epilepsy action

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Menopause and epilepsy

Supporting women with epilepsy across their lifespan

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LivaNova Epilepsy

Welcome to the spring edition of *Epilepsy Professional*. We have a collection of articles to allow you to reflect upon your practice.

The post-partum period is critical to childhood development, but a very difficult time for new mothers with epilepsy. Dr Andrea Cheng-Hakimian outlines the risks for women with epilepsy and their new babies in this period and describes what we can do to reduce those.

As with pregnancy and the post-partum period, the menopause can have a significant impact on seizure control in women with epilepsy. Dr Katherine Zarroli describes the mechanism that may underlay these changes and the difficulties that can be encountered trying to minimise the effects of the menopause on a patient's epilepsy.

On a very different note, Konrad Wagstyl and Sophie Adler, describe the work of the MELD project using artificial intelligence to help identify focal cortical dysplasia on the MRI scans of patients with focal epilepsy. The project aims to ultimately provide a clinical tool to help with the identification of potential surgical resective targets in patients who may originally have been considered lesion-negative.

I hope you enjoy this edition.

Seán Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

22 new mums with epilepsy

Andrea Cheng-Hakimian

Dr Cheng-Hakimian discusses the particular issues affecting women with epilepsy after they have given birth, the care they need during this important period and what best practice may look like

The Epilepsy Research UK Priority Setting Partnership has identified as one of the 10 most pressing issues for the research community to focus on, the hormonal changes in women throughout their lives and the effect this can have on epilepsy. Some issues concerning the female sex appear to have dropped off the research radar, and yet some of these can have a monumental effect on the quality of life, mental health and even the rate of mortality in women with epilepsy.

With this in mind, I'm thrilled that we are able to tap into this research priority with not one, but two of our articles this issue. First up, on page 10, Dr Zarroli catches us up on epilepsy and menopause – a topic that women with epilepsy raise with us at Epilepsy Action more and more often, and yet one for which research seems to have slowed right down in the last 10 or so years. I hope this is a helpful summary of the issues women with epilepsy may well face when going through menopause, and what clinicians can do to support them.

On page 22, we also have an article by Dr Cheng-Hakimian, looking at care for women postpartum, particularly regarding managing anti-seizure medication, achieving seizure freedom and vigilance around sleep.

And finally, on a different note, but equally interesting and important, Konrad Wagstyl and Sophie Adler from UCL discuss how machine learning can help to find focal cortical dysplasia lesions that an MRI might miss (page 16).

I hope you enjoy this issue and that the articles help spark conversations and ideas around these important and fascinating topics.

Kami Kountcheva
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High rate of economic inactivity in people with epilepsy

According to the Office for National Statistics (ONS), more than half of people with epilepsy of working age in the UK are economically inactive. This term refers to people who are not currently in employment and are not looking for work.

The ONS figure shows that 53.1% of people with epilepsy were economically inactive in the year from July 2020 and June 2021. This is a reduction from around two thirds (65.2%) at the beginning of 2020 (January-June).

However, this is still among the highest rates of economic inactivity among disabled people, behind conditions like autism, severe learning disabilities and mental health conditions. In 2021, across England, Scotland and Wales, 22% of working age people in the general population were economically inactive – less than half that of people with epilepsy.

Reports suggest that the reason for the high levels of economic inactivity is "long-term sickness and pressure on the NHS".

Paul Fawcett, 44, from Northumberland has had to give up work because of his uncontrolled epilepsy. He said: "I read about faster access to treatment for people with epilepsy [to help to] possibly get employment or stay in a job. I've been waiting around two or three years now to go into hospital for a week for video monitoring, but with the current situation with the strikes, think I may have to wait a bit longer."

Daniel Jennings, senior policy and campaigns officer at Epilepsy Action, said: "Long-term health conditions can have a huge impact on people's ability to work, as we know that's often the case for people with epilepsy. We know of many instances in which an epilepsy diagnosis has meant having to leave a job, massively reducing hours or changing career paths completely, and that is never easy.

"Not only are people with epilepsy more than twice as likely to be economically inactive compared to the working age population overall, but the delays they're now facing in the Access to Work scheme are making it even harder for them to access and stay in jobs.

"New reports now suggesting the sharp increase in economic inactivity is more likely to be driven by people waiting for treatment, as well as by individuals who permanently live in poorer health, show there is a clear need to re-evaluate and address the causes.

"The NHS struggling to cope with demand may be further delaying or preventing people with a condition from being in work, including those who are waiting to be treated for operations, as well as those who need ways to manage a long-term condition like epilepsy.

"Better and faster access to treatment could mean more people, including those with epilepsy, may be able to re-enter or stay in the workforce."

Communication needed in adult epilepsy care

Better communication is needed across UK hospitals treating adult epilepsy patients admitted after having a seizure, a new National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report said.

The report, released on 8 December 2022, is a review of the quality of epilepsy care for adults who went to hospital with a seizure in 2020, including those who already had an epilepsy diagnosis and those diagnosed after the hospital admission.

The report found that for 42.2% of people, the hospital did not let their usual epilepsy care team know that they had been admitted and 26.1% did not have their epilepsy medicines written in their notes.

NCEPOD also reported that 43.5% left the hospital without input from the neurology team and that in 38.5% of hospitals, specific epilepsy information was not routinely provided until their first clinic appointment, which could be weeks later. Only 12.6% had any information in their notes that the risk of sudden unexpected death in epilepsy had been considered and discussed with them.

NCEPOD said that improved communication is the main theme of the report. It recommended better dialogue with patients' usual epilepsy teams, better documenting of medication and actioning clear plans around investigations. It also raised a need for better neurology advice, as well as discharge and follow-up plans for patients.

The full report is available on the NCEPOD website at: ***bit.ly/3SLvgmf***.

UK epilepsy prevalence and incidence update

A new update on the number of new cases of epilepsy and the number of people with epilepsy in the UK has found differences between the nations.

The new UK study by Wigglesworth and colleagues aimed to provide an update on the incidence of epilepsy (the number of new cases) and the prevalence (the number of people with epilepsy) in the UK between 2013-2018.

The researchers used electronic health records of around 14 million people, representing around one fifth (20%) of the UK population.

The study found that overall in the UK, just over nine people would have epilepsy in every 1,000 people each year. This means that an estimated 633,000 people are living with epilepsy in the UK.

When looking individually at England, Northern Ireland, Scotland and Wales, the team found there were slight differences.

In England this drops to just under nine people in every 1,000 having epilepsy a year. In Scotland, this was just over 10 people, in Wales it was over 11 people and in Northern Ireland it was over 12 people.

The team also looked at the incidence of epilepsy. They found that in the UK there would be around 43 new cases of epilepsy in every 100,000 people in one year.

Reflecting the pattern of prevalence, this was lower in England (37 people), and higher in Northern Ireland (46 people), Scotland (48 people) and Wales (55 people). Overall this means that there are 28,813 new cases of epilepsy each year in the UK, or 79 a day.

The study, published in *Seizure*, found that the prevalence and incidence of epilepsy is similar to that of other high-income countries, with peaks at younger and older age, and a dip in the middle. This is in contrast to the previous survey on incidence and prevalence, which didn't show as much of a peak in older age.

The study authors said that while the prevalence of epilepsy has reduced slightly from 2011, there were significant differences between the different nations and between regions.

The researchers also noted that there was a connection between more deprived areas and a higher level of epilepsy, confirming previous findings. People in the most deprived areas of the UK are more than a third more likely to have epilepsy than those in the least deprived areas, which is something the study authors say needs more research.

You can find the full paper at ***bit.ly/3Jc0lg4***.

Agoraphobia and epilepsy links

A new study published in *Epilepsy Research* has found correlation between agoraphobia and epilepsy.

The study, led by Dr Heidi Munger Clary, looked at 420 adults with epilepsy over a 14-year period, who underwent neuropsychological testing at Columbia University Medical Center in New York. Different cultural and social characteristics were considered, including age, sex, ethnicity and education history.

Of the participants, 36% reported significant phobic or agoraphobic symptoms, which were independently associated with non-White ethnicity and education to less than a college degree. However, they were not linked with any epilepsy-related characteristics such as epilepsy type, seizure frequency or anti-seizure medications.

Epilepsy-related quality of life was also found to be associated with agoraphobic symptoms.

Assessing factors associated with quality of life, the researchers found that age, non-White ethnicity, and depression were also independently associated with poor quality of life. They explained this may suggest that agoraphobic symptoms have a significantly negative impact on quality of life for people with epilepsy.

"Providers might want to consider more robust symptom screening methods to identify and better assist these patients", said Dr Munger Clary. "This may be important to improve health equity, given other key study findings that show those lower education and non-White race/ethnicity had increased odds of significant phobic/agoraphobic symptoms."

For the full study, visit ***bit.ly/3SNdVJF***.

Sodium valproate prescription rules to tighten

Sodium valproate prescription rules will change in the UK for both women and girls, and men and boys, from spring this year.

This will be the first time valproate prescription rules will apply to men and boys, and comes in light of a recent review of the latest safety data by the Commission on Human Medicines (CHM).

The Medicines and Healthcare products Regulatory Agency (MHRA) has announced changes to the way sodium valproate will be prescribed, where no one under the age of 55 should be prescribed sodium valproate, unless two epilepsy specialists independently agree it's the only suitable epilepsy medicine for them.

Anyone currently taking sodium valproate will need to have a review of their epilepsy treatment and ideally be prescribed a different epilepsy medicine, according to the MHRA.

People currently taking valproate are advised to continue taking their medicines as normal in the meantime. Stopping epilepsy medicines could put people at risk of increased or breakthrough seizures.

The MHRA has advised that patients do not need to take any action at this time. However, Epilepsy Action believes that anyone with urgent concerns about their treatment should speak to their epilepsy specialist.

