epilepsy action

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Ketogenic diet
Diet therapies for drug-resistant epilepsy

Manny Bagary

Burnout – Judith Johnson

CBD – Sam Mountney

Q&A – Insights from Mike Kerr

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with drug-resistant epilepsy display depressive symptoms[1]*

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* 515 patients (DRE = 248) were included in the study.

1. Garcia ME et al Epilepsy Research (2015) 110, 157—165
2. Spindler P et al. Seizure: European Journal of Epilepsy 69 (2019) 77–79

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The summer holidays are over, the nights are drawing in and the weather is turning colder. What more to help you get through the cold autumn evenings than the latest edition of *Epilepsy Professional*? Welcome!

We have a fascinating issue for you this time. Professor Mike Kerr is well known in the epilepsy world for his work in the intellectual disability field and received the Excellence in Epilepsy award at the Annual Scientific Meeting of the ILAE British Branch this year – he answers our questions on the challenges and ongoing research in this area.

The ketogenic diet is a well-established treatment for childhood epilepsy. It is increasingly considered as an option in adults with drug refractory epilepsy, but the evidence is sparse and few services are commissioned. Dr Manny Bagary gives us an update on the state of play and how provision of this treatment is moving forward for adults.

Another emerging area of the treatment for drug-resistant epilepsy is in cannabis-based medical products. Sam Mountney gives us an update on where we are now, as we await the decision from the regulatory bodies on a pathway to the safe use of these products in our practice.

We are said to be coming to the end of austerity – whether we believe this or not, I think we can all agree that working in healthcare has become more difficult over the last decade. This puts an extra burden on us as healthcare providers and we risk burnout. Judith Johnson provides a review of burnout and how we can try and prevent and treat it. It is always important to look out for your own and your colleagues' health and wellbeing.

Finally, a shameless plug and plea for sponsorship! The Wessex Neurological Centre Epilepsy team will be getting muddy for charity. With the team, I will be taking part in an Active Warrior run through 5km of mud and water on 19 October 2019. Please sponsor us – half the money will go to Epilepsy Action and half to Smile for Wessex, the charity of the Wessex Neurological Centre, Southampton. *https://uk.virginmoneygiving.com/Team/MyoclonicJerks*

Enjoy the issue.

Dr Seán J Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

It's easy to forget sometimes that we live in a world that's resistant to change. Brexit talks in a stalemate because there's no majority that can decide what leaving the EU will actually look like. Hong Kong in revolt because of the extradition bill. Change takes a long time, and there's a lot of fighting involved, and a lot of waiting.

The waiting and fighting (rinse and repeat) extends to the treatment of epilepsy. Despite a year since cannabis-based products being allowed to be prescribed for medical use, we're still a long way off from GPs widely signing off on those pharmacy slips. More research is needed to bolster clinical confidence in the effectiveness of these products. And it's the tireless work of campaigners, researchers and other stakeholders that will help convert this confidence into public policy. To those people I say keep fighting the good fight. Read more on the current situation on page 16.

It's a similar situation, though arguably less sexy, with ketogenic diets. For nearly 100 years we've been using keto foods to help children with drug-resistant epilepsy. And yet the story turns much more complex for adults with DRE. Dr Manny Bagary outlines where we're at on page 22.

Elsewhere this issue, Judith Johnson talks about burnout on page 12 – sadly an increasingly common scenario in UK healthcare. Finally, we speak to Mike Kerr as he talks about his work on intellectual disability and the future of epilepsy care and research on page 18. Enjoy the issue,

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NICE declines to support CBD treatment for severe epilepsy

Fast-tracked guidance from NICE has ruled that medical cannabis cannot be approved to treat children with severe epilepsy.

Despite reclassifying medicinal cannabis for legal use on the NHS, the health watchdog was unable to recommend these medicines due to the lack of clear evidence of the benefits.

Paul Chrisp, director of the Centre for Guidelines at NICE, said: "We recognise that some people will be disappointed that we have not been able to recommend the wider use of cannabis-based medicinal products. However, we were concerned when we began developing this guidance that a robust evidence base for these mostly unlicensed products was probably lacking."

A separate report by the Health and Social Care Committee says that without a strong research base, products may only be prescribed if there is enough evidence for their safety and effectiveness. The committee recommended that the government and pharmaceutical industry need to ensure that the necessary clinical trials into medicinal cannabis are taken forward.

Dr Sarah Wollaston MP, chair of the Health and Social Care Committee, says: "Changes to government policy on CBD were welcomed. However, there was a failure to communicate what this would mean for the availability of medicinal cannabis. Expectations were unfairly raised that these products would become widely and readily available. There needs to be far clearer communication that this is not the case."

Epilepsy Action deputy chief executive Simon Wigglesworth said: "The initial decision of the NICE technology appraisal committee not to recommend cannabidiol/ CBD (Epidiolex) as an add-on treatment with clobazam for seizures associated with Lennox-Gastaut and Dravet syndromes will come as a major blow to families affected by these severe and debilitating conditions.

"It is particularly disappointing that, despite some high-quality clinical research demonstrating its safety and effectiveness, a number of concerns with the evidence GW Pharmaceuticals put forward in their submission to NICE are preventing it from being routinely available on the NHS.

"These epilepsy syndromes are almost always resistant to the treatments currently available on the NHS. While we recognise the need for rigorous and robust assessments of safety, effectiveness and cost, for many families this will be an extremely challenging situation.

"Epilepsy Action will do all it can to encourage NICE, NHS England and GW Pharmaceuticals to work together to address concerns with the company's evidence as soon as possible. It is vital for people affected by these epilepsy syndromes that an accurate and detailed assessment of the potential of cannabidiol/ CBD (Epidiolex) as an add-on treatment with clobazam for these severe epilepsy syndromes can take place."

To read the full report visit *nice.org.uk/guidance/indevelopment/gid-ng10124*.

Report points to failings in neuro treatment

People with neurological conditions are facing long waiting times, poor access to specialists and a lack of personalised care. That's according to a new report, *Neuro Patience*, published by The Neurological Alliance, based from a survey of more than 10,000 people with neurological conditions.

It found that:

- 39% of people reported seeing a GP five or more times before being referred to a neurologist.
- Following a referral, one in three patients waited more than 12 months for their appointment.
- 55% of respondents said they had experienced delays in accessing healthcare.
- 34% do not believe they see a specialist often enough to meet their needs.

The report also highlighted failings in the social care and welfare system, as well as discrimination in the workplace for people with neurological conditions.

Sarah Vibert, chief executive of The Neurological Alliance, said: "The survey results are shocking. People with neurological conditions are being forgotten and they are running out of patience."

The report has recommended that a national neurology plan for England should be urgently developed to address these shortcomings. It also stated that neurology should be prioritised for mental health improvement initiatives aimed at people with long-term conditions. For the full report visit *https://bit.ly/2kBS5NC*.

Glial cells in zebrafish studied to analyse generalised seizures

The interactions of glia cells and neurons have been studied to help better understand the role they play in seizures.

The study investigated epileptic seizures in zebrafish, a widely used model organism for modelling human brain physiology. Zebrafish contain the same cell types that are present in human brains. Two of these cell types are glia and neurons. Neurons are primarily involved in transmitting signals. The main functions of Glial cells include maintaining a balanced environment and providing support for the neurons, assisting the immune system and increasing the speed of neural signalling.

The study found that just before an epileptic seizure, nerve cells were abnormally active but only in a localised area of the brain. Instead, glial cells showed large burst of synchronous activity that are widely dispersed across the brain. During the actual seizure, the neuronal activity increased abruptly. The functional connections between the nerve cells and glial cells became vigorous. When this happened, generalised seizure spread like a storm of electrical activity across the entire brain due to a strong increase in the level of glutamate, a chemical compound that transmits signals between neuronal cells. Glutamate was secreted by glial cells, which convert themselves from a friend to a foe.

The findings indicate that epilepsy may occur not only due to anomalies in neurons, but also in glial cells. "Our results provide a direct evidence that the interactions between glial cells and neurons change during the

transition from a pre-seizure state to a generalised seizure. It will be interesting to see if this phenomenon is generalisable across different types of epilepsies," says Professor Emre Yaksi. Normally, the glial cells absorb the excess glutamate that is excreted during the increased activity of the nerve cells. This study assumes that the secretion process of the glial cells that we observed in combination with their hyperactivity just before a seizure is a defence mechanism of the brain.

"There are more glial cells than neurons in our brains. Yet, these cells were rather understudied. Our work uncovers an interesting function of the glia and will undoubtedly attract more interest into this cell type", says CRTD research group leader Dr Caghan Kizil. The group conducts its research at the CRTD of the TU Dresden as well as at the German Center for Neurodegenerative Diseases.

In recent decades, a number of new epilepsy drugs have been developed, but a third of patients still do not have good control over their seizures. One reason may be that the current anti-epileptic drugs mostly target the neurons, while the glial cells, which constitute about 80% of the cells in the brain, have been overlooked. For the full study visit *https://go.nature.com/2ZqX8TC*.

