epilepsy action

issue fifty-five / Winter 2019 £3.50
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epilepsy professional

Managing epilepsy in women

The challenges of treating epilepsy across the lifespan

Linda Stephen

Support – Adele Ring | Ann Jacoby | Gus Baker

Epilepsy deaths – Heather Angus-Leppan

ILAE – Roundup of the British ILAE conference

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1. Eggleston KS, et al. Seizure 2014;23(7):496-505. 2. E-36/E-37 Integrated Clinical Study Report. Data on file, Cyberonics Inc Houston, TX

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LivaNova
Health innovation that matters

Sometimes we all need a helping hand, but asking for help may not come naturally to some of us. Amanda Palmer is an alt-rock and art icon who revels in her close relationship with her fans. In her 2013 TED talk, "The Art of Asking", she speaks persuasively on the value of asking for help – not necessarily because you will receive it, but because of the bond that you will make with the person who responds. There is a warm validation in being the friend that someone turns to for help in their hour of need – a strong connection forged when asked to be a confidant.

Professionally, it's flattering to be asked your opinion; whether this is a formal 'second opinion', or when you provide any scrap of advice that may or may not be heeded. The power is held by the person who asks for help, and so the art of asking, is not a weakness.

It is with that in mind that I commend to you the articles in this issue of *Epilepsy Professional*. "What do people want from their treatment and care for epilepsy?" is a great question and one answered by patients with the help of Adele Ring, Gus Baker and Ann Jacoby. Increasingly, we are all demanding more from healthcare (which is good) and more personalised approaches (which is better), and for this we need time. We need listening-time, not clicking or scribbling-time. We need generalists and specialists and shorter waits to receive these specialist opinions – particularly from psychological services.

The second article about asking for support comes from Heather Angus-Leppan and the Epilepsy Action project on epilepsy-related deaths in the UK. This important article is a rallying call to change the way that people live with epilepsy and improve safety. "Knowledge is power, but only if it is acted on." Recognising the existing work in this area, they are working on educational tools with a focus on medication, mental health and drugs and alcohol.

Finally, we have an article on managing epilepsy in women by Linda Stephen. I think this is a great example of something that we all should know more about and should be better at delivering. This form of 'asking' is reflexive – are you sure you are 100% up-to-date on this issue? Whether it's dealing with seizure control in pregnancy or having to contend with bone density in later life, this article provides a framework for the complex challenges you may face before during and after pregnancy.

Enjoy the issue.

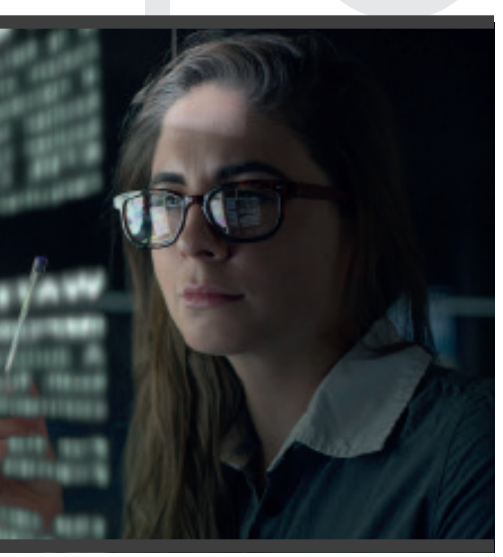
Dr Rhys Thomas
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

18 epilepsy deaths

Heather Angus-Leppan

In this joint project with Epilepsy Action, Dr Heather Angus-Leppan argues for a shift in how we educate and raise awareness of epilepsy-related deaths such as SUDEP.



Sir William Osler said, "The good physician treats the disease; the great physician treats the patient who has the disease."

It's a grand statement in healthcare, but one that resonates fully in epilepsy. Because often specialists need to juggle the provision of anti-epileptic drugs to minimise seizures, ensure adverse effects are limited, and ensure that all treatment options consider short-term and long-term benefits. And if that wasn't enough, manage the patient's expectations and mental wellbeing so that stress and discomfort do not exacerbate in comorbidities. With this in mind, Dr Adele Ring et al explore what's important in the care of epilepsy patients, and what additional support they want to access in order to minimise the effects of epilepsy.

In other news, I came down to Birmingham to cover my first epilepsy event in October, the ILAE 2019 British Scientific Meeting. I enjoyed speaking to our readers and editorial board members who make *Epilepsy Professional* what it is. And having covered conferences in other medical disciplines, I was struck by how engaged the audience was during the various talks. Epilepsy may be a condition that affects a relatively small percentage of the population, but the neurologists, nurses and specialists are no less passionate in finding the best outcomes for their patients. It's that personal connection that develops over the many years that epilepsy patients might need to see their specialists.

Enjoy the year-end festivities and we wish you a happy and successful 2020.

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

Editor/desktop publishing: Matt Ng (mng@epilepsy.org.uk)

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

Publishers: Epilepsy Action (Communications department)

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

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

Epidyolex wins NICE approval for use

The National Institute for Health and Care Excellence (NICE) has recommended Epidyolex for use in the NHS to help treat Dravet syndrome and Lennox-Gastaut syndrome. Epidyolex is the first plant cannabis plant-based medicine to be recommended by NICE for the NHS. It is taken as an oral solution, and does not contain the unapproved tetrahydrocannabinol (THC) psychoactive ingredient.

Epidyolex is recommended as an adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, for patients two years of age and older.

Commenting on the recommendation, Dr Rhys Thomas, consultant neurologist at the Royal Victoria Hospital in Newcastle, said: "This is a significant moment for adults and children with the most difficult to treat epilepsies. NICE's recommendation of cannabidiol oral solution follows a period of great anticipation and enthusiasm for patients and their clinicians. The availability through the NHS is welcome as we badly need additional effective treatments for Dravet and Lennox Gastaut syndromes."

In September, Epidyolex also gained approval from the European Medicines Agency (EMA) for medical use throughout the EU. The approval was based on results from four human trials involving more than 714 people with either LGS or Dravet syndrome. When added to other treatments, Epidyolex was reported to "significantly reduce the number of seizures" in those people, according to manufacturer GW Pharma. The drug was approved in the US more than a year ago and since then has been used on more than 12,000 people. The most common adverse reactions that occurred in patients treated with the medicine were somnolence, decreased appetite, diarrhoea, pyrexia, fatigue and vomiting.

In response to the NICE decision, Epilepsy Action deputy chief executive, Simon Wigglesworth said: "Epilepsy Action are delighted that a new treatment option is now available for people with Dravet syndrome and Lennox-Gastaut syndrome, two severe and treatment-resistant epilepsies.

"Epidyolex is not a silver bullet. However there is high-quality clinical evidence that this treatment can reduce the number of seizures caused by these epilepsies. As the name suggests, new treatment options for treatment-resistant epilepsies do not come about very often. The decision by NICE to recommend Epidyolex offers a potential way forward for people affected. It's not an overstatement to say that it could be life-changing for some."

Though many view this ruling as a step in the right direction for cannabis-based medicines, this hasn't stopped those affected by rare and severe epilepsies to look towards medicines that contain THC as potential treatments. The new NICE guidelines on cannabis-based medicines do not make a recommendation about when, where and how drugs containing THC could be made available on the NHS. Instead the guidelines have made a number of research recommendations.

New gene therapy could help suppress seizures

European scientists have developed a new type of gene therapy for the treatment of temporal lobe epilepsy. Using an animal model, the team have been able to suppress seizures at the site of origin, and are now preparing the procedure for clinical use. The study results are published in *EMBO Molecular Medicine*.

For those with temporal lobe epilepsy (TLE), surgery is often the only effective treatment, though this comes with risks of adverse cognitive outcomes and may not stop seizures altogether. Professor Christoph Schwarzer of the Medical University of Innsbruck and Professor Regine Heilbronn of Berlin's Charité's University have been working to develop a new treatment for drug-resistant TLE.

This technique looks at a selective delivery of a specified gene to nerve cells at the seizure origin site. Once delivered, the gene provides cells with the information needed to produce and store dynorphins, naturally-produced peptides which modulate neural activity. When a seizure begins and high-frequency stimulation of the nerve cells occur, the stored dynorphins are able to dampen the signal transduction, meaning the seizure is not able to spread. In animal models, the team could demonstrate that the therapy can suppress the onset of seizures for several months with no observable side-effects.

For the full study visit *https://bit.ly/2RbNnEr*

New drug hope for those with treatment-resistant epilepsy

A US study has shown that a new drug could offer better seizure outcomes for those with treatment-resistant epilepsy.

The Johns Hopkins University study found that, of 437 patients in 16 countries, the investigational drug cenobamate reduced seizures by 55% across the treatment period. The findings of this trial were published in the 13 November edition of *The Lancet* Neurology.