There are already strict rules in place around the use of valproate for women and girls of childbearing potential because of the significant risks of teratogenic effects, including a higher chance of birth defects or learning disabilities in babies exposed to the medicine in the womb.

The MHRA has reminded healthcare professionals about these risks and the need to ensure that the current Pregnancy Prevention Programme measures are followed, as there are concerns that this is not being done consistently.

The MHRA has also highlighted that some research suggests there may be a risk of reduced fertility in men and boys. Animal studies also suggest there may be effects passed from animals taking valproate to their offspring and future generations, but researchers are not sure if this would be the same in humans.

Alison Fuller, director of Health Improvement and Influencing at Epilepsy Action, said: "While we welcome these new guidelines as set out by the MHRA to improve patient safety and reduce risks around prescribing valproate, we urgently need more detail on how they will work in practice and with ongoing monitoring.

"At a time when the NHS is under more pressure than ever, we are concerned about the challenges people with epilepsy will face in getting opinions from two different clinicians, particularly if valproate is the only effective drug in managing their seizures.

"The proposed new measures will also mean men with epilepsy under the age of 55 are required to undergo a full review prior to the prescribing of valproate. However, we are still waiting to understand the full body of evidence behind these restrictions and its potential impact.

"Patient engagement was a key recommendation in the Cumberlege report, yet we are concerned that these new guidelines have come without adequate consultation from people with epilepsy and how they will impact on people's treatment.

"In the meantime, we will be calling on the MHRA and NICE to ensure these new measures are appropriately implemented, managed, and monitored to ensure that people with epilepsy are able to make informed decisions in a timely and safe manner."

There is more information on the gov.uk website at ***bit.ly/3SKTrkO***.

Northern Ireland epilepsy numbers "highly concerning"

Epilepsy numbers in Northern Ireland have been called "highly concerning" by Epilepsy Action following recently published UK epilepsy prevalence and incidence figures.

A UK research team published findings on the prevalence (number of people) and incidence (number of new cases) of epilepsy in the UK's different nations in *Seizure* journal in January this year. The total number of people with epilepsy in the UK has increased to around 633,000 from 600,000 between 2011 when the last review took place and 2018. But the proportion of people who have epilepsy in the whole population of the UK has dropped slightly In that time.

However, the research also looked at England, Scotland, Wales and Northern Ireland separately. The findings showed higher rates of prevalence and incidence of epilepsy in Scotland, Wales and Northern Ireland compared to England and the UK overall. It also showed that the prevalence of epilepsy has increased in Wale and Northern Ireland when compared to the previous 2011 review.

Epilepsy Action has expressed particular concern about the numbers in Northern Ireland, especially considering the political situation at the moment.

In Northern Ireland, one in 83 people has epilepsy. This is the highest prevalence among the UK nations and compares to one in every 107 people in the UK overall. It is also an increase from the prevalence in Northern Ireland in 2011, which was one in 90 people. The number of new cases in Northern Ireland is just over 45 in every 100,000 people a year. This is higher than the UK overall, which is just over 42 new cases in 100,000 people a year.

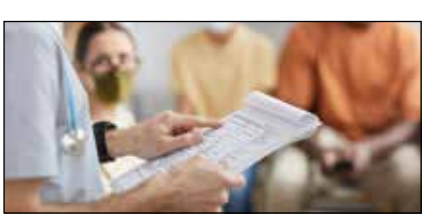
Carla Smyth, Northern Ireland services and project manager at Epilepsy Action, said: "These new figures around the prevalence of epilepsy in Northern Ireland are hugely concerning and highlight a significant difference between Northern Ireland and the rest of the UK.

"This situation is further exacerbated by the fact that waiting times for neurology appointments in Northern Ireland are the highest in the UK. We have heard from some people who have been told they face a wait of over four years for an appointment.

"We urgently need all political parties in Northern Ireland to get back round the table, break the current stalemate, restore power-sharing and work together to address the vast problems facing people with neurological conditions like epilepsy."

The research also found that epilepsy levels were a third higher in poorer areas compared to wealthier areas around the UK. This link has been seen before, with Public Health England figures from 2001-2014 showing a three-times higher risk of epilepsy-related deaths in people living in poorer areas compared to wealthier areas.

The Seizure paper (***bit.ly/3Jc0lg4***) authors said this link between epilepsy numbers and poorer areas needs more research.



Lamotrigine tablets out of stock until April

Lamotrigine 25mg tablets made by Torrent are temporarily out of stock. Torrent have told Epilepsy Action that they expect to be back in stock in April 2023.

Torrent have confirmed that their lamotrigine 50mg tablets are in stock.

Additionally, the Department of Health and Social Care (DHSC) has issued a medicine supply alert for lamotrigine 5mg dispersible tablets.

The DHSC said they expect lamotrigine 5mg dispersible tablets to be out of stock until late March 2023.

Branded lamotrigine (Lamictal) 2mg and 5mg dispersible tablets remain available but are unable to support the increase in demand. Pharmacies may be able to get supply of unlicensed lamotrigine 5mg dispersible or chewable tablets.

The situation will be updated online at ***bit.ly/3IQORNm*** and ***bit.ly/3JaTovn*** as more information becomes available

Levetiracetam 1000mg tablets out of stock

Levetiracetam 1000mg tablets made by Accord are long term out of stock. Accord were not able to give Epilepsy Action a date for when they will be back in stock. The organisation will post an update its website when there is more information (***bit.ly/3YkOLUb***).

Katherine Zarroli

Menopause and epilepsy

Supporting women with epilepsy across their lifespan

Dr Katherine Zarroli discusses the unique challenges that women with epilepsy can face with hormonal changes throughout their life, and what clinicians should focus on when women with epilepsy go through menopause.

Epilepsy affects about 50 million people of all ages worldwide [World Health Organization, 2019]; men and women are affected nearly equally. Therefore, an estimated 25 million women have epilepsy. Women with epilepsy face unique issues across their lifespan. For many women, these issues rise to prominence at three time points: menarche (onset of menses), during pregnancy and menopause. The focus of this piece will be on the issues women with epilepsy face later in life, during menopause. Ageing in women with epilepsy is a somewhat overlooked aspect of research, but is of paramount importance clinically.

There is a complex relationship between sex hormones and seizures in women with epilepsy. This relationship becomes pertinent early in a woman's lifetime and persists through menopause. Many women experience their first seizure at or around the onset of menses, also known as menarche. In the Epilepsy Birth Control Registry, an international web-based survey of women with epilepsy, 8.3% of women had seizure onset during the year of menarche and 49.3% of women experienced seizure onset between two years prior and six years after menarche [Herzog *et al*, 2019]. Oestradiol and progesterone are two key sex hormones that affect neuronal excitability. The rapid increase in oestradiol and progesterone in the years surrounding menarche likely triggered seizure onset in these women.

Oestradol acts as a proconvulsant by increasing excitatory synaptic transmission and neuronal metabolism and discharge rates

Broadly, progesterone (by way of its active metabolite allopregnanolone) has anticonvulsant effects and oestradiol has

proconvulsant effects. Of note, this is a simplified description, as newer research suggests oestradiol may also exert anticonvulsant effects and progesterone may also have proconvulsant effects [Bui, 2022]. The progesterone metabolite allopregnanolone exerts an anticonvulsant effect by binding to the inhibitory gamma-amino-butyric acid (GABA) type A receptor to enhance GABA action and inhibition [Herzog *et al*, 1997; Joshi *et al* 2013]. Progesterone has also recently been found to exert a proconvulsant effect. Shiono *et al* [2019] found that progesterone receptor activation increased seizure frequency in epileptic animals. Oestradiol acts as a proconvulsant by increasing excitatory synaptic transmission [Smith, 1989; Smejkalova and Woolley, 2010] and neuronal metabolism and discharge rates [Hardy, 1970]. These fluctuations in oestrogen and progesterone at the time of menarche likely play a role in triggering a woman's first seizure.

Apart from sex hormones influencing the time of first seizure onset, sex hormones can also influence seizure control throughout a woman's reproductive years. Approximately one-third of women with epilepsy have catamenial epilepsy. Catamenial epilepsy is defined as cyclic seizure exacerbations in relation to the menstrual cycle. In women with normal ovulatory menstrual cycles, catamenial seizure exacerbations can occur during the perimenstrual or the preovulatory phases of the menstrual cycle [Herzog *et al*, 1997; Herzog, 2008]. Perimenstrual seizure exacerbations occur during the time of menstruation and are related to the rapid premenstrual withdrawal of progesterone [Herzog, 2008]. The withdrawal of progesterone impairs GABAergic inhibition to precipitate seizures. Pre-ovulatory seizure exacerbations, alternatively, may be secondary to a pre-ovulatory oestrogen surge. The surge of oestrogen that precedes and leads to ovulation likely triggers seizures due to oestrogen's proconvulsant effects.

Perimenopause presents a potential time for seizure exacerbations, as there is a fluctuating hormonal environment with decreased progesterone secretion by the ovaries

Sex hormones can also influence seizure control as a woman approaches menopause. During the transition to menopause, also known as perimenopause, women start to have irregular menstrual cycles and the levels of oestrogen and progesterone become unpredictable [Santoro *et al*, 1996; Burger *et al*, 2002]. Perimenopause can last around four years. Perimenopause thus presents a potential time for seizure exacerbations, as there is a fluctuating hormonal environment with decreased progesterone secretion by the ovaries. When a woman enters into menopause, the levels of oestrogen and progesterone gradually reduce over time. Menopause is defined as the permanent cessation of menses for at least 12 months.