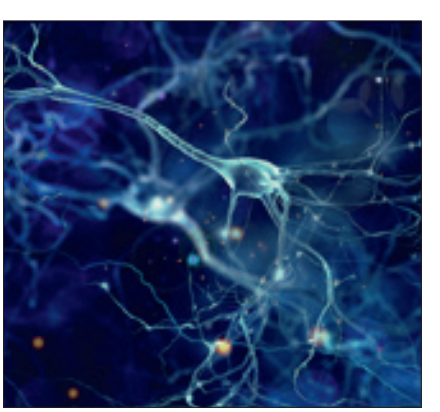
Seizures reduced by removing newborn neurons

Removing new neurons born after a brain injury reduces seizures in mice, according to new research in *The Journal of Neuroscience*. This approach could potentially be key in preventing post-injury epilepsy.

New neurons created following a brain injury often do not develop normally. If left untreated, these cells may contribute to the development of epilepsy.

Researcher Jenny Hsieh and colleagues at the University of Texas continually removed new neurons that formed during the eight weeks following a seizure in mice. The team monitored seizure activity and noticed that the treated mice experienced a 65% reduction in seizures compared to the untreated rodents.

Although these findings support a role for newborn neurons in epilepsy development, they also suggest additional factors are involved. Further research may bring us closer to complete prevention of injury-induced epilepsy. For the full study visit *jneurosci.org/content/39/35/7019*.



Detection of low-level somatic mutation in intractable epilepsy

Scientists have developed an advanced method for detecting low-level somatic mutation in patients with intractable epilepsy. The Korean study showed that deep sequencing replicates of major focal epilepsy genes accurately and efficiently identified low-level somatic mutations in intractable epilepsy.

According to the study, their diagnostic method could increase the accuracy up to 100%, unlike the conventional sequencing analysis, which stands at about 30% accuracy. This work was published in *Acta Neuropathologica*.

Somatic mutations in mTOR pathway genes, SLC35A2, and BRAF are the major genetic causes of intractable epilepsies. A clinical trial to target Focal Cortical Dysplasia type II (FCDII), the mTOR inhibitor is underway at Severance Hospital, their collaborator in Seoul, Korea. However, it is difficult to detect such somatic mutations causing intractable epilepsy because their mutational burden is less than 5%, which is similar to the level of sequencing artifacts. In the clinical field, this has remained a standing challenge for the genetic diagnosis of somatic mutations in intractable epilepsy.

Professor Jeong Ho Lee's team at the Korea Advanced Institute of Science and Technology analysed paired brain and peripheral tissues from 232 intractable epilepsy patients with various brain pathologies at Severance Hospital using deep sequencing and extracted the major focal epilepsy genes.

They narrowed down target genes to eight major focal epilepsy genes, eliminating almost all of the false positive calls using deep targeted sequencing. As a result, the advanced method robustly increased the accuracy and enabled them to detect low-level somatic mutations in unmatched Formalin Fixed Paraffin Embedded (FFPE) brain samples, the most clinically relevant samples.

Professor Lee conducted this study in collaboration with Professor Dong Suk Kim and Hoon-Chul Kang at Severance Hospital of Yonsei University. He said, "This advanced method of genetic analysis will improve overall patient care by providing more comprehensive genetic counselling and informing decisions on alternative treatments."

Professor Lee has investigated low-level somatic mutations arising in the brain for a decade. He is developing innovative diagnostics and therapeutics for untreatable brain disorders including intractable epilepsy and glioblastoma at a tech-startup called SoVarGen. "All of the technologies we used during the research were transferred to the company. This research gave us very good momentum to reach the next phase of our startup," he remarked. For the full study visit *link.springer.com/article/10.1007/s00401-019-02052-6*.

Children's brains can re-map after surgery

The brains of children with severe epilepsy can rewire themselves to compensate for missing regions of the visual cortex following surgery.

"What we're seeing is remarkable," said Erez Freud, assistant professor in York University's Department of Psychology. "The most striking case in our findings was a 14-year-old girl who had severe epilepsy that originated from the left side of the brain. The part of the brain that was removed in the surgery is known to mediate the ability to read. Despite this hemisphere being removed, this patient could read with relatively normal functioning. When we scanned her brain using the fMRI we found that this 'reading region' of the brain had re-mapped to the healthy right hemisphere."

The researchers suggest this provides evidence that children's brains have some degree of plasticity. In adults, if the brain's vision processing centres are injured or parts are removed through surgery, the loss of perception is likely to occur. This makes them unable to recognise faces or locations, or to read. But in children who are still developing, this part of the brain seems to have flexibility to rewire itself.

"It's possible that early surgical treatment for children with epilepsy might be what allows this re-mapping," said Freud. "With early removal of the tissue, the brain may have time to rewire itself to the other healthy hemisphere. It can therefore compensate for the functions that are impaired in the other part of the brain.

For more information on the study, visit *https://bit.ly/2LZ33rR*.

Exposure of babies to topiramate and valproate in womb linked to birth defects, study suggests

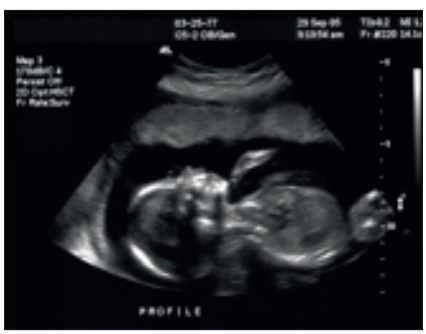
A new study published in *Neurology* has shown an increased risk of birth defects in babies born to mothers taking medicines valproic acid and topiramate.

Study authors Pierre-Olivier Blotière and colleagues wanted to look at risks of birth defects to babies being exposed to 10 different epilepsy medicines in pregnancy. They were lamotrigine, pregabalin, clonazepam, valproic acid, levetiracetam, topiramate, carbamazepine, gabapentin, oxcarbazepine and phenobarbital.

The researchers used French healthcare databases of babies born between 2011 and 2015. They considered babies to have been exposed if the medicines were taken in early pregnancy (between one month before the start of the pregnancy and two months after). From a total of 1,886,825 pregnancies, 8,753 were exposed to an epilepsy medicine.

The study found that babies exposed to valproic acid had a higher risk of having eight types of birth defect, including problems with their spines (spina bifida). Topiramate was also linked to an increased risk of cleft lip.

There have been many studies and news reports highlighting the risk to babies exposed to sodium valproate and valproic acid in the womb. The Medicines and Healthcare products Regulatory Agency (MHRA) has issued specific guidelines around the use of these medicines in women of childbearing age.



Research on the effects of other medicines, including topiramate, continues to take place. Topiramate has been in the news before, when a US study also showed an increased risk in cleft lip and cleft palate in babies exposed to it in the womb.

Simon Wigglesworth, deputy chief executive at Epilepsy Action, said: "We've known for some time that babies born to women taking valproic acid have a high risk of being born with birth defects.

"However, as this study confirms, there are other epilepsy medicines, such as topiramate, which also cause problems. It's vital that topiramate and other medicines which may pose a risk in pregnancy are also investigated by regulators quickly and thoroughly.

"The MHRA has told us that it is planning to carry out a review of the risks of other epilepsy medicines to the unborn child as a priority, including topiramate. We hope this will lead to clear and strong guidance – and regulatory change where this is needed – as soon as possible, to limit the number of babies exposed to these medicines."

The latest study was published in the journal *Neurology* in June.

WHO calls for action to reduce global issues around epilepsy

The World Health Organization (WHO) has released a report highlighting global concerns about epilepsy treatment. The report, *Epilepsy, a public health imperative*, called for action to improve healthcare and reduce stigma and discrimination.

The findings of the report highlight the risk of premature deaths in epilepsy is higher in low- and middle-income countries, compared to high-income countries.

Reasons given by the report include a lack of access to healthcare, leading to problems with continuing seizures and resulting injuries. Dr Tarun Dua from the Department of Mental Health and Substance Abuse at WHO called the treatment gap for epilepsy "unacceptably high".

Within the UK, Public Health England found a similar link between deprived areas and a higher risk of premature deaths in a 2018 report.

Stigma was also highlighted by the WHO report as a global issue in epilepsy. President of the International Bureau for Epilepsy, Prof Martin Brodie, said this is a factor "preventing people from seeking treatment".

The report suggests that public information campaigns can help reduce stigma, and putting laws in place to protect people's rights can decrease discrimination. To reduce treatment gaps, WHO suggests epilepsy treatment from primary care doctors, like family doctors and GPs, may improve access to healthcare and medicines in poorer areas. For the full report visit *https://bit.ly/2JbUlUm*.

Higher levels of serotonin following seizure linked to reduced breathing problems

New research has found that higher levels of serotonin in the blood after a seizure are linked to a lower incidence of seizure-related breathing problems. The study is published online in *Neurology*.

The study involved 49 people with difficult-to-treat epilepsy with an average age of 42. Participants, who had been diagnosed with epilepsy for an average of 17 years, spent time in an epilepsy monitoring unit. Here, researchers examined one seizure for each participant, evaluating the electrical activity in the brain and the heart, oxygen levels in the blood, and changes in blood flow. Blood samples were collected within about 10 minutes after the seizure finished and again at least 12 hours later to measure serotonin levels.

