of memory functions directly. But a reduction in antiepileptic drug load (perhaps made possible by successful epilepsy surgery) was. The study also provided some additional evidence for the concept of 'double winners' and 'double losers' from epilepsy surgery. Patients were more likely to be seizure-free after epilepsy surgery. In those who had become seizure free, a degree of recovery of verbal memory was more and memory decline less likely than among those still experiencing seizures. From a neuropsychological point of view, epilepsy surgery therefore comes out as a good treatment for TLE. But this is as long as it is offered to patients who will become seizure-free with surgery!

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

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# ILAE UK Annual Meeting and European Congress on Epileptology

We take a look at some of the fascinating studies presented at two key ILAE congresses in 2018

As the editor of *Epilepsy Professional*, I am reminded every year how valuable an epilepsy conference is. It provides incredibly rich food for thought and allows colleagues from across the UK – and further afield – to learn from and share in each other's experiences. Conferences are a very efficient and effective way to get up to date with what's going on in the field of epilepsy and come away full of knowledge and ideas.

I was lucky enough to attend two ILAE conferences in 2018 – the 13th European Congress on Epileptology in Vienna and the UK Chapter Annual Meeting in Birmingham. Here, we summarise one session from each meeting.

## ILAE UK Annual Meeting

The ILAE British Chapter – since renamed as the ILAE British Branch – held its Annual Meeting in Birmingham on 26-28 September 2018 at the Birmingham Conference and Events Centre. We look in more detail at Thursday's session on the 'studies which will change our practice'.

### SANAD trial

First up to present on the standard and new anti-epileptic drug (SANAD) trial was Professor Tony Marson from the University of Liverpool. The SANAD trial is the largest to date with 2,500 participants recruited [Marson et al, 2007]. It looked at time to treatment failure or time to 12-month remission in people with focal epilepsy taking lamotrigine, carbamazepine, gabapentin or topiramate. Lamotrigine was found to be better tolerated and therefore less likely to fail, even though it was as effective as carbamazepine. For generalised and unclassified epilepsy, valproate, lamotrigine and topiramate were compared. Valproate emerged as least likely to fail and most likely to put people into 12-month remission.

Professor Marson highlighted that SANAD has helped guide National Institute for Health and Care Excellence (NICE) guidelines and ILAE's thinking. He added that an unblinded trial may lose some internal validity, but it can offer longer follow-up to see if seizure control continues and allow sensible outcomes to be estimated. DNA was collected as part of the trial. Professor Marson explained this now allows the data to be used to answer novel pharmacogenetics questions and to investigate the genetic aetiology of epilepsy.

Professor Marson stressed that we still need bigger and better trials and added that classification is a big problem which needs resolving. SANAD II [2015] has now completed recruiting, and results will be published and presented at meetings in the summer of 2019.

### ESETT study

Professor Hannah Cock from St George's London presented next on the established status epilepticus treatment trial (ESETT) [Cock, 2011]. This is a multi-centre, randomised, double-blind comparative effectiveness study. She started off saying that there is a good evidence base around the use of benzodiazepines as first-line treatment for status epilepticus, but it's not so clear for second-line treatments.

Professor Cock explained that while traditionally, phenytoin or phosphenytoin have been used, newer alternatives are garnering interest, namely levetiracetam and valproate. These may offer a better ease and speed of administration, a broader efficacy and a more favourable safety profile. The primary outcome of the study was the clinical cessation of status epilepticus at 60 minutes, determined by absence of clinically-apparent seizures and improving responsiveness.

Professor Cock explained that results couldn't yet be shared. However, she did present some results on benzodiazepine use. These showed what Professor Cock called a "substantial under-dosing". The results

for older children and adults – anyone over 32kg – showed that less than 20% got an adequate first dose of benzodiazepine based on all the labelling and guidelines. In the paediatric population, parents and carers at home were administering more closely to the correct dose, but again, there was under-dosing by healthcare professionals. Professor Cock said this showed a poor adherence to evidence-based treatment in clinical practice, which has been shown in numerous studies.

## EMPIRE study

Dr Doug McCorry presented next on the anti-epileptic drug management in pregnancy (EMPiRE study) [Thangaratinam et al, 2018]. The EMPIRE study recruited 593 women into the observational cohort study. Women in whom there was a 25% drop in drug level were randomised into two clinical strategies. In one, the woman and clinician were not aware of the fall in drug level, and in the other, they were. This aimed to see if therapy drug monitoring can reduce the risk of seizure deterioration compared to just managing the clinical factors. The drugs the study looked at included lamotrigine, carbamazepine, phenytoin, levetiracetam – but not valproate – and some polytherapies.

