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CURRENT AWARENESS SERVICE

Prevalence and incidence of epilepsy and what it tells us

In recent years, conventional teaching has been that the number of people with epilepsy in the UK is around one in every 100. This figure originated from 2011, when the Joint Epilepsy Council (JEC) published a report on the prevalence and incidence of epilepsy [JEC 2011]. However, there was some variation across the different nations of the UK.

Over the past few years, this figure has been changing. Advances in our healthcare, including new surgery techniques and better imaging and assessment tools, as well as challenges we've faced, such as understaffing in the NHS, are likely to impact on the prevalence and incidence of epilepsy in the UK. There has also been an improvement in the accuracy of the diagnosis of epilepsy and particularly in children. In part, this latter issue reflects the expanding participation of many consultants and trainees in paediatrics in the paediatric epilepsy training (PET) courses established by the British Paediatric Neurology Association (BPNA) almost 20 years ago in 2004. The International League Against Epilepsy (ILAE) and, very recently, the World Health Organisation (WHO) have approved and endorsed the PET programme. The BPNA defines the PET programme as targeting "paediatricians, medical officers and emergency department professionals" and says it "aims to improve the diagnosis of epileptic and non-epileptic events; improve the standard of care; and raise awareness of when to liaise with a paediatric neurologist, a children's epilepsy expert". While there are no data that confirm the hypothesis that this has led to a significant improvement in the accuracy of diagnosis of epilepsy in children, it is highly likely that it has.

In view of the data being over 12 years old, and together with recent advances in epilepsy diagnosis, it seems appropriate to update the prevalence and incidence of epilepsy to reflect where we are in 2023.

Earlier this year, Wigglesworth *et al* [2023] published their retrospective cohort study of UK primary care data in the journal Seizure. Their objective was to provide an update on the overall incidence and prevalence of epilepsy for the UK and each of its individual nations. The study period covered the six years between 1 January 2013 and 31 December 2018.

The data were derived from electronic health records of 14 million patients from primary care practices which represents around 20% of the UK population.

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The results found that overall, in the UK, the epilepsy prevalence was 9.37 per 1,000 persons per year, or one in 107 people, which was a slight reduction compared to one in 103 in previous findings from 2011 [JEC, 2011]. The incidence rate was 42.68 per 100,000 person years, or 79 new cases a day, which was also a reduction from the 2011 findings, which estimated an incidence rate of 51 per 100,000 person years, or 87 new cases per day.

There were some differences between the different UK nations in terms of epilepsy numbers, with the prevalence actually appearing to have increased in some nations. In England, the prevalence was 9.08 per 1,000, or one in 110 (down from one in 105 in 2011), and in Scotland, the prevalence was 10.13 in 1,000, or one in 100 (down from one in 94 in 2011). However, in Wales, the prevalence was 11.4 in 1,000, or one in 88 (up from one in 94 in 2011); and in Northern Ireland, the prevalence was 12.33 in 1,000, or one in 83 (up from one in 90 in 2011) [Wigglesworth *et al*, 2023; JEC, 2011].

As a comparison, the People's Republic of China, the location-specific prevalence in urban and rural areas was 234 and 317 per 100,000, or 2.34 and 3.17 per 1,000, respectively [Gu *et al*, 2013]. A study from sub-Saharan Africa estimated the prevalence to be lower and with a wide range depending on the age: (301 per 100,000, or 3.01 per 1,000, for those aged >60 years; 820, or 8.2 for those aged 40-49 and 1150, or 11.5, for those aged 20-29 years) [Paul *et al*, 2012]. The high rates in Africa are considered to reflect the sequela of infections of the central nervous system (CNS) and particularly neuro-cysticercosis caused by a parasite. The data from China and sub-Saharan Africa must be regarded with caution because of the accuracy of diagnosis as well as the case-ascertainment in resource-poor countries.

In the Wigglesworth *et al* paper [2023], there were also differences in the incidence rates across the different nations. The incidence in England was 41.41 per 100,000 person-years, in Scotland it was 47.76 per 100,000 person years and in Northern Ireland, this was 45.48 per 100,000 person-years. Wales had the highest epilepsy incidence of 54.84 per 100,000 person years.

The estimated incidence of epilepsy in the Nordic countries, as comparison, (primarily Denmark, Finland, Iceland, Norway and Sweden) was 30-60 new cases occur per 100,000 person-years [Syvertsen *et al*, 2015] which is considerably lower than in the UK.