A total of 35% of the people had apnoea during their seizures, and 30% had apnoea after their seizures.

Researchers found that serotonin levels after a seizure were higher than before a seizure in people who did not temporarily stop breathing during a seizure. For 32 people who did not temporarily stop breathing during a seizure, serotonin levels were an average of 140 nanograms per millilitre (ng/ml) higher than an average of 110 ng/ml before seizure. For 17 people who did temporarily stop breathing, their serotonin levels were not significantly higher compared to before seizure.

In 19 people with generalised convulsive seizures who did not temporarily stop breathing after a seizure, serotonin levels were higher after seizure. Their levels were an average of 190 ng/ml, compared to 120 ng/ml. before the seizure, an average of 120 ng/ml. But serotonin levels were not significantly higher compared to before a seizure in eight people with generalised convulsive seizures who temporarily stopped breathing after a seizure.

Researchers also found that a higher heart rate was accompanied by higher serotonin levels after a seizure in people who did not temporarily stop breathing after a seizure compared to those who did.

"Our results give new insight into a possible link between serotonin levels and breathing during and after seizure," said Lhatoo. "This may give hope that perhaps someday new therapies could be developed that may help prevent SUDEP. However, our study was small and much more research is needed to confirm our findings in larger groups before any treatment decisions can be made. It is also important to note that excess serotonin can be harmful, so we strongly recommend against anyone trying to find ways to increase their serotonin levels in response to our study findings." For the full study go to *https://bit.ly/2k46rpZ*.

Alzheimer's linked to recurring seizures

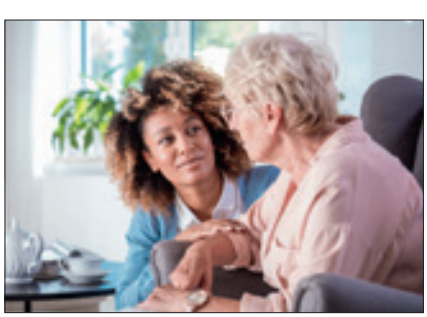
People living with Alzheimer's disease experience epileptic seizures up to six-and-a-half times more often than people without dementia. That's according to new research presented at the Alzheimer's Association International Conference (AAIC) 2019 in Los Angeles.

Alzheimer's disease causes death of neurons, and researchers predict this may contribute to abnormal brain activity that leads to seizures.

Maria Carrillo is chief science officer at Alzheimer's Association. She commented: "There appears to be a mechanism at work that puts people living with dementia at higher risk and recurrence of all types of seizures. Doctors should be aware of how common seizures are in this population to better monitor and treat them.

"At the research level, we need additional studies to understand more about the shared mechanisms between epilepsy and Alzheimer's. This might help us better understand the impact seizures have on the brain in order to better treat both seizures and cognitive decline," Carrillo added.

For more information on the study, visit *https://bit.ly/2YwXy6n*.



Peptide hydrogels could help stimulate healing following traumatic brain injury

Research has reported that a self-assembling peptide hydrogel could stimulate healing following traumatic brain injury (TBI).

The researchers found that when the gel is injected into the brains of rats with TBI, there was increased blood vessel regrowth and neuronal survival. They presented their findings at an annual meeting of the American Chemical Society.

"When we think about traumatic brain injuries, we think of soldiers and athletes," says Biplab Sarkar, who presented the study. "But most TBIs actually happen when people fall or are involved in motor vehicle accidents."

TBIs encompass two types of injuries. Primary injury results from the initial mechanical damage to neurons and other cells in the brain, as well as blood vessels. Secondary injuries, which can occur seconds after the TBI and last for years, include oxidative stress, inflammation and disruption of the blood-brain barrier. "The secondary injury creates this neurotoxic environment that can lead to long-term cognitive effects," Sarkar says. For example, TBI survivors can experience impaired motor control and an increased rate of depression, he says. Currently, there is no effective regenerative treatment for TBIs.

Sarkar and Vivek Kumar, the project's principal investigator, wanted to develop a therapy that could help treat secondary injuries. "We wanted to be able to regrow new blood vessels in the area to restore oxygen exchange, which is reduced in patients with a TBI," Sarkar says. "Also, we wanted to create an environment where neurons can be supported and even thrive."

The researchers, both at the New Jersey Institute of Technology in the US, had previously developed peptides that can self-assemble into hydrogels when injected into rodents. By incorporating snippets of particular protein sequences into the peptides, the team can give them different functions.

Largest ever study finds links in epilepsy genes

Researchers from Austin Health and the University of Melbourne in Australia have taken part in the largest ever study looking at the genetic sequences of people with epilepsy.

The international research, published in the *American Journal of Human Genetics*, involved almost 18,000 people worldwide and identified rare genetic variations that are associated with a higher risk of epilepsy.

Professor Sam Berkovic, Director of Epilepsy with Austin Health and Laureate Professor with the University of Melbourne, said the study found there were genetic links shared by both severe forms of epilepsy and less severe forms of the disease.

"This research is important because the more we understand the genes that are linked to epilepsy, the better we can tailor treatments to reduce the symptoms and let patients live more active lives," Professor Berkovic said.

The study brought together more than 200 researchers from across the world to better understand the genetics of the disease. Researchers used sequencing to look at the genes of 17,606 people from across 37 sites in Europe, North America, Australasia and Asia and found rare genetic variations that are associated with both severe and less severe forms of epilepsy. The coordination of the clinical data occurred in Melbourne with the gene sequencing performed at the Broad Institute, Boston, led by Dr Benjamin Neale. For the full study visit *https://bit.ly/2kNH0sU*.

Burnout

Prevalence, trends and recommendations

Chronic staffing shortages and long working hours are taking heavy tolls on NHS staff. Clinical psychologist Dr Judith Johnson looks at the current state of burnout across our healthcare services, and details the steps health workers can take to help reduce their stress levels.

The scope of the problem

The NHS is the largest single-payer healthcare system and one of the world's largest employers, employing around 1.5 million staff altogether [Nuffield Trust, 2019]. This workforce is the greatest asset the NHS has and it accounts for the majority of NHS Trusts' budgets. Clinical staff make up two-thirds of all staff; the annual bill for employing these staff alone is £43 billion [National Audit Office, 2016]. However, recent years have a seen a growing workforce crisis, with staffing shortages across healthcare disciplines. In 2018, 40,000 nursing posts stood vacant – enough to fill Hong Kong stadium. It has been suggested that this has primarily been caused by too many healthcare professionals leaving their jobs, rather than an inability to recruit staff in the first instance [NHS, 2017].

Burnout could be one factor contributing to this problem [Johnson et al, 2018]. Burnout is made up of two key aspects: exhaustion and disengagement [Demerouti et al, 2008]. Exhaustion describes a state where health professionals feel worn out by work, tired at the thought of going to work and weary at the end of the day. Disengagement, in contrast, involves a sense of detachment from patients and a loss of interest in work. In the UK, recent large-scale surveys have suggested that around a quarter of doctors are experiencing burnout [Medscape, 2018 & GMC, 2018]. Alongside this, broader workforce surveys have

suggested that stress has been steadily increasing in healthcare staff since 2010 [Johnson et al, 2018]. For example, more than 18,000 staff left in 2018-19, citing poor work-life balance as their main reason compared with around 8,000 in 2012-13; over a two-fold increase [NHS Digital, 2019].

A problem for patient care?

In the past, research studies tended to focus on the impact of burnout on clinicians themselves. This work has been valuable, showing that burnout can have a range of negative personal impacts, including alcohol misuse, depression, relationship breakdown and even increased suicide risk [Shanafelt et al, 2012]. However, my work has explored burnout from a different angle – investigating whether burnout in clinicians is also a problem for health organisations and patients.

Together with my colleagues, I have now undertaken a range of studies on this issue. The findings from this work have found the same consistent response to this question: a resounding yes. For example, a review we conducted across healthcare professional groups found 30 papers which tested the link between burnout and patient safety outcomes. Of these, 21 (70%) reported a significant association [Hall et al, 2016].

In a subsequent review which focused only on medical professionals, we found that burnt-out doctors were at twice the risk of being involved in a patient safety incident and at twice the risk of having dissatisfied patients [Panagioti et al, 2018].

These reviews have helped move this area of research forward by showing that burnout is not only a problem for clinicians but for also for health systems and patients.

How is burnout linked to patient care?

While the presence of a link between burnout and patient care is now established, exactly how these two are associated is still being explored.

Research has shown that burnout can have a range of negative personal impacts, including alcohol misuse, depression, relationship breakdown and even increased suicide risk

Research we have conducted suggests that the relationship could be cyclical – burnout contributes to poorer patient care, which then results in patient safety incidents or complaints.

These incidents and complaints then create stress for professionals, further increasing their level of burnout [Hall et al, 2019]. In particular, the GPs involved in this research suggested that burnout contributed to poorer patient care by compromising their concentration and decision-making ability, decreasing their empathy levels and listening skills and by increasing the likelihood that they would inappropriately refer their patients to secondary care [Hall et al, 2019].