Looking at the time to first, second, third and fourth seizure, as well as seizure freedom, Dr McCorry said there was no difference between therapy drug monitoring and managing clinical factors. Secondary outcomes like quality of life and foetal outcome also showed no difference between the management groups. However, in the therapy drug monitoring group, where drug levels were monitored and adjusted, there was higher foetal and neonatal drug exposure.

The study authors also compared the risk of having a seizure between people who didn't have a fall in drug level and those who did. These results also showed no significant difference, which Dr McCorry said was a surprise. Dr McCorry discussed some of the study's weaknesses including a lack of pre-pregnancy AED levels and clinicians being perceived as not being aggressive enough in AED dose escalation. He concluded by noting that good pregnancy care is far more than just checking serum drug levels.

## UKISS and ICISS

Dr Finbar O'Callaghan presented on the UK infantile spasms study (UKISS) and the international collaborative infantile spasms study (ICISS). With epileptic encephalopathies, he said the implication is that ongoing seizures are having a detrimental effect on cognition and development.

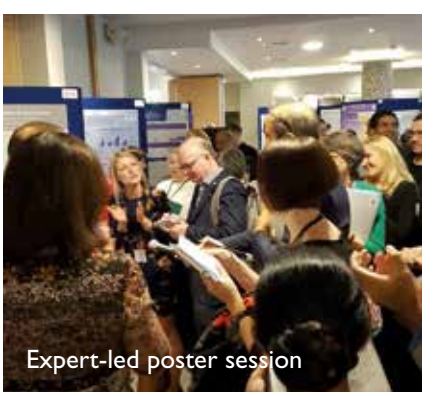
UKISS [Lux et al, 2005] aimed to compare the effectiveness of two courses of hormonal therapy (prednisolone or tetracosactide) and vigabatrin in treating infantile spasms. The primary outcome of this study was an absence of spasms on day 13 and 14 of treatment, and the results showed hormonal therapy as the more effective treatment.

The ICISS study [O'Callaghan et al, 2017] built on the findings of the UKISS study. It aimed to see a cessation of spasms for a four-week period from day 14 to day 42 of treatment with either hormonal therapy or hormonal therapy combined with vigabatrin. The study enrolled 377 children. The results showed that combination therapy was significantly more effective and faster in stopping infantile spasms than hormonal therapy alone.

On looking at the developmental outcomes and epilepsy at 18 months, there was a significant difference between children who responded initially and those who did not respond. Early responders had the


Birmingham Conference and Events Centre


Welcome address from Dr John Paul Leach


Expert-led poster session

Professor Hannah Cock

Dr Danny Costello


The ILAE British Chapter was renamed as the British Branch


Birmingham evening

more favourable outcomes. Similarly, those children without a proven aetiology had better developmental and epilepsy outcomes compared to those with. However, Dr O'Callaghan explained that the team was surprised to see no developmental or epilepsy outcome difference between the two treatment groups. This is despite the fact that the combination therapy group was associated with a better early clinical response.

Finally, Dr O'Callaghan explained that when dividing the population into lead-time-to-treatment groups, they found that the developmental outcomes significantly worsened with a longer lead time. He said that combination therapy has made a big difference to treating infantile spasms.

## CODES study

Professor Laura Goldstein presented at the session on the CODES study on cognitive behavioural therapy (CBT) for dissociative (non-epileptic) seizures.

For the CODES randomised controlled trial, patients were recruited from neurology settings and assessed for suitability. They were then randomised either to the group receiving CBT and standardised medical care, or the group receiving standardised medical care alone. Participants were followed up at six and 12 months by researchers blinded to the treatment. The study's primary outcome measure for the study is monthly seizure frequency at 12 months, compared to baseline.

While Professor Goldstein also could not give the results of the study yet, she shared details of the baseline sample. She said almost three-quarters of the sample were women and the median age was 35 years. She said despite this median age, that the study authors believe there is an early peak in the late teens. The median duration of the disorder before diagnosis was three years with an average of about six years. Over a quarter reported that they had received a previous diagnosis of epilepsy, and 20-21% said they were currently being prescribed AEDs. The majority said they had had previous help for a psychiatric or mental health problem. Professor Goldstein noted that there was a lot of comorbidity in this sample, including anxiety, depression and general psychological distress.