The sex hormonal fluctuations occurring during perimenopause and the gradual reduction in sex hormones during menopause affect

seizure control. In 1999, Harden *et al* sent a questionnaire to menopausal and perimenopausal women with epilepsy; 39 perimenopausal women and 42 menopausal women replied. In respondents, a history of catamenial epilepsy was interestingly associated with an increase in seizures during perimenopause and a decrease in seizures during menopause [Harden *et al*, 1999]. This shows that seizure sensitivity to hormones in the catamenial epilepsy sub-population may persist into the perimenopausal and menopausal phases of life. This is important information for patient counselling; however, further research is needed as this study included only small sample sizes.

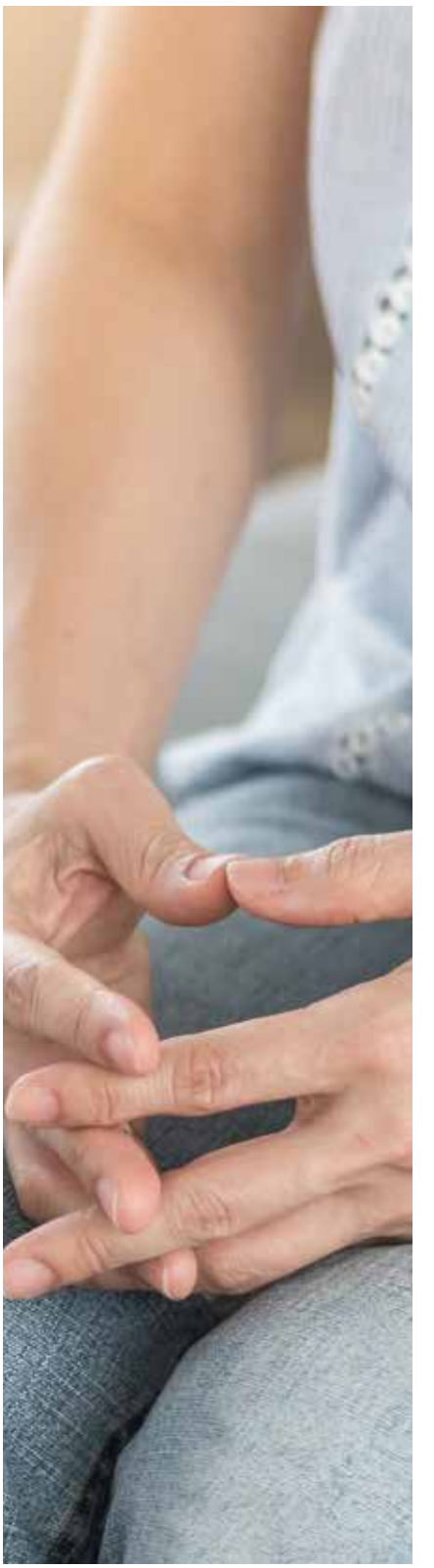
A 2003 survey found that women with epilepsy with a high seizure frequency had an average age of menopause of 46.7 years, while women in the general population had an average age of menopause of 51.4 years

Women with epilepsy are also at risk of earlier menopause. A 2003 survey found that women with epilepsy with a high seizure frequency had an average age of menopause of 46.7 years, while women in the general population had an average age of menopause of 51.4 years [Harden *et al*, 2003]. Seizures can disrupt hypothalamic and pituitary function. This may secondarily affect ovarian function and ovulation, precipitating premature menopause.

Women undergoing menopause may develop symptoms including mood changes, insomnia, night sweats, vaginal dryness, hot flashes, sexual dysfunction and weight gain. To offset these symptoms, hormonal replacement therapy (HRT) can be considered for women in the general population. Unfortunately, HRT may pose risks to women with epilepsy.

The addition of oestrogen is likely why HRT use was associated with an increase in seizures

In a small (n=21) placebo-controlled trial, women with epilepsy were randomised to receive placebo vs Prempro (conjugated equine oestrogens plus medroxyprogesterone acetate) for a three-month treatment period. Use of hormonal replacement therapy was found to be associated with a dose-related increase in seizure frequency [Harden *et al*, 2006]. As detailed above, oestrogen can be considered a proconvulsant and allopregnanolone (a progesterone metabolite) an anticonvulsant. The synthetic progesterone utilised in HRT for this study, medroxyprogesterone acetate, is not metabolised to allopregnanolone, so therefore did not have the anticonvulsant effects of allopregnanolone. The addition of oestrogen is likely why HRT use was associated with an increase in seizures. It is unknown if the synthetic progesterone played a role in leading to increased seizure activity. Low sample sizes did not allow for thorough investigation



into how the use of HRT may affect anti-seizure medication (ASM) levels. It is known that systemic hormonal forms of contraception may interact with ASMs to impact medication efficacy; likewise, this can be applied to HRT [Herzog *et al*, 2016]. While this was a small study, the information is still important and applicable to patient counselling; further research should be conducted. In menopausal women with epilepsy who have debilitating symptoms, alternative options to HRT should also be considered. This can include local vaginal lubricants or psychiatric medications (selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors).

Women in the general population are at an increased risk for osteoporosis and this is especially prevalent in older post-menopausal women. The main contributor to the development of osteoporosis in post-menopausal women is oestrogen deficiency, though other risk factors include genetics, smoking, weight, co-morbidities and use of certain medications [North American Menopause Society, 2021]. Bone health is an important issue for all persons, both men and women, with epilepsy as well. Epilepsy patients on enzyme-inducing ASMs (phenobarbital, phenytoin, carbamazepine, oxcarbazepine and topiramate in dosages greater than 200 mg daily) are at risk of accelerated bone loss, in part because these medications induce metabolism of vitamin D. Use of valproate, an enzyme inhibitor, and gabapentin have also been associated with increased bone loss, though the mechanism is less well understood. Seizures can trigger falls which can lead to bone fractures; this is another reason to keep bone health in mind for epilepsy patients.

As there is an increased risk of osteoporosis independently in post-menopausal women and in women with epilepsy, post-menopausal women with epilepsy pose a sub-population of particular vulnerability. In a survey of women's perceptions and misconceptions relating to having epilepsy and being on ASMs, it was found that 64% of recipients were concerned about ASM therapy and bone health [Vazquez *et al*, 2007]. These survey findings support that bone health is an important issue for women with epilepsy. Women with epilepsy, especially post-menopausal women, should have vitamin D, calcium and phosphate levels monitored. Primary care providers should be closely monitoring bone mineral density as well. Patients should be counselled on preventative measures to improve bone health, such as exercise and improving nutrition. Calcium and vitamin D supplementation should be pursued if needed.

As there is an increased risk of osteoporosis independently in post-menopausal women and in women with epilepsy, post-menopausal women with epilepsy pose a sub-population of particular vulnerability

Overall, menopause is an important time for women with

epilepsy. Fluctuations in sex hormones during perimenopause, followed by a gradual reduction in sex hormonal production in menopause, may impact seizure control. Use of ASMs can affect vitamin D and oestradiol levels, affecting bone health and predisposing women with epilepsy to impaired bone mineral density. Use of HRT in women with epilepsy poses potential detrimental effects on seizure control. It is important to address the unique needs of women with epilepsy throughout their lifespan, and it is of particular importance to have close care continuity during the vulnerable time of menopause.

It is important to address the unique needs of women with epilepsy throughout their lifespan

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Further reading

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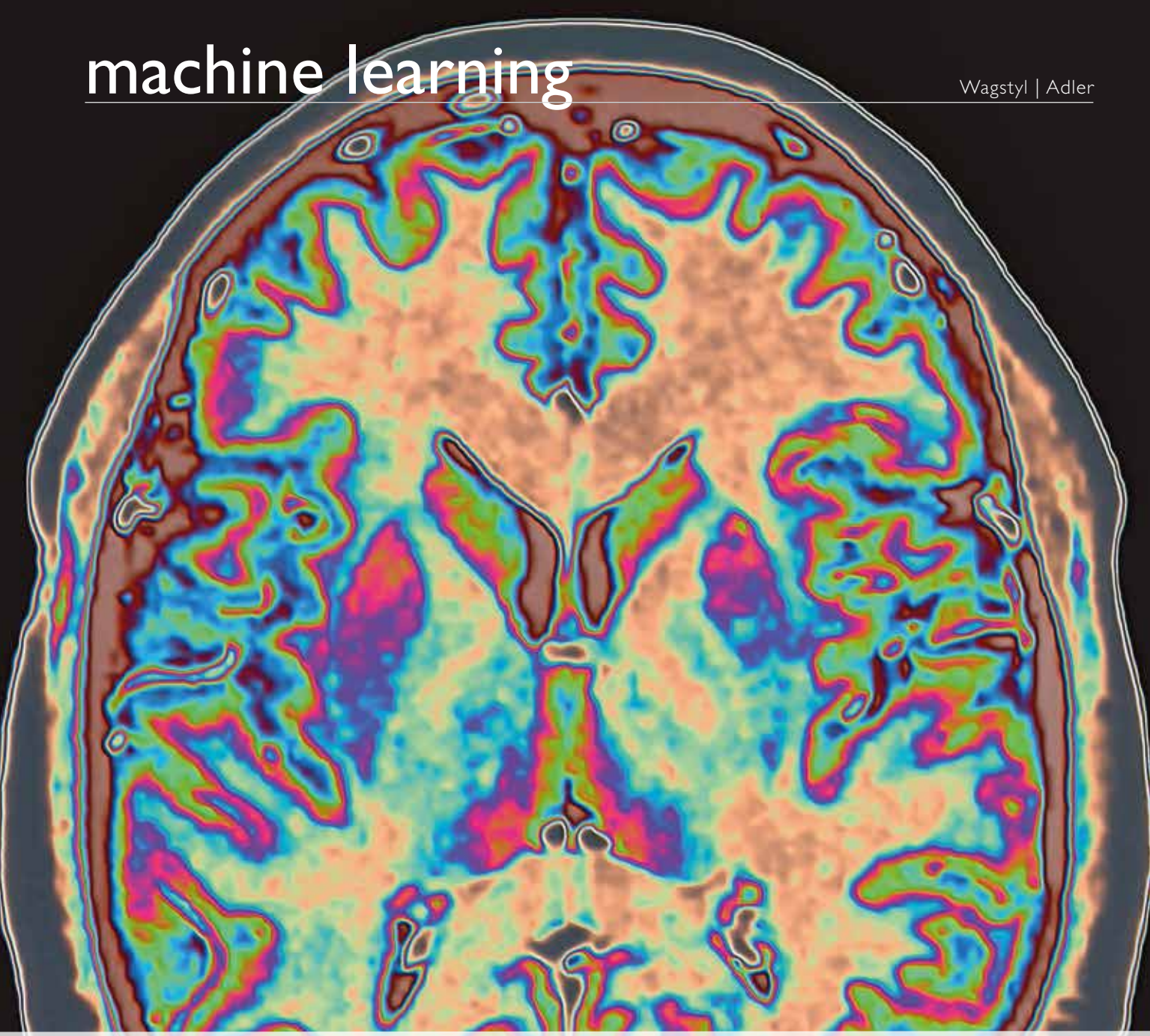
Wagstyl | Adler



