epilepsy action

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epilepsy professional

Medicinal cannabis

The role of medical cannabis in epilepsy

Hannah Cock

Stroke and epilepsy – Emsley | Brigo | Zelano

Intellectual disability care – Watkins | Kerr

Subjective views – Rawlings | Reuber

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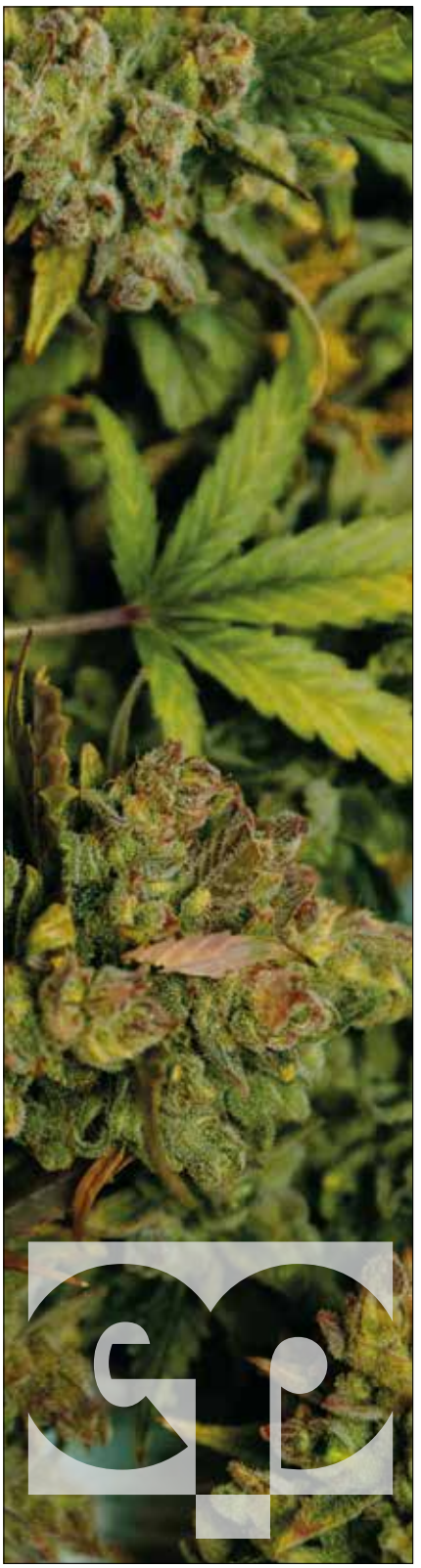


I hope our readers have had an enjoyable and restful summer break. The days already seem to be on the turn and it's with this in mind that we turn our minds to this autumn edition of *Epilepsy Professional*.

No doubt our article on medicinal cannabis will grab your attention, as it dominated the national, European and world news headlines over the last 12 months. And with this, the profile of epilepsy has undoubtedly been raised. Professor Hannah Cock writes candidly, touching on her personal experience, but really revealing the evidence basis for its use, efficacy, side-effects and its legal position. She highlights where we find ourselves with regard to this transforming landscape. She comments that it is not the cure for all and that we must still advocate anti-epileptic drugs. However, she makes a plea to be at the very least well informed about medicinal cannabis if only to provide the hope and confidence that patients and families with epilepsy need.

Stroke services also tend to grab national headlines. In this edition of *Epilepsy Professional*, Professor Emsley, Dr Brigo and Dr Zelano take a turn at unpicking the intimate links between stroke and epilepsy. This encompasses epilepsy in the elderly, an area close to my heart, and is part and parcel of most of our day-to-day clinical practice. I read with interest their proposed disease mechanisms of epileptogenesis, in particular with reference to the blood brain barrier and intricate microstructures.

I think our readers will really enjoy Dr Greg Rawlings' and Professor Marcus Reuber's article on subjective views. This is a fantastic piece of qualitative research unravelling the storytelling in epilepsy and in non-epileptic attack disorder. This piece of work has particular relevance to epilepsy, a condition which lacks a diagnostic test and relies on storytelling and on the interpretation of that story. This article draws out some clinical practice pointers in terms of assisting the diagnostic process and in individualised management. As an epilepsy clinician, I was also reminded of the privileged position I have in helping patients and families make sense of their narrative.

Dr Lance Watkins and Professor Mike Kerr provide another timely article on care in intellectual disability. Again, the themes in this article will be familiar to many, not least the increased mortality from epilepsy in this patient group, behind pneumonia and aspiration pneumonia. The authors highlight areas for change which include an end of fragmented care provision, risk reduction, training and education, and a set of standards for working in generic services. It is pleasing to hear that the Royal College of Psychiatrists is taking this seriously and establishing a set of professional standards/accreditation in the management of people with epilepsy and intellectual disability.

I think you'll agree this autumn edition is jam packed with up-to-date pieces relevant to clinical practice. And so, just in case you have a few days of annual leave left, and, well, especially if an Indian summer beckons, here's your deckchair reading.

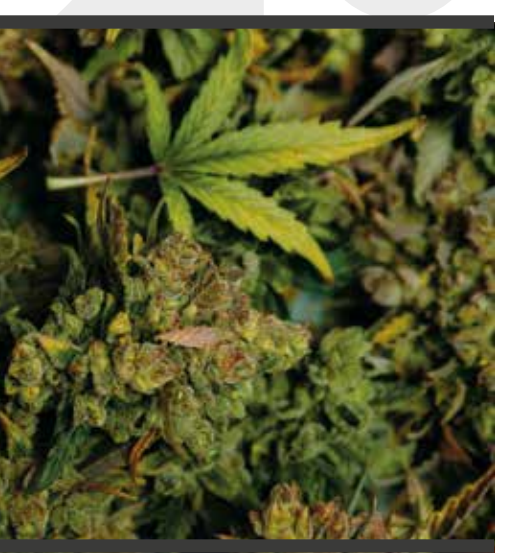
Ann Johnston
Consultant neurologist
Executive medical adviser
Epilepsy Professional

contents

20 subjective views

Gregg Rawlings
Markus Reuber

Dr Rawlings and Prof Reuber discuss the clinical and therapeutic value of the subjective narratives told by patients about their condition



Adapting to change is one thing we have to learn to do. Take this year, for example. One second we are navigating daily life through a rogue snow storm in April, the next, we are trying to construct a makeshift air con from a fan and a few bottles of water. Change came, and we faced it head on.

The fantastic articles in this issue of *Epilepsy Professional* cover a wealth of different topics, but change is something they all have in common – either adapting to it or calling for it. On page 10, you can find Prof Emsley, Dr Brigo and Dr Zelano's article describing the complex relationship between stroke and epilepsy. They stress that more research is needed and that the area deserves more attention, which has led to the creation of the first international congress on epilepsy in cerebrovascular disease (page 35). Meanwhile on page 16, Dr Watkins and Prof Kerr highlight that people with intellectual disabilities and epilepsy have inadequate access to appropriate healthcare. They summarise some recommendations to help improve the situation.

Dr Rawlings and Prof Reuber's article on page 20 looks at the role of patients' subjective narratives in the clinic. They say that in the era of objective and bio-medical approaches to healthcare, subjective accounts are heard less and less. But they argue that these hold important clues about petients. And finally, Prof Cock's article on page 26 helps us keep up with the currently fast-changing landscape of medical cannabis in the UK, offering advice on how to discuss this with patients.

We hope you enjoy this issue and have a great end to the summer!

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UK clinicians will be able to prescribe cannabis-based medicines by autumn

Specialist clinicians will be able to legally prescribe cannabis-based medicines by the autumn, the Home Office has said.

The announcement came on 26 July from Home Secretary Sajid Javid, that cannabis-based medicines will be rescheduled from Schedule 1 under the Misuse of Drugs regulation 2001.

As a result, senior clinicians will be able to prescribe cannabis-based medicines to those with an "exceptional clinical need", Mr Javid stated.

In the meantime, clinicians can still put in applications for cannabis-based medicines to the expert panel that was set up last month. This was put together by Prof Dame Sally Davies, Chief Medical Officer for England, as a measure in the interim, while the review was taking place. The Home Office has added that it will waive any licence fees for applications already made and future applications.

The next step is to develop a clear definition of what cannabis-based products are, the Home Office has said. The Department of Health and Social Care (DHSC) and the Medicines and Healthcare products Regulatory Agency (MHRA) have been tasked with this. Only those products that meet those specifications will be moved out of Schedule 1.

The Home Office's decision has come after last month's government review into cannabis-based medicines. This review found evidence of their effectiveness for some health conditions. The review was sparked when Mr Javid used an exceptional power to issue a 12-year-old boy a licence for cannabis oil.

Billy Caldwell's cannabis oil was confiscated at Heathrow airport in June. His mother Charlotte had travelled to Canada to source the medicine for him. Billy's seizures worsened and he was admitted to hospital a few days after his medicine was taken. This prompted the government to issue a licence and set up the review.

In the first part of the review, Prof Dame Sally Davies looked at evidence of the effectiveness of cannabis-based medicines. She concluded that they should no longer be classed as Schedule 1. In the second part of the review, the Advisory Council on the Misuse of Drugs (ACMD) provided some short-term advice. It agreed with Prof Davies, that the medicines should be rescheduled.

The ACMD made a few recommendations to the government about cannabis-based medicines, including creating a clear definition of what they are. It also recommended that clear clinical guidelines should be put together to ensure safe prescribing of these medicines.

The ACMD stressed that a lot more research and clinical trials are needed on the effectiveness and safety of these medicines. It will also be providing longer-term advice to the UK government.

Cannabis for recreational use will remain illegal in the UK.

Interactions in enzyme-inducing anti-epileptic drugs

A new study from Italy has found that patients treated with enzyme-inducing anti-epileptic drugs (EIAEDs) are at a high risk of medicine interactions.

Zaccara and colleagues set out to look at how often EIAEDs are prescribed to people with epilepsy alongside other medicines.

The researchers included people in the study who had been treated with at least one first-generation EIAED – carbamazepine, phenytoin, phenobarbital and primidone. Study participants had also received prescriptions for non-epilepsy medicines from a list of 103 compiled by the researchers, the metabolism of which is induced by EIAEDs.

The study included 9,221 people with epilepsy. The authors explained that there were 2,538 combinations of EIAEDs and non-epilepsy medicines found, which could result in "serious clinical consequences". Another 3,317 combinations were found with moderate interactions.

The study authors said that few studies have looked into medicine interactions in outpatients with epilepsy. They concluded that people treated with EIAEDs are at a very high risk of interactions with other medicines they may be prescribed. The study was published in the August issue of *Epilepsy & Behavior*.

Tribunal rules against £89m fine over medicine price hikes

A UK Competition Appeal Tribunal has overturned the decision to fine two pharmaceutical companies over price hikes of their phenytoin sodium capsules.

The Competition and Markets Authority (CMA) issued a record £89 million fine to Pfizer and Flynn Pharma in December 2016. This was a result of the two pharmaceutical companies raising the prices for their epilepsy medicine by 2,600% overnight in 2012.

In June, the tribunal ruled that he CMA did not correctly apply the legal test when they found that the hiked-up prices of the medicine were unfair.

However, the tribunal said that there is "much in the [CMA's] decision with which we agree". It also highlighted that this ruling "does not imply any finding by the tribunal as to whether there has been an abuse by Pfizer or Flynn of their respective dominant positions".

In a statement, the CMA said that it is disappointed with the judgement but is considering issuing an appeal of the decision. It said its decision to issue the fine was in order to protect the NHS, patients and taxpayers.