This multicentre, double-blind, randomised, placebo-controlled trial demonstrated that cenobamate at doses of 100 mg, 200 mg, and 400 mg/day significantly improved seizure control versus placebo in patients with focal-onset seizures taking 1-3 anti-epileptic drugs (AEDs). Cenobamate demonstrated significantly higher responder rates (percentage of patients achieving ≥50% reduction in seizures) across all doses during the 12-week maintenance phase compared to placebo. The responder rates were 40% ($p=0.036$), 56% ($p<0.001$), and 64% ($p<0.001$), for the 100 mg, 200 mg, and 400 mg groups, respectively, compared to 25% for placebo. Furthermore, 4% (not significant), 11% ($p=0.002$), and 21% ($p<0.001$), of patients treated with cenobamate 100 mg, 200 mg, and 400 mg, respectively, reported zero focal-onset seizures (100% seizure freedom) compared with only 1% of placebo-treated patients during the maintenance phase.

Overall, most treatment-emergent adverse events (TEAEs) were mild or moderate in severity, and similar to those observed with

other AEDs. The most common TEAEs reported were somnolence, dizziness, headache, fatigue and diplopia and the incidences increased with the dosage. One serious case of drug reaction with eosinophilia and systemic symptoms occurred in the 200 mg cenobamate group.

For the participants in the maintenance period on the placebo, 25% saw a 50% or more reduction in the number of seizures. On the 200 milligram dose during the maintenance period, 56% of participants had a 50% or more reduction in the number of seizures. On the highest dose (400 milligrams), 64% of participants had a 50% or more reduction in the number of seizures, and up to 21% had no seizures at all during the maintenance period.

There are currently more than 20 anti-seizure drugs available in the US, though around 40% of people with epilepsy do not become seizure-free on these medications. Cenobamate has not yet received Food and Drug Administration approval, but is being tested for its effectiveness in treating partial-onset seizures.

For the full study visit *https://bit.ly/2Lga0Uf*

Better seizure control with ketogenic diet

Young children with epilepsy due to genetic causes respond better to ketogenic diet treatment compared to people with other types of epilepsy. This is according to a review of cases across 10 years at a Chicago hospital in the US. The results were published in *Scientific Reports* in June 2019.

The study author is John Millichap, Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine, US. He said: "Overall, we observed that the ketogenic diet continues to be a safe, effective and well-tolerated treatment for patients under three years of age with drug-resistant epilepsy."

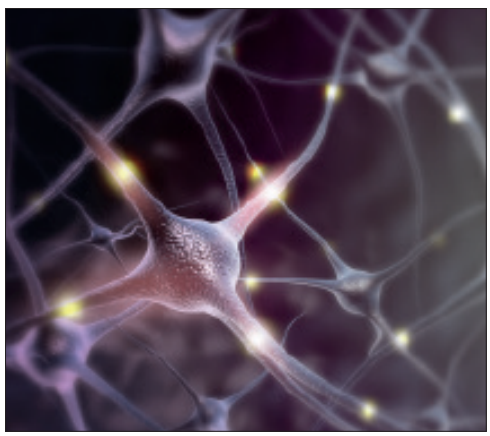
"Clinicians could consider offering the ketogenic diet earlier to infants diagnosed with genetic epilepsy, perhaps even before it becomes clear that the patient is not responding to anticonvulsant medication."

"The ketogenic diet helps control seizures by reducing fluctuations of blood sugar, which reduces hyper-excitability in the brain," explained Dr Millichap.

This latest research looks at the ketogenic diet in 109 young patients with various types of epilepsy that began in infancy. In the study, the youngest patient to start on the diet was three weeks old. Of the children in the study, nearly 20% achieved complete seizure control after three months on the diet and nearly 40% had significant seizure reduction. In children with genetic causes of epilepsy, the results were even better. Nearly half reported to have more than 50% fewer seizures.

For the full study visit *https://bit.ly/32RFGGg*

New therapy helps stops seizures after injury



American investigators have developed a new form of cell therapy to help prevent seizures in mice models following a traumatic brain injury.

Traumatic brain injuries can cause cell death and inflammation in the brain. People with head injuries often have memory loss and can develop epilepsy.

The University of California study saw the transplantation of embryonic progenitor cells in mice with traumatic brain injury. These cells are capable of generating inhibitory interneurons, a specific type of nerve cell that controls the activity of brain circuits. They targeted the hippocampus, a brain region responsible for learning and memory.

The investigators found that the transplanted neurons migrated into the injury site and created new connections with the injured brain cells. Within one month, the mice exhibited signs of memory improvement, performing as well in a memory task as mice without a brain injury. The cell transplants also prevented the mice from developing epilepsy, which affected more than half of the mice who were not treated with new interneurons. The study is published in *Nature Communications*.

"Inhibitory neurons are critically involved in many aspects of memory, and they are extremely vulnerable to dying after a brain injury," said Robert Hunt, professor of anatomy and neurobiology at UCI School of Medicine who led the study. "While we cannot stop interneurons from dying, it was exciting to find that we can replace them and rebuild their circuits."

This was an exciting discovery for the researchers. "The idea to regrow neurons that die off after a brain injury is something that neuroscientists have been trying to do for a long time," Hunt said. "But often, the transplanted cells don't survive, or they aren't able to migrate or develop into functional neurons."

To further test their observations, Hunt and his team silenced the transplanted neurons with a drug, which caused the memory problems to return.

"It was exciting to see the animals' memory problems come back after we silenced the transplanted cells, because it showed that the new neurons really were the reason for the memory improvement," said Bingyao Zhu, first author of the study.

Currently, there are no treatments for people who experience a head injury. If the results in mice can be replicated in humans, it could have a beneficial outcome in patients who have a risk of developing epilepsy. The researchers say that the next phase will involve creating interneurons from human stem cells.

For the full study visit *https://go.nature.com/37ZSMUM*

AI model developed to predict seizures

A new artificial intelligence model has been developed that can predict the onset of seizures up to one hour before they occur, with near perfect accuracy. Researchers at the University of Louisiana in the US looked at long-term EEG data from 22 patients to develop and test their deep learning model, achieving a 99.6% accuracy rate in predicting seizures.

"Due to unexpected seizure times, epilepsy has a strong psychological and social effect on patients," said Hisham Daoud, a researcher who co-developed the model.

There have been other attempts to analyse brain activity and predict seizures using EEG tests, but this has been challenging because each person exhibits unique brain patterns. In these attempts, the brain patterns have to be manually extracted, before a classification system is used.

In the new model, the two processes are combined using an automatic system, enabling earlier and more accurate seizure prediction. The investigators also incorporated another classification approach where a deep learning algorithm extracts and analyses the spatial-temporal features of the patient's brain activity from different electrode locations, boosting the accuracy of their model. The team also applied an additional algorithm to identify the most appropriate predictive channels of electrical activity, which makes the prediction process faster.

The model is described in a study in *IEEE Transactions on Biomedical Circuits and Systems*.

Repeated febrile convulsions linked to epilepsy

A new study from Aarhus University in Denmark has found that febrile convulsions can result in a higher risk of developing epilepsy later in life. Febrile convulsions are convulsions experienced by children with a high body temperature or fever caused by illness.

Around 4% of Danish children have febrile convulsions. The risk of having febrile convulsions increases with the child's fever. The study highlighted a link between repeated febrile convulsions and the risk of epilepsy later in life.

The study, published in the scientific journal *JAMA Pediatrics* in October 2019, was based on two million Danish children born between 1977 and 2011. The researchers have data for around 17,000 children that have had more than one febrile convulsion.

The study's lead author is Julie Werenberg Dreyer of Denmark's National Centre for Register-based Research. She said:

"Research has shown an increased occurrence of epilepsy among children with febrile convulsions. However this is one of the first studies to demonstrate such a correlation between febrile convulsions and psychiatric disorders. Not least due to the size of the study, the long period of time that the study covers and the valid data."

The researcher noted that the study shows a link between febrile convulsions and epilepsy and some psychiatric disorders. However, it does not prove that febrile convulsions actually cause epilepsy. Further research is needed to understand what the link is.

Julie Werenberg Dreyer said: "There are still many unknown factors that we don't know enough about. It may be in genes that we find an explanation for why some children have repeated febrile convulsions and then develop epilepsy and psychiatric disorders."

The study found that children who have three or more febrile convulsions have a 15% chance of developing epilepsy over the next 30 years. This compares with a risk of just 2% for children who have had no febrile convulsions.

For information on the full study visit: *https://bit.ly/2paCZRP*

Insights on the effects of cannabidiol on severe epilepsy

Results from a study published in the *British Journal of Clinical Pharmacology* may help explain why cannabidiol, a chemical component of marijuana with no psychoactive properties, reduces the frequency of seizures in patients with severe forms of epilepsy. The effect may be explained by a drug to drug interaction between cannabidiol and the anti-seizure medication clobazam.