Detecting lesions using AI

Using machine learning to localise lesions on MRI

Konrad Wagstyl and Sophie Adler describe the MELD project and the benefits of machine learning in better detecting 'MRI negative' focal cortical dysplasia.

Focal cortical dysplasia (FCD) is a leading cause of drug-resistant epilepsy in both children and adults. It is a malformation of cortical development which causes recurrent drug-resistant seizures. Accurate diagnosis and localisation of FCD using MRI is essential for enabling and planning potentially curative neurosurgical resection. However, FCDs can occur anywhere in the cerebral cortex and are often missed on visual inspection of MRI due to the subtlety of the lesions – the 'MRI negative' lesions. For these MRI negative patients, accurate diagnosis and subsequent surgical planning remain a clinical challenge.

Why might machine learning help?

Machine learning describes a group of computational methods aimed at learning patterns from input training data which are useful for performing a particular task. One subset of machine learning, called deep learning, aims to simulate a network of neurons that activate in response to specific patterns in the input data. Multiple layers of these neurons can be combined in different structures to perform a wide variety of tasks, such as recognising faces in images or words from voice recordings. These tools are behind the current boom in AI applications to healthcare. In some cases, such tools have been able to match or even outperform human experts.

Detecting FCDs is an ideal task for deep learning, as FCDs are characterised by quantifiable structural abnormalities on MRI

Detecting FCDs is an ideal task for deep learning, as FCDs are characterised by quantifiable structural abnormalities on MRI whose patterns could be learnt by neural networks.

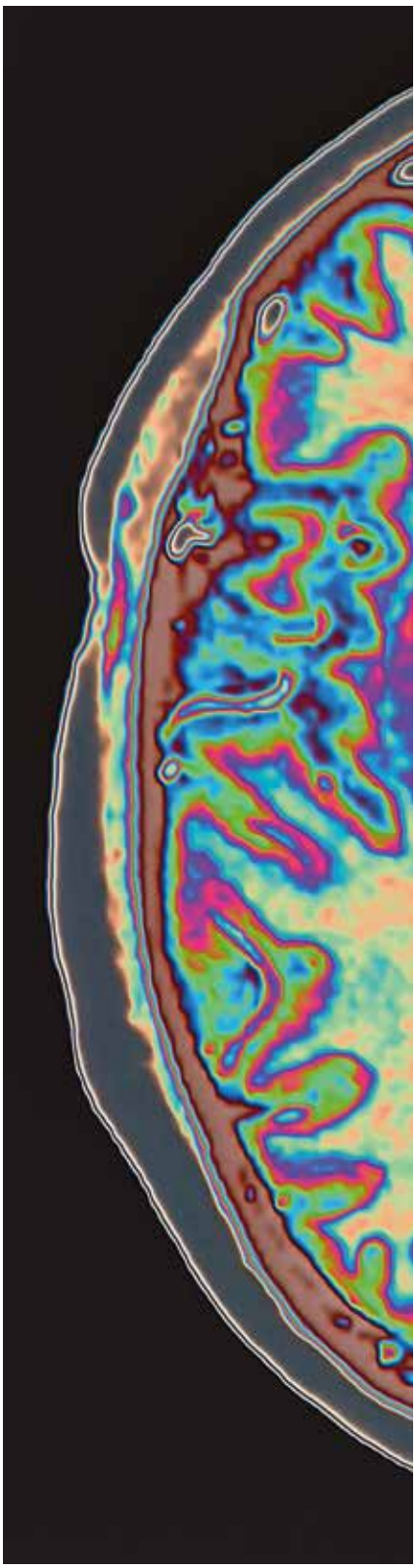
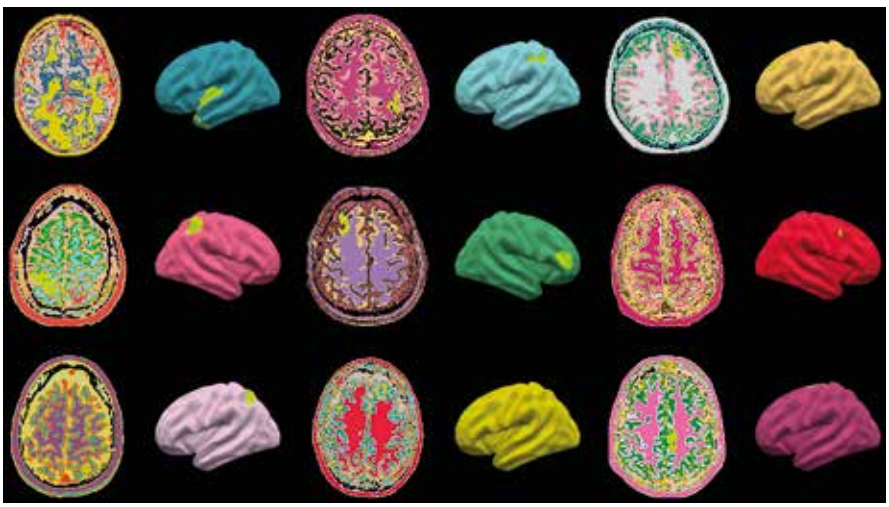


Figure 1. Brain abnormalities identified by the MELD AI algorithm (highlighted in lime green) on MRI scans of children and adults with epilepsy from around the world.



Furthermore, the visual identification of FCDs is a clinical challenge where a machine learning solution would provide an invaluable diagnostic aid and tool for neurosurgical planning. Indeed, FCDs are often subtle abnormalities on first review of MRI scans, but once highlighted become much easier to verify. This makes them an ideal use case for machine learning-driven localisation where putative abnormalities can be reviewed by expert clinicians.

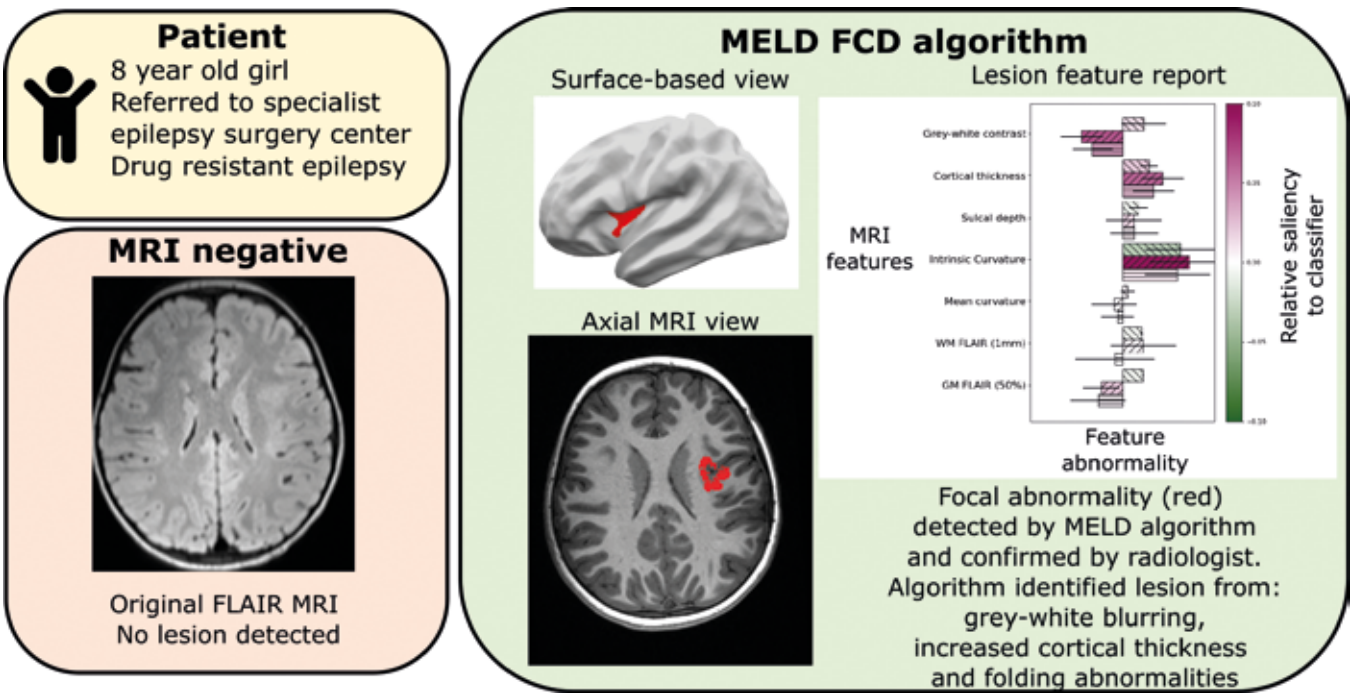
One criticism of machine-learning technologies is that they are 'black boxes', meaning they provide an output, such as a prediction of where in the cortex a lesion is, without any explanation as to how this decision was made. This lack of interpretability is challenging for clinical translation of AI technologies, as clinicians need to be able to understand AI predictions and independently assess whether they are correct or not. For example, in the case of using AI for automated FCD detection, false positive predictions can occur and may be due to factors such as MRI artifacts or motion. A new field of machine-learning, called 'Explainable AI' involves analysing how an algorithm arrives at a prediction and what it has learnt – opening the 'black box'.

