Protocadherin 19 (PCDH19) is currently considered to be one of the most frequently mutated genes in epilepsy. It is possibly second only to mutations in SCN1A, the gene associated with Dravet syndrome. Some specialists in paediatric epilepsy include it as one of the infantile epileptic encephalopathies. However, it is certainly not in the same league as Ohtahara, West and Dravet syndromes, or epilepsy of infancy with migrating focal seizures. In view of how common it is reported to be and its better-defined semiology (clinical features and EEG findings) [Trivisano et al, 2018], I thought it would be a useful topic for this editorial.

What is its genetic basis?

The gene that codes for PCDH19 is on the X chromosome at position q22. This means that females are predominantly affected, as indicated in its early reports in 2008. Females are affected because they have two X-chromosomes, one healthy and one mutated. This would usually protect them from an X-chromosome-borne disease, but in this case, it actually causes the disorder. Males with the same mutation have also been reported, although rarely, and show similar clinical and EEG features to those seen in females. Mutations may be of different types and include ‘missense’, ‘nonsense’ and a ‘frameshift’ or ‘rearrangement’. Based on very limited evidence, there does not seem to be a clear genotype-phenotype correlation. This means that the type of mutation (the ‘genotype’) does not seem to be associated with a particular pattern of seizures, presence or absence of learning difficulties or psychiatric disorders, or EEG findings (the ‘phenotype’). This may change as and when more is known about this specific epilepsy. As with most mutations, it would be rare for the same biological parents to have another affected child.

How common is it?

Its incidence (new cases diagnosed per year) and prevalence (cases in all females and all individuals with epilepsy), are unknown. The US Epilepsy Research Foundation estimates it might affect 15,000-30,000 females with epilepsy in the US. Limited studies of large cohorts of females with epilepsy have shown a wide range of PCDH19 mutations, ranging from 2-20%. The actual figure of prevalence in females with epilepsy is likely to be 15-20%. This has become clearer because of increased genetic testing of females with epilepsy that have onset in the first five years of life.

Electro-clinical features

This condition was initially called ‘epilepsy and mental retardation limited to females’ [Dibbens et al, 2008].
Scheffer et al, 2008]. This emphasised the intellectual difficulties and exclusive occurrence in females that were found in early cases with the disorder. With time and knowledge, it is now clear that, although it is far more common in females, it may occur in males. In addition, up to 30% of individuals are said to have normal cognitive (and educational) function.

Seizures: Most seizures start within the first two years of life with a mean age of 9-10 months. However, the range at seizure onset is wide, from one month to five years. The seizures usually occur in clusters, often on a daily basis and usually in relation to fever or a febrile illness, similar to infants with Dravet syndrome. Seizure frequency is very high in the first 6-24 months after it starts. Multiple seizure types occur during the course of the child’s life but focal seizures are the most common type at onset and during the first couple of years of evolution. Initially, the focal seizures are mainly non-motor but focal motor seizures occur slightly later. Non-motor seizures are manifest as behavioural arrest with or without automatisms, loss of muscle tone, eye-deviation, hypopnoea and cyanosis. Motor seizures show predominantly tonic or clonic features. Children may appear scared or frightened during the seizures, suggesting an origin from the temporal or, slightly less likely, the frontal lobes. Generalised seizures may occur and are considered to be ‘secondarily’ generalised, rather than ‘primary’ generalised, in nature. Generalised seizures include myoclonic, absence and tonic-clonic seizures. Status epilepticus (SE) is uncommon and tends to be non-convulsive rather than convulsive; serial seizures, either motor or non-motor, are more common than SE.

The EEG: There is no specific inter-ictal (between-seizure) or ictal (during a seizure) EEG pattern seen in this genetic epilepsy. The background recording is either normal or immature (showing focal or multi-focal slow wave activity). Epileptiform activity is relatively common, whether in the waking or sleeping state. It shows focal, multi-focal or diffuse, but no generalised sharp waves/spikes/spike and slow wave activity. Rarely, an ictal EEG that is done during a cluster of seizures may show different seizures originating from either cerebral hemisphere, resembling epilepsy of infancy with migrating focal seizures. The presence of inter-ictal abnormalities, specifically spikes and spike and slow waves, does not appear to correlate with either the occurrence, or the degree, of learning difficulty. Consequently, PCDH19-related epilepsy should perhaps not be classified as an ‘epileptic encephalopathy’.