Is burnout just another word for 'depression'?

There is much debate in the literature as to whether 'burnout' is a valid concept, or whether it is simply another take on the problem of 'depression'. This has been driven by the observation that the two concepts overlap and can behave similarly – for example, both are known to be linked with perceptions of patient care in clinicians. However, the consequences of this possibility are significant: depression is an individual problem, treated primarily with individual-level interventions such as psychological therapy. Burnout, on the other hand, is an organisational problem – it suggests that workers are unhappy in their work, and the system may need to change.

My research in this area has rejected the possibility that burnout and depression are the same [Johnson et al, 2017]. In fact, when considered together in relation to perceptions of patient care, a study I conducted in nurses suggested that when burnout is accounted for, depression is no longer linked with patient safety perceptions [Johnson et al, 2017].

While this study was a small, cross-sectional piece of work, it suggests that burnout could be the more relevant concept to focus on when seeking to improve patient care.

When considered together in relation to perceptions of patient care, a study I conducted suggested that when burnout is accounted for, depression is no longer linked with patient safety perceptions

Becoming aware of burnout

The first stage in addressing burnout is being able to recognise it. If you are concerned about your own risk of burnout, it might help to start by asking yourself the following questions:

- Am I regularly feeling tired before I even arrive at work?
- Do I usually feel worn out while working?
- Do I feel too worn out after work and during days off to do the things I enjoy?
- Have I lost interest in my work?
- Am I talking about work in a more negative way than I used to?
- Am I feeling disconnected from my patients?

These questions have been adapted from the Oldenburg Burnout Inventory, one of the most widely used burnout questionnaires. If you responded 'yes' to the first three, you may be experiencing exhaustion. If you responded 'yes' to the last three, you may be experiencing disengagement.

Tackling burnout

There have been three significant reviews since 2016 which have investigated the effectiveness of burnout interventions. Two of these reviews focused on doctors [West et al, 2016 & Panagioti et al, 2017] and one focused on mental healthcare providers from all health disciplines [Dreison et al, 2018]. These reviews found broadly similar results, with all concluding that interventions are effective, but only to a limited extent. One estimated that across the board, interventions will reduce burnout in professionals by 10% [West et al, 2016]. The headline news is that burnout can be reduced – and in general, interventions are likely to be effective. The specifics, however, are hazier. For example, interventions are often split into two main types: those which focus on the individual (such as stress management workshops and psychological therapy) and those which focus on the organisation (such as changing shift patterns and providing continuing professional development opportunities). When it came to the question of which type of intervention is likely to be more effective, the results conflicted. One review suggested that both types of intervention were equally effective [West et al, 2016], one suggested that organisation-level interventions were more effective [Panagioti et al, 2017] and the last suggested that individual-level interventions were more effective [Dreison et al, 2018].

The first possibility for these conflicting results is that these categories are not clearly defined – for example, whereas one review considered training interventions to be an individual-level intervention [West et al, 2016], another regarded these as organisation-level interventions [Dreison et al, 2018]. Furthermore, these categories are overly broad and could be criticised for lumping too many different types of interventions together.

Practical recommendations

It's clear that further research is needed into the effectiveness of burnout interventions before clear conclusions can be drawn regarding the best form of intervention to use.

However, given the urgent nature of the problem of burnout, there are established principles that managers can draw on in the meantime:

- Where possible, base interventions on the challenges that your staff are reporting, rather than seeking off-the-shelf solutions. Interventions which aim to tackle stress directly without considering its causes could increase the risk that your staff will feel they are not being listened to.
- Jobs with high workload and less flexibility are known to contribute to burnout. Interventions which moderate workload and increase flexibility (in relation to hours worked or tasks completed within the job) will likely be effective in reducing burnout.
- Lack of in-work support is a consistent burnout factor. Considering the nature of support networks which your staff have, and intervening to enhance these could reduce burnout.

It's clear that further research is needed into the effectiveness of burnout interventions before clear conclusions can be drawn regarding the best form of intervention to use

Burnout can be regarded as an organisational problem, but there are steps that individual clinicians can take to help contribute towards their own wellbeing:

- When possible, take breaks. Our research in GPs suggests that taking regular breaks during the working day and having even brief positive conversations with colleagues is linked with lower burnout.
- Diversify your skillset. Combining direct patient care provision with other activities including teaching and research is linked with lower rates of burnout.
- Seek support. Clinicians who report higher levels of support also report experiencing lower burnout. Ideally you will feel supported by your organisation, but if not, network with other clinicians to help create your own support system.
- Beware of perfectionism. Having perfectionistic attitudes increases risk for most types of mental health problems, and leads individuals to cope less well when they make mistakes. Those who are low on perfectionism are able to adapt to their situation; they know when to aim high and when to let themselves off the hook. They cope better when things go wrong and report better mental health. So, if you know you are prone to perfectionism, then go easy on yourself! No one is perfect all the time.

Judith Johnson is a Clinical Psychologist and Lecturer at the University of Leeds. She is an expert in psychological resilience and the healthcare workforce.

Dr Judith Johnson

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Cannabis-based medical products

Where are we now?

As we near the year anniversary of the decision to allow CBMPs to be legally prescribed in the UK, Epilepsy Action's senior policy and campaigns officer Sam Mountney offers a retrospective view of where we are and how we got here.

In early summer 2018, the debate around cannabis-based medicinal products (CBMPs) for epilepsy took centre stage in the UK press. While the media spotlight has dimmed, discussions have continued behind clinicians' doors and in the offices of UK regulators.

August 2019 saw the publication of two important documents from the National Institute of Health and Care Excellence (NICE). The first was the draft NICE guidance on CBMPs, this was followed shortly after by the draft NICE recommendations on Epidyolex (CBD), as an add-on treatment for seizures associated with two intractable epilepsy syndromes, Dravet and Lennox-Gastaut Syndrome (LGS).

Epidyolex

Epidyolex is the CBMP with the most robust clinical evidence for epilepsy. There is some randomised clinical trial (RCT) evidence demonstrating the safety and efficacy of the purified CBD oral solution for the indications noted above. Epidyolex is currently under appraisal by NICE through the Single Technology Appraisal (STA) process, this is separate from the NICE CBMP guideline process.

The NICE appraisal committee recently returned a draft decision not to recommend Epidyolex as an add-on treatment for seizures associated with

Dravet syndrome or LGS. A number of concerns were raised by NICE around the clinical modelling submitted by the manufacturer, GW Pharmaceuticals. There are also questions around the long-term efficacy of Epidyolex in light of a lack of long-term clinical evidence and existing clinical knowledge around long-term variance in the efficacy of some antiepileptic drugs.

This is a draft decision and the final decision will be published later in the year. It is worth noting that both NICE and GW Pharmaceuticals have noted their respective commitments to working together to address these issues [Epilepsy Action, 2019]. The need for new safe and efficacious treatment options for intractable epilepsies is clearly recognised by all involved, not least patients and clinicians, and as such the ongoing efforts of NICE and GW Pharmaceuticals are very welcome.

Despite some positive anecdotal evidence, including the experiences of Alfie Dingley and Billy Caldwell, there is currently insufficient evidence around the safety and efficacy of CBMPs for NICE to make a recommendation.

Other CBMPs

The high-profile cases of Alfie Dingley and Billy Caldwell, two young boys with intractable epilepsies whose families were campaigning for access to CBMPs, caught the attention of the nation. Last year's change in the law came about in no small part due to the efforts of these ardent campaigners. Both families were pushing for access to CBMPs containing Tetrahydrocannabinol

(THC), a psychoactive compound present in the cannabis plant associated with the feeling of being 'high', and CBD.

NICE recently published draft guidance on CBMPs, including for severe and treatment-resistant epilepsies. The remit of these guidelines includes CBMPs containing THC and CBD. The draft NICE guidelines note that the guideline committee have been unable to make a recommendation on the use of CBMPs for severe and treatment-resistant epilepsies.

Despite some positive anecdotal evidence, including the experiences of Alfie Dingley and Billy Caldwell, there is currently insufficient evidence around the safety and efficacy of CBMPs for NICE to make a recommendation.

In the absence of a clinical recommendation, the draft NICE guidelines instead proposed a number of research recommendations. These include research into CBD and separately into THC in combination with CBD. The research recommendations posited by NICE have subsequently been supported by NHS England and NHS Improvement in a recent report on the barriers to accessing CBMPs on the NHS [NHS England, 2019], commissioned by Secretary of State for Health Matt Hancock MP. The report also notes that research into CBMPs for intractable epilepsies should include alternative research studies alongside RCTs.

Conclusion

The final NICE decisions on the CBMP guidelines and recommendations for Epidyolex are expected later in the year. It is clear that all the key stakeholders in this debate, from clinicians to regulators and from patients to government, are committed to making CBMPs that are safe and effective available on the NHS for those who could benefit.

While debates will continue and differences persist around how and when CBMPs should be made available for intractable epilepsies, the commitment to working hard in the best interests of patients is clear.