The differences between the nations of the UK may imply different healthcare provision for people with epilepsy across the different UK nations. Following the publication of the new figures, Epilepsy Action expressed particular concern about the prevalence of epilepsy in Northern Ireland, particularly in view of the long-standing political situation. There is currently no devolved government in place in Northern Ireland following elections in May 2022 after which the two main political parties, Sinn Féin and the Democratic Unionist Party (DUP), failed to agree on a new speaker for the Northern Ireland assembly. This has meant important decisions around health policy have not been made. The prevalence has increased compared to 2011, and is the highest among the UK nations, and the incidence of epilepsy is also higher than that of the UK overall.

Carla Smyth, Northern Ireland services and project manager at Epilepsy Action, commenting on the findings of Wigglesworth *et al*, stated: "These new figures around the prevalence of epilepsy in Northern Ireland are hugely concerning and highlight a significant difference between Northern Ireland and the rest of the UK.

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

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

There are very limited paediatric-specific data. An interesting population-based study from Scotland of 390 children recruited over a three year period examined the prevalence and incidence of early-onset (beginning before three years of age) epilepsy [Symonds *et al*, 2021]. The adjusted incidence of epilepsies presenting in the first three years of life was 239 per 100,000 live births. There was a socio-economic gradient to incidence, with a significantly higher incidence in the most deprived quintile (301 per 100,000 live births) compared with the least deprived quintile (182 per 100,000 live births). However, the relationship between deprivation and incidence was only observed in the group without an identified aetiology which the authors suggested reflected the fact that populations that live in higher areas of deprivation have a larger number of risk factors for epilepsy [Symonds *et al*, 2021]. Intuitively, this seems a paradox. This is because early-onset health-related stressful events such as pre-term and/or light for gestational age births, severe febrile illnesses including meningitis and sepsis and non-accidental injury (including traumatic brain injuries) are more likely to be seen in socially-deprived areas and therefore disadvantaged children. The authors recognised this unusual finding and said this requires further research.

When it came to the different age groups, the researchers found that there is a flattening of the well-recognised U-shaped age-related incidence curve (which indicates peak incidences in early childhood and older age) and

especially at the younger age range [Wigglesworth *et al*, 2023]. They couldn't account for the reasons of this flattening, but suggested: "It could be linked to improved guidance for clinicians, better obstetric care, more effective treatment of febrile seizures and more accurate differential diagnosis in the younger age groups."

However, the study did suggest a link between social deprivation and epilepsy, with the prevalence and incidence of epilepsy a third higher in poorer areas of the UK compared to wealthier areas. They found that the incidence and prevalence in England and Wales increased "from the lowest to the highest indices of multiple deprivation (IMD) deciles, with an over 40% increase".

A correlation between level of deprivation and epilepsy levels has been seen before, with Public Health England (PHE) figures from 2001-2014 showing a near three-fold higher risk of epilepsy-related deaths in people living in poorer areas of England compared to wealthier [PHE, 2018]. The report stated: "It is well documented, but not as yet well explained, that epilepsy prevalence varies with social deprivation; it is not clear whether this inequality in mortality is the consequence of prevalence of poor care, or both."

Looking at different regions in England, Wigglesworth *et al* [2023] also found that the highest epilepsy prevalence and incidence corresponded to the area that a recent Association of British Neurologists (ABN) survey found had the lowest number of consultant neurologists – the Northern Region (primarily the North East). In contrast, the lowest prevalence was found to be in London, the area which the ABN survey identified as having the highest number of consultant neurologists. However, these data must be regarded with some caution because it is the number of neurologists per head (e.g. per 1,000 or per 10,000) of population rather than the absolute number of neurologists that is the more important figure. It is possible that the number of neurologists per head of the adult population is higher (and therefore 'better') in the much lower populated Northern Region than in London.

The researchers in *Seizure* [2023] emphasised that their study was not designed to investigate the factors or reasons for this apparent correlation between the prevalence and incidence of epilepsy and deprivation. They said that long-term and prospective cohort data would be required to understand if the incidence and prevalence of epilepsy changed over time (i.e. increased) with an increase in those defined as being socially-deprived.

Keeping a clear eye on the changes in prevalence and incidence of epilepsy across the country can give us some indication of where care needs to be improved institutionally. Care must begin with the establishment of a correct diagnosis of epilepsy, before then considering the standard of care in terms of investigation and treatment and specifically holistic treatment which must include the provision of epilepsy specialist nurses. The recently-published data also provide us with an idea of the possible gaps in care that exist in pockets around the country that result not only in a higher rates of incidence and prevalence but also a potentially higher risk and rate of epilepsy-related mortality. These gaps in care are not unique to the UK and will be global but greatest in the developing countries. However, addressing and trying to resolve these gaps is important, irrespective of the country. Finally, one must also never lose sight of the ideal in disease management, which is to continue to strive to prevent the development of epilepsy in the first place.