The CMA said: "The tribunal has provisionally decided to remit the

case back to the CMA for further consideration, after ruling against its finding of abuse. The tribunal's judgment makes it clear that a finding of abuse remains possible given the size of the price increase that occurred."

Following the decision of the tribunal, Pfizer issued a statement saying the company is pleased with the decision. It added: "Our priority has always been to ensure a sustainable supply of our medicines to UK patients and this was at the heart of our decision to divest this medicine."

Epilepsy Action chief executive Philip Lee said: "Anything that might jeopardise the continuity of supply of epilepsy medicines must be avoided and protected against. That includes the potential for unfair pricing of medicines which could affect their affordability to the NHS and limit their availability."

Teva discontinues lamotrigine tablets

Pharmaceutical company Teva has decided to discontinue a number of its lamotrigine tablets in the UK once current stocks run out. The 50mg, 100mg and 200mg tablets are already out of stock. The 25mg tablets and the 100mg dispersible tablets are available until January 2019. The dispersible 25mg tablets are available until August next year.

The company has no plans to discontinue the 5mg dispersible tablets.

For updates on epilepsy medicine availability, visit *bit.ly/2uR6WWD*.

Auras and surgery

A study from India has looked at the role of auras in predicting surgical outcomes in drug-resistant temporal lobe epilepsy (TLE).

Study authors Radhakrishnan *et al* compared surgical outcomes in 456 people with and without auras who underwent anterior temporal lobectomy (ATL) between 2009 and 2014. They were followed up after three months, 12 months and the annually.

Of these people, 344 had auras. The study found that there was no difference in surgical outcome between people with and without auras. But auditory and vertiginous auras in people were linked to poorer surgical outcomes, the authors explained.

The study, published in *Epilepsy Research*, concluded that while presence of aura itself does not affect outcome, particular types are linked to poorer outcomes. The researchers suggest more extensive screening of the seizure onset zone.

Rosemont phenytoin oral suspension discontinued

Pharmaceutical company Rosemont has discontinued its version of phenytoin oral suspension in the UK. Anyone taking this medicine should speak to their doctor.

Safety, effectiveness and predictors of outcomes in epilepsy surgery in children under three years old

A new study from Germany has looked at the epilepsy surgery in children in the first three years of life. The study aimed to look at predictors for long-term seizure freedom and cognitive development after surgery in this age group.

Study authors Kadish *et al* explained that the majority of children who end up undergoing epilepsy surgery are diagnosed with epilepsy before the age of three. However, only a few of these actually undergo surgery in early childhood.

As well as finding predictors for a positive outcome, the researcher also wanted to try to determine the appropriate timing for surgery in this age group.

The authors analysed data from 48 children aged around one year old at surgery. The surgical treatments included hemispherotomies, as well as multilobar and intralobar resections. The causes for the children's epilepsies included cortical malformations in the majority, ischemic lesions, benign tumours or tuberous sclerosis.

At the last follow up, 60% of children were found to be seizure free, and 38% had been taken off anti-epileptic drugs (AEDs). Children undergoing intralobar surgery were more likely to have seizure control than those undergoing other types of surgery. The researchers also found that seizure freedom was associated with the completeness of resection. Seizure recurrence was found to be linked with early post-surgical seizures.

As well as seizure control, the researchers also looked into development. Before undergoing surgery, they found that adaptive and cognitive development was impaired in 89% of the children. They found that development was worse in children who had had epilepsy longer or in whom the lesion was larger. This determined the developmental outcome after surgery.

The study authors concluded that epilepsy surgery in very young children is safe and efficient. They added that their findings support the use of early surgical intervention, as epilepsy duration was found to be a modifiable predictor of development outcomes.

The study was published in August in the journal *Neurosurgery*.

US FDA approves cannabidiol

On Monday 25 June, the US Food and Drug Administration (FDA) approved the new cannabis-based medicine Epidiolex for use in Lennox-Gastaut syndrome (LGS) and Dravet syndrome.

GW Pharmaceuticals' medicine has been approved for use for the two rare and severe forms of epilepsy in two-year-olds and above. According to reports, it is set to become available in the US in the autumn.

A decision is expected from the European Medicines Agency (EMA) on the use of Epidiolex in the UK and Europe early next year. If approved, the medicine will become available later in the year.

Cannabidiol (CBD) is derived from cannabis and does not contain the psychoactive part of the plant. CBD has recently undergone a number of clinical trials to assess its effectiveness and safety when treating LGS and Dravet syndrome. It has been shown to have beneficial effects in both.

The FDA said the most common side-effects from the clinical trials included sleepiness, loss of appetite and diarrhoea. People also sometimes experienced a rash, weakness, poor quality sleep, infections and an impact on the liver.

Epilepsy Action's position statements on cannabis-based medicines can be found online at *epilepsy.org.uk/cannabis*.

Termination of pregnancy in women with epilepsy

A new study from Israel has looked at the reasons pregnancies in women with epilepsy were terminated at the Rabin Medical Center between 2004 and 2016.

Study authors Goldstein *et al* explain that terminated pregnancies are often not included in studies looking at medicine teratogenicity or the effects of recurrent seizures. They said that this has meant that this may have reduced the measured incidence of congenital malformations and effects of anti-epileptic drug (AED) exposure.

The study looked at medical records in their medical centre and identified 58 terminated pregnancies in women with epilepsy in the research timeframe. The main reason for terminating pregnancy was spontaneous abortion requiring medical intervention (46.6%). Other reasons included patient's request (31%) and medical recommendation (10.3%). The reason was unknown in 12.1% of cases.

The researchers added that the reasons why patients requested a termination included AED exposure and uncontrolled epilepsy.

The study was published in *Epilepsy & Behavior*.

Rufinamide approved for use in children over age of one

The European Commission (EC) extended the approval for the epilepsy medicine rufinamide on 24 August, to include children as young as one year old. This medicine can now be used in this age group as adjunctive therapy for treatment of Lennox-Gastaut syndrome (LGS).

Rufinamide, produced by the company Eisai and marketed as Inovelon, was initially authorised as an add-on treatment for LGS in children over four years old. Eisai, explained that symptoms of LGS are sometimes observed in younger children.

The EC's decision is based on studies into the medicine specifically in children one year of age or older. The latest study, from Arzimanoglou *et al*, looked at the safety and pharmacokinetics of rufinamide treatment for LGS in children younger than four. This found that the medicine was safe and well-tolerated in this group, and the effects were comparable to those in children over four years old.

The study was published in the *European Journal of Paediatric Neurology* in 2016.

Anxiety common issue in people with some types of epilepsy

Anxiety is common in epilepsy and is linked with some clinical features of the condition, a new US study has found.

Dr Heidi Munger Clary and her colleagues wanted to look at the links between anxiety and epilepsy localisation. They also wanted to look at the association between anxiety and other epilepsy-related and demographic factors.

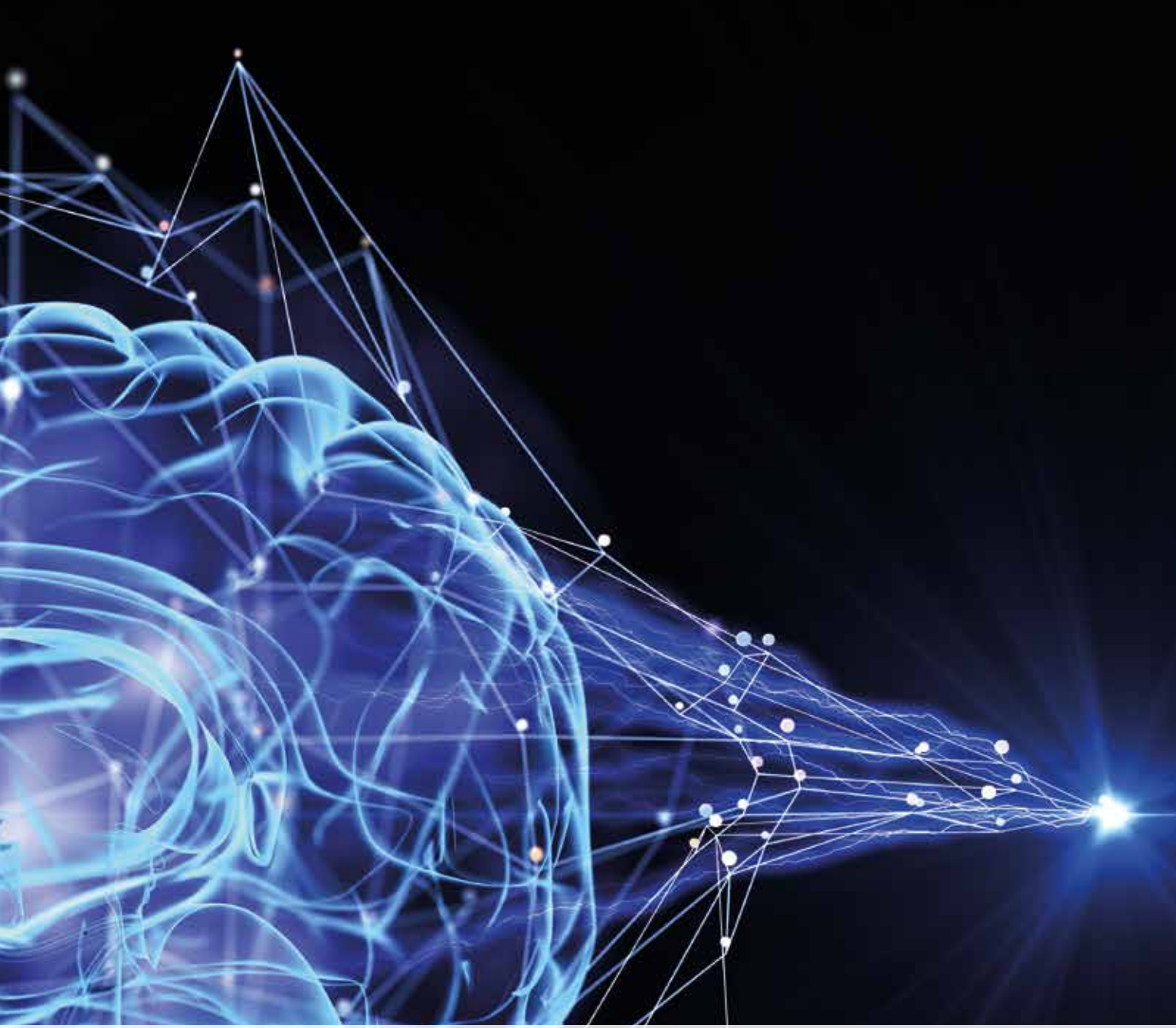
They looked at 540 adults from specialist care. They assessed anxiety symptoms, demographic information, the types of epilepsy and the seizure focus, and depression levels.

The results showed that 46.1% of people had anxiety symptoms. Focal or unknown types of epilepsy were independently linked with anxiety. This was especially so for people with mesial temporal sclerosis. Higher depression scores were also independently linked to anxiety.

Other factors were also linked to anxiety. They included lower education, non-white ethnicity, taking more than one epilepsy medicine and previous head trauma.

Of those who scored high for anxiety, 18.4% did not score high for depression. The researchers also found that only 26% of people with high anxiety were taking an anxiety medicine.

The *Epilepsy & Behavior* study concluded that the results show the importance of screening specifically for anxiety in epilepsy clinics. People should be offered appropriate treatment, the researchers added.



Stroke and epilepsy

Current understanding and approach to management

Professor Emsley, Dr Brigo and Dr Zelano describe the complex relationship between epilepsy and stroke, the treatment of post-stroke epilepsy and the further research necessary in this area

There is a complex relationship between stroke and epilepsy. This article seeks to summarise our current understanding and approach to management, as well as offering some insights into areas of uncertainty where further research will be required.