In concluding, Professor Goldstein said a number of services were created for the study and some will continue.

## Epilepsy incidence in Cork

Dr Danny Costello from Cork University Hospital was last up, presenting on the prospective study on incidence of first seizures newly diagnosed and seizure mimics in Cork, Ireland [Maloney et al, 2018].

Ireland has a good prevalence study [Linehan et al, 2010], Dr Costello said, suggesting that about 33,000 people in Ireland are actively treated for epilepsy in a population of 5.5 million. However, he highlighted that there has never been an epilepsy incidence study in Ireland. He said that this type of study is important in informing on details of the condition and resource allocation.

Cork county has a population of 550,000 people. The study aimed to determine the incidence of first unprovoked seizures, first provoked seizures, new diagnosis of epilepsy and seizure mimics there. The study was carried out over the calendar year 2017, enrolling 1,541 patients and excluding neonatal or febrile seizures.

The most useful channels for identifying patients were the emergency department, the EEG database and radiology, Dr Costello explained. However, he added that their experience showed them that using multiple sources for screening for patients was necessary so as not to miss patients.

The team estimated that the incidence in the study cohort is 280 presentations in 100,000 population. Dr Costello added that there is no reason to believe the population in Cork is different to other parts of Ireland or most parts of Europe. He said this number could be used to estimate how many people will present in hospitals and can be used for resource allocation and healthcare planning.

## European Congress on Epileptology

The end of August this year saw the 13th European Congress on Epileptology (ECE) take place in Vienna Austria. Among many thought provoking talks and presentations over the five days, we summarise one of the platform sessions of the congress on the topic of epidemiology.

### Mortality ratios, risks and interventions

First to present was Dr Gashirai Mbizvo, with a study looking at trends in SUDEP and other epilepsy-related deaths (ERDs) in adults in Scotland. The research he and his group carried out aimed to find out what the rates, causes and risk factors were of epilepsy-related deaths in this population.

Dr Mbizvo said his group focused on epilepsy-related deaths that they believed could be avoided, including from epilepsy itself, treatment and comorbidities. The study wanted to include less-often recognised ERD risk factors too, such as increased risks of aspiration pneumonia and suicide. They used death certificates, which are well scrutinised in Scotland, and medical records linked to individuals through a community healthcare index number (CHIN). They compared adults with epilepsy above 16 years old who had died from an ERD between 2009 and 2016, with adults with epilepsy who were still alive.

Just over 2,000 epilepsy-related deaths were found in the study period. Overall mortality rate remained the same, despite advances in medical care. The findings, split by age group, showed that in 16-44-year-olds, the observed deaths were far more than the expected deaths. Dr Mbizvo noted that 60% were found to be from Scotland's most deprived areas. Not all were cases of SUDEP, with suicide, drowning, alcohol and drug problems, and aspiration pneumonias also seen.

Dr Mbizvo added that these deaths can be prevented with more access to neurology services and better education about treatable conditions like pneumonia. He concluded that perhaps the younger age group should be a target for intervention.

Also presenting on mortality risk factors in epilepsy in the session was Dr Lizbeth Hernandez Ronquillo. She presented on a study examining patterns of mortality in a population with epilepsy in Saskatchewan, Canada, and assessing mortality risk factors. Dr Hernandez Ronquillo explained that between 2001 and 2010, administrative data were used to identify people with epilepsy through a set of criteria such as hospitalisation with a diagnosis of epilepsy.

Between 2005-2020, 1,470 deaths occurred. The standardised mortality ratio (SMR) showed that mortality remained constant over the study period, similar to Dr Mbizvo's findings. However, in contrast, the study found that people over the age of 65 were at the highest risk of mortality.

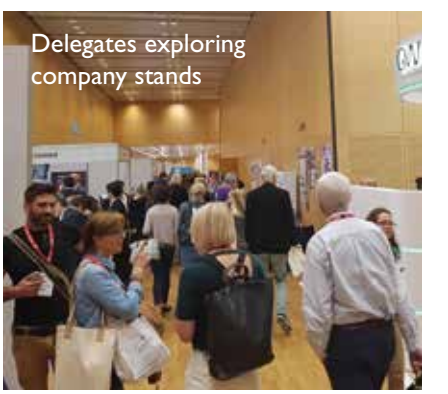
Dr Hernandez Ronquillo concluded that the SMR, mortality rate and proportionate mortality were similar to those of other developed countries. She said that risk factors for mortality in epilepsy in this study included being aged 15-59 and over 60 years, and having a Registered Indian status stratified by income support.