Investigators conducted clinical trial simulations for the effect of 20mg per kg per day cannabidiol on seizure frequency in patients with Lennox-Gastaut syndrome.

"The effects of cannabidiol on seizure frequency in Lennox-Gastaut patients could be explained entirely through estimated elevations of blood levels of clobazam, which might mean that cannabidiol in itself may not have any, or at best limited, antiepileptic effects," said senior author Geert Jan Groeneveld, MD, PhD, of the Centre for Human Drug Research, in The Netherlands.

For the full study visit *https://bit.ly/34R2QxL*

ILAE British Branch Annual Scientific Meeting 2019

Birmingham, 2-4 October 2019

Epilepsy researchers, clinicians and specialists gathered for the annual ILAE British Branch Scientific Meeting on 2-4 October in Birmingham.

The three-day conference was packed with speakers and poster presentations regarding the latest epilepsy updates. Topics included SUDEP, the teenage brain and the definition of seizure, among many more.

Below are summaries from just a few of the presentations.

Valproate versus levetiracetam for generalised and unclassifiable epilepsy: Results from SANAD II: Tony Marson, University of Liverpool

The end goal of epilepsy treatment is to maximise quality of life by eliminating seizures, while minimising side-effects. In the last 20 years, new AED drugs have come to the market based on positive findings from short term trials, but longer term outcomes are difficult to discern.

Professor Tony Marson presented results from the ongoing trial A study of Standard and New Antiepileptic Drugs (SANAD) II.

SANAD II's aim was to highlight the most effective epilepsy treatment for adults and children aged five years and older, which was measured as an outcome of 12 months' remission from seizures.

This trial is a follow-up to the original SANAD I trial which began in 1999 to compare treatments available at that time.

SANAD II has been designed as a phase four multicentre pragmatic randomised controlled trial for comparing levetiracetam and zonisamide against standard treatments such as lamotrigine and valproate. There were 520 patients randomised into the trial – 396 had generalised epilepsy with the remaining 124 documented as having unclassified epilepsy.

Valproate was concluded to be significantly more effective than levetiracetam in both time to one and two-year remission, including treatment failure for inadequate seizure control. With those on

levetiracetam, 24% had an immediate 12-month remission, compared to 33% of those on valproate.

Despite this, there were some uncertain data that suggests that levetiracetam performed better than valproate in patients with unclassified epilepsy.
sanad2.org.uk

EcLiPSE: 'and now there is light…' Richard Appleton, Alder Hey Children's Health Park

Paediatric neurologist Professor Richard Appleton wished to investigate what next stage treatment options were if children in convulsive status epilepticus (CSE) were not responding to first-line anticonvulsants such as benzodiazepine. Second-line treatments for many years have recommended the use of phenytoin, but this is associated with rare yet dangerous adverse effects.

He touched upon two medico-legal cases that occurred within 18 months of each other, where two children had died due to phenytoin intoxication causing fatal arrhythmia.

Given the dangers of phenytoin, he led the (Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children) EcLiPSE team to ascertain the best courses of second-line treatment.

This national study looked at the effectiveness of 40mg per kg levetiracetam versus 20mg per kg phenytoin in treating this neurological emergency. The clinical trial took place across 30 UK emergency departments from July 2015 to April 2018.

After discounting ineligible patients and those not providing consent, the study had assigned 286 children aged from six months to 18 years, presenting with CSE requiring second-line treatment. It was found that though levetiracetam was not statistically superior to phenytoin in stopping CSE (69.7% vs 64.2% respectively), the former was shown to be associated with a safer and simpler treatment profile, with a faster infusion time (5-10 minutes vs at least 20 minutes) and fewer serious and adverse events. Therefore, the study recommended that levetiracetam should be considered as an alternative to phenytoin for the second-line treatment of paediatric CSE.

For the full study visit *https://bit.ly/33pK3YH*

The next meeting of the British Branch of the ILAE will take place on 28 September – 1 October 2020 at City Hall, Cardiff.
ilaebritish.org.uk

Debate underway at ILAE 2019

Professor Mike Kerr received the Excellence in Epilepsy Award

Additional support:

A study of patient preferences

Adele Ring, Ann Jacoby, Gus Baker explore what epilepsy patients want from their treatment and care

Introduction
Currently, the evidence about what people with epilepsy consider important in terms of the treatment for their condition is limited, with only a small number of primary research-based studies and reviews exploring this topic. However, decisions about the treatment for epilepsy are increasingly complex, as the range of available strategies grows. Although antiepileptic drugs (AEDs) are the first-line treatment for epilepsy [Cockerell et al, 1995], other treatments for refractory seizures include surgery [Engel et al, 2008], vagal nerve stimulation [Schachter et al, 2008] and dietary control [Stafstromet et al, 2008]. The role of psychological interventions [Ramaratnam et al, 2005, Cross, 2017] and alternative therapies such as yoga and acupuncture are increasing in interest [Cheuk et al, 2014, Panebianco et al, 2015]. In addition, the use of psychological and educational interventions and counselling have been strongly advocated for management of the psychosocial impacts of epilepsy [May et al, 2002, Gandy et al, 2013].

"Taking two [AEDs] is better than taking one. Because my life has been different last year…I could go out for a meal without worrying if I was going to have a seizure."[1]

Adverse effects of AEDs [Lloyd et al, 2005] and other treatments [Langfitt et al, 2007] are well documented, adding to the level of complexity of treatment decisions. The study we report here aimed to add to the evidence base about optimal treatment provision by exploring the views, understandings and preferences for treatment of adults with epilepsy themselves. This is an important question, given that previous research has highlighted that the views of patients and health professionals are not always concordant [Kwoh et al, 2001, Dilorio et al, 1995].

Methods
Adults with epilepsy were recruited from three major epilepsy centres across England. To be eligible, those wishing to participate had to be aged 18 years and over, and not experiencing other long-term health conditions. We excluded those with a learning difficulty, who would have found the tasks unreasonable, as well as those who were non-English speakers, and those who were unable to provide informed consent or who were currently participating in other research.

Based on these criteria, 56 adults were recruited and took part in in-depth interviews about their experiences and views about treatment. These interviews helped us clarify which treatments and outcomes of treatment were considered important, and why. Based on these findings, we developed a series of statements about treatment preferences which were then included in a web-based survey, hosted on the Epilepsy Action website.

"I'm a mum – do you think I am going to put myself through surgery, when there is a risk of death?"[1]

The in-depth interviews were audio-recorded and transcribed. Our analysis of what participants said aimed to identify important themes and the relationships between them, using a recognised approach. Themes included those articulated by participants themselves and ones defined by the research team. Data

from the survey were analysed using the quantitative analysis package SPSS. Ethical approval for the study was given by the UK Health Research Authority NRES Committee North West.

Interview findings
In explaining their views and preferences for treatment and what outcomes of treatment were important to them, many participants described the impact of epilepsy and its treatments on important aspects of daily life. Consequently, being able to 'live a normal life' was a key desired outcome. For many people, living a normal life was synonymous with complete seizure control, but even for those people where seizure freedom had not been possible, it was important that treatment enabled them to gain a degree of normalcy.

Life roles, particularly those related to work and family were central to epilepsy and treatment experience, and consequently it was from highly individualised perspectives that the benefits and risks of treatment were assessed.

Effectiveness and risk
For many people, AEDs were the first-choice treatment – either because they had been effective in stopping seizures or because other treatment options were considered to be no more effective or too risky. Key risks included that of further seizures (with both physical and psychological consequences), side-effects of medication and in extremes cases, the risks of brain damage and death. It was because of these latter risks that most people considered surgery a last resort treatment. Conversely, a key consideration in views about the possibility of AED withdrawal was what this would mean in the context of daily life.

Psychological support and help with memory problems
Given the impact of epilepsy on people's daily lives, it is perhaps unsurprising that many participants highlighted the need for greater psychological support. Several also expressed the need for help with memory problems.

These findings relating to treatment preferences and outcomes are discussed in greater detail in two recently published papers [Holmes et al, 2018, Ring et al, 2019].

"My safety net is knowing that taking that medication keeps me safe and keeps the rest of the public safe."[1]

Preferences for healthcare
Several aspects of healthcare beyond the matter of specific treatments were identified as important in supporting people with epilepsy to manage it within their daily life.

Getting rapid access to care and expert advice in times of need and the provision of appropriate information and care, tailored to individual need, was important. For people with a recent diagnosis, information about their seizures (type, management), their medication (e.g. what to expect in terms of common side-effects, how long these might last, what to do if a dose is missed and medication regime), and availability of financial support (e.g. prescription cost exemptions) were important.

A personalised approach, where clinicians listened and responded to specific views and concerns, along with expert advice, was important in supporting people to manage epilepsy on a day-to-day basis. The physical health benefits (managing seizures and medication side-effects) and psychological benefits (reassurance and helping to reduce worry) of expert advice were self-evident.