In the context of an ageing population, there is little doubt that the field of stroke and epilepsy will become an increasingly important area of practice. Seizures can complicate clinically overt stroke, in the form of early post-stroke seizures or late post-stroke seizures, or as post-stroke epilepsy (PSE). Seizures can also arise as a result of otherwise occult cerebrovascular disease (CVD) and be associated with a significantly increased stroke risk.

Seizures and epilepsy following clinically over stroke

Seizures may occur at the time of, or in close temporal association with, clinically overt stroke. When these occur within seven days of stroke, these are generally termed early post-stroke seizures (provoked or acute symptomatic). Late post-stroke seizures (unprovoked or remote symptomatic seizures) are those occurring after a variable interval (days to years) following stroke. These are generally regarded as seizures occurring at least seven days after the stroke. Even a single late post-stroke seizure implies a diagnosis of PSE. This is due to the probable enduring predisposition to generate epileptic seizures. It is also taking into account the occurrence of 'one unprovoked seizure and a probability of further seizures of at least 60% over the next 10 years' as a defining condition for epilepsy [Fisher *et al*, 2014]. Seizure freedom can often be achieved in PSE, with some studies reporting this in more than 80% of cases. It is not known if appropriate treatment is always pursued.

Even a single late post-stroke seizure implies a diagnosis of post-stroke epilepsy due to the probable predisposition to generate epileptic seizures

With regard to treatment of seizures after stroke, different approaches are taken depending on the timing of the seizures. An isolated short-lived early post-stroke seizure may require no specific treatment, given that the risk of a further early post-stroke seizure is low. Status epilepticus requires urgent intravenous anti-epileptic drug (AED) treatment. Recurrent early post-stroke seizures may be treated with an AED in the short-term. There is a paucity of studies of treatment of late post-stroke seizures. For instance, the difference between policies of immediate versus deferred AED treatment has not been investigated in PSE. But given the fact that virtually all patients with a first unprovoked late post-stroke seizure are at a high risk of seizure recurrence, AED treatment should be considered. Of course, it is necessary to consider whether a seizure is in keeping with a post-stroke seizure, based on semiology and correlation with the stroke lesion. The risk of seizure recurrence and the potential benefit of prophylactic AED treatment should be discussed with the patient, taking into account individual circumstances. There may be situations where AED treatment should be deferred. For instance, this could be in situations where the patient is constantly supervised, the risk of seizure-related injury is low (eg if the patient is non-ambulant), or the seizures are very mild.

The overall evidence supporting the use of AEDs in post-stroke seizures is of low-quality and insufficient to provide clinical recommendations. There is evidence of some AEDs adversely affecting risks of cardiovascular events and death. Enzyme-inducing AEDs can interact

with cardiovascular prophylaxis, while some AEDs are associated with atherogenic serum lipid profiles. Based on clinical experience, lamotrigine and levetiracetam appear to be suitable AED choices, but further studies are required to provide robust evidence on the efficacy and tolerability of AEDs for treating PSE [Brigo *et al*, 2018]. It is worth considering individual patient factors as well as AED characteristics. These may be things such as pharmacokinetic properties, ease of use, patient preference, effects on cognition, behaviour and functional motor recovery following stroke.

Late-onset seizures and late-onset epilepsy in clinically occult CVD

Late-onset epilepsy (LOE) refers to the onset of epilepsy in later life – most often defined as being after the age of 60. CVD is widely believed to be the single most important cause of late-onset epilepsy.

LOE is important for a number of reasons. With an ageing population, its prevalence is increasing. Older adults are more likely to develop seizures than younger individuals. The annual incidence of epilepsy rises from 86 per 100,000 people aged 65-69 years to 135 per 100,000 people aged over 80 years. Older adults with epilepsy have significantly increased mortality. Late-onset seizures predict subsequent stroke. Epilepsy in later life has been expertly reviewed [Brodie *et al*, 2009]. There is sometimes a tendency for the importance of LOE to be diminished, at least anecdotally. There can be a perception that because seizures in older adults can often be controlled with AEDs rather more easily than in younger adults, this may contribute to less attention being given to LOE than it deserves.

Determining the true incidence and prevalence of LOE is difficult, not least because the diagnosis of epilepsy in older adults is often not straightforward. LOE may not be considered when the patient is first assessed even in specialist settings. We know, for instance, that seizure is the commonest alternative diagnosis among patients initially suspected to have stroke or transient ischaemic attack (TIA). It accounts for 20% of non-stroke or TIA diagnoses [Gibson & Whiteley, 2013]. Seizure presentations in older adults can be surprisingly varied and can include falls, confusional states, amnesia and focal neurological symptoms. A number of factors contribute to diagnostic difficulties in older adults. They include differences in clinical features of seizures in older adults by comparison with younger adults, the frequent coexistence of cognitive impairment and a lack of a witness description.

Given the increased risk of subsequent stroke in those developing LOE, it seems reasonable for vascular risk to be addressed and managed. This has been advocated for more than a decade [Sudlow, 2004], but the extent to which this is actively pursued in routine practice is not known. It is perhaps surprising, given the likelihood that occult CVD is a frequent cause of LOE, that this whole field has not received more attention. Further research is needed to better describe the epidemiology and natural history, as well as to understand the mechanisms of epileptogenesis and opportunities for intervention.

Determining the incidence and prevalence of late-onset epilepsy (LOE) is difficult, not least because the diagnosis of epilepsy in older adults is often not straightforward

CVD and epilepsy: a bidirectional relationship

There does seem to be clear evidence of a bidirectional relationship between LOE and CVD. Stroke is the most important risk factor for the development of LOE, while LOE confers a nearly three-fold increase in the risk of stroke [Cleary *et al*, 2004]. In the first year after a stroke, the risk of epilepsy may be

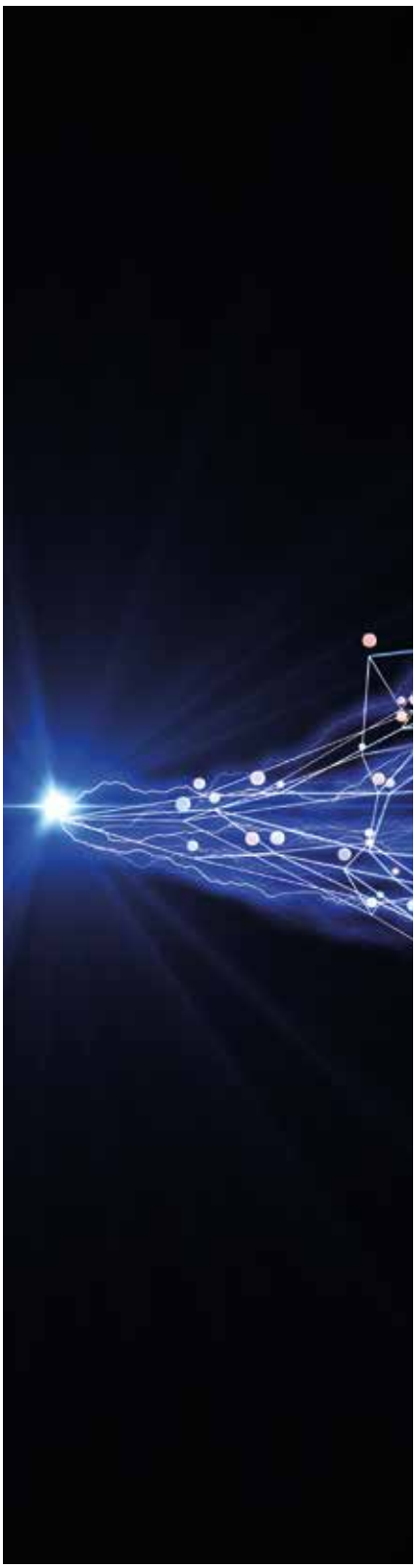
increased by up to 20 times [So *et al*, 1996]. Epilepsy occurs more often after stroke involving the cortex, or in the context of haemorrhage, large or multiple lesions, or where acute symptomatic seizures have occurred [Lancmann *et al*, 1993]. The long-term cumulative risk of PSE after a cerebrovascular event varies from 2-15%, with differences in reported rates reflecting differences in study cohorts. These include stroke aetiology, follow-up time, outcome measures, loss to follow-up, definitions (including that of epilepsy), or whether survival was corrected for [Zelano, 2016].

Apart from those with epilepsy complicating clinically overt stroke, there is compelling evidence that occult CVD accounts for a significant proportion of otherwise cryptogenic LOE [Gibson *et al*, 2014]. Previous studies suggest that there is a relationship between vascular risk factors and the risk of LOE, apart from the relationship that exists through clinically overt stroke. In addition, there is evidence from several studies of an excess of clinically unsuspected, radiological CVD, particularly cortical infarction but apparently also excess subcortical small vessel disease changes. The study by Cleary *et al* [2004] reported a highly significant difference in stroke-free survival between older people with LOE and without. The study compared 4,709 individuals who had seizures beginning after the age of 60 years, and 4,709 randomly selected matched controls with no history of seizures ($p<0.0001$). The data were based on the UK General Practice Research Database. The relative hazard of stroke at any point for people with seizures compared with the control group was 2.89 (95% CI 2.45-3.41) [Cleary *et al*, 2004]. Thus, the onset of seizures in later life was found to be associated with a striking increase in the risk of stroke. Similar findings were reported in a recent study based on the Swedish stroke register (Riksstroke). It involved data from 1,372 patients with a first seizure or epilepsy diagnosis within 10 years of the index stroke [Zelano *et al*, 2017]. This study

Stroke is the most important risk factor for the development of LOE, while LOE confers a nearly three-fold increase in the risk of stroke

A typical case: seizures initially misdiagnosed as transient ischemic attacks

An 80-year-old man had been seen at various transient ischemic attack (TIA) clinics with episodes of speech disturbance. He had been managed as having recurrent TIAs. Review of his clinical history, including a verbal account by a witness, revealed the occurrence of numerous episodes (more than would be typical for embolic TIAs). These were stereotyped (seizures are often repetitive, with stereotyped features), and lasted several minutes (can occur with seizures or TIAs). They comprised mutism (aphasia can be an ictal phenomenon) followed by gradual recovery of speech. During the episodes, he would be vacant and be plucking at his clothes (automatism), and exhibit confused behaviour afterwards (post-ictal confusion). He could not recall the episodes (amnesia). These episodes were clearly in keeping with focal impaired awareness seizures. The patient was initially reluctant to accept a diagnosis of epilepsy, having previously been told the episodes were TIAs. However, after further discussion, he did accept anti-epileptic drug (AED) treatment, not least because of the potential to resume driving if seizure freedom was achieved. A magnetic resonance imaging (MRI) brain scan showed diffuse small vessel CVD changes and involutional change, but no other lesions. A clinical seizure with epileptiform changes arising from the left temporal region was captured on a routine scalp electroencephalogram (EEG). The electrical event lasted approximately 50 seconds, during which the patient vocalised, became agitated, started to fiddle with clothing and was not responsive.



found 5-20% of incident cases of seizures or epilepsy after 60 years of age could herald stroke. Further research is needed on how to reduce the risk of stroke in patients with late-onset seizures or epilepsy.