### Trends and differences

Dr Julie Dreier took to the podium, to describe her group's study examining sex differences in febrile seizures and the risk of recurrent febrile seizures and subsequent epilepsy.

They looked at children born between 1977 and 2011, identifying those who had hospital contact for febrile seizures. The study defined

Messe Wien Congress Center in Vienna


Delegates exploring company stands


Outside the congress centre

Dr Gashirai Mbizvo


The 13th ECE congress spanned across five days


ECE Forum on valproate

Dr Julie Dreier


Posters

febrile seizures as occurring between three months and five years. Children with a previous diagnosis of epilepsy, cerebral palsy, head trauma, or intracranial tumours or infections were excluded.

The study found around 75,000 children who had at least one hospital admission with febrile seizures. The hazard ratio of febrile seizures was found to be 21% higher in boys than girls.

In looking at the incidence of recurrent seizures, the researchers found that the more seizures the children had had, the higher the likelihood of recurrence. The risk of recurrent seizures was also higher in children who had their previous seizure before the age of two years old. The 30-year risk of developing epilepsy was similar in girls and boys. However, girls who had more seizures early on were more likely to develop epilepsy than boys.

Dr Dreier concluded that, in line with previous studies, boys were at a higher risk of febrile seizures than girls throughout all the ages. They were also at a slightly higher risk of recurrent seizures. However, girls who had multiple febrile seizures had a slightly higher risk of developing epilepsy than boys who had multiple febrile seizures.

On a very different subject, but again looking at trends and patterns, Dr Andrew Neal discussed his group's study on the characteristics of motor vehicle crashes associated with seizures [Neal et al, 2018]. He said if it's a person's first seizure or if there is no witness, it can be difficult to identify a seizure-related crash.

Using medical records and the police crash investigation database in Victoria, Australia, 71 seizure-related crashes were identified, involving 62 patients. Of these, the majority had focal epilepsy and had a seizure including tonic-clonic semiology. Of these 9% had a crash linked to a first seizure. Retrospectively applying the fitness to drive guidelines, 65% would be deemed fit to drive up until the crash, and 24% would have been deemed unfit to drive, Dr Neal said.

Between seizure-related and not seizure-related crashes, there was no difference in age, sex of drivers, time of crash, speed zone or road conditions. However, the majority of seizure-related crashes involved a single vehicle, had a single occupant, involved an out-of-control movement and tended to veer off path on a straight road. Any collisions tended to occur with fixed objects, as opposed to non-seizure-related crashes, which tended to involve another vehicle. Dr Neal said that while these characteristics should not be used to rule out the possibility of a seizure-related crash, they should be incorporated into assessments of crashes from suspected seizures.

## Quality of life and quality of care

Dr Jakob Christensen from Denmark addressed the room about quality of life in individuals with epilepsy. The study was based on the national cohort from Denmark of about 5-5.5 million people, from 1995-2010. The researchers invited 250,000 people into the study – including more than 2,000 people with epilepsy. The response rate from people with epilepsy was around 61%.

The study looked to compare quality of life in people with epilepsy with that in people without epilepsy. The quality of life was stratified by two wellbeing aspects – physical component summary and mental component summary. Comparing males with epilepsy to males without epilepsy, quality of life from a physical wellbeing point of view was lower in

the epilepsy group. This was also found to be the case for women.

The study also looked at quality of life from a mental wellbeing perspective. Again, men with epilepsy had a lower quality of life than men without, and the same was seen in women. The study also looked at people with epilepsy who also had psychological comorbidities. Psychological factors lowered the quality of life of both the epilepsy and the non-epilepsy group in terms of both physical and mental wellbeing. But for men and women with epilepsy, it was still lower than people without epilepsy.

Dr Christensen added that the findings may even be an underestimate, as the patients who were worst off were less likely to respond.

Last up, Professor Tony Marson from Liverpool presented on the improved patient outcomes and potential cost savings from best management of epilepsy [Marson et al, 2017]. He started off highlighting that if services aren't properly coordinated, there can be a delay in access to treatment, access to specialist expertise and more advanced treatment options. Without this access, outcomes would be expected to be poorer, resulting in a greater economic burden.