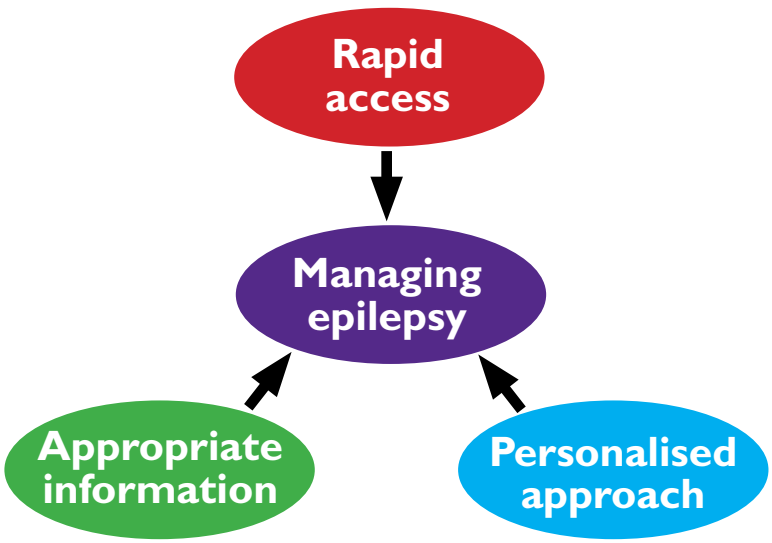
Access to clinicians with specialist knowledge about epilepsy was considered very important, as was continuity of care. Seeing the same clinician during clinic visits helped to avoid time wasted in repeating past history, leaving more time to focus on current issues and future treatment. Joined-up services, with improved communication across the system, was seen as important in facilitating rapid and effective management and reducing confusion regarding treatment.

"The cognitive behaviour [therapy] was useful, because you are going to need it to be able to deal with actually having it."[2]

Survey findings
Findings from qualitative interviews were supported by the responses of those taking part in the survey, who were asked to register their agreement or disagreement with a series of statements using a five-point scale (strongly agree, agree somewhat, don't know, disagree somewhat, strongly disagree).

Summary
Views and preferences of PWE about treatment reflected the lived context within which they experienced having epilepsy and its treatment. Parental responsibilities and social and work-

Statement	Number of responders to statement	% Agreement
Appointments		
I would like more time in my appointments with the hospital doctor/specialist	319	62.7
It is important that I see the same doctor/specialist when I go for my hospital appointments	320	92.2
Communication		
It is important that the doctors and nurses involved in my care listen to what I have to say	323	98.1
It is important to have caring and supportive health professionals involved in helping me to manage my epilepsy	325	96.3
Good communication is important in helping me to manage my epilepsy	318	96.2
Information provision		
It is important that it is explained to me what I might expect when starting on a new medication (such as likely side-effects, plans for treatment etc)	324	98.8
It is important for people with epilepsy to be given practical information about living life with epilepsy (such as information about driving, bus pass, prescription costs exemption and travel insurance)	324	98.5
It is important for people with epilepsy to be given information about sources of support	322	98.4
Accessibility and responsiveness		
Being able to speak to the epilepsy nurse quickly when problems arise is very important in helping a patient to manage their epilepsy	321	93.5
Having contact with the epilepsy nurse is very important for the day-to-day management of my epilepsy	320	67.5
It is important that the doctors and nurses who make decisions about my treatment have specialist knowledge about epilepsy	322	98.8
Patient education		
Having an educational session(s) provided soon after diagnosis (about epilepsy, its treatment, its management and support services) would have helped me to manage my epilepsy	323	84.5



related roles were key lenses through which benefits versus risks of treatment were assessed. For many, the serious risks associated with surgery meant it was generally not considered to be a viable option, despite recent arguments for its use earlier in the condition trajectory [Kingwell, 2012]. The level of tolerability of medication side-effects was reflected in their perceived

"I would have liked clearer information about what to do if you miss your tablets… either told to you or in the medicine packaging, because in all the medicine it just says speak to your GP."[3]

impact on daily activities. Conversely, the psychological consequences accruing from the effectiveness of medication in stopping seizures was apparent. This balance between adverse effects and efficacy of AEDs has also been addressed elsewhere using a structured approach [Lloyd et al, 2005]. Where seizure control proved unattainable, limiting treatment side-effects was paramount. As reported by others [Poole et al, 2000, Mills et al, 1997], a personalised approach to treatment and care, with timely and appropriate information provision and advice were all

"The support I got from the nurse was useful – she gave me good clinical advice, allowed me to talk about my issues and she suggested practical things that have made a huge difference."[2]

important to people in managing epilepsy and treatment effects. Access to clinicians with specialist knowledge about epilepsy was critical, particularly in the context of the limited knowledge among primary care personnel. Overall, our findings point to some important targets for optimal treatment and healthcare for people with epilepsy in the UK.

Recommendations for healthcare

- A personalised approach to healthcare, focusing on the individual and their lived experience
- Early follow-up of the first diagnostic appointment, allowing time for processing information and early questions to emerge
- Continuity of clinicians providing specialist advice and care
- Specialist nurse support for all, including rapid telephone contact
- Timely and appropriate information provision
- Improved access to psychological services
- Better support for people experiencing memory problems
- Improved communication across the healthcare system

Adele Ring, Ann Jacoby, Gus Baker

"It would be nice to have one doctor that you could discuss things with, so you are not just reiterating what you told the last person. That in itself gets really frustrating."[2]

[1]Women with Established Epilepsy
[2]Women with Recent Diagnosis Epilepsy
[3]Male with Recent Diagnosis Epilepsy

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Living better, living safer with epilepsy: Time for a paradigm shift

Dr Heather Angus-Leppan discusses the Epilepsy Action project on epilepsy-related deaths in the UK

Introduction

We have known about premature mortality among people with epilepsy for more than 150 years. Despite this, it was a real struggle, in the UK and elsewhere, to get this recognised.

Charities such as SUDEP Action and Epilepsy Action, along with many individuals, have campaigned for change over the last few decades.

Since the 1800s, we've had clear evidence that epilepsy carries an increased rate of mortality [Devinsky et al, 2018]. Research has focused on sudden unexpected death in epilepsy (SUDEP), but half the deaths are from other factors (the underlying cause of the epilepsy, social deprivation, accidents, especially drowning, suicide, dependence, especially alcohol, or pneumonia) [Mbizvo et al, 2019]. It is estimated that about half of these deaths are preventable. Many of them are potentially avoidable with better education of patients and clinicians, and better care.

About 1,000 people a year die in the UK because of epilepsy [Epilepsy Action]. These deaths send ripples beyond the loss of that person's future. They are tragedies for the person, for their families, their loved ones and for the whole community. Many deaths happen in young people who had their whole life ahead of them. The average age of death in the North American SUDEP registry is 26 years [Verducci et al, 2019]. Worldwide epilepsy-related deaths have not reduced over the last decades. In the UK, deaths of people with epilepsy increased by 70% between 2001 and 2014, with mortality in the most deprived areas nearly three times that in the least deprived [Public Health England, 2018].

Many of these deaths are potentially avoidable with better education of patients and clinicians, and better care.

The epilepsy-related deaths project

This year, Epilepsy Action is working on a project to ensure that people understand the risk of death from epilepsy, and what they can do to be safer. Despite a lot of excellent research the problem remains and it is time to do more about it.

The key questions we asked

- Do people talk about deaths from epilepsy?
- What are the knowledge gaps?
- What can we do now?
- What is needed for the future?
- What are the barriers to further progress?

How have we gathered information?

1. We have adapted the approach based on National Institute for Clinical Excellence (NICE) using existing research, stakeholder engagement and meetings.
2. We have reviewed the literature on epilepsy-related deaths, looking at both quantitative and qualitative work. The latter is often neglected and gives important information about communication techniques, examples of good practice, innovations and individual experience. We have not been as worried about the statistical significance of information as clinical significance.
3. Interviews with key stakeholders have provided ideas of excellent practice and innovations.
4. We have completed a survey about understanding epilepsy-related deaths and future innovations, involving people with epilepsy, as well as their family, carers and health professionals. This has helped with ideas about the timing of information about

epilepsy-related deaths including SUDEP, and what is missing from the current available support. It's given us a basis for developing appropriate guidelines and resources for the future.

5. In July 2019 we met with people with epilepsy and epilepsy professionals. We explored short-term and long-term goals. We learned and gained insight from places where there is excellent care for people with epilepsy.

Key outputs

Medium to long term goals: shifting the paradigm

Our findings this year suggest part of the solution is taking a different angle, instead of presenting SUDEP as an unexplained phenomenon. If we shift to living better and living more safely, we can reduce epilepsy risks and also improve people's quality of life.