Photosensitivity, the internationally-defined presence of a ‘photoparoxysmal response’ on an EEG, has been reported in approximately 5-10% of individuals. It is usually seen at between 3.5 and 12.5 years of age. This figure is probably unreliable because of poor or no cooperation with intermittent photic stimulation in children and young people with this disorder. It appears unlikely that photosensitivity is common in PCDH19-related epilepsy, unlike in Dravet syndrome.

Cerebral magnetic resonance imaging (MRI): This is usually normal. However, a report published in 2018 described five children (all girls) with infantile-onset epilepsy and a PCDH19 mutation. MRI in these five children showed cortical malformations, including areas of focal cortical dysplasia [Kurian et al, 2018]. The authors predictably concluded that a structural abnormality should be searched for in patients with a pathogenic PCDH19 mutation. Conversely, they also recommend that PCDH19 analysis should be considered in all children with a cortical malformation and who are undergoing evaluation for epilepsy surgery. I think this is unnecessary and an inappropriate investigation and should be restricted to only females with cortical dysplasia as the disorder is rare in boys. An earlier retrospective study of 58 females found cortical dysplasia in two of 48 patients that had undergone MRI and was “suspected” in another seven patients [Lotte et al, 2016]. Protocadherin-19 has a role during brain development and this might support the theory that PCDH19 mutations may lead to structural malformations [Merwick et al, 2012].

Associated difficulties: learning difficulties and autistic spectrum disorder

It was initially thought that learning difficulties were a constant feature of this epilepsy, occurring in almost all patients [Dibbens et al, 2008; Scheffer et al, 2008]. However, a recent study of 61 Italian children and young people, together with a review of the earlier literature, showed that up to 30% of affected individuals had normal cognitive development [Trivisano et al, 2018]. The degree of learning difficulties ranges from mild to profound. A figure of 30% normal cognition is somewhat optimistic, given the early onset of the epilepsy and high frequency of the seizures in the first couple of years of life. This might reflect how ‘cognitive development’ was defined and diagnosed. I think that with additional data and more formal psychological assessments, the number with ‘normal’ cognitive function is likely to be much lower. Psychiatric comorbidities, including hyperactivity, autism spectrum disorder (ASD) and obsessive compulsive disorders (OCD) are reported to be common features in both females and males. Reported prevalence rates range between 60 and 80% [Breuillard et al, 2016]. Further research is clearly required to clarify these non-seizure aspects of the disorder.

Prognosis (outcome)

There is no single or combination of anti-epileptic drugs (AEDs) that have been shown to be particularly effective in treating the different seizure types in PCDH19-related epilepsy. A recent report retrospectively described 58 females with this epilepsy collated from 12 European countries [Lotte et al, 2016]. It suggested bromide (the most ancient AED, and only extremely rarely used in the UK) and clobazam were the most effective drugs at three
Sodium valproate was the next most effective AED. Recent and preliminary research has suggested a neuro-steroid called ganaxolone might be beneficial. Ganaxalone is related to a naturally-occurring sex hormone called allopregnanolone which has anticonvulsant properties and seems to be low in pre-pubertal females with PCDH19-related epilepsy. The hypothesis is that by giving ganaxalone, which resembles allopregnanolone, this may reduce seizure frequency during the pre-pubertal years [Tan C et al, 2015].

As stated above, the epilepsy is reported to become less troublesome from the age of 10-15 years onwards. Some patients had been seizure free for six years at the time of their last follow-up. However, there is no information as to whether this remains the case throughout adult life and whether seizure-freedom is spontaneous or only because of the continuing use of AEDs.

The one factor that has been shown to be closely linked with developmental and cognitive (ie educational) outcome is the age at onset of the epilepsy. The earlier the epilepsy starts, the worst the cognitive outcome. Seizure frequency and seizure control do not seem to be as important [Trivisano et al, 2018] as the age at onset.

Clearly, more information is needed to confirm this current optimistic outcome that individuals may become and remain seizure free. This includes the possibility of ‘resolution’ of their epilepsy (ie seizure free for 10 years and not having received an AED for at least the last five of these 10 years) [Fisher et al, 2014].