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Richard Appleton
Co-Editors

References

Gu L, Liang B, Chen Q, *et al*. 2013. Prevalence of epilepsy in the People's Republic of China: a systematic review. *Epilepsy Res*. 105: 195-205.

Joint Epilepsy Council (JEC). 2011. Epilepsy prevalence, incidence and other statistics. [online] Available at: *https://d3imrogdy81qei.cloudfront.net/instructor_docs/373/29_05_2016_Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11.pdf*

Nitkunan A, Lawrence J and Reilly MM. Neurology Workforce Survey conducted by the Association of British Neurologists 2018-2019. [online] Available at: *https://cdn.ymaws.com/www.theabn.org/resource/collection/219B4A48-4D25-4726-97AA-0EB6090769BE/2020_ABN_Neurology_Workforce_Survey_2018-19_28_Jan_2020.pdf*

Paul A, Adeloye D, George-Carey R, *et al*. 2012. An estimate of the prevalence of epilepsy in Sub-Saharan Africa: A systematic analysis. *J Glob Health*. 2: 020405. doi: 10.7189/jogh.02.020405.

Public Health England. 2018. Deaths associated with neurological conditions in England 2001-2014. [online] Available at: *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/683998/Deaths_associated_with_neurological_conditions_data_briefing.pdf*

Symonds JD, Elliott KS, Shetty J, *et al*. 2021. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain* 144: 2879-2891.

Syvertsen M, Koht J, Nakken KO. 2015. Prevalence and incidence of epilepsy in the Nordic countries. *Tidsskr Nor Laegeforen (Journal of the Norwegian Medical Association)*. 135: 1641-1645. (article in English and Norwegian)

Wigglesworth S, Neligan A, Dickson JM, Pullen A, Yelland E, Anjuman T, Reuber M. 2023. The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data. *Seizure* 105: 37-42.

Forthcoming courses and conferences

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

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

September 2023
2-6
35th International Epilepsy Congress
Dublin, Ireland
bit.ly/3S5ANDj

October 2023
2-4
ILAE British Branch Annual Scientific Meeting Gateshead
Gateshead, UK
ilaebritishconference.org.uk


Madrid


Prague

March 2024
3-8
4th International Training Course on Neuropsychology in Epilepsy
Lyon, France
bit.ly/3VvHu2Z

May 2024
5-8
Seventeenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3fdKAbT

September 2024
7-11
15th European Epilepsy Congress
Rome, Italy
ilae.org/congresses/15th-european-epilepsy-congress

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epilepsy.org.uk/yourchild

Your child and epilepsy

Grow your confidence managing epilepsy in your family

Your child and epilepsy is a new online course for parents and carers of children with epilepsy. It's been developed with parents, epilepsy nurses and psychologists.

This course is a helping hand to support families on their epilepsy journey. It's full of advice and stories from parents. It aims to give parents and carers the confidence, skills and knowledge to support their child to manage their epilepsy.

There are eight parts that cover:

- Understanding epilepsy
- Supporting your child with their epilepsy
- Keeping your child safe
- The impact of epilepsy on family life
- Your child's wellbeing
- Learning and behaviour
- Growing up and independence
- Sources of help and support

Free course

The course is free and flexible. It can be accessed at any time on a computer, tablet or smartphone with internet access.

Leaflets about the course to give to families can be requested by emailing **nurseorders@epilepsy.org.uk**

To view the course go to: **epilepsy.org.uk/yourchild**
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An update on the clinical phenotype and management of Dravet syndrome

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Dravet syndrome (DS) is a developmental and epileptic encephalopathy (DEE) associated with pathogenic variants of the SCN1A gene in nearly all cases. DS is associated with lifelong drug resistant seizures, early developmental impairment/intellectual disability, pervasive neurodevelopment disorders, and sleep impairment and gait difficulties. Importantly, DS is associated with an almost 2-fold increase in sudden unexpected death in epilepsy (SUDEP) patients compared to the other drug resistant epilepsies persisting into adulthood [Cooper *et al*, 2016].

A recent prospective study showed SCN1A-related epilepsy is the second most common monogenic epilepsy in children under three years of age [Symonds *et al*, 2019]. An incidence of DS in 6.5/100,000 live births was observed in a recent prospective cohort study across Scotland [Symonds *et al*, 2021].