Knowledge is power, but only if it is acted on. A lot of epilepsy mortality research is on SUDEP: mechanisms, risk factors (many unclear and not agreed between studies). We need more research to understand why people die during a seizure. But let us focus in the meantime on what we can explain, sometimes even predict. Sometimes the cause of a death is quite clear, for example by drowning. It is time to do more about the things that we can solve now.

Sometimes people don't realise how important it is to take their epilepsy medicines, avoid triggers and avoid dangerous situations. For example, advise people to take showers rather than baths.

We can't prevent all deaths from epilepsy, but many are caused when people take unnecessary risks or lack support. Perhaps the person's seizures have worsened and they haven't seen their doctors or nurses. Remediable factors include struggles with mental health problems, potential changes to their lifestyle which will increase safety, such as better sleep patterns, reducing alcohol use. Many relate to not getting or taking their epilepsy medicines, or remembering to take them on time. EPSMON is an example of a focus on preventing deaths by signalling the need for support and consultation with a professional [EPSMON]. There is scope for more interventions.

Some think healthcare professionals and charities should stay out of politics, and leave it to the politicians. Should we keep ourselves detached?

Short-term actions: guidelines and training for professionals

Talking about epilepsy deaths

The current survey suggests many of us are still not comfortable with this, as do previous studies [Keddie et al, 2016]. Some families who have lost a loved one feel they and the person who died didn't have enough information about the risks. People talk about death in other conditions such as heart disease or asthma, so it is possible to be open about risk in epilepsy. Doctors and nurses may struggle with the best way to talk about this. A barrier to openness is the clinician's fear of overloading bad news. The newly diagnosed person has been told at their appointment that they have epilepsy and they can't drive. This is life-changing, and may have major implications for work and family activities. Medications, side-effects, tests and follow-ups loom ahead. It can seem "too much" to add the fact

that seizures are dangerous and you can die during one. Online and in-person training will provide practical teaching on how to talk about epilepsy-related deaths, and how to help people with epilepsy to live more safely.

Epilepsy medicines
Missing a dose or running out of epilepsy medicines is an important but avoidable problem that is pertinent as Brexit looms. It is hugely stressful if someone is running out of their epilepsy medicine and doesn't know how to get more. People are often unclear about what to do if they miss a dose, and sometimes this includes the doctors and nurses. My team are working on guidelines for individual plans so people with epilepsy know what to do if they miss a dose or are unexpectedly running low on their epilepsy medicine. No one would think it is okay for someone with diabetes to miss a dose of insulin. In the same way, no one with epilepsy should be left without their regular epilepsy medication.

Mental health
Mental health issues are common in all of us, and even more common in people with epilepsy. Talking about this is a first stage to getting support and seeing improvements. We are working on guidance to help with this, and we'll incorporate a checklist to alert doctors and nurses of the signs to look out for.

Drugs and alcohol
Life stresses and mental health problems may cause people with epilepsy to misuse alcohol and recreational drugs, to lose hope and to neglect self-care. Advice and contact with support services is essential and the team are preparing a webpage to flag what support is out there.

Educational YouTube videos
We have devised scripts for brief videos on hot topics, including talking about epilepsy-related deaths, what to do if someone has a seizure and what to do if they run out of epilepsy medicine. This is a particularly challenging part of the project. The aim is to reach people who are more at home with social media than they are reading booklets and advice sheets.

Stresses about PIP and benefits are a major and growing source of worry for some people with epilepsy

Goals for the future

Social change

Stresses about PIP and benefits are a major and growing source of worry for some people with epilepsy, and streamlining and adapting the process would make a real difference to reducing stress. These stresses can make people unwell and less able to deal with their health needs.

Poverty and social deprivation are strongly linked to severe epilepsy [Public Health England]. It is the elephant in the room, and if this is not solved, the problem of epilepsy related-deaths will remain. It is the same across many neurological conditions, and health in general.

Better joined-up patient records for all to see

We need better patient and medication records, so that GPs, hospital nurses and doctors and the person with epilepsy can all see them easily. This improves communication and allows problems to be dealt with quickly and efficiently. Worries about confidentiality have been a barrier,

but these can be overcome. Other countries such as Spain have achieved this.

Monitoring this issue
In Scandinavia, Scotland and Wales, government systems allow us to track epilepsy mortality, what is happening with the numbers of people dying from epilepsy, including how and why. This is lacking in England, and is important in monitoring and analysing progress. This is going to take some time to fix.

Campaigning and political action
Some think healthcare professionals and charities should stay out of politics, and leave it to the politicians. Should we keep ourselves detached? Clearly political action is complicated, outside the comfort zone of most nurses and doctors, and can be misinterpreted. I argue that if we don't take political action then we accept the status quo and things will not change. Social deprivation, which is clearly linked

This research project is in response to another project which may provide you with further information: Epilepsy-related and other causes of mortality in people with epilepsy: A systematic review of systematic reviews. Gashirai K. Mbizvoa, Kyle Bennett, Colin R. Simpson, Susan E. Duncan, Richard F.M. Chin. *Epilepsy Research* 157 (2019) 106192 *https://bit.ly/31RKhHa*

Abstract
- This systematic review of epilepsy mortality systematic reviews evaluates comparative risks, causes, and risk factors for all-cause mortality in people with epilepsy (PWE) to specifically establish the burden of epilepsy-related deaths.
- MEDLINE and Embase were searched for systematic reviews evaluating all-cause mortality in PWE of any age. A narrative synthesis of review findings was used to present results, including from a secondary analysis of individual epilepsy-related death risk factors.
- Deaths were separated into epilepsy-related and unrelated, using a classification system (Devinsky et al, 2016)
- Six moderate or high-quality systematic reviews were included in the primary analysis, evaluating 103 observational studies. Common epilepsy-related causes included alcohol, drowning, pneumonia, and suicide.
- Nine additional systematic reviews were included in the secondary analysis. Epilepsy-related death risk factors were reported for sudden unexpected death in epilepsy (SUDEP), drowning and suicide.
- Conclusions: Premature all-cause mortality remains a major problem in PWE globally, particularly in children and young adults. Most are epilepsy-related and potentially preventable. SUDEP is only one of several other common and important epilepsy-related causes of death.

Dr Heather Angus-Leppan is the Epilepsy Action Lead, Epilepsy-related deaths project; Epilepsy Advisory Group member, and representative, MHRA Valproate Stakeholders' Network meeting (2018), Association of British Neurologists; UK representative on the Sanofi European Valproate educational programme Advisory Board. She holds Eisai Investigator initiated non-pharmaceutical grants and has received honoraria for non-promotional lectures from Eisai and UCB. Some of the views expressed in this article, particularly the political ones, are her own, and it is hoped they will encourage further debate.

This project is being supported by the Octavia Morris Memorial Fund.

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Management of epilepsy in women

Dr Linda Stephen looks how we can improve quality of life for women with epilepsy across their lifespan

Introduction
Worldwide, epilepsy is a common neurological condition in women with a prevalence of 6.85 cases per 1,000 women [Fiest et al, 2016]. This article discusses the issues which arise at different life stages for female patients with epilepsy, including the menstrual cycle, fertility, contraception and pregnancy and the menopause.

Hormonal influences
Approximately one third of women experience a variation in seizure frequency across the menstrual cycle, referred to as catamenial epilepsy [Herzog et al, 2012]. The most common time for seizure control to worsen is around menstruation, but deterioration can also occur pre-ovulation and during anovulatory cycles with inadequate luteal phases [Herzog et al, 2012]. A diary can be useful in establishing a seizure pattern. Progesterone and its metabolites can exert a neuro-inhibitory effect via post-synaptic GABA-A receptors. To test the hypothesis that a pre-menstrual reduction of progesterone concentrations results in catamenial seizures, 130 women with and 164 women without catamenial epilepsy were given an adjunctive natural progesterone supplement in a randomised, double-blind, placebo-controlled study [Herzog et al, 2012]. There was no statistically significant difference between progesterone and placebo in the proportion of patients who reported a ≥50% seizure frequency reduction, although a significant reduction occurred in a small subgroup with a three-fold worsening of perimenstrual seizures [Herzog et al, 2014]. Clobazam is commonly prescribed for catamenial seizures, although robust efficacy data are lacking.

Contraception
Effective contraception for women with epilepsy is particularly important, given that many antiepileptic drugs (AEDs) interact with steroid hormones [Brodie et al, 2013] (Table 1) and have associated teratogenicity [Tomson et al, 2018]. UK guidelines recommend that, when possible, contraception should be discussed before a woman with epilepsy becomes sexually active and should be reviewed regularly [NICE, 2019, SIGN, 2019]. Despite this, hormonal contraceptive use is low in this population [Farmen et al, 2016].