Mechanisms of epileptogenesis

Mechanisms of epileptogenesis due to CVD remain relatively obscure [Gibson *et al*, 2014]. Radiological lesions involving the cerebral cortex in clinical stroke would generally be assumed to cause epileptogenesis via cortical irritability. As discussed above, clinically occult CVD may be deemed responsible for the development of otherwise cryptogenic LOE. Radiological markers of small vessel CVD may be present – such as white matter lesions, enlarged perivascular spaces and atrophy. But in the absence of previous cortical infaction or haemorrhage, it can be difficult to reconcile principally subcortical small vessel CVD with the development of epilepsy typically deemed to derive from the cerebral cortex. CVD may cause structural or functional disruption of corticocortical or subcorticocortical circuits which cannot be identified on conventional neuroimaging. Some abnormalities may be overlooked as a result of imaging modality or sequences. For example, subtle structural lesions may not be seen on computed tomography and haemosiderin (eg microbleeds) may not be identified without appropriate MRI sequences (eg susceptibility weighted imaging). Other abnormalities may be undetectable as a result of lack of sensitivity of conventional sequences (eg microinfarcts, disrupted white matter integrity).

CVD may cause a number of changes potentially responsible for epileptogenesis. These might include loss of regulation of processes such as coupling of neural activity and cerebral blood flow (CBF) or transport across the blood-brain barrier (BBB). Such processes depend on the coordinated activity of the 'neurovascular unit' comprising the microvascular endothelium, and neuronal and glial cell elements in close proximity. The disordered neurovascular unit may contribute to LOE [Gibson *et al*, 2011]. Significant alterations in cerebral perfusion and metabolism are seen in patients with extensive CVD; changes in these measures are likely to contribute to acute symptomatic seizures in stroke. We have reported structural and physiological imaging correlates of occult CVD in LOE [Hanby *et al*, 2015], but this area merits further study.

Much more needs to be done, both in routine practice and to expand our understanding of epidemiology, natural history, approaches to management and mechanisms

The relationship between seizures and cerebral perfusion is undoubtedly complex and incompletely understood. The microvasculature is abnormal in small vessel CVD, with loss of smooth muscle cells, vessel wall thickening, luminal narrowing, and increased vessel stiffness. Recently, BBB breakdown has received considerable attention as a cause of small vessel CVD. BBB dysfunction can certainly occur as a consequence of seizures but BBB opening is also recognised to promote seizures in humans. Therefore, BBB dysfunction is likely to represent an area worthy of further investigation in the clinical context of

PSE and LOE associated with CVD. Inflammation is also an integral part of diseased hyperexcitable brain tissue, and it may be a key determinant of epileptogenesis, potentially in part due to BBB disruption and haemodynamic changes. At the current time, epileptogenic mechanisms in CVD are incompletely understood but are deserving of further study.

Receiving the attention it deserves

This important area of practice is rightly receiving more attention. But much needs to be done, both in routine practice and to expand our understanding of epidemiology, natural history, approaches to management and mechanisms. A forum entitled 'Epilepsy and Stroke – Can we do better?' was held at the recent 13th European Congress on Epileptology in Vienna, Austria. A dedicated conference, the first of its kind – 'Seizures and Stroke – 1st International Congress on Epilepsy in Cerebrovascular Disease' will be held in Gothenburg, Sweden, 20-22 February 2019 (*seizuresandstroke.com*).

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Intellectual disability care

Care provision for adults with epilepsy and intellectual disability

Dr Lance Watkins and Professor Mike Kerr describe some issues that affect the access to healthcare that people with intellectual disability and epilepsy get, and how care can be improved for this population

People with intellectual disability (ID) and epilepsy often have complex needs and are at an increased risk of physical and psychiatric co-morbidity. The healthcare outcomes for people with epilepsy and ID are confounded by risks associated with seizures, the nature of which is more likely to be severe and treatment resistant. They may also face difficulties accessing the specialist care. Access to appropriate healthcare services may be influenced by factors related to ID. They may include level of cognition, communication difficulties and a lack of capacity to take part in the decision-making process around care needs. The care provision for this complex population is often fragmented and inadequate. It may not always be clear who is responsible for epilepsy management for people with ID, and the reasonable adjustments required to facilitate access to services are often not routinely considered [Kerr *et al*, 2018].

Morbidity and mortality

There is a clear yet complex relationship between epilepsy and ID with a wide range of aetiological influences. An estimated prevalence for epilepsy in the population is 0.8% evidenced by the Quality of Outcomes Framework: Primary Care Domain Report, 2015. For people with ID there appears to be a correlation with severity of ID. The prevalence of epilepsy in people with mild ID is approximately 10%, for people with moderate, severe or profound ID the prevalence is at least 30% [Robertson *et al*, 2015]. Not only is epilepsy a common and significant co-morbidity for people with ID, but people with ID are more likely to experience complex, treatment resistant seizures [McGrother *et al*, 2006]. The clinical picture is further complicated by the fact that people with epilepsy and ID are more likely to experience other comorbidities. These could be physical (sensory impairment, mobility problems, cerebral palsy, vascular and gastrointestinal disease) and psychiatric (depression, anxiety, psychosis, neurodevelopmental disorders, behavioural changes)[Turky *et al*, 2011; Robertson *et al*, 2015].

The combination of ID and epilepsy raises the mortality ratio significantly to at least five times that of the general population

The recent report published by Public Health England [2018] on deaths associated with neurological conditions in England has exposed a concerning trend. There has been a significant increase in the age-standardised mortality rate (ASMR) associated with epilepsy related deaths, exacerbated in recent years (ASMR 6.1 per 100,000 population in 2003-5 and 8.1 in 2012-14). These results are in direct contrast to the downward trend in ASMR for all-cause deaths.

ID and epilepsy are independently associated with increased risk of morbidity and mortality [Heslop *et al*, 2013; Hitiris *et al*, 2007]. The combination of ID and epilepsy raises standardised mortality ratio significantly to at least five times that of the general population [Forsgren *et al*, 1996]. Seizures are the most frequent cause of potentially avoidable hospital admissions in people with ID, comprising 40% of all emergency admissions [Glover and Evison, 2013]. Identification and stratification of risk in this population is currently not optimally managed, as rates of potentially avoidable deaths are higher than other chronic conditions such as asthma [Office for National Statistics, 2013]. In the annual report from the Learning Disabilities Mortality Review (LeDeR) Programme [2017] epilepsy was recorded as the third most common individual cause of death. It was behind pneumonia and aspiration pneumonia, and associated with 5% of the overall deaths reviewed.

People with ID have poorer healthcare outcomes than the general population as a result of inequitable

access to appropriate healthcare. These health inequalities are in part related to difficulties in receiving accurate and timely medical diagnoses and management [Heslop *et al*, 2013].

Service provision

The British Branch of the International League Against Epilepsy (ILAE) working group on services for adults with epilepsy and ID have published a special report on care provision for this population [Kerr *et al*, 2018]. The report recommendations are based on survey results from key stakeholders involved in the delivery of care to this population through their affiliated professional bodies.

The results from this survey highlight the wide range of different healthcare professional, services and service levels that people with ID and epilepsy are interacting with. Services include primary care

provision, intellectual disability community services, secondary neurology led services and specialist tertiary epilepsy centres. The level of experience of treating people with epilepsy and ID within these services and of professionals involved can vary significantly.

At present, people with epilepsy and ID are waiting far longer for investigations than the National Institute for Health and Care Excellence (NICE) Clinical Guideline 137 [2012] recommends. The survey results show that waiting times for routine investigation such as electroencephalogram (EEG) and magnetic resonance imaging (MRI) are commonly at least one to three months. According to NICE, MRI brain imaging should be completed within four weeks of a request by a specialist. People with epilepsy and ID often have co-morbid communication and behavioural difficulties that will affect their ability to tolerate prolonged investigations. Therefore, it may be necessary for such investigations, like MRI, to be conducted under general anaesthetic. The lack of adjustment in current service provision means that this can increase waiting times to over six months.

As we have discussed people with epilepsy and ID are more likely to suffer with complex treatment resistant epilepsy. However, the survey results suggest that there is still a minority of clinicians working in this field that would not consider evidence-based interventions for this population. These include epilepsy surgery, vagus nerve stimulation (VNS) and the ketogenic diet.

The British Branch of the International League Against Epilepsy (ILAE) working group on services for adults with epilepsy and ID have made a number of recommendations based upon their findings [Kerr *et al*, 2018].

1. **End fragmented care provision**
   People with epilepsy and ID often have contact with healthcare professionals from a number of specialities as a result of the complexity of their co-morbidities and challenges of treatment. It has been recommended that the ILAE work to promote collaboration between the key stakeholder professional bodies to develop pathways of care delivery for this population. These care pathways should be auditable and there should be a forum for discussion and further work between relevant bodies and their affiliated clinicians

At present, people with epilepsy and ID are waiting far longer for investigations than the NICE Clinical Guideline 137 recommends

2. **Risk reduction**
   People with epilepsy and ID should have standardised risk assessments in place that are accessible to all clinicians across primary and secondary care. There is a specific increased risk of sudden unexpected death in epilepsy (SUDEP) and therefore further robust research in this area is required. Strategies such as night monitoring devices should be considered where appropriate to mitigate risk.
3. **Equitable access to care**
   People with epilepsy and ID should have equitable access to appropriate investigations in a reasonable timeframe. This includes the use of MRI under general anaesthetic.
4. **Training and education**
   Training should be provided for

those individuals involved in the prescribing and administration of rescue medication. People with epilepsy and ID are often reliant on family members and carers to provide information on their current needs. Therefore, it is important that seizure recording is accurate and standardised.

5. **Working in generic (not ID specific) services**
   There should be guidance on appropriate standards of care for people with epilepsy and ID which includes the need for reasonable adjustments. Some considerations include the role of ID liaison nurses in secondary care, longer clinic appointments, and shared clinical reviews (between ID services and general services/neurology).

The future

The report from the Neurological Alliance [2014] explores the barriers for people accessing appropriate specialist neurology support. As we have discussed, access to specialist services for people with ID is further confounded. The care of people with epilepsy and ID is currently shared between ID services, neurology, and primary care. The care provision an individual receives and from which service will vary dependent upon location and the expertise in that area. In order for such a system to operate effectively there needs to be clear care pathways in place with open communication between all services and healthcare professionals involved. For individuals with complex physical and psychiatric co-morbidities there may be a role for having one named individual to co-ordinate care between specialist services. This co-ordination may be best allocated to ID services who can take an overview of care. The Royal College of Psychiatrists (RCPsych) Faculty of ID Psychiatry is in the process of developing a strategy to help support psychiatrists in the management of people with epilepsy and ID [RCPsych CR203, 2017]. A three-tiered competency model (bronze/silver/gold) has been proposed which has been mapped against NICE outcome indicators for epilepsy and the Scottish Intercollegiate Network (SIGN) guidance [2015].