One criticism of machine-learning technologies is that they are 'black boxes', meaning they provide an output without any explanation as to how this decision was made

Big data for AI in healthcare

One challenge for machine learning approaches in healthcare is that they require large training datasets, necessitating the coordinated efforts of clinical teams and machine learning scientists to aggregate and curate datasets that can be used to train these algorithms. This is why we created the Multicentre Epilepsy

Figure 2. Case vignette of an eight-year-old patient.

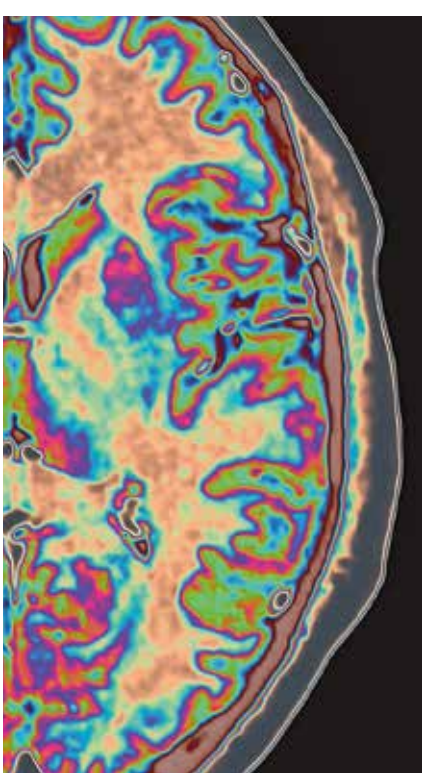


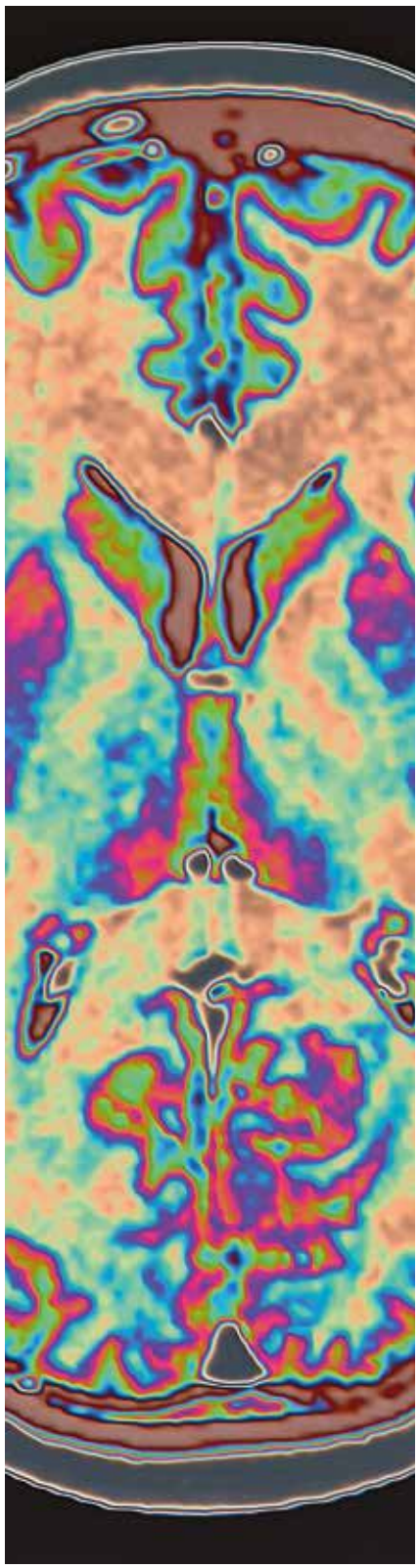
Lesion Detection (MELD) project, to collate a large dataset of MRI data from patients with FCD, to create AI tools to help their automated detection.

The MELD project has been studying FCD using a combination of clinical, imaging and machine learning techniques [Wagstyl *et al*, 2021; Spitzer *et al*, 2022]. One goal of the project was to create a machine-learning algorithm to automatically identify these lesions. Importantly, we wanted any developed algorithm to be interpretable, meaning clinicians would be able to understand why the algorithm had identified particular cortical areas.

Twenty two epilepsy centres around the world collaborated to create an MRI cohort of over 600 patients with FCD. With this large dataset, we identified that although FCD lesions can occur throughout the cerebral cortex, they were more frequently located in particular areas, including the temporal pole and superior frontal sulcus [Wagstyl *et al*, 2021]. Interestingly, the clinical characteristics of patients varied depending on the location of their FCD. For example, FCDs in primary sensory and motor areas were associated with earlier age of epilepsy onset, likely reflecting earlier cortical

We need machine-learning algorithms capable of detecting all major causes of focal epilepsy and differentiating them





maturation in these regions [Cohen *et al*, 2022]. Lesions located near eloquent areas were associated with worse post-surgical outcomes [Wagstyl *et al*, 2021]. This is likely due to deliberate neurosurgical caution when resecting lesions in these areas to avoid damaging cortical function.

Each of the 22 collaborating epilepsy centres conducted advanced neuroimaging processing on the MRI data of their patients. This involved extracting 21 features, such as the thickness of the cortex, at over 300,000 points across the cerebral cortex per patient. We used this data to train a machine-learning algorithm to learn patterns of features that identified FCDs [Spitzer *et al*, 2022]. The algorithm was able to identify 69% of the lesions across the full cohort and 63% of the lesions in patients who were at some point considered 'MRI negative'. Importantly, the algorithm is interpretable. It outputs putative lesion locations as well as which features were abnormal in these cortical areas and how important this was to the algorithm. We capture how important the feature was to the algorithm's prediction using a form of 'Explainable AI' called saliency.

Open science

One key feature of the MELD project is that all code, including the tool to identify an FCD on a new patient's MRI scan, is open source (***https://github.com/MELDProject***). This enables any epilepsy centre to download and install the algorithm and evaluate it on their own patients. This must be done as part of research as the algorithm is not a medically licensed device and is still solely a research tool. In the case vignette, we demonstrate how the algorithm has been applied, as a research tool, to help detect the lesion of an 'MRI negative' patient. The MELD FCD detection algorithm is currently being evaluated at Great Ormond Street Hospital, the National Hospital for Neurology and Neurosurgery, and other NHS, European and international epilepsy centres.

Limitations and future directions

The algorithm predicts an average of two clusters per patient. This means that it does make some inaccurate predictions – false positives. Furthermore, as previously mentioned, the algorithm is still a research tool and must be carefully interpreted in view of the full clinical

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context. Further work is needed to improve the algorithm, including reducing the number of false positives, and evaluate its utility.

Finally, FCD is only one cause of 'MRI negative' focal epilepsy, alongside other structural abnormalities such as hippocampal sclerosis and polymicrogyria. We therefore need machine-learning algorithms capable of detecting all major causes of focal epilepsy and differentiating them. To this end, we have now launched the MELD focal epilepsies project, aiming to create a larger, more heterogeneous cohort of patients with focal epilepsy due to a wide range of structural lesions. We will be using this dataset to train AI algorithms to better detect causes of focal epilepsy and predict surgical outcome.

If you'd like to get involved with the MELD project, contact ***meld.study@gmail.com***.

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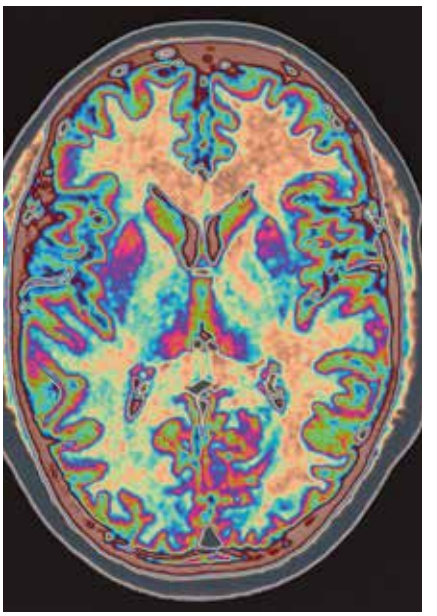


Andrea Cheng-Hakimian

New mums with epilepsy

Best practice postpartum care for mothers with epilepsy

Dr Cheng-Hakimian discusses the particular issues affecting women with epilepsy after they have given birth, the care that they need in this important period and what best practice may look like.

What is your first reaction when the next patient on your clinic schedule is a pregnant woman with epilepsy? I find it exciting. Not only do I help the mother, but I get to help kick-start a brand-new life. However, I wouldn't blame anyone for feeling otherwise. Maybe you feel a bit like Odysseus, battling danger after danger, in a long, circuitous journey towards a healthy mother and child. Worldwide, more than 15 million women with epilepsy are of childbearing age. Each year 600,000 become pregnant [International League Against Epilepsy, 2019]. These women have an increased risk of a long list of adverse outcomes in pregnancy, including preeclampsia, placental abruption and death [MacDonald SC, 2015; Razaz N, 2017; Artama M, 2017; Salman L, 2018]. Their infants, meanwhile, face an increased risk of major congenital malformations, prematurity, low birthweight and requiring NICU admission [MacDonald *et al*, 2015; Razaz *et al*, 2017; Artama *et al*, 2017; Chen *et al*, 2017; Veiby *et al*, 2009]. No wonder that after delivery, practitioners breathe a sigh of relief, knowing that worrying can end. Or can they?