**Summary**

Table 1 provides a pragmatic summary of the three most common ‘seizure-related’ conditions that may present in the first 6-12 months in association with a high body temperature.

---

<table>
<thead>
<tr>
<th></th>
<th>PCDH19-related epilepsy</th>
<th>Dravet syndrome (SCN1A mutation)</th>
<th>Febrile seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Females (≥95%)</td>
<td>Females and males</td>
<td>Females and males</td>
</tr>
<tr>
<td><strong>Age at onset of seizures</strong></td>
<td>Under 12 months (3-12 months)</td>
<td>Under 12 months (6-9 months)</td>
<td>12-36 months (rare under 10 months)*</td>
</tr>
<tr>
<td><strong>Seizure type</strong></td>
<td>Focal &gt; generalised</td>
<td>Focal ≥ generalised</td>
<td>Generalised</td>
</tr>
<tr>
<td><strong>Seizure frequency</strong></td>
<td>Cluster/serial &gt; single</td>
<td>Single &gt; cluster</td>
<td>Single</td>
</tr>
<tr>
<td><strong>Seizure duration</strong></td>
<td>Brief (&lt;5 minutes)</td>
<td>Prolonged (&gt;15 minutes; status epilepticus common)</td>
<td>Brief (&lt;5 minutes)</td>
</tr>
<tr>
<td><strong>Inter-ictal EEG</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Photosensitivity on EEG</strong></td>
<td>Rare (&lt;5%; usually aged 5-12 years)</td>
<td>Common (~30%; usually aged 1-4 years)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Development at seizure onset</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* be extremely cautious about diagnosing a febrile seizure in an infant <10 months of age

---

References


Scheffer IE et al. (2008) Epilepsy and mental retardation limited to females: an under-recognised disorder *Brain* 131: 918-27.


Forthcoming courses and conferences

The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

**March 2019**
25-28
EEG in the first year of life
Cambridge, UK
ilae.org/congresses/eeg-in-the-first-year-of-life

**April 2019**
7-9
7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures
London, UK
statusepilepticus.eu

**May 2019**
5-11
6th Residential International Course on Drug Resistant Epilepsies
Rome, Italy
ilae.org/congresses/6th-residential-international-course-on-drug-resistant-epilepsies

26-28
12th International Epilepsy Colloquium (IEC)

**June 2019**
22-26
33rd International Epilepsy Congress
Bangkok, Thailand
epilepsycongress.org/iec/

**September 2019**
14-15
ILAE British Branch 17th SpR Epilepsy Teaching Weekend
Oxford, UK
epilepsyteachingweekend.com

**October 2019**
2-4
ILAE British Branch Annual Scientific Meeting
Birmingham, UK
ilaebritishconference.org.uk

**July 2020**
4-8
14th European Congress on Epileptology (ECE)
Geneva, Switzerland
epilepsycongress.org/ece
Branded and generic anti-epileptic drugs

Dr Maria Moran, consultant paediatrician with expertise in epilepsy, Nottingham University Hospitals NHS Trust
Dr William P Whitehouse, clinical associate professor, University of Nottingham and consultant paediatric neurologist, Nottingham University Hospitals NHS Trust

Introduction
Generic prescribing has been a priority within the NHS for some time. Yet there has often been concern expressed by patients with epilepsy and their clinicians about the use of generic anti-epileptic drugs (AEDs). Are they really equivalent to branded products in their efficacy? Is switching to a generic worth the risk for a patient who is seizure-free? What about the risk of adverse effects?

Benefits of generic prescribing
The primary driver for use of generic prescriptions is cost. The patent on a newly invented branded pharmaceutical drug may typically last 20 years, after which other companies are free to produce a generic version. The cost of a generic drug will usually be less than a branded product as there is no need for the manufacturer to re-coup the expenditure on research and development. Furthermore, expanding the number of manufacturers should provide market competition to lower prices. Between 1976 and 2015 the proportion of generic prescriptions for all medications issued by GPs in the NHS has increased dramatically. It has risen from around 20% to over 84%, with estimated cost saving to the NHS of £7.5 billion [Appleby 2015].