Professor Marson said to provide the best services, we need to invest in those services, staff training, equipment and coordination of care. He and a team of researchers sought to use an economic model to find out if investment in services would result in savings to health services and society.

Better management was represented using National Institute for Health and Care Excellence (NICE) guidelines. Current management was identified using a number of studies, and data were used from the SANAD trial. The model was run over a 70-year time horizon.

The model estimated that there would be a significant reduction in the number of seizures people might experience if they were managed more quickly and adequately. It estimated a significant reduction in injuries and epilepsy-related deaths. Discounted savings over the 70-year time horizon, per 1,000 patients, may be in the order of £7m, Professor Marson said. However, he added that if we invest, the savings will be realised a long time into the future.

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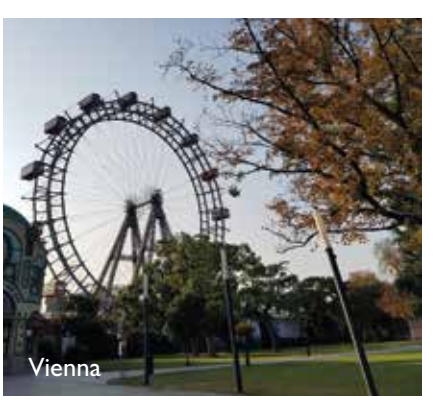
Dr Lizbeth Hernandez Ronquillo


Vienna

# Tech revolution in medicine

Technological advancements are set to revolutionise our relationship with healthcare. Increasingly, we are moving healthcare from the hospital to the home – this being particularly relevant for long-term conditions such as epilepsy.

Technology is also helping us move away from cure and towards prevention. And conveniently, a number of these advancements are using devices we already own to bring this technological revolution into our pockets.

The Luddites will likely revolt but the potential of technology is unavoidable. Just as your calculator can outperform you in basic arithmetic, artificial intelligence (AI) outperforms you in pattern recognition. But fear not – an Oxford University report found that physicians and surgeons are among the safest jobs come the AI revolution (although apparently not as secure as choreographers!).
Here we discuss the challenges and opportunities provided by a number of higher-profile apps, and where the future of medicine is heading.

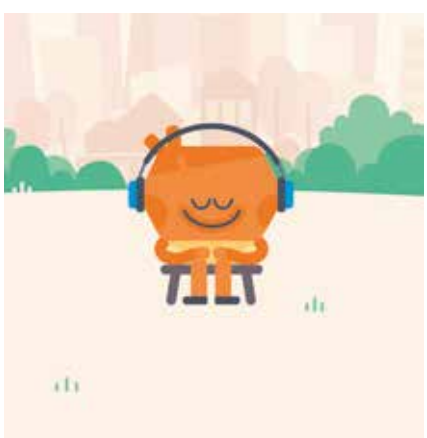
**Babylon** – *4.8 stars from 12,354 reviews on the Apple App Store | £5 a month for unlimited GP consultations*
Babylon is an app which contentiously promises to bring the power of AI and snappy consultations with a doctor to your phone, thus democratising healthcare and cutting GP waiting times. Users are able to chat to Babylon's AI about their symptoms, and after a series of questions, Babylon will output its diagnosis. The system errs on the side of caution,


preferring to erroneously send you to the emergency department than miss something serious. Indeed, a trial performed by Babylon revealed that the system is safer than the average doctor when triaging patients. The trial showed it as almost equivalent when forming a differential diagnosis. One has to take a trial designed and performed by Babylon employees with a generous pinch of salt, but the results are promising.

Where Babylon truly excels is as 'the Uber' of healthcare. Patients are able to book video call appointments with GPs and specialist doctors. These calls are recorded for your perusal later on, and patients are able to order prescriptions and tests through the app. The app is being piloted in London under the 'GP at Hand' scheme. Patients of the practice use the app for free, and can be seen at a physical location if needed. It is designed for "people with episodic, well defined needs" and those who are "digitally confident". One could envision such services being used for simple medication review appointments for those with epilepsy.

The Health Secretary, Matt Hancock, is a user, though the scheme has not been without criticism. Some claim that this is another step towards the privatisation of the NHS. Others criticise the barriers of entry of 'telemedicine' for some of the NHS's most vulnerable users. A furore broke earlier this year with users apparently unclear that by using 'GP at Hand', they were de-registered from their usual surgery.