Women with epilepsy are more likely to have unplanned pregnancies than women without epilepsy and are not satisfied with their knowledge of pregnancy and birth issues

Fertility
Information on fertility and epilepsy is lacking. A Norwegian database study of >25,000 women found similar birth numbers for women ≤20 years with and without epilepsy, but for those with epilepsy, birth numbers fell with rising age [Farmen et al, 2016]. However, it is not known whether women in this broad population were trying to become pregnant and how fertility was influenced by psychosocial factors. A US prospective, observational study of 89 women with epilepsy and 108 controls without epilepsy trying for pregnancy found that 61% and 60% respectively became pregnant within 12 months of enrolment [Pennell et al, 2018]. Prospective, randomised controlled trials examining fertility in this population would provide useful information.

Preconceptual counselling
Given that women with epilepsy have many more issues surrounding pregnancy and childbirth to consider than women without epilepsy, preconceptual counselling is recommended [NICE, 2019, SIGN, 2019] (Table 2). This includes advice on folic acid supplementation. Although evidence for congenital malformation prevention with folic acid supplementation is inconclusive for children born to women with epilepsy, there are associated neurodevelopmental benefits [Meador et al, 2013, Baker et al, 2015, Bjørk et al, 2018]. Optimal dosing remains unclear, but UK guidelines recommend at least 400mcg daily and up to 5mg daily in the preconceptual period and for at least the first trimester [NICE, 2019, SIGN, 2019].

Epilepsy specialist nurses are ideally placed to provide counselling and support prior to, throughout and after pregnancy. However, women with epilepsy are more likely to have unplanned pregnancies than in women without epilepsy and are not satisfied with their knowledge of pregnancy and birth issues [Stephen et al, 2019]. This highlights the importance of preconceptual counselling in this population.

Valproate
Although valproate has been shown to be a very effective AED in many patients with epilepsy, evidence of its teratogenic potential is growing [Tomson et al, 201, Hernández-Diaz et al, 2012, Campbell et al, 2014]. Valproate has a higher major congenital malformation risk than

other AEDs. The risk is dose-related, increasing from 500-750 mg daily. Genetic factors or individual susceptibility may also be implicated [Stephen et al, 2019]. Valproate use during pregnancy has been associated with poorer neurodevelopmental outcomes in offspring, with more children experiencing cognitive, psychomotor or language developmental delay, compared with children of untreated women with epilepsy [Bromley et al, 2014, Bromley et al, 2017]. Exposed offspring may also be at increased risk of autism spectrum disorder, dyspraxia and attention deficit hyperactivity disorder [Veroniki et al, 2017, Christensen et al, 2013, Cohen et al, 2013]. Valproate should therefore be avoided, when possible, in women of childbearing potential and use is restricted by the US Food and Drug Administration (FDA) [FDA DSC, 2019] and the European Medicines Agency (EMA) [EMA, 2019]. Unless there are compelling reasons to indicate there are no risks of pregnancy, women in Europe of childbearing potential who are prescribed valproate are required to comply with the EMA pregnancy prevention programme on an annual basis [EMA, 2019]. As valproate has been recommended as the drug of first choice for many women with unclassified and genetic generalised epilepsies who may achieve seizure control with low dosing, these restrictions create a dilemma. A comprehensive assessment and discussion of options can aid decision making [Angus-Leppan et al, 2018].

Pregnancy

Epilepsy is one of the most common neurological disorders in pregnancy, with a prevalence of 0.3-0.7% [MacDonald et al, 2015]. Pregnancy registers, including the UK epilepsy and pregnancy and EURAP registers, provide invaluable information to assist management decisions [Tomson et al, 2018, Hernández-Diaz et al, 2012, Campbell et al, 2014].

Epilepsy is still one of the leading indirect causes of maternal death with sudden, unexpected death in epilepsy being the commonest cause

Seizure control in pregnancy

EURAP data [Herzog et al, 2014] showed the majority of women with epilepsy had reduced seizure frequency or remained seizure-free during pregnancy. Women with genetic generalised epilepsies were significantly more likely to remain seizure-free compared to those with localisation-related epilepsies [Battino et al, 2013]. The incidence of status epilepticus was much higher (21 [0.6%] of 3,451 women) during pregnancy than in the general population (12.6 [0.013%] of 100,000 men and women with epilepsy) although register results may be subject to reporting bias [Battino et al, 2013]. In the UK, epilepsy is still one of the leading indirect causes of maternal death with sudden, unexpected death in epilepsy being the commonest cause [Edey et al, 2014, Knight et al, 2017]. This highlights the importance of pre-pregnancy planning with optimisation of seizure control and AED treatment prior to conception [Stephen et al, 2019].

Antiepileptic drug metabolism in pregnancy

During pregnancy physiological changes affect AED absorption, distribution, metabolism and excretion [Pariente et al, 2016]. This can result in falling concentrations of lamotrigine, levetiracetam, topiramate, zonisamide and oxcarbazepine as the pregnancy progresses [Stephen et al, 2019]. Therapeutic drug monitoring can aid AED dose adjustment, but this may not be readily available in some areas [Stephen et al, 2019]. It is recommended that AEDs are continued throughout pregnancy and in the post-partum period with the aim of controlling seizures, in particular, tonic-clonic events [SIGN, 2019].

Comorbidities in pregnancy

Women with epilepsy are more at risk of peripartum psychiatric comorbidities compared to women without epilepsy [Bjørk et al, 2015]. Epilepsy has been associated with a significantly increased prevalence of obesity [Kolstad et al, 2016], binge eating disorder and impaired body image [Kolstad et al, 2015] during pregnancy. Pre-eclampsia is more common in women with epilepsy and eating disorder in pregnancy, compared to those with neither condition [Kolstad et al, 2015]. Lower global satisfaction scores, poor self-esteem and adverse socio-economic circumstances such as single parenting, financial difficulties, low education and unemployment are more likely in women with epilepsy, both during and after pregnancy [Stephen et al, 2019].

Pregnancy-related complications

The majority of women with epilepsy will have a straightforward pregnancy, labour and delivery and will give birth to a healthy baby [Artama et al, 2017]. However, database and registry data have shown an increased risk of complications for some women with the condition,

compared to women without epilepsy. These include pre-eclampsia, gestational hypertension, gestational diabetes, preterm labour and birth, premature membrane rupture, induction of labour, caesarean section, ante- and post-partum haemorrhage, placental abruption and chorioamnionitis [Stephen et al, 2019]. It is therefore recommended that women with epilepsy should be delivered in a consultant-led maternity unit, ideally with one-to-one midwifery care during labour and close post-partum observation [SIGN, 2019]. A low threshold for admission should be adopted for those presenting in early labour, with every effort made to reduce seizures in labour, including effective analgesia [SIGN, 2019].

Post-natal issues

During the post-natal period regular, assured contact with clinicians can be a support to new mothers with epilepsy [NICE, 2019, SIGN, 2019] (Figure 1). As the physiological changes of pregnancy reverse, AED dose reduction may be required to prevent toxicity [Stephen et al, 2019]. Anxiety and depression are common at this time, particularly in women with a past history [Bjørk et al, 2015]. Previous anxiety and depression and a history of physical and sexual abuse are poor prognostic indicators [Bjørk et al, 2015]. Despite this, women with epilepsy are less likely to receive antidepressants compared to those with other chronic diseases [Bjørk et al, 2015]. Clinicians should therefore have a high awareness of these issues and liaise promptly with psychiatry services when required.