Further reading

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Q&A with Professor Mike Kerr

Professor Mike Kerr is due to receive the Excellence in Epilepsy award at the ILAE British Chapter meeting in October. We speak to him to find out more about his work in epilepsy and his research outlook for the future.

Your work focuses on epilepsy and intellectual disability. How did you get into this field in the first place?
There was an epilepsy clinic I had to take when I was training as a psychiatrist in intellectual disability. I had trained as a GP and therefore knew that I had incredibly little knowledge of epilepsy, so I started to learn and was hooked by the experience of working with the patients and families.

Can you tell me a little bit about what you are currently or have recently been researching or working on?
My main epilepsy work is with the Epilepsy Death Register, trying to understand the experiences and nature of epilepsy-related deaths. I have been lucky enough to work with Swansea University on routine data and epilepsy, as well as the healthcare of people with an intellectual disability.

With colleagues there, we have highlighted important information of the association between deprivation and epilepsy and also information on the very high levels of antipsychotic medication use in children with an intellectual disability.

What are some of the biggest challenges people with epilepsy and intellectual disabilities, and their families, face today?
The biggest challenge is equity in care experience for adults. The individuals and their families, if living in the right area, can have a world-class clinical experience. Sadly, there is far too much of a postcode lottery and they can instead be left without specialist support and with poor health support in general. People with intellectual disability should be prioritised as the most in need of expert care, yet unfortunately all too often it seems more as if they are ignored.

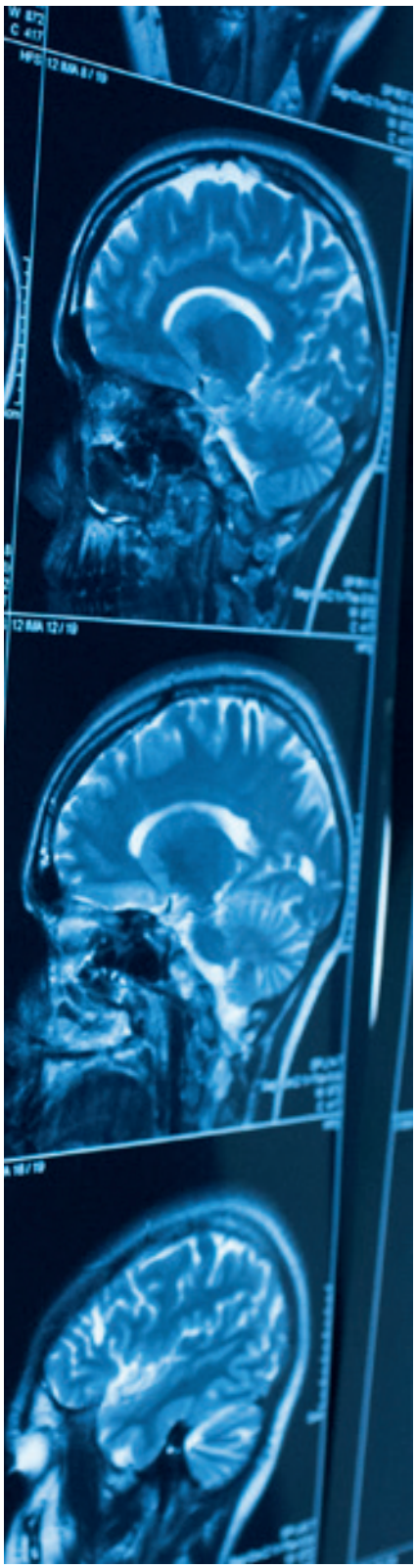
People with intellectual disability should be prioritised as the most in need of expert care, yet unfortunately all too often it seems more as if they are ignored

Individuals and families should have a right to expert epilepsy care either from neurology or learning disability psychiatry services, high-level support from community teams and excellent primary care.

What makes this group of patients different in terms of treatment and healthcare requirements?
Every patient is an individual with individual needs, but as a group there are several key areas that make the delivery of care different and often complex. These include:

1. Communication issues that can lead to difficulties in understanding individual choice and often a reliance on carer knowledge and a use of best interest decision making.
2. Complex co-morbidity; both physical, intellectual and psychiatric.
3. In particular, psychiatric or behavioural comorbidity making investigation and assessment of treatment difficult, especially when major behavioural challenges are present or significant autistic traits.

Very individual causations from genetic conditions, ensuring treating clinicians need to continue to update a rapidly advancing body of knowledge.



In what ways can good healthcare provision improve their quality of life, and what does best practice look like?
Good healthcare in terms of epilepsy can reduce seizure impact through less injury, less time lost in seizures, less cognitive impact of seizures, less psychiatric impact of seizures and reduced risk of epilepsy related death, including SUDEP. It also reduces treatment impact through supporting an understanding of epilepsy medications and their side-effects.

Best practice has the individual placed in the centre of care, with high-quality epilepsy skills supported by skilled nursing professionals – these can be within epilepsy or intellectual disability care. The individual, carers and family need easy rapid open access. Meanwhile, the support will link to broader health facilitation with secondary and primary care, and integrate with employment and other care providers to minimise the negative impact of epilepsy.

What services exist for this group of patients and in what way can we improve services further?
The key health services outside specialist epilepsy care and primary care are the community learning disability teams who will be integrated with social care services. These teams at their best provide expert support of epilepsy through risk and safety plans, rescue medication plans, carer training, health facilitation, support of comorbidity and many other impacts.

To improve services, we need to set standards and audit and improve the quality of these services to ensure access and high-quality of care for people with epilepsy. There is too much variation in practice that leads to inequality of care experience. The Learning Disabilities Mortality Review (LeDeR) project has shown some stark findings about premature deaths in people with learning disabilities.

To improve services, we need to set standards and audit and improve the quality of these services to ensure access and high-quality of care for people with epilepsy

What needs to be done to reduce this and improve the situation for this group of people?
The message that I take from LeDeR is that premature deaths have multiple causality, but certain avoidable factors are present including poor practice, discrimination, uneven access to care and poor health facilitation. Approaching such a big issue is multifactorial but if we look at it from a service level we could:

In primary care: Ensure full access to annual health checks by GPs. Further support for the primary healthcare teams in managing health interventions and ensure easy referral pathways to clinical support. The Community Learning Disability Teams can be fantastic in doing this and in addition support broader health facilitation.

In secondary care: Ensure measurement and audits of patient experience. In particular we need to audit do not resuscitate plans and equality of access to health interventions. Health liaison nurses

can help improve care, though like all new interventions their impact needs assessing. I think national audits of care are needed.

In specialist epilepsy care: ensure people with an intellectual disability are prioritised and that health funders acknowledge the need for more time and input in clinic for this group. Finally, where care is provided by neurology, learning disability teams should integrate and support clinics to help support the provision of holistic care. In particular I think it is very hard to deliver good epilepsy care without good communication of the person's health status and support of their psychiatric comorbidity.

Much of our understanding of intellectual disability has come from genetic advancements and the linking of genetic syndromes to the health profile of a person and subsequent precise interventions

What are some of the biggest research findings and advances in the last 10 years in the area of epilepsy and intellectual disability in your opinion?
Much of the advancement in understanding intellectual disability has come from genetic advancements and the linking of known genetic syndromes to the health profile of a person and subsequent precise interventions.

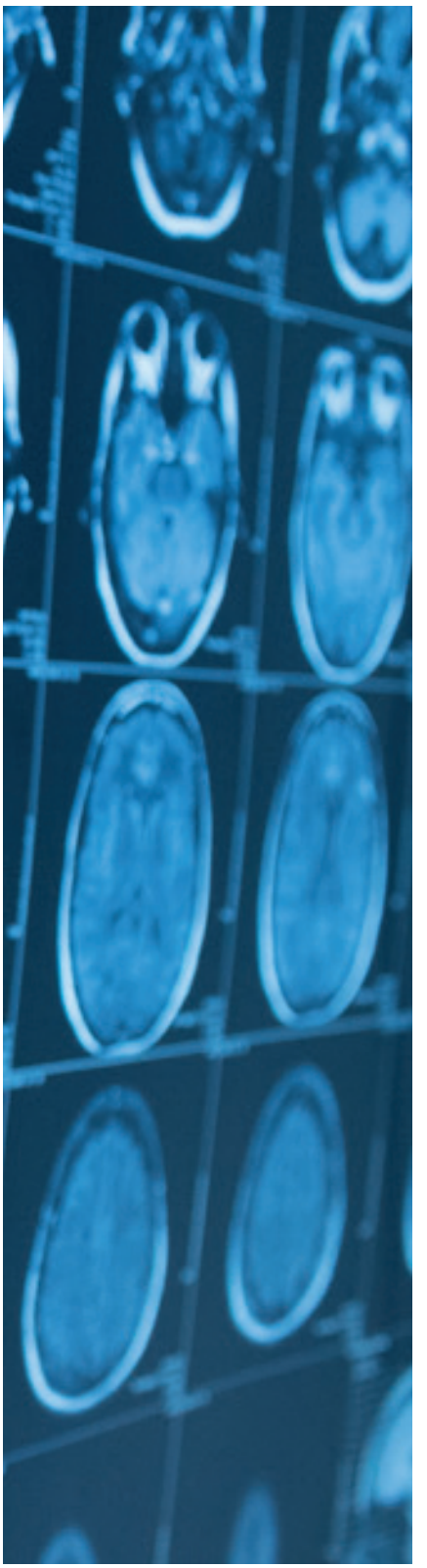
This "personalised medicine" can be best seen in a condition like tuberous sclerosis where the scientific understanding of this genetic condition has led to the precise intervention through the mTOR inhibitors, which now seem to be promising therapies in epilepsy within these individuals.