DS presents in the first year of life in an infant with initially normal development usually with prolonged, febrile and afebrile seizures which can be focal hemiclonic seizures on alternating sides and generalised tonic-clonic seizures [Zuberi *et al*, 2022].

DS is a clinical diagnosis but in the era of whole exome and genome sequencing, and next generation genetic panels, one would expect to confirm a pathogenic variant of SCN1A resulting in haploinsufficiency of the NaV1.1 alpha-1 subunit of the sodium channel in almost all cases [Harkin *et al*, 2007].

SCN1A pathogenic variants may also be related to other phenotypes, particularly generalised epilepsy with febrile seizures plus (GEFS+) linked with recurrent febrile and afebrile seizures in childhood, associated with a family history of febrile seizures. The phenotypic spectrum of GEFS+ is broad and the label of DS may be considered appropriate on the more severe end of it in individuals with SCN1A pathogenic variants [Scheffer *et al*, 2009].

In the era of precision medicine, DS can be considered the prototypical monogenic epilepsy. DS has probably been studied more than any other monogenic epilepsy. Several DS-specific precision treatments have been developed that have been shown to improve seizure outcome.

In addition, there are several common anti-seizure medications (ASMs) that worsen seizures in DS that must be avoided. Therefore, it is fundamental that all paediatricians with an interest or expertise in epilepsy and all neurodevelopmental and neurodisability paediatricians have a good working knowledge about DS.

Early phenotypic recognition, genetic diagnosis and initiation of precision treatment strategies are fundamental to improve outcome and reduce the risk of SUDEP. In the UK, early referral of DS children to a tertiary paediatric neurology centre with access to these therapies is crucial.

Holistic and integrated care of children with DS involving a multi or inter disciplinary team of paediatricians or paediatric neurologists, therapists, educationalists, nurses and child psychiatrists or psychologists is important to optimise the intellectual and psychosocial potential of every child with DS. Clearly, this may be difficult depending on the child's postcode and available resources.

We will review the clinical phenotype of DS, and the diagnostic approach, management of co-morbidities, and epilepsy treatment strategies. We summarise the many recently-published guidelines and studies and suggest a practical approach to management.

Clinical features

Seizures

Seizure onset is usually between 3-9 months of age with a median age of six months [Zuberi *et al*, 2022]. In a study from Australia, a tonic-clonic seizure was the initial seizure in 52% of children, while focal hemiclonic seizures were seen in 35% [Li *et al*, 2021]. Prolonged seizures (seizures over five minutes) and status epilepticus are usually seen at the onset (age ranges 5-8.5 months and 5-11 months respectively), as shown in a recent systematic literature review [Sullivan *et al*, 2022].

Febrile seizures at onset were seen in 55% of children [Li *et al*, 2021] which indicates that febrile seizures may be part of the syndrome [Dravet, 2011]. The common triggers for seizures are viral or bacterial infections resulting in fever, post immunisation fever, hot baths, a hot environment, flashing lights and over-excitation [Wirrell *et al*, 2017]. More specifically, the history of an early and prolonged hemiclonic seizure following a routine childhood immunisation in infancy is highly suggestive of DS.

Absence and myoclonic seizures develop between the age of 1-2 years [Sullivan *et al*, 2022] with other seizure

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types also then occurring between 1-5 years of age. These include focal impaired awareness seizures, atonic seizures and non-convulsive status epilepticus [Zuberi *et al*, 2022]. In half of children and at an average age of seven years, tonic and tonic-clonic seizures start to occur during sleep and in clusters, and often persist into adulthood [Sullivan *et al*, 2022; Zuberi *et al*, 2022]. The prolonged and clusters of seizures tend to lessen with increasing age [Sullivan *et al*, 2022].

It is important to note that although the onset of DS has been reported between the age ranges of one and 20 months, the ILAE guidelines highlight those children that present at the extremes of this range (1-2 months or 15-20 months) and recommend that an alternative diagnosis should be considered, including metabolic (mitochondrial), structural or other genetic epilepsies/disorders (such as PCDH19 or glut-1 deficiency) [Dravet, 2011; Zuberi *et al*, 2022].

Approach to investigation

All children with suspected DS should have an EEG, MRI brain scan and genetic testing, not just to confirm the diagnosis of DS, but to exclude alternative diagnoses including a structural, genetic or metabolic epilepsy.

In DS, the MRI brain scan initially is usually normal but cerebellar atrophy may develop over time. Hippocampal sclerosis has occasionally been reported. Some children with DS may show evidence of cerebral and cerebellar atrophy over time on subsequent MRI scans [Guerrini *et al*, 2011].