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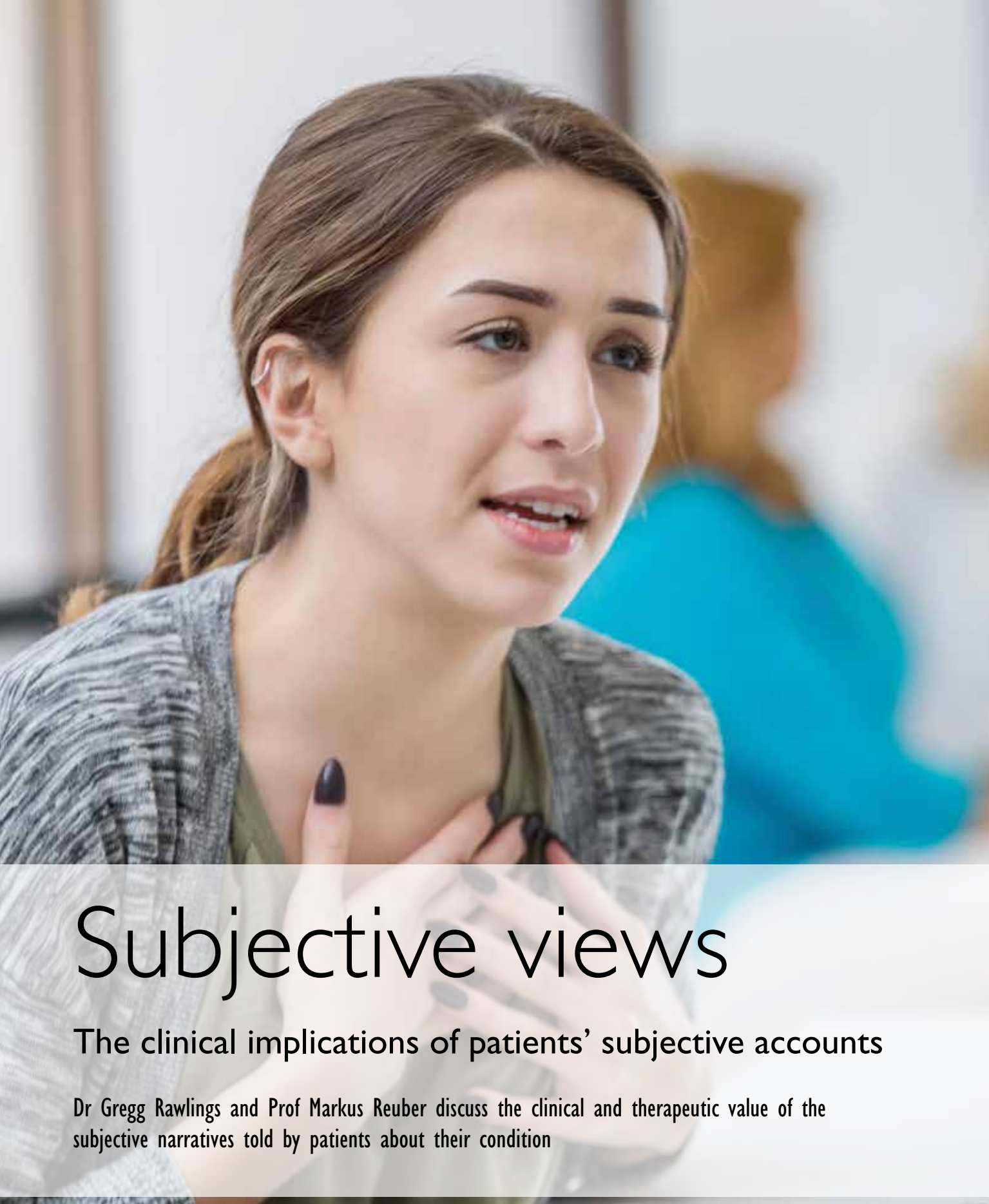


Subjective views

The clinical implications of patients' subjective accounts

Dr Gregg Rawlings and Prof Markus Reuber discuss the clinical and therapeutic value of the subjective narratives told by patients about their condition

Human beings are natural storytellers. Telling stories is an important mode of transmission of cultural and personal identity, and a key feature of what it is to be human. Although the age of acquisition is debated, the ability to construct stories is known to develop at an early stage.

Stories hold a special importance when people are ill. In illness, narratives allow individuals to make sense of a potentially chaotic and all-embracing mix of personal experience and emotion. Narrative enables people to work out how they think and feel about their condition. This is seen as an important first step towards achieving a state of acceptance, understanding and, ultimately, healing. Communicating accounts of illness helps others to understand the inner experiences of those affected, and enables those living with an illness to gain validation and support from the outside world [Frank, 1995].

Healthcare professionals are in a position of privilege in that they get to listen to patients' narratives. Illness accounts provide rich and unequalled insight into patients' subjective experience. However, the impressive advances in medical technologies mean that clinicians are at increasing risk of forgetting this. Patient narratives have been central to diagnostic and treatment processes throughout the history of medicine. But there is now a real risk of patient accounts being ignored, and even supressed, as clinicians prioritise 'objective', bio-medical approaches to interpreting illness to those based on 'subjective' narratives. This is particularly poignant for patients whose symptoms cannot be easily explained by 'objective' tests.

Patient narratives have been central to diagnostic and treatment processes throughout the history of medicine

Fortunately, there is also increasing recognition of the limitations of a purely bio-medical approach and a growing interest in the uses of patient narratives in medicine. Incorporating the implications of subjective accounts in clinical practice is essential to providing care that is personalised and responsive to the needs of individual patients. Revealing and understanding a patient's story requires a set of skills. Training on narrative competency such as history taking has become routine in medical education. Without these skills, it can be difficult to make sense of patient narratives and use them in clinical settings. Accounts of illness can be disorganised, erratic and emotionally challenging. Patient narratives may fail to follow typical patterns or plotlines. Confusing accounts can leave healthcare professionals feeling

Table 1. Five different narrative types

Narrative typology	Key narratological characteristics
Losses of Illness	Focused on events, activities or behaviours missed out on as a result of their condition. Struggled to accept or live with seizures. Most negative and difficult to read. Resembled a list of frustrations or restrictions. Individuals with epilepsy or NEAD told these types of stories in similar numbers.
Feeling Lost	Appeared to be in search of something, such as a diagnosis that better explained their experiences, or greater understanding and acceptance of their condition. Focused on how people react to their condition. Descriptions of feeling isolated and ostracised. Only those with NEAD told this type of story.
Tackling Adversity	Seizures have a profound and negative impact. However, authors were keen to express that they are coping with this and were determined to not let their disorder stop them. Appeared to have come through an initial period of turmoil after their diagnosis and now be in a position to manage their condition. Most common type of story told by those with epilepsy.
Overcoming Challenges	Focused on seizure-related challenges that they have overcome. The condition must be fought or battled with, and with the support from others, treatments and their own personal qualities, it can be beaten. Stories were the longest and most detailed. As a reader there is a feeling that participants told this story so they themselves could hear it as well as others. More common in epilepsy than NEAD.
A Normal Life	While affected by the condition, they manage the challenges calmly and with little need to fight. Described some benefits of having a seizure condition, explaining that it has made them stronger or provided them with greater insight into their sense of self. Only those with epilepsy told this type of story.

frustrated and doubting whether they fully understood a patient's experiences or worries.

Narratives of patients with seizures

We conducted a study to help clinicians make more sense of the stories they may encounter. The study set out to identify some of the different types of narratives that individuals who live with seizures are likely to tell. We invited people with epilepsy or non-epileptic attack disorder (NEAD) to write for 20 minutes about their very deepest thoughts and feelings about their condition. We used a form of narrative analysis that looks at both the content and structure of the story. This method is used to identify common storylines or plots, alternatively known as narrative typologies. In addition, we asked patients to complete a series of self-report demographic and clinical measures. These examined levels of anxiety, depression, health-related quality of life, seizure frequency and severity, and illness perceptions.

Although all patients have their own unique story to tell, we identified some key characteristics of their accounts that allowed us to differentiate between five different types of illness narratives (*Table 1*).

Practical importance

Our study demonstrated that individuals with epilepsy or NEAD tend to produce different narratives, suggesting that they have dissimilar experiences with their condition. Participants with NEAD commonly

described feeling lost, uncertain about their condition and in search of something like acceptance or understanding. Individuals with epilepsy, on the other hand, tended to narrate stories in which they encounter challenges and hurdles associated with their condition on a regular basis. However, they were keen to communicate how they are coping and living well (or 'normally') with their condition [Rawlings *et al*, 2018b; Rawlings *et al*, Manuscript Submitted].

This means that the differences characterising the narratives of individuals with epilepsy or NEAD could well be of diagnostic use. It can be difficult to differentiate between these two seizure disorders. Many patients with NEAD are initially misdiagnosed as having epilepsy. Delays in the correct diagnosis mean that the most suitable treatment is not provided straightaway, and that many patients initially receive inappropriate and ineffective treatment. Although our study was based on the analysis of written narratives, the types of stories participants told could perhaps also be picked up by clinicians when they talk to patients in outpatient settings. This is especially likely if they take the time to explore patients' feelings about their seizure disorders. While the narratives in this study represent the feelings and perceptions of people who knew their diagnosis, some of the findings of the narrative analysis were certainly reminiscent of a conversation analysis study by Reuber *et al* [2009]. In this study, conversation analysis of doctor-patient interactions in seizure clinics were carried out on people admitted for video/EEG telemetry because their diagnosis was uncertain. Linguists were found to be able to predict the seizure diagnosis with a high level of accuracy (85%) on the basis of linguistic and interactional observations alone [Reuber *et al*, 2009].

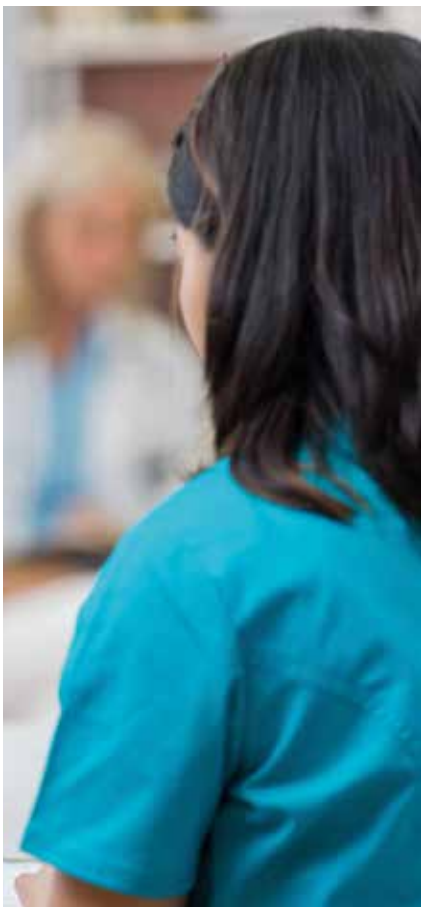
Individuals with epilepsy or NEAD tend to produce different narratives, suggesting that they have dissimilar experiences

Qualitative analyses and the quantitative clinical and self-report data combined suggest that narratives can offer insight that go beyond the question whether patients have epilepsy or NEAD. The narratives also say a lot about how authors are handling their condition.

Losses of Illness plots were the most negative and difficult to read as patients appeared to be most disabled by their condition. In line with this, authors who told this story scored highest on self-report measures of depression, anxiety and seizure severity. They also reported the lowest health-related quality of life and were more likely to be unemployed or in receipt of disability benefits.

Authors who told a story of Feeling Lost appeared to be in a state of searching instigated by their condition. These individuals most commonly reported their condition as threatening, suggesting that they do not understand it. Those who contributed a story of Tackling Adversity were the youngest.

It is important to note that the narratives we tell are not fixed. They are transient and subject to change as we mature, reflect and are influenced by psycho-social factors. The narratives of individuals in this group reflected that there was an initial period of turmoil soon after the development of their condition. As such, at one time they may have told a Losses of Illness narrative. However, compared to those authors, Tackling Adversity narrators had been living with their condition on average a decade longer. Therefore, it may be that they have had the opportunity to learn to cope better with the demands of their condition.



Individuals who provided A Normal Life narrative reported the highest health-related quality of life and scored lowest on measures of depression, anxiety and illness perceptions. This is consistent with the notion that they are managing their condition well. Authors of these narratives also described developing epilepsy in childhood, which could suggest that they have also had a greater opportunity to adapt to their condition. However, and more likely given the narrative, it may also suggest that they cannot grieve for a life

without their condition or adapt to a new one with it. These results suggest that the perceptions of particular narratological types may allow clinicians to identify additional treatment needs of their patients outside of their seizures. These could be interventions addressing adjustment problems, depression or anxiety.