There is mounting evidence that the postpartum period holds continued risk. All maternal deaths in the UK have been reported to a central database since the 1950s [Healthcare Quality Improvement Partnership, 2014]. A review of maternal deaths associated with epilepsy in this database from 1979-2008 was conducted by Kapoor and Wallace [2014]. Maternal deaths were defined as "death of a woman while pregnant or within 42 days of termination of pregnancy". Ninety two maternal deaths related to epilepsy were found, one-third of which occurred postpartum. The 92 deaths represent 0.43 deaths per 100,000 maternities, and increased over time (0.05 during 1979-1981 to 0.61 during 2006-2008). The most common causes of maternal death in women with epilepsy were SUDEP (sudden unexplained death in epilepsy), generally considered due to a terminal epileptic seizure, (41%), aspiration of gastric contents during seizures (21%), unknown (16%) and drowning while bathing (9%). Simple addition tells us that complications of seizures accounted for 71% of maternal deaths. In other words, approximately 70% of maternal deaths could have been prevented by controlling seizures.

Ninety two maternal deaths related to epilepsy were found one-third of which occurred postpartum

Evidence of increased postpartum mortality is not confined to the UK. A case control study in Denmark showed that maternal mortality (to 42 days postpartum) was more than five times greater when associated with epilepsy [Christensen *et al*, 2018]. In our recent retrospective cohort study with US data, we identified linked vital-hospital discharge-death records of all women with epilepsy and compared them to records of randomly selected women without epilepsy. We then compared the occurrence of adverse maternal and infant outcomes during the first two years postpartum. A seven-fold increased risk of maternal mortality and a greater than two-fold increased risk of maternal rehospitalisation were observed [Mueller *et al*, 2022]. Although cause of mortality or rehospitalisation could not be explored, the number of deaths was consistent with that expected from the reported SUDEP rate of 1.16/1000 [CDC, 2020].

Other causes of preventable postpartum maternal mortality can be suggested. Epilepsy triples the baseline risk of depression [Fiest *et al*, 2013]. Postpartum depression is significantly more common among women with epilepsy [Turner *et al*, 2009; Bjork *et al*, 2015; Meador *et al*, 2002]. Epilepsy increases risk of suicide [Thurman *et*

al, 2016]. Is there especially increased risk of suicide among women with epilepsy in the postpartum period? Although one study found no increased risk of suicide, it is limited by a small sample size [Meador *et al*, 2002]. Increased suicide risk is unfortunately plausible and needs to be further researched. Finally, greater levels of pregnancy-related complications among women with epilepsy, such as eclampsia, could plausibly increase maternal mortality risk postpartum.

Hopefully, I've convinced you by now that the postpartum period is not the time to relax vigilance. What should the practitioner concentrate on during this time? For me, achieving seizure control is far and away most important. We've seen that women with epilepsy are at a 5-10 times greater risk of death, with a majority of deaths likely due to conditions resulting from uncontrolled seizures. Known contributors to inadequate seizure control include sleep deprivation, reduced anti-seizure medication (ASM) compliance, and suboptimal ASM regimens, all of which are more likely in the postpartum period.

Infants require round-the-clock care for many months, notoriously causing severe, chronic sleep deprivation in caretakers. Optimally before delivery, practitioners should encourage mothers to enlist alternative caretakers from among friends and family. Newborns wake to feed typically every 2-3 hours. An alternative caretaker for just one night-time feeding would allow the mother to sleep uninterrupted for about six hours. Practitioners can emphasise that mothers are doing this as a medical necessity rather than a luxury.

In the hectic postpartum period, even the most conscientious patient will sometimes forget to take her ASMs. Practitioners can counsel patients to set up multiple layers of reminders, including using weekly pillboxes, setting alarms on smartphones and having another adult verify pill intake at the end of each day. Extended-release formulations of ASMs can also be considered as a once-daily intake is likely to reduce forgetful noncompliance. Our study also suggests that infants have increased risk of rehospitalisation, with greater numbers during their first two years. It seems prudent to counsel mothers about postpartum infant safety precautions. Mothers should be advised to change or feed their baby strapped to a chair or table (so that their baby doesn't roll or crawl into danger during a seizure), to use a baby carrier or pram even around the home (so the baby isn't dropped during a seizure), and to never cook on the front burners of a stove, iron clothing, or bathe the baby unsupervised (babies can drown in just a few inches of water if the mum loses consciousness).

Still with the goal of seizure freedom in mind, the mother's ASMs should be re-examined postpartum. This is particularly true if the regimen includes lamotrigine. Lamotrigine and levetiracetam are commonly preferred ASMs in pregnancy, as they are associated with low teratogenicity risk [North American Antiepileptic Drug Pregnancy Registry, 2022; Tomson *et al*, 2011]. Lamotrigine clearance, however, dramatically increases in pregnancy, then quickly returns to pre-pregnancy baseline in the first few weeks postpartum [Pennell *et al*, 2008]. If lamotrigine dose is not adjusted during pregnancy, the level is likely to drop, with increased likelihood of breakthrough seizures if the drop is by

A case control study in Denmark showed that maternal mortality (to 42 days postpartum) was more than five times greater when associated with epilepsy

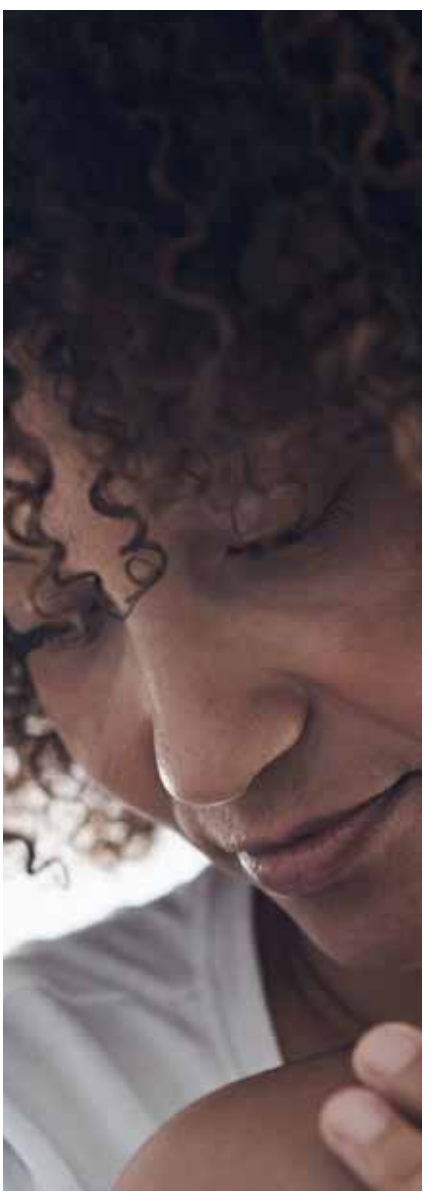
more than 35% [Pennell *et al*, 2008]. A striking finding in the UK maternal morbidity study discussed above was that the majority of ASM levels checked at time of death were subtherapeutic or undetectable [Kapoor and Wallace, 2014]. The reasons are unclear, and no breakdown by ASM was available. Although teratogenicity concerns and stress-related behaviour change are entirely plausible alternative explanations, this finding suggests it may be especially important to check levels in women taking lamotrigine during pregnancy.

With the goal of seizure freedom in mind, the mother's ASMs should be re-examined postpartum, particularly if the regimen includes lamotrigine

The way lamotrigine is metabolised also means that a well-tolerated dose prior to delivery may produce toxicity after delivery. Postpartum toxicity can be prevented by frequently checking lamotrigine levels in the first few weeks and adjusting dose to achieve pre-pregnancy baseline serum levels. Levetiracetam clearance also increases during pregnancy, though not as dramatically as lamotrigine, and may also benefit from close serum level surveillance [Berlin *et al*, 2019]. Serum monitoring of other ASMs is less well established but is of potential clinical benefit and should be considered.

Practitioners should also counsel mothers about contraception soon after delivery to prevent accidental pregnancies. Hormonal contraceptives and enzyme-inducing ASMs hold sometimes bidirectional interactions that risk both contraceptive efficacy and seizure control (Schwenkhagen and Stodieck, 2008). Neurology, and obstetrics and gynaecology specialists should work together to select the contraceptive least likely to interfere with seizure control and with the greatest contraceptive efficacy. Hormone-based and copper IUDs do not interact with ASMs and are very effective contraceptives [Bounds and Guillebaud, 2002; Davis *et al*, 2016]. These should be among the first contraceptives to be considered.

Practitioners should also address breastfeeding with new mothers. Our study found that mothers with epilepsy are three times less likely to breastfeed their infants [Mueller *et al*, 2022]. In an earlier, adequately powered, prospective study, breastfed, six-year-old children of women with epilepsy taking any of four medications (carbamazepine, lamotrigine, phenytoin, or valproic acid monotherapy) showed a slight but statistically significant increase of mean IQ scores compared with their formula-fed peers [Meador *et al*, 2014]. The study was not powered to make comparisons within ASM groups, but no medication group demonstrated a significant decline in IQ with breastfeeding. The valproic acid group data even suggested slightly increased IQ scores with breastfeeding, although this did not reach statistical significance and no firm conclusion can be drawn as there was only 36 mother-child pairs in this group. Generally low infant-to-maternal serum ASM ratios provide one explanation for the lack of adverse effect of breastfeeding on neurocognitive development [Birnbaum *et al*, 2020]. A Norwegian study also suggested improved developmental outcomes of children of mothers taking ASMs who were breastfed [Veiby *et al*, 2013]. Overall, multiple, well-conducted research studies report no harm and likely benefit from breastfeeding. The benefits of breastfeeding in the general population (decreased subsequent maternal breast and ovarian cancer risk, decreased childhood infections, etc.) are well known. Thus, there is no reason to discourage it among women



with epilepsy, especially if the ASM is in monotherapy or low dose.