Epilepsy is a common neurological condition. Point prevalence of active epilepsy in a recent meta-analysis of international studies was 6.38 per 1,000 persons [Fiest et al, 2017]. In the US, there are thought to be around 2.2 million people with epilepsy, and in the UK an estimated 600,000 receiving treatment for epilepsy [JEC, 2011]. The expenditure on AEDs is therefore sizeable. It is estimated to be over £400 million for community prescriptions in the UK, with potential cost savings of around £25 million if more generic prescriptions were used [PrescQIPP, 2014].

Regulating generic medications
The fear of using generic AEDs has arisen from two main concerns: inferior efficacy and risk of adverse effects. An unfortunate episode in the 1960s in Australia was an early illustration of the risk of adverse effects. Following an apparently small change in manufacturing practice, a number of patients developed phenytoin toxicity after the excipient was changed in one brand of phenytoin capsules. This led to an unexpected increase in active drug absorption [Tyrer et al, 1970]. Since that time, regulations governing the manufacture of drugs have evolved substantially to protect patients. Generic medications must contain the same active ingredients and use the same dosage form and route of administration as the branded version. They must be manufactured and monitored to the same standards of quality and safety as all medicines, following ‘Good Manufacturing Practice’ [Give.uk, 2019; European Commission]. Furthermore, to receive marketing approval — the ‘license’ to advertise and promote a medicinal product for specific indications — manufacturers must demonstrate that the generic drug shows good bioequivalence. It needs to have the same acceptable range in bioavailability as different batches of the original branded product.

Pharmacokinetic (PK) studies must be undertaken, measuring serum or plasma concentration over time after a single dose. They establish the Cmax and AUC for both the branded reference product and generic product. Cmax is the peak concentration reached after a single oral dose. The time after swallowing the dose to reach Cmax is Tmax. The Area Under the Curve (AUC) is the area under a plot of concentration (y-axis) versus time (x-axis) after a single oral dose. It corresponds to the amount of medicinal product absorbed into the circulation (see Figure 1).

The 90% confidence interval (CI) for the log-transformed ratio of generic versus branded product for Cmax and AUC

Figure 1. A PK study showing the plot of drug concentration in serum over time following a single oral dose of two different medicinal products of the same drug, each on a single occasion in a single person.
Switching between brands of AEDs may involve a change of colour, size or appearance, which has the potential to confuse patients with multiple medications and cause medication errors. There may be a difference in taste and palatability, which is an important factor in concordance with medication, particularly for paediatric patients.

Most importantly, for AEDs, the impact of a small difference in efficacy compared to other medications may be much more deleterious for the patient if it leads to a breakthrough seizure. Particularly for patients who have been seizure-free for some time, a single breakthrough seizure may cause injury or death, or adversely affect employment, driving and other daily activities.

**Generic AEDs: evidence of harm?**

A number of studies have explored the risk associated with using generic AEDs. Surveys of both patients and their physicians have reported problems when they switch from branded to generic AEDs. Crawford et al [1996] surveyed 40 GP practices that reported 10% of the 251 patients that switched (for sodium valproate, carbamazepine, phenytoin) experienced problems with seizure control or side-effects. An Epilepsy Foundation online survey [2009] received 1,085 responses, with 59% of people reporting a worsening of seizures and 49% worse side-effects following a switch to a generic preparation. Wilner [2004] surveyed 301 US neurologists who reported 68% of patients had breakthrough seizures after switching, although the response rate for the survey was only 4%. A further survey of 550 patients and 606 physicians [Berg et al, 2008] found 88% of physicians were concerned about an increase in breakthrough seizures when switching. A survey including 594 responses from European branches of the ILAE [Kramer et al, 2007] found 49% reported problems when switching. Conclusions from these surveys suggest a significant risk in switching to generic AEDs. However, such retrospective, invited response surveys have clear limitations and likely associated bias. Nevertheless, they illustrate well the perception of the risk held by patients and their clinicians at the time.