Therapeutic use of patient narrative

The National Institute for Health and Care Excellence (NICE) recommend the use of psychotherapy in conjunction with other treatments for seizure disorders. While such approaches to care can be very effective, these treatments are resource intensive and few patients have routine access.

The seizure narratives discussed above were extracted from a writing programme intended to help patients with epilepsy or NEAD, who had emotional problems related to their seizure disorders. These were from the first writing task, which was to write about the deepest thoughts and feelings about their condition. The intervention also involved participants writing about different aspects of their experiences on three further occasions for at least 20 minutes. For the other tasks, patients were instructed to write a letter to their condition, a letter to their younger self about their condition and to complete a self-affirming task.

The findings of this part of our research project demonstrated that participants chose to write for longer than the 20 minutes recommended. This suggests that the writing requests were acceptable, and perhaps also that patients experienced an unmet need to tell their story. In our study, completion of the writing intervention resulted in a significant improvement in patients' health-related quality of life at one-month follow-up [Rawlings *et al*, 2018a].

This supports the notion that helping people with seizures to explore, formulate and express their experiences of living with seizures should be an important goal in the therapeutic journey. A study testing a one-day communication training intervention developed for doctors in seizure clinics provides an example of how this can be achieved practically. This intervention aimed to help doctors to adopt an unusually open approach to their questioning style. The more open question format was intended to give patients the space to formulate their narrative and voice their own concerns. Following training, the overall appointment length did not increase, but doctors went longer without interrupting patients. The patients, in turn, were better able to determine their own agenda of the encounter, and enjoyed greater opportunity to present their problems and expectations [Jenkins *et al*, 2015].

In our study, completion of the writing intervention resulted in a significant improvement in patients' health-related quality of life at one-month follow-up

Perceptions and outcomes

Narratives are devices that we use to understand ourselves and the world around us. Personal accounts are a representation of what we experience and therefore reflect a subjective truth and interpretation, which can differ from historical or factual truth. This however, does not mean that they are any less important. When individuals are diagnosed with a medical disorder, they naturally make a subjective evaluation, which will shape their perceptions of the condition. This process is influenced by personal, social and cultural factors. There is likely to be a bi-directional relationship between these factors and the stories people tell themselves and others about their experiences. Patients' beliefs are powerful and can help to determine how they will go on to manage their condition.

In a previous study, we looked at the

perceptions of patients with epilepsy or NEAD of their condition (as measured by the Brief-Illness Perception Questionnaire). We found that perceptions were a significant predictor of health-related quality of life, second only to anxiety and depression. In contrast, clinical factors, such as seizure frequency or severity, did not make a significant contribution to this variance [Rawlings *et al*, 2017]. These findings demonstrate the importance of appreciating and attempting to shape patients' understanding and representation of their condition.

Clinicians' perceptions

In our qualitative exploration of the content of patient narratives, we found that many greatly valued clinicians who listened to them. Reflected in the study investigating the one-day training intervention, patients also appreciated professionals who created an environment that encouraged them to be more open to sharing their experiences.

Even the most 'scientific', 'objective' and dispassionate approaches to medical practice are likely to be influenced by the way patients solicit help or advice

However, healthcare professionals also need to consider their own position in their relationship with patients. In recent years, there has been a growing emphasis to practice reflectively. Healthcare professionals are encouraged to use information gathered from feedback and self-reflection to improve their practice. They should therefore think about their own reactions and responses to the stories that patients tell them, and consider sharing their reflections with others. Even the most 'scientific', 'objective' and dispassionate approaches to medical practice are likely to be influenced by the way patients solicit help or advice.

For those professionals interested in reflecting on how patient stories affect them, the Brainstorms series of books provides an excellent resource. These include narratives collected and edited by Professor Steven Schachter at Harvard University (published by Oxford University Press). This series, which previously focused on epilepsy, has recently been extended with a book on NEAD. It contains over 100 contributions from patients, relatives or friends of patients affected by NEAD [Reuber *et al*, 2018]. The Brainstorms series also includes one book with contributions from professionals about their experiences with providing care and advice for people with epilepsy [Schachter, 2007]. All of these books can provide clinicians with insights, which are difficult to gain from textbooks or scientific papers. As recently demonstrated by our review of attitudes of clinicians, such insights may be particularly urgent in relation to understanding NEAD [Rawlings and Reuber, 2018].

We hope that this article has helped show the value of subjective narratives both for clinicians delivering care and for patients with seizure conditions.

If you have had experience managing people with NEAD, you can contribute to an upcoming new addition to the Brainstorms series – *Non-Epileptic Seizures In Our Experience: Accounts of Health Care Professionals*. If you are interested in adding your own writing to this book, please contact Gregg Rawlings at ghrawlings1@sheffield.ac.uk or visit *sites.google.com/site/brainstormshcp* for more information.

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Medicinal cannabis

The role of medical cannabis in epilepsy

Professor Hannah Cock looks at the evidence around cannabis-based medicines in epilepsy and describes the current situation in the UK

How many people have asked you to prescribe cannabis for epilepsy this week? Things have been moving quickly. Mainstream media championed two particular children with severe drug resistant epilepsy during the first six months of 2018 [Gayle, 2018]. In parallel in April 2018, US authorities recommended approval of the first cannabis based treatment to treat drug resistant seizures in Dravet and Lennox Gastaut Syndrome. This was based on trial data supported by selected case videos, and "emotional testimony" from parents [Dyer, 2018]. By June 2018, the UK government announced a review into 'medicinal cannabis'.

Around 350,000 people in the UK were already known to be using artisanal preparations, representing a four-fold increase since October 2016 [Grierson and Busby, 2018]. Within a month, the intention to reclassify 'medicinal cannabis' and ensure it was available on prescription in the UK by autumn of this year followed. Specialists can already apply to an expert advisory panel for cases of "exceptional and unmet clinical need" [Torjesen, 2018]. This article reviews the truth behind the hype, to support clinicians in discussions with patients.

How did we get here?

The medicinal potential of cannabis has been recognised for thousands of years, in parallel with which cannabis has become the most consumed illegal recreational drug worldwide [Santos *et al*, 2015]. Scientific interest dates to the 1960s, since when the many active components of the cannabis plant have been identified, and the endogenous (endocannabinoid) system characterised [Santos *et al*, 2015; O'Connell *et al*, 2017]. Cannabis has several strains, and contains hundreds of chemicals that occur naturally in the plant. The two most important are tetrahydrocannibidiol (THC) and cannabidiol (CBD).

The term 'medicinal cannabis' covers a range of products. Some contain CBD only, others have both CBD and THC in varying proportions, in addition to a large number of other cannabinoids and compounds. There are, of course, already some licensed agents (box 1). A further THC rich

compound, Rimonabant looked promising in early studies, but was then withdrawn in 2008 due to psychiatric side-effects, including increased suicidality [Whalley, 2014]. Over the last few years approval for medicinal cannabis preparations was achieved in 29 US states and 40 other countries. This was due to a largely lay-led movement, driven by unmet need, alongside anecdotal reports in social media and mainstream news. Laws vary from simple decriminalisation to full legal medical use [Barnes, 2018], now also under review in the UK.

Why might it work?

The endocannabinoid system is an attractive target for drug development in epilepsy. Endocannabinoids are small lipid messengers synthesised 'on demand' in an activity-dependent manner through cleavage of membrane phospholipids. They are intimately involved in the regulation of cortical excitability. To date, two cannabinoid receptors (CB1 and CB2) have been identified. CB1 receptors are widely expressed in the central nervous system (CNS), mainly localised on presynaptic terminals. CB2 receptors are mainly located outside the CNS but are expressed by microglia during inflammatory processes as well as in brainstem neurons [De Caro *et al*, 2017].

Numerous in vitro and in vivo studies support that modulation of the system can alter seizure activity, and potentially epileptogenesis in a range of models [Santos *et al*, 2015]. Of the hundreds of plant-derived cannabinoids, THC, delta-9-tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), delta-8-tetrahydrocannabinol (delta-8-THC), cannabinol (CBN) and especially CBD have anticonvulsant effects. THC is a partial agonist for CB1 and CB2 receptors. However it has demonstrable pro-convulsant effects in some models, in addition to which studies in rodents with spontaneous seizures suggest tolerance can develop [Santos *et al*, 2015]. THC also has a definite neurobehavioural effect. It is the component that makes people feel 'high' and can also cause negative effects such as anxiety and paranoia [Rcpsych.ac.uk]. Most interest in epilepsy has thus been on CBD. The recently US approved product Epidiolex, manufactured by the UK company GW Pharmaceuticals, is an oral formulation of near pure CBD in sesame oil (<0.1% THC).

Pre-clinical studies indicate CBD is a relatively potent anticonvulsant in a range of acute provocation and spontaneous seizure models

The oral bioavailability of CBD is less than 10%, with low water solubility and significant first pass metabolism. It then undergoes rapid distribution into fat including into the brain. It is highly protein bound, reaching peak serum levels within 90-120 minutes. It has a half-life of 18-32 hours. The pharmacology of CBD is not completely understood, and seems to be largely independent of CB1/2 binding for which it has low affinity. However, it antagonises CB1/2 agonists (including THC) at nanomolar concentrations.

CBD does have multiple other known actions on other CNS receptors/signalling systems [Santos *et al*, 2015], supporting its potential in a range of disorders. Pre-clinical studies indicate it is a relatively potent anticonvulsant in a range of acute provocation and spontaneous seizures models. In contrast to THC, there are no studies suggesting pro-convulsant effects. Anticonvulsant effects may be mediated by activation of the endocannabinoid system (reduced uptake and breakdown of anandamide) or other mechanisms. This may also promote defence against acute excitotoxicity, and be neuroprotective also via non CB1 mechanisms.

Safety and effectiveness of CBD in clinical studies

The first reasonably solid evidence came in 2016 [Devinsky *et al*, 2016]. Data from an open label trial (expanded access programme) were published, suggesting possible efficacy in treatment resistant patients with a range of etiologies. This was quickly followed by double blind studies in Dravet Syndrome [Devinsky *et al*, 2017], Lennox Gastaut Syndrome [Devinsky *et al*, 2018; Thiele *et al*, 2018], and more extensive open label data [Szaflarski *et al*, 2018]. This is summarised in *Table 1*. All studies relied on diary data of countable (motor) seizures for the primary endpoint, with a four-week pre-CBD baseline without other treatment changes.

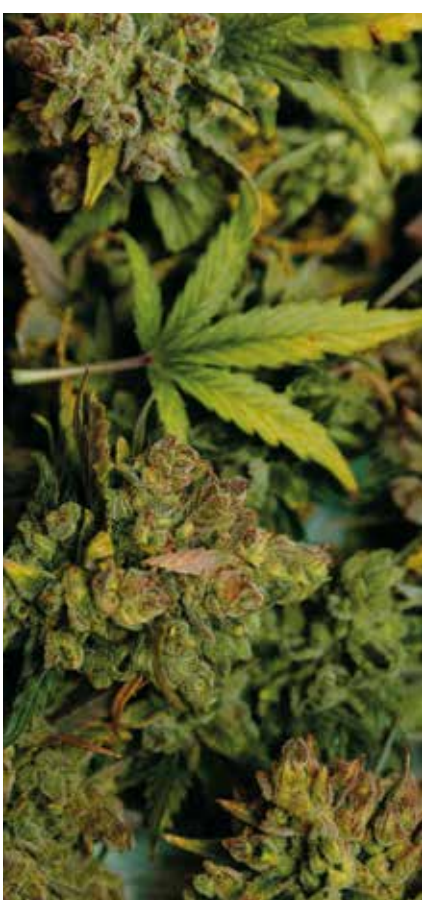
The most recent comprehensive review by Stockings *et al* [2018]

Nabilone™, a synthetic mimic of THC has been available for chemotherapy induced nausea and vomiting since the 1980s, and is also sometimes used (off license) for pain.
Sativex™, a 1:1 mix of CBD and THC licensed in 2005 for spasticity in Multiple Sclerosis, though not recommended by NICE due to lack of cost-effectiveness (Barnes, 2018). Both are contraindicated in epilepsy.