A general neurologist would hardly be blamed for feeling out of practice with these multidisciplinary issues. The Multispecialty UK Epilepsy Mortality Group [Leach *et al*, 2017] recommends a team-based approach to care. Consistent and comprehensive care messaging repeated by different practitioners within the team can only increase patient compliance. Built-in communication between team members would optimise interdisciplinary decisions, such as the selection of contraceptives. In an ideal world, the team would consist of a neurologist, obstetrician and gynaecologist, psychiatrist, counsellor and lactation specialist. At every postpartum visit, a depression screen would be performed. Referral to psychiatry or counselling would be made as appropriate. The psychiatrist would be familiar with the special needs of this population such as teratogenicity risk and medication effects on seizure thresholds, and would follow up for at least a year postpartum. The lactation specialist would be able to provide details of breastfeeding techniques consistent with postpartum seizure precautions, help the patient plan for daily alternate caregiver feedings and provide routine breastfeeding assistance.

In the past, a single six-week follow-up clinic visit was common for the postpartum period. More frequent follow-up may be needed. In 2018, the American College of Obstetrics & Gynecology changed their recommendations to shorten follow-up intervals [ACOG Committee Opinion No 736, 2018]. Follow-up schedules should be individualised to the patient, but one schedule may look like this:

Before or during hospitalisation for delivery: discuss contraceptive methods, review postpartum seizure

Further reading

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precautions, ASM dose reduction plan (if applicable) and lactation consultation.
Postpartum day 7-14: phone call/ telemedicine visit to administer depression screen, review seizure count and sleep schedule, obtain ASM levels, and adjust regimen as needed. Refer to psychiatry or lactation specialist as needed.
Postpartum weeks 3-6: in-person visit to obtain contraception and perform gynaecological and/or neurological exam. Repeat depression screen, review seizure count and sleep schedule, obtain ASM levels, and adjust as needed. Refer to psychiatry or lactation specialist as needed.
Postpartum months 3-6: Telemedicine visit or phone call to repeat depression screen, review seizure count and sleep schedule, obtain ASM levels, and adjust as needed. Refer to psychiatry or lactation specialist as needed.
Postpartum months 6-18: in-person visit to optimise ASM regimen or refer for consideration of epilepsy surgery in anticipation of the next pregnancy, obtain exam and labs as needed.

The postpartum period is best envisioned as the "fourth trimester" [ACOG Committee Opinion No 736, 2018]; a period of heightened risk that calls for continued practitioner vigilance and, perhaps, a new, multidisciplinary team-based paradigm. Odysseus must ply the wine-dark sea, but with these tools Ithaca is in sight.

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Tom Shillito

Research update

Epilepsy Action health improvement and research manager, Tom Shillito shares updates from Epilepsy Action's research work

Quality improvement

At Epilepsy Action, we are expanding our support for healthcare quality improvement projects. We will be starting an improvement project around maternity care for people with epilepsy in certain areas of the UK very soon, and we will be looking to assist on other epilepsy related quality improvement projects in the future.

The areas we are most interested in are:

- Older people with epilepsy
- Transition to adult epilepsy services
- Mental health and epilepsy
- Pregnancy and hormones
- Seizure control and management
- Healthcare inequalities

We will be offering quality improvement coaching and practical support with improvement projects. There may also be funding available to support projects at certain times. For more information, please get in touch with the Health Improvement and Influencing team at ***researchadmin@epilepsy.org.uk***.

We can also help with access to tools, information and advice.

The Step Together benchmarking toolkit for epilepsy and learning disability services will be rolled out nationwide this spring, and can be used as a starting point for quality improvement projects. The toolkit is based on the Step Together guidance written by Prof Rohit Shankar, and was created in collaboration with Epilepsy Action using a grant from UCB. It asks questions about many different aspects of care for people with epilepsy and learning disabilities and gives an overall score and scores for different aspects of care, such as transition, workforce, user involvement, etc. The toolkit can be the first step in a quality improvement journey, with the results being used to find areas for development that could be improved. The toolkit is currently being piloted in the Midlands and has already inspired quality improvement projects in the systems using it.

Patient and public involvement

We have been recruiting new Research Development volunteers and have doubled our number in just a month of recruitment. These volunteers can give feedback on research proposals, review patient-facing documents, attend focus groups to discuss ideas, and sit on patient boards and steering committees. They are all either living with epilepsy themselves, or have a close family member who has epilepsy. They are trained on research essentials and are enthusiastic about being the voice of people with epilepsy in the research world.

What our volunteers have been involved with recently:

- A group of volunteers have recently given feedback on proposed focus group questions, to ensure when the focus group is held the questions will be appropriate to ask and easy to understand, and will generate useful conversations among the attendees

Further reading

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- Some of our volunteers took part in a filmed panel discussion to disseminate the results of a project they had been involved in
- A number of our volunteers attended focus groups to give feedback on a new technology and how they would like to see it implemented within the NHS
- Our volunteers are currently helping us to write our new research strategy, giving their input on what our priorities should be and how we can achieve our goals

If you would like our volunteers to get involved with your research, or to find out how else Epilepsy Action can assist researchers, please email ***researchadmin@epilepsy.org.uk***

Research and Quality Improvement strategy

We are currently writing our Research and Quality Improvement strategy for 2023-2026. The new strategy will look different from previous ones, as healthcare quality improvement will be embedded within it. We have made this choice as we believe both new research findings and implementing those findings within healthcare practice are vital to improving the lives of people with epilepsy.

Our new strategy will set out the priority areas that we want to impact. These will be based on a large body of evidence, including the Epilepsy Priority Setting Partnership, NICE guidelines, NASH3, GIRFT Neurology Report, Epilepsy 12 audit, and many others. However, the most important voice in our strategy comes from our members and volunteers, who are letting us know what their priorities are and what they would like to see improved for people with epilepsy. Listening to these voices will ensure our research and quality improvement projects can have the maximum benefit for people living with epilepsy.

We will share the highlights of the new strategy with you in the next edition of *Epilepsy Professional*.

Markus Reuber

Highlights

Top picks from *Seizure*

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

In 2005, the ILAE defined epilepsy as "a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" [Fisher et al, 2005]. This definition did not fully recognise epilepsy as a complex neurobiological disorder of the brain in which the development of seizures is often preceded by cognitive, psychological or psychiatric symptoms [Hesdorffer et al, 2012]. However, it did embrace the most important non-seizure consequences of epilepsy which, at least for those individuals whose epileptic seizures cannot be stopped completely with treatment, typically have greater effects on health-related quality of life than seizure frequency or severity itself [Rawlings et al, 2017].

The 2014 ILAE definition of epilepsy dropped any reference to non-seizure manifestations of epilepsy. Epilepsy is currently defined as "a disease of the brain defined by … at least two unprovoked (or reflex) seizures occurring >24 h apart, …one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years … [or the] diagnosis of an epilepsy syndrome" [Fisher et al, 2014].

The failure to mention the neurobiologic, cognitive, psychological and social aspects of this multifaceted disease more prominently in the most recent definition of epilepsy is particularly regrettable because, as the authors of the 2014 definition point out, "the definition of epilepsy will affect diagnosis and treatment in both resource-rich and resource-poor societies". By not characterising epilepsy more broadly as a complex neuropsychiatric disease, and by restricting the focus to seizures, the 2014 definition represents a missed opportunity. It does a disservice to individuals with epilepsy and clinicians interested in offering a holistic treatment service aiming to improve patients' quality of life rather than simply reducing their seizures.

My editor's choice from *Seizure* volume 103 is a prospective clinical study by Rui Zhong et al [2022], exploring predictors of the development of drug resistant epilepsy – including depression and anxiety – in patients newly presenting with seizures at the time of their epilepsy diagnosis. Confirming the findings of a previous study [Hitiris et al, 2007], this paper demonstrates that the presence of depression at the point of diagnosis of epilepsy makes it three times more likely that the seizure disorder will prove drug resistant. Patients with depression and anxiety at diagnosis were five times more likely not to respond readily to anti-seizure medications (ASMs) than patients with neither of these common 'comorbidities' of epilepsy.

This paper should help to make future prediction models of drug-resistant epilepsy more accurate and facilitate an earlier consideration of treatments such as epilepsy surgery. Perhaps this paper will also persuade more clinicians to assess the mental health of their patients with seizures. Additionally, it will hopefully make it more likely that the next ILAE definition of epilepsy will recognise the fallacy of reducing epilepsy to a disease characterised just by seizures. Perhaps it will help to ensure that the next definition fully embraces all aspects of epilepsy (seizure and non-seizure),

By not characterising epilepsy more broadly as a complex neuropsychiatric disease, the 2014 definition represents a missed opportunity

including the bidirectional relationship between seizures, mental health, cognitive issues and social problems. Last but not least, this paper may motivate researchers to study whether tackling depression and anxiety therapeutically at the point of epilepsy diagnosis can improve anti-seizure treatment outcomes.