**Headspace** – *4.8 stars from 130,894 reviews on the Apple App Store | Free initially and then £9.99 a month*
Mindfulness has its roots in Eastern culture, and has recently emerged in evidence-based medicine, showing benefits in managing stress. It is effective in helping deal with symptoms of depression and anxiety – common in epilepsy – as well as a myriad of physical symptoms. Headspace incorporates a guided meditation programme to get you started. Studies show that online mindfulness interventions, such as Headspace, can be as effective as face-to-face programmes. It has mindfulness regimes for both adults and children.



**SeizAlarm** – *4.4 stars from 17 reviews on the Apple App Store | two-week free trial and then £4.99 a month*
This app was created by Greg Pabst, someone with epilepsy who saw the potential of the Apple Watch for detecting seizures. Previous solutions required the purchase of expensive


devices to monitor for seizures. However, SeizAlarm harnesses the power of the Apple Watch's accelerometer and heart rate monitor to detect seizures and call for help. Help from emergency contacts can be set to be requested immediately, or after a pre-set time-delay. The seizures are logged into a seizure diary which can easily be displayed to a healthcare professional.

The scope for advanced health monitoring technology like this is monumental. Apple has already sponsored a study by Stanford University to use the Apple Watch to detect dangerous heart rhythms. Apps like SeizAlarm have the potential to pick up on underreported nocturnal seizures. One day, they could even form the basis of epilepsy management. Data from a person's seizure diary could be sent to their healthcare professional and worsening outcomes could trigger more frequent check-ups.

**EpSMon** – *Free on the Apple App Store and Google Play for Android*

EpSMon is an award-winning initiative by the University of Plymouth, SUDEP Action, Cornwall Partnership NHS Foundation Trust and Royal Cornwall Hospitals. The app encompasses data from a six-year research project to help prevent sudden unexpected death in epilepsy (SUDEP). Every three months, the app collects information about known risk factors for epilepsy mortality including SUDEP, such as epilepsy control and lifestyle. A person's answers to these questions form a recommendation for their care, for example, booking an earlier appointment with their healthcare professional. The app also provides essential information on each risk factor to support risk management.

Researchers found that many people who died from SUDEP had a deteriorating condition preceding their death, but only 20% were in touch with their specialist. EpSMon can help monitor a patient in between review appointments and encourage at-risk patients to seek help to prevent deaths.


**QuitGenius** – *4.4 stars from 263 reviews on the Apple App Store | two-week free trial and then £9.99 a month*

Created by Medical Students at Imperial College, QuitGenius uses cognitive behavioural therapy (CBT) to help quit smoking. CBT challenges and alters your beliefs around smoking and has shown a 36% quit rate, with a 60% reduction in cigarette consumption in those who did not quit (in trials performed by the staff).

CBT has traditionally been used to treat depression and anxiety; common comorbidities of epilepsy. Studies show that depression and anxiety in epilepsy are more strongly related to how people cope with the disease, rather than the actual disease pathology itself. CBT can help teach people effective coping mechanisms and previous studies have found it to reduce depression, anxiety and disability in epilepsy.

Face-to-face CBT with a therapist can involve a hefty waiting list or cost between £40-100 privately. Therefore bringing these methods to your smartphone for a relatively affordable fee is a big step forward. It's true that CBT on a smartphone app may take away the personal touch of a therapist. However, it may also be more convenient for the person with epilepsy with a busy work schedule or without a driving licence. No such app currently exists for epilepsy comorbidities, but promising results from QuitGenius in smoking cessation give hope that something similar can be developed for epilepsy.

## Patient safety

Following last year's WannaCry cyberattack on the NHS, many harbour concerns about the safety of patients and their data. The attack brought some NHS trusts back into the stone age. They were unable to access electronic patient records, test results and even important equipment such as MRI scanners. Five hospitals had to divert ambulances elsewhere and nearly 20,000 appointments were cancelled. Fortunately, the extent of the impact was more disruption than desecration. NHS England reported no patient harm coming from the attacks – in part due to staff being able to use manual workarounds for routine tasks such as prescribing medication. The motives of this attack are a mystery, though it was unlikely to have been a targeted attack on the NHS; rather

the NHS was caught in the crossfire. If an undirected cyberattack could bring an institute with a 12-digit budget to its knees, what chance does an individual developer's app have? In the privatised healthcare system of the US, Reuter's reported that your healthcare data is worth 10 times more than your credit card. Indeed, the London Bridge Plastic Surgery clinic made headlines when hackers claimed that they had stolen highly sensitive photos of their celebrity clientele.