Box 1. Currently licensed cannabis-based products in the UK

*Table 1: Summary of CBD clinical studies on safety and effectiveness. AE = adverse events AtS = atonic/drop seizures. DBRCT = double blind randomised control trial LGS = Lennox-Gastaut syndrome. NA = not applicable. n,n = number on active treatment, n on placebo. NS = not stated. RR = responder rate (%)m defined as >50% reduction in motor seizure frequency (in the Dravet study this was convulsive seizures, in the first LGS study atonic (drop) seizures). SAE = serious adverse events. SF = seizure free. TRE = treatment resistant epilepsy. *Efficacy sustained over up to 96 weeks. Safety data based on f/u range 2-146 weeks.*

Study design	Condition (n, n)	Age (years)	Median current, previous AEDs (range)	Duration efficacy phase (weeks)	Target Dose (mg/kg)	% RR CBD vs Placebo (SF)	% Withdrawals due to AEs, CBD vs Placebo
Devinsky 2016, EAP	TRE 162	1-30	3 (0-7), 3 (1-7)	12	25-50	39	7
Devinsky 2017, DBRCT	Dravet 61, 59	2-18	3 (1-5), 4 (0-26)	14	20	43 vs 27 (5 vs 0)	13 vs 1.4
Devinsky 2018, DBRCT	LGS (AtS) 76, 73	2-55	3 (1.5), 6 (0-22)	14	10 or 20	42 vs 37	13 vs 1.3
Thiele 2018, DBRCT	LGS 86, 85	2-55	3 (1-5), 6 (0-28)	14	20	44 vs 20	14 vs 1.2
Szarlarski 2018, EAP	TRE 607	0.4-62	3 (0-10), NS	12-96*	10-50	52	5



included all but the newest of these observational studies. It totalled data on 555 patients in randomised controlled trials, and over 3,000 in open observational studies. The authors estimated that of every eight patients with these severe treatment-resistant epilepsies given CBD (2/3 in the pure formulation), one will have a greater than 50% reduction in seizures. Only one in 171 will have sustained seizure freedom. Reductions in severe seizure types, including tonic-clonic, tonic and atonic seizures were seen as particularly beneficial.

Side-effects, most commonly including drowsiness, diarrhoea, reduced appetite, vomiting and fatigue, will affect one in three. However, these are often mild, improve over time or with dose reduction, and were rare at doses of <10-15mg/kg/day. Status epilepticus, SUDEP and pneumonia were also not uncommon (5-10%), likely reflecting the patient population. However, one in 23 experience serious side-effects such as extreme somnolence (risking aspiration, postural difficulties, falls), severe diarrhoea, or abnormal (>3 times normal limits) liver function tests. Drug interactions with valproate (increasing the risk of hepatotoxicity) and clobazam (contributing to somnolence) are currently recognised, though may be manageable with dose changes [De Caro *et al*, 2017]. Epidiolex is licensed for up to 50mg/kg/day (usually split in two doses), but a dose of 20-25mg/kg/day has been used most commonly, limited by tolerability.

There are, of course, problems with open label observational data. Studies with highest risk of bias methodologically were the most likely to report better outcomes [Stockings *et al*, 2018]. The role of the placebo response is of particular importance in this context. This is due to the intense social and traditional media attention, as well as the strong belief held by many that a natural product is inherently safer and more effective than licensed pharmaceutical agents [O'Connell *et al*, 2017]. Furthermore, in some sites, access to the expanded

access programme was dependent on seizure diary data, so baseline over-reporting can't be excluded. Nonetheless, there is clear evidence of efficacy and a reasonable safety profile, justifying the use of CBD for adjunctive use in some people with severe treatment-resistant epilepsies.

How does this compare with other newer AEDs?

Unsurprisingly, as remains the case for most of our licensed adjunctive treatments in treatment-resistant epilepsy, there are no comparative studies. Furthermore, current trial designs are inherently flawed. This is due to reliance on seizure diaries, strict inclusion/exclusion criteria and short durations which may fail to adequately account for the inherent variability of treatment-resistant epilepsies [Shorvon and Schmidt, 2016].

The best indicators for indirect comparisons is also debated. Clinicians often favour number needed to treat (or harm), licensing authorities require responder rates or percent reduction in seizures, and statisticians argue for odds ratios [Lesaffre *et al*, 2000]. As a broad-brush comparison, estimates of the number needed to treat (NNT) for other recently licensed AEDs average around 10 (range 10-19). Responder rates are mostly in the 30-40% range, withdrawals due to adverse events are typically around 10% (5-15), and the number needed to harm is around 25 (10-26) [Costa *et al*, 2011]. One year retention rates for CBD appear very favourable at up to 76% [Szaflarski *et al*, 2018] compared, for example, to 65% for levetiracetam in early studies [Bootsma *et al*, 2008]. But these may not be insignificantly influenced by the cultural attachment to the idea of cannabis derived products as a "non-drug" option [Press *et al*, 2015].

Only CBD has been well studied in clinical epilepsy trials thus far

CBD isn't thus strikingly different on current evidence. It's effective for some and sometimes well tolerated, yes; potentially useful in severe drug resistant cases – certainly. But the magic answer for most people with drug-resistant epilepsy, or better than existing drugs, it is clearly not on current evidence.

What about artisanal CBD preparations, including those with THC?

The Stockings 2018 review, included 10 observational studies of CBD:THC preparations, four predominantly CBD, and six using Sativex (1:1). In all instances, these were used as adjuvant treatment, with up to seven years of follow-up data. These were all of – at best – low methodological quality, so, at most, they are evidence of experience rather than effectiveness. Therefore, there is insufficient evidence to draw firm conclusions on whether THC is of any added specific benefit (or harm) in epilepsy over and above that of CBD. There are, however, concerns about dependence on THC, estimated to affect around 9% of recreational cannabis users (compared to 14% for alcohol, and 32% for tobacco [Nutt *et al*, 2007]). These might explain some anecdotal reports of worsening seizures when cannabis preparations are discontinued.

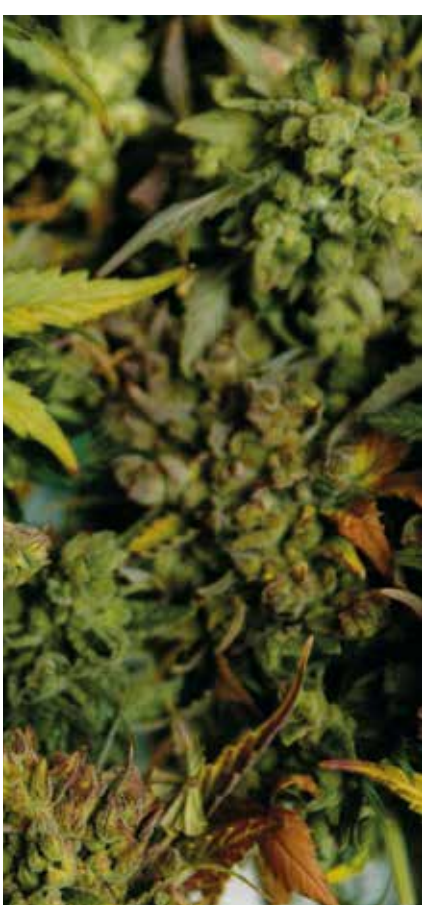
The bigger concern relates to possible adverse effects. It is known that THC carries severe risks for some, especially if taken regularly, and in children and adolescents. They include depression, psychosis and anxiety [Hawkes, 2018]. Cognitive impairments, poor school performance and potentially irreversible structural changes have also been reported [Detyniecki and Hirsch, 2016]. Proponents may argue that CBD offsets the effects of THC via pharmacodynamics and pharmacokinetic mechanisms [Huestis, 2007]. Improvements in motor skills, language and cognition are also often reported, by parents especially, but might, in part, be natural maturation over time. People with epilepsy are already vulnerable to psychiatric and cognitive disorders. Only CBD has been well studied in clinical epilepsy trials thus far.

Ultimately, we don't know if there is a 'safe dose' of THC, meaning that on current evidence it is difficult to recommend preparations including THC. There are several high CBD and

very low (typically <0.3%) THC preparations available commercially. This is clearly a big business, including different flavoured oils, capsules and even a pet formulation [MarijuanaBreak, 2017]. They all contain other cannabinoids and purportedly "beneficial" compounds, for which there is an absence of good-quality safety or long-term data. Also, unless a formulation has been pharmaceutically prepared and controlled, it is not known what is (or isn't) in it, and there can be significant variation between batches.

Legislation, licensing and supply

Prior to recent events, CBD was unscheduled, and continues to be legally available as a nutritional supplement in the UK. Cannabis and THC-containing products, other than those in Box 1, are still listed under Schedule 1 of the Misuse of Drugs Regulations 2001. This means they are (or were) considered of no therapeutic value, could not be lawfully possessed or prescribed and need a home office licence for research [Barnes, 2018]. We now know the UK intention is for cannabis derived medicinal products for use in treatment resistant conditions, including epilepsy, to be moved to Schedule 2, meaning they could be lawfully prescribed [Torjesen, 2018]. The Department of Health and Social Care for England (DHSC) and the UK Medicines and Health products Regulatory Agency (MHRA) have been tasked with defining exactly what constitutes a cannabis derived medicinal product. It seems very likely that this will at least include Epidiolex, with a European Medicines Agency (EMA) decision on licensing also expected by early 2019 [Torjesen, 2018].



There has been a clear message that this is not a first step towards legalising cannabis for recreational use. Beyond this, whether a broader range of compounds will be moved, or only individual preparations considered one by one, remains to be seen. With several different plant strains, a very wide range of formulations, multiple routes of ingestion and varying bioavailability, this would be a significant hurdle. Many jurisdictions, both in the US and other countries, have addressed this by approving specific suppliers, monitoring the quality of products, and ensuring availability only on prescription through licensed pharmacies [Barnes, 2018]. Meanwhile, specialists treating patients with "exceptional and unmet clinical need" can already apply to the home office panel. The 11-page form [GOV.UK, 2018] must specify the product, supply source, pre-defined intended outcomes, how these will be assessed and over what time period, including stopping criteria. This is alongside a full treatment history and summary of the evidence justifying the application. This must be approved by the medical director, and, of course, someone has to pay. The cost implications cannot and should not be ignored. Better quality artisanal preparations can still cost £1,000s a year [ILAE, 2018], and the cost of Epidiolex has recently been announced as around $32,500 a year [Brodwin, 2018].

Clear explanation of the evidence is needed, and pointing to sources of reliable information

What should I say to my patient?

A blanket refusal may prove harmful to the therapeutic relationship, and risks the patient or family disengaging and seeking support from perhaps less appropriate prescribers. Clear explanation of the evidence is needed, and pointing to sources of reliable information. This, together with emphasising the known safety and efficacy of alternative licensed drugs will be sufficient for most, and can be delivered in primary and secondary care settings.