Further studies exploited database information to explore this issue further. Andermann et al [2007] used pharmacy claims data from Ontario. The study showed that commonly used medications, such as statins and SSRIs, when switched to generic forms, had a low rate of switching back to branded product – around 1.5-2.9%. However, AEDs had higher rate of switch back: 12-20% for Depakene (valproic acid), Frisium (clobazam) and Lamictal (lamotrigine). It was not possible from this study to attribute cause for this. It may well have reflected perceived risk, and the unpredictability and variability of seizure rates in epilepsies, as much as genuine adverse effects. A study of claims data from Quebec [LeLorier et al, 2008] showed a similar switch-back rate for patients switched from Lamictal to generic lamotrigine (27% switched back). This study reported a higher rate of

---

**Figure 2. Schematic of 90% confidence interval for the log-transformed ratio of branded versus generic product for Cmax for four different medicinal products of the same drug. Medication 1, 2, 3 would be considered bioequivalent; Medication 4 has a confidence interval that lies outside the accepted range.**
medical visits (9.8 versus 8.7 per person-year), longer length of stay (4.6 versus 3.3 days per person-year), and higher prescriptions of all medications in the group taking generic lamotrigine. Labiner et al [2010] analysed health insurance claims data (from 2000-07) for adults with epilepsy and compared time periods of branded prescriptions with generic. They reported increased use of all prescription drugs, 20% increased risk of injury and increased epilepsy-related medical utilisation rates. A retrospective study of patients prescribed levetiracetam [Chaluvadi et al, 2011] found 42% of 245 patients switched back to the branded product after a hospital policy was introduced to only use generic prescription. An increase in seizures was reported by 19%. These studies all conclude a potential significant risk of using generic AEDs. However, they were all retrospective observational studies without clear account of possible confounding factors, and mainly highlight the significant perception of risk.

**Evidence to reassure us**

There has been a call for high quality evidence to inform the debate over whether generic AEDs should be used. In response to concern regarding bioequivalence studies, the FDA examined 127 in vivo bioequivalence studies and confirmed that the mean difference in AUC was 3.5% and in Cmax 4.3% for those tested [Henney, 1999]. Furthermore, it has been shown that there is less than 15% variability in 99% of AUC and 89% Cmax values in bioequivalence studies for AEDs [Krauss et al, 2011].

A number of observational studies offered a more reassuring picture than those outlined above. Polard et al [2015] reported a review of health insurance database information for 8,379 patients which showed no increased risk of seizure-related hospitalisation when taking generic medications. Hartung et al [2012] examined Medicaid claims data in the US between 2006 and 2009 for 616 patients that had switched to generic lamotrigine. They found no increased risk of emergency department visits or hospital admissions. A prospective study [Vari et al, 2016] of 59 patients who switched from Keppra to generic levetiracetam showed no increase in seizures or adverse effects during six months of follow-up. The switch back rate was only 3.4%.

Given the concern of possible increase in seizures after switching to a generic AED, two studies explored the risk of collecting a new prescription of medication (a refill), regardless of whether branded or generic. One showed an increased risk of seizures requiring emergency treatment (OR 2.31) when a refill had been collected within 21 days [Gagne et al, 2010]. A second study reported health insurance data for 83,000 patients using generic AEDs. It found collecting a refill was associated with an 8% increase in seizure-related emergency attendances or admissions, with no associated change when switching between generic products [Kesselheim et al, 2016]. Reasons for this are unclear, but may be related to a pause in medication use between prescriptions.

A randomised double-blind study comparing branded and generic carbamazepine in 40 patients showed no statistical difference in seizure frequencies, AUC and Cmax measurements [Oles et al, 1992]. An open label study [Markkola et al, 2017] in 12 patients comparing Keppra with generic levetiracetam also showed no difference in seizure frequency and AUC and Cmax values.

Despite these reassuring results, concern remained that there was, until recently, insufficient robust prospective evidence to support using generic AEDs. Two recent studies sought to address this for generic lamotrigine. The BEEP study (BioEquivalence in Epilepsy Patients) compared generic lamotrigine with Lamictal in 34 patients who had not previously used generic preparations [Ting et al, 2015]. It used a randomised, double-blind, crossover design with trough and 12-hr sampling periods to measure AUC and Cmax, as well as the secondary outcome of seizure frequency. No significant differences were found.

The Equigen study compared generic to branded lamotrigine change in 33 patients and also found no difference for AUC, Cmax or seizure frequency [Berg et al, 2017].

**National guidance**

Previously, national guidance has advised caution in the use of generic AEDs. In the UK, the National Institute for Health and Care Excellence (NICE) guidance 2012 stipulates that:

“Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer’s AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side-effects.” [NICE, 2012]

The American Epilepsy Society (AES) has similarly previously advised against using generic AEDs without explicit approval of the clinician and patient.