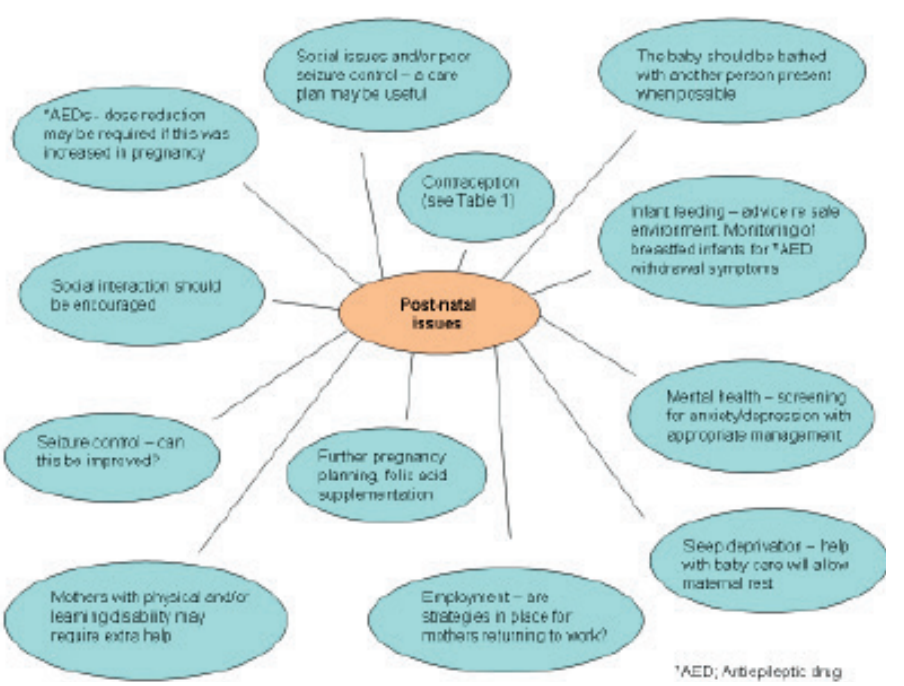
Breastfeeding

Fewer women with epilepsy breastfeed compared to those without epilepsy and many are concerned about the safety of breastfeeding [Meador et al, 2014]. However, although lipid soluble AEDs are present in breastmilk, quantities are generally too small to produce unwanted effects [Veiby et al, 2015] Exceptions may be barbiturates, benzodiazepines, lamotrigine, zonisamide and ethosuxmide [Veiby et al, 2013]. Mothers receiving these AEDs should be advised to monitor their infants for symptoms such as lethargy and sedation [Meador et al, 2014] Two prospective longitudinal studies of breastfed children revealed no adverse effects on motor and social skills, language and behaviour for those whose parents took carbamazepine, lamotrigine, or valproate [Meador et al, 2014, Veiby et al, 2013]. The NEAD study found no adverse neurodevelopmental effects of breastfeeding in 181 children at three and six years whose mothers received phenytoin, carbamazepine, valproate or lamotrigine [Meador et al, 2014]. Given these positive outcomes, women with epilepsy should be encouraged to breastfeed when possible [Stephen et al, 2019].

Menopause

There are few data available on epilepsy and the menopause. Two small questionnaire-based studies found women with epilepsy to be more susceptible to early perimenopause and menopause [Stephen et al, 2019]. One suggested a link between greater lifetime seizure frequency and earlier menopause, as much as three to four years earlier for women with more than 20 seizures. In women with epilepsy of reproductive age, antimüllerian hormone, a direct measure of ovarian reserve, was

Figure. Post-natal issues for women with epilepsy requiring discussion



found in lower concentrations in those with uncontrolled seizures, compared to women who were seizure-free [Harden et al, 2016]. Rapid changes in oestrogen and progesterone concentrations may increase seizure frequency during perimenopause [Koppel et al, 2014]. At menopause, a seizure reduction can occur in some women, perhaps due to higher oestrone concentrations, which have been linked with fewer seizures in patients with catamenial epilepsy and in experimental models [Koppel et al, 2014]. Exogenous hormones might also influence seizures around the menopause. A small randomised, placebo-controlled study found use of conjugated equine oestrogens with medroxyprogesterone acetate as hormone replacement therapy was associated with a dose-related increase in seizure frequency in six of 15 women [Koppel et al, 2014]. Oestrogen-containing hormone replacement therapy reduces lamotrigine concentrations which may necessitate an increase in lamotrigine dose [Reimers et al, 2017]. Current management strategies for women with epilepsy going through the menopause focus on optimisation of AED regimens, but greater understanding of hormonal influences on neuronal excitability should assist novel therapy development [Stephen et al, 2019].

Bone density

During the menopause bone turnover increases and bone loss is accelerated, leading to reduced bone mineral density and risk of fracture [SIGN, 2014]. AED use is associated with low bone mineral density, making post-menopausal women with epilepsy particularly vulnerable to fractures [SIGN, 2014]. As found in a UK general practice analysis, bone loss can occur before the menopause – for every 10,000 women (median age 48.2 years) with epilepsy on enzyme inducing AEDs for one year, 48 additional fractures occurred [Nicholas et al, 2013]. While hepatic enzyme inducing AEDs have a particular association, other AEDs such as valproate are also linked with reduced bone mineral density [Albaghdadi et al, 2016].

Although the majority of women with epilepsy have favourable pregnancy outcomes, research is needed to explore reasons for pregnancy complications

Mechanisms remain unclear and are likely to be multifactorial, occurring at various stages in the bone metabolism pathway [Stephen et al, 2019]. Management is complex – change of AED to one with less risk may be an option for some women [Stephen et al, 2019]. Bone densitometry screening is advised, but there is no robust evidence regarding frequency or minimum screening age [SIGN, 2014]. Vitamin D supplements are beneficial, although dosing is not clear [Fernandez et al, 2018]. Daily doses of 800IU have been suggested in combination with calcium and 1800-4000IU when used alone [Fernandez et al, 2018]. Long-term trials of bone densitometry with varying vitamin D and calcium doses are needed to shine a light on this area.

Conclusions

There are many challenging issues facing women with epilepsy at different life stages. Younger women may encounter seizure variations during their menstrual cycle. Unravelling causes for this phenomenon may lead to effective management strategies. Mechanistic and genetic studies exploring the causes of AED-related congenital and neurodevelopmental abnormalities will allow more informed preconceptual counselling. Although the majority of women with epilepsy have favourable pregnancy outcomes, research is needed to explore reasons for pregnancy complications, including physical and psychiatric morbidities and mortality. Perimenopause and menopause appear to occur earlier in women with epilepsy compared to women in the general population. Reasons have yet to be fully ascertained. Long-term bone mineral density studies would help establish optimum therapies for those at risk of fracture. Answers to these many questions will lead to improved quality of life for women with epilepsy.

Dr Linda Stephen
West Glasgow Ambulatory Care Hospital

Correspondence to:
Dr Linda Stephen
Associate Specialist
Honorary Clinical Senior Lecturer
West Glasgow Ambulatory Care Hospital
Dalnair St, Glasgow
G3 8SJ
Tel: +44 141 201 0511
Email: *linda.stephen@ggc.scot.nhs.uk*

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Table 1. Contraceptive pathways for women receiving antiepileptic drugs (AEDs)[a]

Hepatic enzyme inducing AEDs	Non-enzyme inducing AEDs
Carbamazepine **Eslicarbazepine acetate** **Oxcarbazepine** **Perampanel (≥12mg/day)** **Phenobarbital** **Phenytoin** **Primidone** **Rufinamide** **Topiramate (≥200mg/day)**	**Acetazolamide** **bBrivaracetam** **Clobazam** **cClonazepam** **Ethosuximide** **Gabapentin** **Lacosamide** ***Lamotrigine** **Levetiracetam** **Pregabalin** **Retigabine** **Sodium valproate** **Tiagabine** **Vigabatrin** **Zonisamide**
Hormonal Combined oral contraceptive pill must have at least 50micrograms/day oestrogen If breakthrough bleeding occurs with no other obvious cause, consider increasing to 70 micrograms/day and tricycling Progesterone-only pill, progesterone implant, combined contraceptive patches, vaginal ring are not recommended due to reduced efficacy. Depot/subcutaneous progesterone and levonorgestrel intrauterine system are suitable for use as efficacy is maintained Risk of bone loss with depot/subcutaneous progesterone **Non-hormonal** Barrier contraception is less effective than combined oral contraceptive pill Non-hormonal intrauterine device may be contraceptive of choice **Emergency contraception** Single dose of levonorgestrel 3mg (as opposed to 1.5mg) as soon as possible within 72 hours of unprotected intercourse (off licence in UK) Ulipristal acetate is not recommended due to restricted efficacy Insertion of a non-hormonal intra-uterine device within 5 days (120 hours) of intercourse is an alternative	**Hormonal** **As for women not taking an AED** Non-enzyme inducing AEDs do not alter the effectiveness of combined contraceptive patches, combined oral contraceptive pill, progesterone-only pill, progesterone implant, vaginal ring, or emergency contraceptives Lamotrigine clearance is doubled by ethinyloestradiol/levonorgestrel; an increased lamotrigine dose may be required **Non-hormonal** As for women not taking an AED **Emergency contraception** As for women not taking an AED

Table 2. Preconceptual counselling issues for women with epilepsy

ISSUE	ACTION
Review of diagnosis	Is the diagnosis correct? Are any investigations needed prior to pregnancy?
Review of seizure control and AED* treatment	An effort should be made to optimise seizure control and rationalise AED* regimen prior to conception. If possible, valproate should be discontinued. Aim for monotherapy if feasible.
Epilepsy surgery	If the woman is a candidate for epilepsy surgery is preconceptual referral worthwhile?
Comorbidities	Are there any physical or mental comorbidities which are under/untreated?
Weight reduction	Obesity is associated with adverse outcomes for women with epilepsy. Weight reduction counselling should be offered to relevant women.
Eating disorders	Women with a history of eating disorders and epilepsy have a higher prevalence of pre-eclampsia compared to the general population. Psychiatric liaison should be arranged for relevant women.
Contraception	Women not wishing to conceive should be using an adequate contraceptive method with no AED* interactions.
Reassurance	Parents can be reassured that most women with epilepsy will have a normal pregnancy, labour, delivery and a healthy baby.
*AED teratogenicity	Discussion regarding AED* teratogenicity should take place
Folic acid	Women wishing to become pregnant should be advised to take folic acid, ideally preconceptually and for at least the first trimester.
History of congenital malformations/other inherited conditions	Women with epilepsy who have had a previous child with, or who have a first/second degree relative with neural tube defects or other major congenital malformations, are at risk of giving birth to a child with anomalies compared to the general population. These women should be referred for preconceptual genetic counselling.
Smoking cessation	Women with epilepsy who smoke during pregnancy have a substantially higher risk of premature contractions, pre-term labour and delivery compared to those who do not smoke. Smoking cessation should be encouraged.
Pregnancy registers	Information on pregnancy registers should be given to women, together with the underpinning rationale.
Written information	Where possible, women should be provided with written information – these enable greater retention of information.