It's not clear where the onus lies for the protection of data. For example, in the case that data from your portable pacemaker is breached (dubbed a MEDJACK), who is to blame? The regulatory body? The NHS? The manufacturer? You? As medical technology continually permeates into our lives, it'll be important to address these questions to ensure patients can trust these services and devices with their data.

## The future

The tech revolution will reshape the patient's role in their healthcare: from 'doctor knows best' to 'my smartphone knows better'. With currently available technology, a diabetic patient can add glucosalarm to their toilet and monitor their urine glucose. They can then discuss results with their endocrinologist on Babylon and even send them a detailed snapshot of their retina for clinical assessment using the D-EYE for iPhone. The revolution isn't limited to the patient either. A stay-at-home parent can work remotely as a Babylon GP, working evenings and weekends for £100,000 a year.

While we want to stay optimistic about innovations, they can frequently result in even more cost to a cash-strapped NHS. A trial of a telemedicine service not dissimilar to 'GP at Hand' found that virtual visits doubled while face-to-face visits remained about the same. It's all well and good having a watch that tracks every seizure from every patient, or a smart toilet that analyses your urine glucose. But who is going to analyse the data and deal with the follow-up? This is where we need to be smart about how we apply this technology. Not every seizure needs to be reported to the GP, but – as EpSMon has shown us – patterns can be analysed for red flags and recommendations made in-app. Future advancements in deep-learning AI will mean that everything from the initial diagnosis to the interpretation of imaging and management plan will be handled by AI.

CheXNet, a Stanford University AI, has already surpassed the average radiologist when interpreting chest X-rays for pneumonia. AI can analyse histopathology slides and give a more accurate prognosis than pathologists are currently able to. This is significant, because AI in medicine is going beyond trying to imitate clinicians: it's transcending them.

AI will augment the role of the future doctor. Just as today's physicians will refer to a NICE pathway, they will refer to AI as part of their information gathering procedure. The AI will use knowledge gained from assessing data from millions of patients and output a recommendation, but the ultimate decision will always be the clinician's. After all, CheXNet can spot the pneumonia, but it can't consider the complex biopsychosocial needs of the patient and communicate them... yet.

## Conclusion

Challenges remain. Often the most likely to embrace this technology are the 'worried well', while those who are most in need of it are least able to use it – furthering health inequality. Hopefully, progress can encourage more 'set it and forget it' solutions which can work in the background to monitor health. Nevertheless, healthcare technology may provide a portal into the lives of the most vulnerable patients and help manage their disease.

*This issue's opinion piece was put together by Mustafa Sultan and Dr Rhys Thomas*

## Dates for the diary

### February 2019

20-22
Seizures and stroke 1st international congress on epilepsy in cerebrovascular disease
Gothenburg, Sweden
*seizuresandstroke.com*

22
Cannabinoids in the treatment of epilepsy
Freiburg, Germany
*www.ilae.org/files/dmfile/Flyer_Cannabionoide-Epilepsiebehandlung-FINAL.pdf*

### April 2019

4-7
13th World Congress on Controversies in Neurology (CONy)
Madrid, Spain
*www.comtecmed.com/cony/2019*

6
EEG in Status Epilepticus and on the Intensive Care Unit Teaching Course
London, UK
*bit.ly/2ODcMqq*

7-9
7th London-Innsbruck Colloquium on Status Epilepticus & Acute Seizures
London, UK
*statusepilepticus.eu/index.php*

### June 2019

16-20
XV Workshop on Neurobiology of Epilepsy WONOEP 2019
Ayutthaya, Thailand
*internationalepilepsycongress.org/wonoep*

22-26
33rd International Epilepsy Congress (IEC)
Bangkok, Thailand
*internationalepilepsycongress.org*

### September 2019

14-15
ILAE British Branch 17th SpR Epilepsy Teaching Weekend
Oxford, UK
*epilepsyteachingweekend.com*

## Mental health in children

Dr Ailsa McLellan discusses mental health problems in children and young people relating to epilepsy, as well as screening and treatment.

## Stress and epilepsy

Dr Christophe Bernard describes research around the effect of stress on epilepsy and what this relationship might mean for clinicians treating people with epilepsy.

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