Neurodiversity in epilepsy

The last two decades have witnessed a steady increase in the prevalence of autistic spectrum disorders. While

other interpretations of this trend are possible, it is likely that most of this increase is due to a greater recognition of autism and autistic spectrum disorders [Zeidan et al, 2022]. Previously largely viewed as manifestations of disability, some authors have more recently conceptualised autistic features as one of several manifestations of neurodiversity. This is an important change which recognises that, while autism affects the ways in which individuals perceive and interact with their world, these differences of perception and behaviour are not invariably distressing or disabling. Indeed, while vigorous debate about concepts and terminology continue, it has been argued that – akin to biodiversity – neurodiversity, and the particular contributions neurodiverse individuals can make on the basis of their particular perceptional and behavioural tendencies, are a bonus to society at large.

It has been argued that neurodiversity, and the particular contributions neurodiverse individuals can make on the basis of their particular perceptional and behavioural tendencies, are a bonus to society at large

Regardless of whether autistic tendencies are pathological (in the sense of causing distress or disability) or whether they simply reflect manifestations of interindividual variance of neurodevelopment, it is important to recognise such traits. Those individuals who struggle with the effects these traits have on their lives may need support or intervention. Those who don't struggle may still benefit from a better understanding of the ways in which they differ from the 'neurotypical' majority. The recognition of autistic tendencies may also help others by allowing them to optimise their interactions with people with such traits and to minimise the risk of misunderstandings.

The recognition of autistic tendencies is of particular importance in people with epilepsy, in whom such traits are likely to be present in more than one in three individuals with intellectual disabilities and one in 20 of those who are cognitively able [Berg and Plioplys, 2012].

Not surprisingly, the lack of clear, categorical differences between autistic and non-autistic individuals poses a significant challenge to the 'diagnosis' (or recognition) of autistic spectrum disorders [Stenning and Bertilsdotter Rosqvist, 2021]. This is further exacerbated by the ongoing evolution of the concept of neurodiversity and its relationship with autism. However, in view of the importance of identifying autistic tendencies, it is important to try and characterise such features. This is especially so when there are concerns about a person's level of social functioning or when an individual experiences distress which could be related to their (unrecognised) autistic traits.

My editor's choice from *Seizure* volume 104 is a narrative review by Martina Giorgia Perinelli and Monique Cloherty [2023]. This summarises what we know about the performance of screening and diagnostic tools for autistic spectrum disorders in populations of cognitively able adults with epilepsy. A range of self-report questionnaires and interview methods

have been used in this population. Despite some deficits in terms of specificity, the broader use of screening instruments like the Autistic Spectrum Quotient (AQ) and the Sensory Reactivity Scale (SRS-AS) could help to raise greater awareness of the relatively common association of epilepsy with autistic spectrum disorders. It may also alert clinicians to adapt their interactions and interventions appropriately. This, in turn, might lead to more (and urgently needed) research on the performance of 'gold-standard' interview techniques for the characterisation of autistic tendencies in people with epilepsy.

The fate of topiramate

It is now well-recognised that the exposure of babies to sodium valproate in the womb may cause major malformations, detectable at birth, that are likely to result from teratogenic effects in the early parts of pregnancy. Also, it may lead to more subtle abnormalities of brain development manifesting as slight deficits of cognitive or social functioning in later life [Davies et al, 2020]. However, the journey from the discovery of the anti-seizure properties of the drug to the implementation of policies to reduce the risk of in-utero exposure to valproate has been a long one. Valproic acid was first synthetised in 1882, but its seizure suppressing effects were only discovered by serendipity in 1963 [López-Muñoz et al, 2012]. Valproate was first approved for the treatment of epilepsy in France in 1967, with a first controlled trial proving its effectiveness in 1975 [Richens and Ahmad, 1975]. A dose-dependent risk of major malformations in babies exposed to valproate in the womb was initially reported in the early 1980s [DiLiberti et al, 1984]. The link between intra-uterine valproate exposure, a reduction in verbal IQ and increased risk of behavioural problems in children was first described in 2004 [Adab et al, 2004]. However, it was not until 2018 that the European Medicines Agency recommended that valproate should only be used in women of childbearing age if their epilepsy has not responded to other ASMs, and if they are enrolled in a pregnancy prevention programme [Davies et al, 2020].

Regulatory agencies are currently considering whether they should respond more quickly to similar concerns about topiramate. Topiramate was first synthesised in 1979. Its anticonvulsant potential was surmised because of its chemical structure and promising results in limited animal experiments, and its development as an ASM started in 1986. It became a great commercial success after its FDA approval in 1996 [Maryanoff, 2016]. However, by 2008, pregnancy registers had identified topiramate as a likely cause of congenital malformations (especially cleft palate) [Hunt et al, 2008], and by 2014 a link with reduced birth weight had been demonstrated [Veiby et al, 2014].

Regulatory agencies are currently considering whether they should respond more quickly to similar teratogenicity concerns about topiramate

My editor's choice from *Seizure* volume 105, is a cohort study of 28 children whose exposure to topiramate in utero had been captured by the UK pregnancy register [Knight et al, 2023]. In this study, Rebecca Knight and her collaborators interviewed mothers

about their children aged 2.5 to 17 years at the time of assessment. Six topiramate-exposed children were born small for gestational age, and four had been diagnosed with autism spectrum disorder (considerably more than expected, given a UK background prevalence rate of about 1%). Significant associations were observed between birthweight, topiramate dose and Vineland Adaptive Behaviour Scale-Third Edition (VABS-III) assessment scores.

The study by Knight et al. adds to recent evidence from two other studies suggesting a link between topiramate and neurodevelopmental disorders. One is a population-based healthcare records study from the Nordic countries, demonstrating an increased risk of autistic spectrum disorder [Bjørk et al, 2022]. The other is a previous cohort study indicating an increased risk of learning disability among topiramate-exposed children (n= 27) [Bech et al, 2018]. While confirmation of these findings would be desirable, it may well be that topiramate will soon join valproate as an ASM which should not be used in pregnancy if alternative treatment is possible.

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A plan for efficiency

I'm starting with apologies to Oscar Wilde, who, in the *Picture of Dorian Gray*, said "There is only one thing in the world worse than being talked about, and that is not being talked about". I say, the only one thing in the world worse than causing disruption to the NHS when you strike, is not causing disruption to the NHS when you strike.

"*Broken, embarrassing, dangerous*" – no, not a description of the locks on the Glastonbury Portaloo doors, but how commentators are describing the NHS in 2023. *Epilepsy Professional* is not a political journal and I may have pushed editorial policy to the very limit with thinly veiled Br*xit innuendos in previous columns. However, it would be remiss of me not to allude to the strikes that have hit the NHS over the Winter of 2022 and Spring of 2023.

I think we have unintentionally hit upon a method of massive efficiency savings that I want to rebrand as the 'Thomas plan'. (I would like my medal to be WhatsApp-ed to me (efficient communication) by Liz Truss (efficient leadership – short and memorable tenure), and for the medal to be based on the Ashes urn (tiny in its efficiency)).

The basis of the 'Thomas plan' is that not every striking professional will have the same impact to services. For example, when the highways agencies, who place orange cones across motorways, went on strike for 24 hours, the net impact was that the road system worked more smoothly for a day.

The plan is loosely based upon faddy exclusion diets where you stop eating major food groups one by one, and see whether your tendency towards mild irritable bowel syndrome is marginally better. It is up to the reader to decide whether they feel that the NHS is chronically constipated, or whether the work force is numerically wasting away, as these are political statements that I can neither support nor disavow. I digress. The plan is that each major area of the work force withdraws their labour for seventy-two hours and we assess the increase in workload for colleagues, and the reduction in healthcare delivery for patients. Any healthcare group where we are equivocal about the disruption then strikes for a month and we assess whether we need them back at work at all.

Who would you suspect would be the most likely to be permanently laid off? Who amongst your colleagues do you secretly feel creates more work than they resolve? Is there a nepotistic job somewhere where someone's only role is to test the NHS custard cremes?

I am a rational man with a scientific mind, so far be it from me to prejudice the results of the 'Thomas plan' by trying to second guess the outcomes. However, my Google for 'who is the most useless person in the NHS' brought up a quote from a Conservative MP for Shipley, Philip Davies, who blames the current "shambles of the NHS" on "far too many overpaid and utterly useless senior managers" [Pearson, 2023]. Which I think brings me to the coup de grâce of the 'Thomas plan' – if we discover that instead of being over-staffed with luxury services and over managed by fat cats, that we are instead a tightly knit highly-motivated and under-staffed service, then we get immediate pay restoration and a historic reinvestment to NHS services.

Further reading

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Dates for the diary

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

2023

29-31 March
International Congress on Structural Epilepsy & Symptomatic Seizures
Gothenburg, Sweden
bit.ly/3ezBJRs

5-8 May
Seventeenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3FIlgdw

23-24 May
KetoCollege Advance
East Grinstead, UK
ketocollege.co.uk

20-24 June
15th European Paediatric Neurology Society Congress (EPNS)
Prague, Czech Republic
epns.info/epns-congress-2023

2-6 September
35th International Epilepsy Congress
Dublin, Ireland
bit.ly/30Spwk8

8-13 October
10th Eilat Educational Course: Pharmacological treatment of epilepsy
Jerusalem, Israel
eilatedu.com

2024

3-8 March
4th International Training Course on Neuropsychology in Epilepsy
Lyon, France
bit.ly/3gLFWD4

5-8 May
Seventeenth Eilat Conference on new Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3u7Mzm6

Next issues:

Prof Patrick Kwan

Prof Kwan discusses self discontinuation of anti-seizure medications and managing this in patients.

Dr Joseph Anderson

Dr Anderson describes the use and importance of population level health monitoring in epilepsy.

If you are interested in submitting a research paper for inclusion in *Epilepsy Professional,* please contact the Editor:

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