Current UK Medicines and Healthcare Products Regulatory Agency (MHRA) guidance specifies different levels of caution according to category of AED [Gov.uk, 2013] (Table 1).

This was updated in 2017 to include advice to prescribers that, as well as the classification, when evaluating whether continuity of supply should be maintained, they should also consider:

- Perception by patients of differences in supply for example differences in product presentations
Table 1. Medicines and Healthcare Products Regulatory Agency guidance on different level of caution when switching between different manufacturers’ products according to category of anti-epileptic drug

<table>
<thead>
<tr>
<th>Category</th>
<th>Advice for doctors</th>
<th>Anti-epileptic drugs in category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Doctors are advised to ensure that their patient is maintained on a specific manufacturer’s product</td>
<td>Phenytoin, carbamazepine, phenobarbital, primidone</td>
</tr>
<tr>
<td>Category 2</td>
<td>Doctors are advised to use their judgement (in consultation with their patient and/or their carer) to determine whether it would be advisable for them to be maintained on a specific manufacturer’s product</td>
<td>Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate</td>
</tr>
<tr>
<td>Category 3</td>
<td>Doctors are advised that it is usually unnecessary to ensure that their patients are maintained on a specific manufacturer’s product</td>
<td>Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin</td>
</tr>
</tbody>
</table>

- Comorbid autism, mental health issues, or learning disability [Gov.uk, 2017]

With the growing evidence in support of the safety of generic AEDs, guidance is moving forward. Following publication of the BEEP and Equigen studies, the AES re-issued an updated position statement in 2016. This recognised these as well-designed, prospective studies in patients with epilepsies [Vossler et al, 2016] and acknowledged “that drug formulation substitution with FDA-approved generic products reduces costs without compromising efficacy”.

The statement points out that a bioequivalent generic product should be used (that is, consistency between immediate and modified-release). It says there should be communication regarding difference in appearance but confidence in efficacy and quality.

Local perspective

Recently, in our own hospital trust, paediatric and adult neurologists agreed a transition to generically dispensed levetiracetam, lamotrigine and topiramate unless otherwise specified by the prescriber. A hospital registered clinical audit of this practice showed that generic prescription was achieved for the majority of patients. It was the case in 75/97 (77%) taking levetiracetam, 14/15 (93%) taking topiramate and 31/41 (76%) taking lamotrigine. Patients or their parents or carers were also contacted by telephone to collect information regarding seizure control, adverse effects, and thoughts or concerns regarding the change to generic AED. Numbers were small to draw firm conclusions regarding any effect on seizure control or adverse effects, although there was no suggestion of a difference between generic and branded preparation. Of more interest was the finding that many had already used generic preparations dispensed in the community, and very few had any concerns about the use of generic AEDs generally, or switching between preparations. For topiramate, 11/15 (73%), and for lamotrigine, 32/41 (78%) expressed no specific opinion about generic substitution and switching. Only 5/56 (9%) said they preferred to have branded topiramate or lamotrigine to generic products.

Conclusion

It is clear that prescribing generic AEDs offers the potential for cost savings. Having the confidence and flexibility to use generic preparations is an important consideration for a resource-challenged health service. It is important to understand the role of bioequivalence studies in ensuring quality of preparation, the limitations of studies which have reported adverse effects from using generic AEDs, and the current reassuring evidence to the contrary, limited though this is. This will hopefully help inform clinicians and patients in making their decision about prescribing, and being compliant with, generic AEDs. Finally, wherever possible, it would seem reasonable to use the same generic product in hospital and the community. This would help minimise the potential for confusion and drug errors due to switching on an individual patient.

References


Epilepsy Foundation. (2009). In Their Own Words: Epilepsy Patients’ Experiences Changing the Formulation of the Drugs They Use to Prevent Seizures. [online] Available at: https://www.epilepsy.com/sites/core/files/atoms/files/In-Their-Own-Words.pdf [Accessed 22 Feb 2019]


This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

Maragkos GA, Geropoulos G, Kechagias K, Zogias IA, Mylonas KS. 
Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis 

Shorvon S. 
Paediatric status epilepticus—A series of timely reviews 

Shaukat Q, Hertecant J, El-Hattab AW, Ali BR, Suleiman J. 
West syndrome, developmental and epileptic encephalopathy, and severe CNS disorder associated with WWOX mutations 

Patient satisfaction with epilepsy surgery: what is important to patients? 