There have been major advances in primary healthcare through the continually expanding use of health checks for adults with an intellectual disability in primary care. Myself and colleagues at Cardiff University designed and investigated the Cardiff/Welsh Health Check in the 1990s and this is now national policy in England and Wales with over 100,000 adults receiving it annually. Research has shown its impact on improved health promotion and disease finding.

As well as these positive research findings and intervention, the messages from LeDeR on mortality and SUDEP research have shown stark and unpalatable findings but these have been very impactful in influencing changes in care delivery.

What does research need to focus on going forward in your view?
Reducing death, reducing morbidity and increasing quality of life. I think the path to this is through research on impact, research and improvements in care access and a constant focus on new interventions.

Congratulations on receiving the Excellence in Epilepsy award at the ILAE this year! How does it feel to receive this accolade?
I really am so honoured to receive this. I think it is reflection of the importance of the people I care for and of course is very much down the support I receive, and have received, from so many colleagues and my family.



Ketogenic diets

Therapies in adults with drug-resistant epilepsy

Dr Manny Bagary explains the promising applications of the ketogenic diet in adults.

Ketogenic diet therapies (KDT) are a range of high-fat and low carbohydrate diets which mimic the metabolic effects of prolonged fasting. They are used in the treatment of epilepsy in children with drug-resistant epilepsies (DRE). There is an increasing interest in application of KDT in adult populations with DRE. The major KDT are described in Table 1.

Ketogenic diet variants

KDT were initially developed following observations that starvation was helpful in reducing seizure frequency. In 1921, Wilder [Wilder, 1921] induced ketosis using a high-fat, low-carbohydrate diet to mimic a state of starvation. This led to the development of the classical ketogenic diet (CKD) with a 4:1 ratio of fat (in grams) to protein and carbohydrate for DRE. Lower ratios such as 3:1 can also be used depending on required levels of ketosis, protein requirements and tolerability.

Interest in KDT waned following the discovery of phenytoin in 1938 and subsequent antiepileptic drug (AED) development. In 1971, to improve adherence, Huttenlocher [Huttenlocher et al, 1971] introduced medium chain triglyceride (MCT) oil. MCTs are more ketogenic per calorie than long chain triglycerides (LCTs), hence allowing more protein and carbohydrate in this version of KDT. Despite the development of many new AEDs, seizure freedom rates have disappointingly failed to improve. Over the last 20 years, there has been a resurgence of interest in non-AED treatment options in drug-resistant epilepsy. KDT have evolved to include the modified Atkins diet, MAD (also known as the modified ketogenic diet, MKD). The MKD involves a 1:1 ratio of fat (in grams) to protein and carbohydrate with a carbohydrate restriction of 10–30 g/day. There is no requirement to weigh food portions and also no restriction of calories or protein. The Low Glycaemic Index Diet (LGIT) allows for the highest proportion of carbohydrates (40–60 g/day) in KDT with 60% of calories from fat. However, carbohydrates are restricted to those with a glycaemic index (GI) of <50. The GI index ranges from 0-100 and usually uses pure glucose as the reference which has a GI of 100. Slowly absorbed carbohydrates have a low GI rating.

Mechanisms of action

Glucose is the main metabolic substrate for neurons. Under certain conditions such as starvation,

Table 1: Ketogenic Diet Therapies (KDT)

Ketogenic Diet Therapies (KDT)	% total energy			Ratio of Fat to Protein and Carbohydrate (grams)
	Fat	Protein	Carbohydrates	
Classical KD (CKD)	90	6	4	4:1 version 3:1 version 2:1 version
Medium Chain Triglycerides Diet (MCTKD)	73 (MCTs 30-60)	10	17	03:01
Modified Atkins Diet (MAD) or Modified Ketogenic Diet (MKD)	65	30	5	01:01 10-30g carbohydrates/day
Low Glycaemic Index Diet (LGIT)	60	30	10	0.6:1 40-60g carbohydrates/day Glycaemic index <50

glycogen depletion or low insulin levels, ketone bodies can supply much of the required neuronal energy requirements. Ketone bodies are produced in liver mitochondria from the fatty acids derived from dietary sources or alternatively body fat stores if there is insufficient dietary supply. Free fatty acids in the liver undergo beta-oxidation to form acetyl CoA. Two molecules of acetyl CoA form acetoacetyl CoA, which is then further metabolised to produce acetoacetate. Beta-hydroxybutyrate and acetone are produced from acetoacetate. Ketone bodies (mainly acetoacetate and beta-hydroxybutyrate) cross the blood brain barrier via monocarboxylic acid transporters, MCT1 and MCT2. The regulation of MCT transporters is not fully established but prolonged fasting (several days) increases cerebral Ketone body uptake [Hasselbalch et al 1994 & Hongyan et al, 2018]. A range of mechanisms of action have been proposed for KDT. Ketosis is necessary for efficacy but there does not appear to be a linear relationship between ketosis and efficacy. Potential direct mechanisms include enhanced brain energy reserves through alterative provision to glucose. Reduced glycolysis is also associated with reduced neuronal excitability. Proposed indirect mechanisms include altered DNA methylation, increased mitochondrial biosynthesis, direct AMPA receptor inhibition through decanoic acid, enhanced GABAergic inhibition, decreased concentration of reactive oxygen species and altered gut biome.

Efficacy

KDT in drug-resistant epilepsy was recently subject to a further Cochrane review [Martin-McGill et al, 2018]. Eleven randomised or quasi-randomised controlled trials were reviewed comprising 712 children and adolescents with an additional 66 adults with a follow-up of between 2-16 months. A meta-analysis could not be conducted due to trial heterogeneity. Seizure freedom rates for KDT were 0-15% compared to 0-9% in controls. The ≥ 50% responder rate was 35-56% for KDT compared to 0-18% for controls.

The single adult study included in the Cochrane review was an Iranian prospective study of patients with DRE with ≥ 2 seizures/month using MAD with a 15g carbohydrate restriction compared to DRE controls and two-month follow up [Zare et al, 2017]. No patients became seizure free in either the control or MAD group. The ≥ 50% responder rate was 35% (12/ 34) for MAD compared to 0% (0/32) for controls.

A more recent 12-week RCT of MAD (n =37) compared to habitual diet (control group, n=38) used an intention to treat relative risk analysis for seizure reduction which did not demonstrate any difference between the groups. The attrition rate was 35% in the MAD group and 16% in the control group [Kverneland et al, 2018].

The most recent meta-analysis [Hongyan et al, 2018] of KDT in adults with refractory partial or symptomatic generalised DRE identified 16 published studies open-label, prospective studies from eight countries (n= 338) of adult patients, aged ≥16 years. The seizure freedom rate was 13% and ≥ 50% seizure reduction rate was 53%. As with many studies using meta-analysis methods, there was significant heterogeneity among the studies [Wilhelmina et al, 2017].

Tolerability

The recent Cochrane review [Martin-McGill et al, 2018] of 11 randomised or quasi-randomised controlled trials with 2-16 month follow up reported attrition rate for KDT of 8-35%. This was similar to the control group attrition rate of 0-40%. Common adverse effects included vomiting and constipation. Other reported adverse events included gastrointestinal (diarrhoea, dysphagia, weight loss,

nausea, gallstones, acute pancreatitis, fatty liver), metabolic (hypoglycaemia, hyperammonaemic encephalopathy, decrease in bone matrix density), infections (pneumonia, sepsis), altered lipid profiles, renal (nephrocalcinosis, metabolic acidosis) and reduction in height (children).

Why is the evidence base so limited in adults?

Although evidence for efficacy in children and adolescents is well established, there remains a lack of an adequately powered RCT in adults. In the absence of an RCT, there are concerns regarding efficacy and tolerability. The duration of treatment is not established in adult DRE populations. In particular, the long-term cardiovascular risk of a high-fat diet is not established, although the evidence to date does not support a sustained rise in lipid profiles. Funding and commissioning of KDT services for adults is problematic in the UK with only a handful of established services.