**AED; Antiepileptic drug*

[b]When brivaracetam 400mg/day was co-administered with an oral contraceptive containing 0.03mg ethinylestradiol and 0.15mg levonorgestrel, oestrogen and progestin concentrations decreased by 27% and 23% respectively without an impact on ovulation suppression [FDA DSC, 2019]. No such change was observed with 100mg/day [Christensen et al, 2013].

[c]Clonazepam clearance is reduced by the progesterone only pill via the nitroreduction pathway [Christensen et al, 2013]

*When 300mg lamotrigine was administered to women receiving a combined contraceptive containing 30mcg of ethinylestradiol and 150mcg of levonorgestrel circulating lamotrigine concentrations were halved through glucuronidation induction [Christensen et al, 2013]. There was a 19% reduction in levonorgestrel concentrations, although no evidence of ovulation was seen [Christensen et al, 2013].

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Highlights

Top picks from *Seizure*

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

It is now well-established that epilepsy is much more than seizures. At least in temporal and epidemiological terms there is a clear bidirectional relationship between epilepsy and mental health problems including depression, anxiety and suicidality – and it is highly plausible that there is a causal bidirectional relationship between these problems as well [Hesdorffer et al, 2012]. Aside from this, epilepsy is a social disorder. Indeed, the social consequences of having epilepsy exceed the medical impact of the condition for most people living with seizures [Jacoby et al, 2005]. Furthermore, epilepsy and its treatment have many implications for people's lives – affecting important personal matters such as family planning and employment opportunities but also more mundane issues such how to cook, clean themselves or look after their young children.

Despite the recognition of the broad impact of epilepsy on the lives of those affected, epilepsy services (even or perhaps especially in high income countries) struggle to provide support with the non-seizure manifestations of epilepsy. Neurologists or psychiatrists (the professionals who most commonly diagnose epilepsy and oversee its pharmacological treatment) may screen for mental health symptoms but rarely offer meaningful advice on the social consequences of epilepsy or any practical questions their patients have to deal with because of their epilepsy, and patients may not consider it appropriate to ask a doctor about these matters. Non-epilepsy experts (for instance in primary care or non-medical professions such as social work) may feel that they lack the knowledge to offer advice on questions related to epilepsy. This leaves many people with epilepsy to their own devices and means that they do not have access to high quality individualized advice about epilepsy-related questions, which may well affect their quality of life more than the seizures themselves.

My editor's choice paper from the current volume of Seizure is a study by Agnes Higgins et al. describing and assessing the role of epilepsy nurse specialists (ENSs) [Higgins et al, 2019]. Of course, ENSs know a lot about seizures, but they are also ideally placed to fill the gaps in service provisions for non-seizure manifestations of epilepsy, which exist in many medically dominated epilepsy services. This qualitative study based on data from 12 ENSs, 24 multidisciplinary team members as well as 35 people with epilepsy and their family members captured working practices across five Irish epilepsy services. The findings indicate how crucial the support is which ESNs provide in terms of empowering people to self-manage their illness, performing comprehensive needs' assessments, providing person-centred education, monitoring the impact of care and treatment, providing education to significant others and psychosocial care to optimise psychological wellness, co-ordinating care and quality assuring patient information. However the findings also show that, in order to function ESNs need to be embedded in and complemented by a multidisciplinary team. ESNs enhance medically oriented services they do not replace them. As such, this paper makes a useful addition to the evidence-base for ESN services, which has recently been summarized by the ESPENTE team [Campbell et al, 2019]. My editor's choice paper should be read in the context of all the other evidence underlining the importance of ESNs for comprehensive epilepsy services. This evidence has recently been compiled and beautifully presented by the ESPENTE collaborators in a freely available interactive evidence map (do take a look at: *espente.epilepsy.org.uk*).

Further reading

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I thought for this edition of *Epilepsy Professional*, we could stop and focus our attention on epilepsy carers. Some charities invest in supporting carers, but often they are overlooked by the medical profession. I hope to use this short piece of writing to illustrate some of the compromises carers make. I also want to highlight some of the recent government schemes, health policies and training programmes which start to address some of the challenges they face.

I wonder how acutely aware we are of the position of being a child carer, or a sibling carer for a person with epilepsy? It's not uncommon to see a school age or a young adult carer in my adult epilepsy clinics taking on such a role for one of their parents or siblings. Or even seeing an older or middle-aged adult in the prime of their life caring for a brother or sister with epilepsy.

Sometimes it's hard to comprehend the different personal experiences we have had to these children and young adult carers. It's probably a world away from our formative years. As outsiders we probably view their role as one of commitment and sacrifice, but yet for the individual the motivating factors are probably quite complex. Maybe it's a role of individual and family expectation, of doing the right thing, or driven out of devotion, love and support. Perhaps they step into the role because often some external care agencies struggle to find regular committed trained staff to deal with the sometimes complex epilepsy and personal care needs. To me, it seems these children, teenagers and young adults live their lives around other people's needs. They perhaps downplay significant events in their own lives, such as birthdays, school achievements, holidays and maybe even sacrifice certain friendships, relationships, their career and own path in life.

On a practical note, it's pleasing to see the blue badge scheme has been extended by the government to include hidden disabilities such as epilepsy. This is obviously a great step for people with epilepsy and their carers. It acknowledges the effect of a condition on an individual level, and also helps to recognise comorbidities such as anxiety and depression. The real benefit of the scheme for people with epilepsy is that the badge is awarded to an individual. This means they do not need to have a driving license, or be over 17 years of age. So those with uncontrolled epilepsy who are not legally eligible to drive can apply for a blue badge which can be used by their carer, family or friend, as long the badge holder is in the vehicle. The benefits here to carers, families and the individual with epilepsy are obvious.

Finally, it's worth mentioning the new Epilepsy Nurses Association guidelines on administering emergency and rescue medications. This is a new online assessment tool, which provides best practice training for professionals and carers involved in acute seizure management. This training can not only help save lives of people with epilepsy, potentially reduce accident and emergency attendances but also will give carers increased confidence, safety and independence, and autonomy in their caring role.

I hope this short section illustrates some of the unseen and sometimes unspoken work of carers. I trust in our clinics that we can give them an opportunity and a voice, even if only for a short time. I wonder, can we also start to think laterally about some social prescribing, such as the blue badge scheme, and also write to councils for a request of a free bus pass for individuals and/or carers of people with epilepsy. It causes me to stop and think; in what other areas can we utilise and in time legislate social prescribing for people with epilepsy?

Dates for the diary

January 2020

20-24
10th EPODES Advanced II Paediatric Epilepsy Surgery, Palliative surgery & Neuromodulation
Brno, Czech Republic
ilae.org/congresses/10th-epodes-advanced-ii

29-31
2020 British Paediatric Neurology Association (BPNA) Annual Conference
Belfast, Northern Ireland
bpna.org.uk/conference/2020

February 2020

24-25
30th International Conference on Neurology and Cognitive Neuroscience
London, UK
neurocognitivedisorders.neurologyconference.com

March 2020

16-17
25th International Conference on Neurosurgery and Neuroscience 2020
Berlin, Germany
neurosurgery.insightconferences.com

24-26
7th International Conference on Non-Invasive Brain Stimulation (NIBS)
Baden-Baden, Germany
nibs-conference.de

26-28
4th ILAE British Branch Epilepsy Neuroimaging Course
Chalfont St Peter, UK
https://bit.ly/2rbePH9

26-29
14th World Congress on Controversies in Neurology
London, UK
cony.comtecmed.com

29 – 3 April
3rd International Training Course on Neuropsychology in Epilepsy
Bordeaux, France
https://bit.ly/2O2wlq0

The tiny fish making a splash

Dominic Burrows and Richard Rosch explore how zebrafish can offer an unprecedented look into the dynamics of the epileptic brain.

Seizure forecasting

Vicky Byrne and Pauline Heslop look at the quality of care of epilepsy patients with learning disabilities, what improvements are necessary and how we can help reduce mortality rates in the UK.

Epilepsy Professional's advisory panel

Adele Ring
Andrew Curran
Andrew Nicolson
Catherine Robson
Claire Isaac
Colin Dunkley
Gus Baker
Heather Angus-Leppan
Howard Ring
Ivana Rosenzweig
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