Yasumoto S, Ohtsuka Y, Sato K, Kurata A, Numachi Y, Shimizu M. 
Long-term efficacy and safety of lamotrigine monotherapy in Japanese and South Korean pediatric patients with newly diagnosed typical absence seizures: An open-label extension study. 

Treatment of infantile spasms by pediatric neurologists in Japan 

Unterberger I, Trinka E, Kaplan PW, Walser G, Luef G, Bauer G. 
Generalized nonmotor (absence) seizures—What do absence, generalized, and nonmotor mean? 

Donos C, Malia MD, Dömpelmann M, Schulze-Bonhage A. 
Seizure onset predicts its type 

Invasive monitoring after resection of epileptogenic neocortical lesions in multistaged epilepsy surgery in children 

Dietze CS, Ekosso-Ejangue L, Israel CW, Bien CG, Fauser S. 
Benefits of additional cardiologic examination in patients admitted for differential diagnosis to the Epilepsy Center Bethel 

Ali S, Scheffer I, Sadleir LG. 
Efficacy of cannabinoids in paediatric epilepsy 

Cognitive outcomes following epilepsy in infancy: A longitudinal community-based study. 

Kalliani L, Sun X, Peligrims B, Noack-Rink M, Villanueva V. 
The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis 

Carlson S, Kandler RH, Moorhouse D, Ponnusamy A, Mordekar SR, Alix JJP. 
Home video telemetry in children: A comparison to inpatient video telemetry 

Hirsch M, Hintz M, Specht A, Schulze-Bonhage A. 
Tolerability, efficacy and retention rate of Brivaracetam in patients previously
treated with Levetiracetam: A monocenter retrospective outcome analysis

Cohen NT, Chamberlain JM, Gaillard WD. Timing and medication of first antiepileptic medication in patients with pediatric status epilepticus


Gill D.
Dealing with a first seizure: accurate diagnosis and good management

Brorson LO, Eriksson M, Blomberg K, Stenning E.
Fifty years’ follow-up of childhood epilepsy: Medical outcome, morbidity, and medication

Angione K, Eschbach K, Smith G, Joshi C, Demarest S.
Genetic testing in a cohort of patients with potential epilepsy with myoclonic-atonic seizures

Functional neuroimaging in Rasmussen syndrome

Abraham AP, Thomas MM, Mathew V, Muthusamy K, Yogananth S, Jonathan GE, Prabhun K, Daniel RT, Chacko AG.
EEG lateralization and seizure outcome following peri-insular hemispherotomy for pediatric hemispheric epilepsy

Ryvlin P, Rheims S, Lhatoo SD.
Risks and predictive biomarkers of sudden unexpected death in epilepsy patient

Haut SR, Gursky JM, Privitera M.
Behavioral interventions in epilepsy

Shimamoto S, Wu C, Sperling MR.
Laser interstitial thermal therapy in drug-resistant epilepsy

Brikell I, Chen Q, Kuja-Hallkola R, D’Onofrio BM, Wiggs KK, Lichtenstein P, Almqvist C, Quinn PD, Chang Z, Larsson H.
Medication treatment for attention-deficit/hyperactivity disorder and the risk of acute seizures in individuals with epilepsy

Devinsky O, Bundock E, Hesdorffer D, Donner E, Moseley B, Cihan E, Hussain F, Friedman D.
Resolving ambiguities in SUDEP classification

de Lange IM, Gunning B, Sonsma ACM, van Gemert L, van Kempen M, Verbeek NE, Nicolai J, Knoers NVAM, Koeleman BPC, Brilstra EH.
Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN1A-related seizure phenotypes

Chewing induced reflex seizures (“eating epilepsy”) and eye closure sensitivity as a common feature in pediatric patients with SYNGAP1 mutations: Review of literature and report of 8 cases

"Breath holding spells" in a child with SCN8A-related epilepsy: Expanding the clinical spectrum

Different types of suppression-burst patterns in patients with epilepsy of infancy with migrating focal seizures (EIMFS)