Patient selection

KDT do seem to be effective for all seizure types. There is good evidence for the efficacy of KDT in a range of childhood-onset epilepsy syndromes, many of which will transition into adult services. KDT is the treatment of choice for Glucose Transporter Type 1 (GLUT 1) Deficiency Syndrome, which has a broad phenotype but is often associated with early onset absence seizures and later onset movement disorder. The response rate is approximately 86% for epilepsy but less convincing for the movement disorder [Wilhelmina et al, 2017]. Ketone bodies provide an alterative source of energy and cross the blood brain barrier through monocarboxylic acid transporters bypassing the reliance on the impaired glucose transporter system. KDT is also recommended for Pyruvate Dehydrogenase Complex (PDC) Deficiency. In PDC deficiency, pyruvate (the end product of glycolysis) is not optimally metabolised through the tricarboxylic acid cycle, leading to the increased production of lactate and impaired production of adenosine triphosphatase (ATP) via the mitochondrial respiratory chain. During carbohydrate deprivation in KDT, ketone bodies generated by fatty acid oxidation serve as an alternative neuronal energy substrate. Further subgroups with evidence for efficacy include Infantile spasms, Lennox-Gastaut syndrome, Dravet syndrome, Angelman Syndrome, Myoclonic-Astatic Epilepsy and CDKL5 Deficiency Disorder.

Funding approval for patient treatment with KDT from local Clinical Commissioning Groups remains problematic in the context of many competing demands for scarce resources.

With regard to adult data informing our patient selection process, a recent retrospective analysis reported higher responder rates than many other centres for 55 adults (>17 years old) treated with KDT for three months. The > 50% responder rates were 56% for those who had prior failed surgery, 57% in focal epilepsy and 83% in generalised epilepsy [Roehl et al, 2019]. The authors reported that structural brain abnormalities, vagal nerve stimulation and surgical resection did not reduce efficacy of KDT [Falco-Walter et al, 2019].

Conventional pharmacotherapy for refractory status epilepticus is associated with persistent or re-emergent status epilepticus in up to 20% of cases. The prognosis for super-refractory status epilepticus (SRSE) is poor. After evidence-based treatment options have been exhausted, there is some encouragement to consider the use of KDT in (S)RSE for both adult [Thakur et al, 2014] and paediatric population [Arya et al, 2018]. There is sufficient evidence to support a prospective RCT for KDT in SRSE. However, there are a number of challenges that will need to be addressed such as the concomitant use of propofol.

In those patients undergoing enteral feeding, KDT using a liquid formula may be used. The KDT phase in this is straightforward and adherence rates are high in such circumstances.

KDT is contradicted in adults with disorders of fatty acid transport and oxidation, organic acidurias, porphyria and inborn errors of metabolism. These disorders generally present in childhood and adolescence rather than in adult populations. Caution should be exercised in hyperlipidaemias, osteopenia/osteoporosis, nephrolithiasis, pregnancy, cachexia and carnitine deficiency.

Initiation of KDT

An initial joint assessment with an epilepsy clinician and dietitian is essential prior to KDT initiation to clarify baseline seizure frequency, understanding of KDT, establish commitment and motivation, identify outcome targets, manage expectations and clarify support needs. Food preferences, energy requirements, nutrient intake, meal plans and use of supplements will need to be discussed.

Monitoring of KDT

Most centres take baseline bloods to include FBC, U+E, LFTs, lipids, total/free carnitine and vitamin D levels. Carnitine is required for the transport

of long-chain fatty acids from cytoplasm to the site of beta-oxidation of fatty acids for energy generation in the mitochondrial matrix. Some centres also check a range of other parameters such as vitamins A, E and B12.

Ketosis is usually monitored by capillary testing of blood beta-hydroxybutyrate or urine testing of acetaoacetate. Although urine acetoacetate is less invasive, capillary beta-hydroxybutyrate is more accurate. The aim is to provide optimum seizure control with acceptable tolerability of KDT.

Duration of treatment

There is no established consensus for duration of treatment. Most adult centres offer an initial three-month course of treatment. If efficacy and tolerability are deemed to be acceptable, the treatment is then extended. The experience of our centre is that long-term treatment in adults is often necessary to maintain seizure control, whereas in paediatric services KDT is often gradually tapered and withdrawn over several weeks at 24 months.

Where can I refer my adult patients for KDT?

At present there is very limited capacity in service provision for adult KDT in drug-resistant epilepsy. Matthew's Friends provides invaluable resources including finding a local adult centre (www.matthewsfriends.org/medical-section/keto-centres). Funding approval for patient treatment with KDT from local Clinical Commissioning Groups remains problematic in the context of many competing demands for scarce resources. The capacity and funding of adult KDT services remains a particular problem for patients transitioning from paediatric services.

Next steps

An RCT in adults with DRE is necessary to support the case for commissioning KDT services. Experts across the UK are currently collaborating to apply for funding for an adult RCT.

In the interim, there are a small number of clinical services that can provide KDT treatments. The development of dedicated clinics is necessary for paediatric patients transitioning to adult services. There is some variability in practice across adult KDT centres. Consensus recommendations based on current international clinical practice in established adult KDT services are being developed.

Acknowledgments

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Conflicts of Interest

Dr Bagary has received research funding/honoraria from Eisai, GWPharma, LivaNova, Nutricia, Pfizer, UCB, Zoginex.

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Conference report

Genetic Generalised Epilepsies: From Basic Science to Clinical Practice

The Genetic Generalised Epilepsies: From Basic Science to Clinical Practice conference took place at King's College London, on June 21. Academics, medical professionals and nursing specialists gathered to discuss the latest techniques in the management of neurological disorders. Below are summaries for two of the day's sessions.

Impulsivity in GGE – predictors and consequences

Dr Marte Syverten presented her comprehensive study of 92 people with juvenile myoclonic epilepsy (JME). The aim was to see if psychosocial issues linked with impulsivity occurred more in people with JME than those with other types of epilepsy. Impulsivity is defined as the tendency to act with little or no thinking of the consequences.

JME was first described by German researchers Janz and Christian back in 1957. At the time, it was thought to be an easily manageable and treatable form of 'benign' epilepsy. However, the researchers claimed that people with JME tended to have an engaging yet emotionally unstable and immature personality. This didn't receive much attention until 40 years later, when Swartz and his team compared working memory in frontal lobe epilepsy. He found that there was some degree of frontal lobe impairment and therefore personality disorders, which seems to match up to Janz's claims. To date, there have been limited studies looking at the mental and social issues of JME, despite JME comprising 10% of all epilepsies.

The Norwegian researchers interviewed 92 people with JME and 45 with other types of epilepsy, all between the ages of 14 and 40. These people were recruited from Drammen Hospital in Norway. They looked at their background, family history, epilepsy history and were interviewed on their social history. They also asked questions that could highlight potential effects of risk-taking behaviour. This included the use of recreational drugs, being charged by the police and smoking while under the age of 18.

Despite having quite different backgrounds, the researchers found that these people had something in common, other than their seizures. From their interviews, the researchers got the impression that within these people's lives were some challenges in their relationships within schools and social services. Their study questioned how to describe this similarity, and how to measure and study it.

The researchers found that people with JME were slightly more likely to take high reward but high-risk gambles. There was also a link with more run ins with the law, recreational drug use, underage smoking, risk-taking and criminal behaviour. In females also, there was a slightly higher incidence of attention-deficit hyperactivity disorder.

Despite this, Dr Syvertsen explained impulsivity wasn't always a negative trait, repeating Janz's claim that people with JME were engaging. This can make them fun to be around, and that new ideas or creativity comes naturally to them. Dr Syvertsen says that perhaps it depends on their environment and their upbringing, which determines how their actions play out in their lives.

Dr Syvertsen said that these conditions could potentially have more of an influence on the lives of people with JME than seizures alone. She concluded therefore JME should be seen as a condition of the brain that takes a broader scope than that of a "pure" epilepsy.

The BIOJUME Study – Analysis of 600 JME deep phenotypes

Many common long-term conditions begin in young people, such as diabetes and epilepsy. Therefore, the key to preventing a lifetime of symptoms and long-term therapies is to understand the causes and workings of these conditions. Therefore, decoding the genetics of common epilepsies may be the key in understanding and potentially curing them.

In JME, many symptoms go hand-in-hand with the typical lifestyle of young people – sleep disturbance, stress and drinking alcohol. Unfortunately, to avoid being labelled this long-term condition, there is a tendency for teens to deny or 'hide' from their diagnosis. Treating JME is often challenging because of this.

The Biology of juvenile myoclonic epilepsy (BIOJUME) study is the largest genetic study for juvenile myoclonic epilepsy (JME). Now in their fourth year, the researchers aim to explore the causes and workings of JME. They'll be doing this by looking at more than 1,000 people across Europe and the US.

For the study, people aged between 10 and 40 years old who showed symptoms of JME between the ages of 10 and 25 took part. They had a single blood test and EEG recording. The genetic code of these people will be compared with those without epilepsy, which should hopefully find the genetic cause for JME. This will in turn lead to better treatments and earlier detection, improving quality of life. Dr Deb Pal, lead researcher, has said there are valuable insights to be had in looking at the genetics behind JME.

To date, the researchers have collected 742 phenotypes that will help in their analysis of JME. A phenotype is defined as the set of perceived traits of an individual resulting from the interaction of its genotype with the environment. A genotype is the genetic makeup of an individual organism.

Professor Pal provided an update on the latest findings, adding they found women at a higher risk of side effects from medication, including weight gain. He also highlighted there was a treatment gap in some age groups. Also, while sodium valproate was a common medication for JME, the drug response was unpredictable. In fact, in 15% of people drugs had a less than satisfactory effect. With sodium valproate having links with birth defects in foetuses, their use is not encouraged in young women.