For individuals who nonetheless choose to use CBD products privately, it's better to know about it than not. This is so as to minimise the risk of harm from drug interactions with, or discontinuation of, other prescribed medications. It is also important to try to help patients or carers define and more objectively assess response, as far as possible. The change in licensing will likely support and enable more clinical

trials, which I will always encourage eligible individuals to participate in.

For those few with ongoing devastating seizures despite all other options, at some point a 'trial of one' may be justified. In this case, it will be tertiary epilepsy specialists who are best placed to seek approval and funding. Even if not successful, the importance of hope and confidence in a patient's treating professional can be immeasurable, including sometimes helping to "facilitate the transition to palliative care" [Rosemergy *et al*, 2016].

Professor Cock's now deceased son was on cannabidiol for around 18 months as part of a UK trial, prior to his death (unrelated) in 2016. The author is the site PI for a GWPharma sponsored multicentre international clinical trial for epilepsy in tuberous sclerosis, and has recruited so is prescribing cannabidiol as part of this. The author has received no direct payments for this activity. The author reports personal fees Sage Pharmaceuticals Ltd, Eisai Europe Ltd, UCB Pharma Ltd, European Medicines Agency, UK Epilepsy Nurse Specialist Association, non-financial support from Special Products Ltd, grants from U.S NIH Institute of Neurological Disorders and Stroke, non-financial support from International League Against Epilepsy, Status Epilepticus Classification Task Force and Epilepsy Certification (education) Task Force, and non-financial support from European Academy of Neurology. Full disclosure at www.whopaysthisdoctor.org. The author does not consider any of the above to have influenced her impartiality as an advisor beyond personal experience reinforcing the importance of good quality advice/information for families and professionals

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Highlights

Top picks from *Seizure*

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

One well-established way of characterising the adequacy of provisions for people with epilepsy is the epilepsy treatment gap (ETG). The ETG is defined as the percentage of people with active epilepsy who are not receiving appropriate treatment in a given population at a particular time. One comprehensive review, based on the analysis of 74 studies, found considerable variations of the ETG between and within countries, linked to the wealth of the country or area [Meyer *et al*, 2010].

My editor's choice paper from *Seizure issue 59* is about a different and less established kind of gap – the evidence gap. In their systematic review, Sharika Raga and Jo Wilmshurst [2018] deal with the evidence gap relating to treatments for infants and young children with epileptic spasms (ES). They focus on evidence for treatments which may be available in countries in which the first line treatments recommended in international guidelines and reviews are simply not available.

With an incidence of 0.25 to 0.42 per 1000 live births per year, ES are the most common seizure type in the infantile period in high income countries. They are likely to be more common still in Lower Middle Income countries (LMICs) and Low Income countries (LICs) [Cowan and Hudson, 1991]. Rapid and effective treatment of ES (and the hypsarrhythmia in the EEG

which ES are associated with) is of great importance because it is associated with better developmental outcomes. Reviews of the available research (largely carried out in High Income countries (HICs)) suggest that ACTH is the treatment of choice for ES (unless ES are caused by tuberous sclerosis when vigabatrin should be used [Hancock *et al*, 2013].

The problem with this recommendation is that a course of ACTH in a country such as South Africa will cost over 11,000 times as much as a course of oral steroids. However, it is much less certain whether drugs likely to be available in poorer countries (prednisolone or prednisone) are as effective as ACTH or vigabatrin [Raga and Wilmshurst, 2018]. The good news is that the cheaper drugs may work for many children. The bad news is that we can't be sure of this and that the evidence gap may turn out to be as difficult to close as the treatment gap!

Seizure sounds

Neurophysiologically, vision is the most important sense for humans. Not surprisingly, visible information is also predominant in medicine – including the assessment and differentiation of seizures through clinical manifestations, EEG or brain imaging. However, my editor's choice by Hartl *et al* from *Seizure issue 60* [2018] focuses specifically on seizure manifestations we can pick up with our sense of hearing. It reminds us that an optimal diagnostic process requires us to use all of our senses [Hartl *et al*, 2018].

Audible features can help distinguish between epilepsy and non-epileptic seizures (NES) when sound recordings of seizures are available. For example, in one study, the laryngeal sound differentiated bilateral tonic-clonic seizures (BTCS) from NES with a sensitivity of 85% and a specificity of 100% [Millichap, 2010].

The study by Hartl *et al* examines ictal vocalisations more closely and focuses on their localising value in patients with epilepsy. Ictal vocalisation was observed in nearly 40% of seizures. Although the phenomenon occurred with similar frequency in patients with temporal and frontal lobe epilepsies, the combination of vocalisation and other seizure-related automatic actions identified patients with temporal seizure onset with a sensitivity of 92% and specificity of 70%. Quantitative analysis of vocalisation intensity provided more information of localising value. Frontal lobe seizures were characterised by a greater intensity range, intensity variation and intensity increase at the beginning of the vocalisation. Epileptologists do not just need to keep their eyes open: they need to stop, look and *LISTEN*.

Further reading

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CONTRAINDICATIONS: The VNS Therapy system cannot be used in patients after a bilateral or left cervical vagotomy. Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with the VNS Therapy system. Diagnostic ultrasound is not included in this contraindication. Cardiac arrhythmia (Model 106 only)—The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias or who are using treatments that interfere with normal intrinsic heart rate responses.
WARNINGS: Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy Physician Manuals, including information that VNS Therapy may not be a cure for epilepsy. Since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, or in strenuous sports that could harm them or others. A malfunction of the VNS Therapy system could cause painful or direct current stimulation, which could result in nerve damage. Removal or replacement of the VNS Therapy system requires an additional surgical procedure. Patients who have pre-existing swallowing, cardiac, or respiratory difficulties (including, but not limited to, obstructive sleep apnea and chronic pulmonary disease) should discuss with their physicians whether VNS Therapy is appropriate for them since there is the possibility that stimulation might worsen their condition. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. MRI can be safely performed; however, special equipment and procedures must be used.
ADVERSE EVENTS: The most commonly reported side effects from stimulation include hoarseness (voice alteration), paresthesia (prickling feeling in the skin), dyspnea (shortness of breath), sore throat and increased coughing. The most commonly reported side effect from the implant procedure is infection.

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

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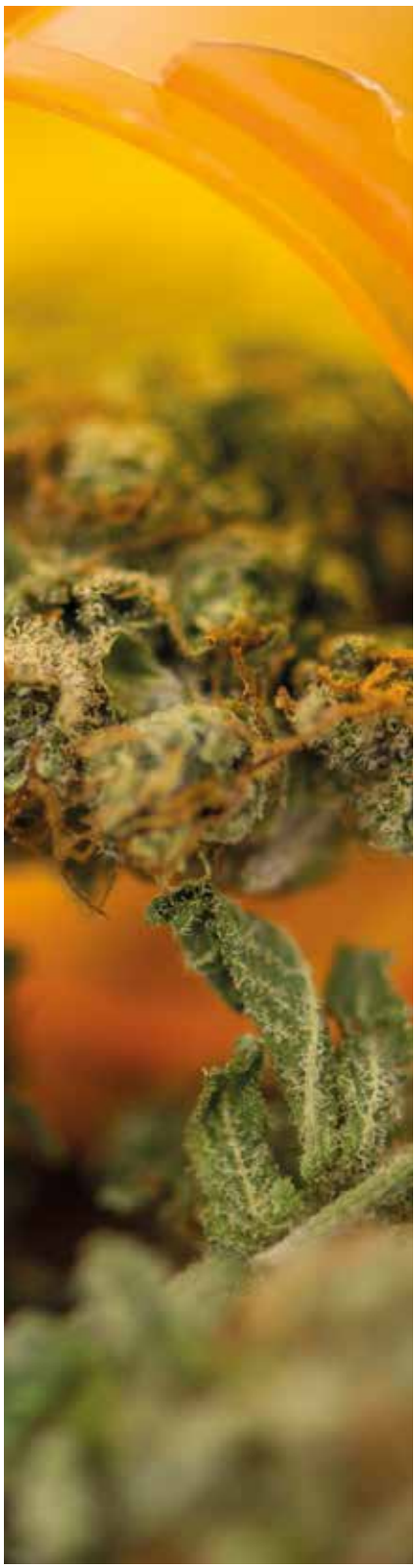

Am I your dealer?

I don't think I have had an epilepsy clinic in the last year or so, where I haven't, in at least one consultation, been asked "But what about cannabis Dr Slaght?" I strive, as we all do, to enable my patients to make informed choices about their treatment options. These can be complex and difficult, often with limited or confusing clinical evidence regarding the risks and benefits. This of course takes time. What makes answering the question about medical cannabis especially hard is that its culturally perceived benefits are significantly out of step with the medical evidence. Most patients and carers expect there to be no risk as it is a 'natural product'. So, it can be one of those questions that can make my heart sink. And this is particularly so when I'm running 40 minutes late and it is the third time I've been asked this question in the same clinic.

Prof Cock from St George's University has provided an excellent summary of the evidence regarding the use of medical cannabis in epilepsy in this edition of *Epilepsy Professional*. It has certainly helped to better equip me to inform my patients and their carers. Prof Cock explains that a blanket refusal to discuss the issue is potentially harmful to the therapeutic relationship. I fully agree with this. It is always best to know if the patient is self-medicating with cannabidiol oil or smoking marijuana. There are potential interactions with some AEDs and we need to help our patients navigate these and other issues.

Another useful resource is the brief and very understandable statement on the use of medical marijuana from the British Paediatric Neurology Association (*bit.ly/2CbKb5x*). I have copies of this statement handy in the clinic to give to patients and carers as a summary of our discussions.

Medical cannabis is going to become part of our prescribing landscape, in epilepsy and for many other conditions. However, I feel that it needs to be given as much scrutiny as any other medical product. We need many more trials to establish where different types of medical cannabis fit in our therapeutic pathways and how much potential for harm they have.

I fear that the impending change in the scheduling of medical cannabis will lead to increasingly more (and more assertive) demands for its use from patients and carers. This may be even in situations where tried and tested medicines with more robust clinical data may well be more appropriate and have less potential for harm.

To combat this, we need more clinical trials of medicinal cannabis products in different types of epilepsy, so that their place in the AED armament can be established robustly.

Dates for the diary

September 2018

20-22
19th International Symposium on Severe Infantile Epilepsies: Old and New Treatments (ISSET) 2018
Vatican City in Rome, Italy
bit.ly/2EZlmdi

26-28
ILAE British Chapter Annual Scientific Meeting
Birmingham, UK
www.ilaebritishconference.org.uk/

28
Irish Chapter of the ILAE 8th Annual Expert Day
Dublin, Ireland
www.ilae.org/files/dmfile/Ireland-Expert-Day-Programme-Sept2018.pdf

October 2018

5-9
6th Global Symposium on Ketogenic Therapies for Neurological Disorders
Seogwipo, Korea
keto2018jeju.org/

November 2018

1-2
SUDEP Action prevent21summit
Oxford, UK
sudep.org/sudep-actions-prevent21-summit

1-3
Video-EEG in Paediatric Epilepsies: From seizures to syndromes
Madrid, Spain
bit.ly/2LiOBrP

February 2019

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

April 2019

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

Misdiagnosis in epilepsy

Dr Maria Oto discusses the causes and rates of misdiagnosis in epilepsy and how these can be avoided.

Sodium valproate and exceptional circumstances

Dr Heather Angus-Leppan describes the new guidelines around use of sodium valproate in women of childbearing age and suggests exceptional circumstances in which it could be used in this group.

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