Professor Pal also linked his study with Dr Marte Syvertsen's analysis on impulsivity in JME. If the findings from the study are shown to be robust, it could further help find and match up genetic similarities in those with JME.

Professor Pal added the link in genetics in JME, stating that there was an 80% chance that twins would develop JME. And if a person had JME there was a 10% chance that their siblings would have the same condition.

Decoding the genetics of common epilepsies across a large clinical group is still an ongoing challenge. But there's much hope that this long-term study will the door to personalised early treatments for people with JME.

www.childhood-epilespy.org

Markus Reuber

Highlights

Top picks from *Seizure*

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

Over the last three decades many neurologists will have gained first-hand experience of how the treatment of a neurological emergency can change completely: the management of suspected stroke has metamorphosed from tucking people up in bed with an aspirin to an investigation and treatment pathway bearing closer resemblance to the Formula One pit lane than the management which was still established practice one generation ago.

Although the detrimental effects of delaying the treatment of convulsive status epilepticus (CSE) have been recognized for much longer than thirty years, and despite the fact that effective treatments for most presentations with status epilepticus have been available throughout this period, improvements in the actual clinical management of CSE have been much more sporadic. The lack of focus on CSE cannot be related to the rarity of the condition: with an incidence of 6.8–41/100,000 per year, status epilepticus (SE) is one of the commonest neurological emergencies, especially among children where the incidence is 135–156/100,000 per year. The relatively low investment in service improvements is also not explained by the benign nature of the condition: while mortality from SE is lower in children than in adults, it is still high at 3-9% within 30 days and 7% in the long-term. Delayed treatment is also associated with greater morbidity and long-term care costs.

It can only be hoped that the current Special Issue of *Seizure* "Paediatric Status Epilepticus" offering a collection of comprehensive review articles will help clinicians and patient representatives to attract more attention to the question how the gap between the clear evidence for rapid and adequate treatment of SE and the actual provision of this treatment can be closed. My editor's choice from issue 68 of *Seizure*, a narrative expert review by Marina Gaínza-Lein et al. summarises the arguments for service improvements most clearly by demonstrating how changes in the composition and localisation of GABA-A and NMDA receptors can render interventions much less effective if they are not administered in a timely manner.

Changing perceptions of epilepsy

Unhelpful and factually erroneous ideas about epilepsy are common around the world and not exclusively a problem encountered in Lower and Middle Income Countries (LaMICs). Stigma continues to affect the opportunities and life chances of individuals with epilepsy in all countries, and superstitions about epilepsy survive even in High Income Countries (HICs) where the persistence of such inaccurate and negative beliefs cannot readily be blamed on lack of access to educational opportunities.

In 2015 the World Health Assembly (WHA) recognised this continuing global problem when it adopted a resolution on epilepsy, WHA68.20, which urges coordination of action at country level to address the health, social and public knowledge implications of this disease. This resolution should be a powerful tool, directing countries to implement improvements to medical and social services for people living with epilepsy, and to promote public awareness about epilepsy.

A Global Information Kit on Epilepsy has been developed to support the implementation of WHA68.20 recommendations showing how myths like "epilepsy is contagious", "epilepsy is a punishment or caused by spirit possession", "people with epilepsy should not work" or "people with epilepsy should not get married" can be tackled.

While such documents are important to shape global awareness, policy and funding priorities, the implementation of any programme will have to take account of local social and cultural factors as well as medical and educational resources. To this end I am pleased to select a randomised controlled trial by Unyime Eshiet, Matthew Okonta and Chinwe Ukwe as my Editor's Choice from issue 69 of *Seizure*. They adapted the MOSES educational programme for people with epilepsy, originally developed in Germany, for their local Nigerian context and used pharmacists as a locally available resource to deliver the intervention.

Valproate prescriptions analysed

It has been recognised for several decades that the use of antiepileptic drugs during pregnancy can harm foetal development. Several antiepileptic drugs (AEDs) have been linked to diverse major congenital malformations including cardiac abnormalities, spina bifida and other skeletal abnormalities. In addition, over the last fifteen years, it has become increasingly clear that exposure to AEDs in utero can have a detrimental effect on the intellectual development of babies born to mothers with epilepsy. Valproate, one of the most widely used antiepileptic drugs, has been shown to put babies at particularly high risk of suboptimal cognitive development. Early reports of adverse effects on verbal IQ have been confirmed by further studies and meta-analyses. It is now clear that children exposed to valproate in the womb have a lower IQ than those born to untreated women with epilepsy, or those exposed to carbamazepine, lamotrigine, levetiracetam, topiramate or phenytoin in pregnancy.

My editor's choice article from issue 70 of *Seizure*, an interrupted time series analysis of valproate prescriptions issued by the public health service in Lithuania by Kristijonas Puteikis, Irma Medziausaite and Ruta Mamensikiene, shows how these scientific discoveries and the regulatory responses which they prompted have led to change in the use of an antiepileptic drug, which continues to be the most effective drug for genetic generalised epilepsies.

We learn that valproate use began to decline gradually in women and girls even before the first interventions from European regulators in 2013. The first intervention by regulators in 2013/14 did not significantly accelerate the overall trend – except in girls below the age of 15 – a relevant group, but arguably not the most important target population. In contrast the regulatory tightening of the valproate prescription procedures in 2017/18 had a much more dramatic effect on the use of valproate in female patients of all age groups.

The fact that the drop in valproate prescriptions to women above the age of fifty was as great as that in younger women suggests that the new prescription guidelines may be a fairly blunt tool. Perhaps the guidelines have caused clinicians to review the prescription or continuation of inappropriate medication. However, it is also possible that women who are not at risk of having children who could be harmed by valproate exposure are now inappropriately deprived of a highly effective antiepileptic drug.

Further reading

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www.who.int/mental_health/neurology/epilepsy/epilepsy_global_toolkit.pdf

Epilepsy Professional is politically neutral. This is not unusual for a professional magazine or a patient organisation. If you tied your colours to the mast of a certain ideology then you would be in trouble, perhaps, when the tide turns. You would vacillate between having the ear of those in power, to the opposite – being lost in the political wilderness and unable to lobby for people with epilepsy.

I am not politically neutral. But I am – whenever you see me. When I am in clinic discussing the PIP (Personal Independent Payment) system I am politically neutral. The not-politically-neutral *Guardian* described the PIP system in June of this year as leaving epilepsy patients 'high and dry'. But my public personal is politically bland. When I am advocating for epilepsy charities or advertising new posts on Twitter I project the most anodyne and anaemic version of myself. I avoid discussion of the royal family, religion or football.

I even – and I find this very hard to square – discuss B****t with patients and colleagues with the mental-handbrake on. An ideological schism splits the nation and unless I am explicitly asked in clinic whether someone should be stockpiling meds in a lead-lined bunker – I provide a dispassionate shrug. But when does my natural inclination to project a public persona need to crack? When is activism needed?

Dr David Nicholl is a consultant neurologist from Birmingham and the Association of British Neurology Secretary. In April he turned 'whistle-blower' when discussing the country's ill-preparedness for a no-deal B****t on Newsnight. Specifically he was reflecting the concerns of his patients who may find shortages in the supply of anti-epilepsy medication. David is not a crank, or pessimist, or conspiracy theorist; he helped draw-up the risk register of epilepsy drugs for the government's Operation Yellowhammer no-deal plans.

To cut a long story short 'David from Birmingham' asked a direct question about mortality to the Leader of the House of Commons, Jacob Rees-Mogg MP on LBC radio in September. One thing led to another thing which led to Mr

Rees-Mogg comparing Dr Nicholl to the disgraced and struck-off Dr Andrew Wakefield (or to give him his full title, Andrew Wakefield), which led to David calling Jacob a muppet. An apology was forthcoming (for the Wakefield comment). Philip Lee MP that week left the Conservatives and crossed the floor to the Liberal Democrats citing the patronising mistreatment of Dr Nicholl as the straw that broke the camel's back.

I am politically agnostic in public for fear of making a scene. Dr Nicholl is a careful political campaigner and connects with the hearts and minds of government and becomes a force for good at a time when his patients need this of him.

We all have a duty to speak truth to power and to advocate for our patients when there are clear patient safety issues. When I am weak, I am pleased that David Nicholl is strong.

Dates for the diary

November 2019

7-8
13th Global Neurologists Meeting on Neurology and Neurosurgery
Frankfurt, Germany
neurologists.conferenceseries.com

14-15
9th International Conference on Brain Injury & Neuroscience
Geneva, Switzerland
braininjury.conferenceseries.com

18-19
2nd International Congress on Neurology and Psychology
Rome, Italy
neurology.neurologyconference.com

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

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

Additional support

Adele Ring discusses what really affects the quality of life of people with epilepsy and how clinicians can take that into consideration when treating patients.

Epilepsy deaths project

Heather Angus-Leppan is working to understand the risks of epilepsy-related deaths, in the hope of developing best practice guidance for healthcare professionals.

Epilepsy Professional's advisory panel

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