The interictal EEG in children with DS is typically normal prior to two years of age. After two years, background slowing tends to be seen with inter-ictal focal, multifocal and generalised discharges (spikes or sharp waves). A photo-paroxysmal discharge is seen in at least 15% of children [Specchio *et al*, 2012].

It is recommended that there should be confirmation of a suspected diagnosis by DNA analysis. How this is undertaken will depend on the available policy in your area. Options include sequencing of the single SCN1A gene, a next generation bespoke epilepsy panel or whole genome or exome sequencing. A chromosomal microarray should also be undertaken to identify any rearrangements on chromosome 2q encompassing SCN1A and a number of contiguous genes, such as SCN2A, SCN3A, SCN7A and SCN9A. A chromosomal rearrangement might be missed on Sanger or genomic sequencing [Marini *et al*, 2011].

In England, the two currently available options for SCN1A genetic testing are through routine trio whole genome sequencing (applying the R59 epilepsy of childhood onset gene panel) or rapid trio whole genome sequencing (R14) (see *england.nhs.uk/genomics/nhs-genomic-med-service/*).

Routine whole genome sequencing involves sequencing the genome of the child and both parents followed by an initial targeted analysis of over 300 curated genes associated with epilepsy. If no pathogenic variant is identified, this is followed by a 'limited gene agnostic analysis' of genetic variants of interest by bioinformatic software based on correlation with phenotypic data. The rapid R14 whole genome provides a 'gene agnostic' analysis with a two-week turnaround time (*exeterlaboratory.com/genomics/exome-sequencing-services/*).

In requesting genetic testing for DS, it is important to highlight specifically that a variant of SCN1A is being looked for. In addition, when performing trio testing (involving samples of the child and parents) it is important to take a detailed family history to clarify whether parents might also be affected by an SCN1A-related epilepsy or other condition. Most cases of DS occur de novo but it is important to ask if parents had child-onset febrile/afebrile seizures, features of hemiplegic migraine, autism or intellectual disability. SCN1A pathogenic variants might be missed using gene agnostic technologies if the variant has been inherited from a parent. It is important to obtain an accurate family history to ensure that an incomplete penetrance (when a proportion of people with a genetic variant do not develop features of the condition) filter or panel-based analysis is used to avoid the variant being missed.

If a genetic variant is identified in a parent, then genetic counselling should be sought early as there is a 50% chance of passing on the variant in affected individuals. The SCN1A gene can show variable expressivity with a more severe DS phenotype seen in offspring of parents with a milder febrile seizure phenotype [Marini *et al*, 2011]. Preimplantation genetic diagnosis might be available if further pregnancies are being considered [Sermon *et al*, 2004].

A recent consensus guideline has highlighted that all children under 12 months with prolonged febrile seizures lasting more than 30 minutes should have genetic testing for SCN1A [Wirral *et al*, 2022]. We would recommend that a rapid genetic diagnosis for possible DS should be sought in all infants that present with recurrent febrile/afebrile status epilepticus in infancy and in all infants with drug-resistant early-onset seizures and with no obvious abnormality on neuroimaging. The genetic finding of a pathogenic SCN1A variant may allow precision treatment options as outlined later.

Other genes associated with DS like phenotypes include SCN2A, SCN8A, SCN9A, SCN1B, PCDH19, GABRA1, GABRG2, STXBP1, HCN1, CHD2 and KCNA2 [Steel *et al*, 2017]. In around 20-30% of cases children with a DS-like phenotype a pathogenic variant may not be identified [Marini *et al*, 2011].

Approach to treatment of seizures

There are currently a number of treatment options available to treat children with DS and novel ones are likely to be identified in the future. Consequently, it is advisable

to adopt a rational and systematic approach. Seizures are typically drug resistant, with minimal chance of long-term seizure freedom. Acceptable (to parents and the doctor) seizure control may be achieved early or late in any systematic approach. Not all patients will need all the treatment options. The choice of treatment might be influenced by specific factors, including adverse side effects, medication tolerability and the ability to comply with routine monitoring (blood tests and echocardiograms).

Although various trial data are presented, it must be stated that there is a skew towards recent pharmaceutical industry sponsored randomised control studies. Data for older, well-established ASMs are derived predominantly from retrospective studies with a lack of head-to-head comparison between and within newer and older generations ASMs. Consequently, the sequential approach to the use of ASMs is primarily based on expert consensus guidelines.

In England, cannabidiol (Epidyolex) and fenfluramine (Zogenix, Fintepla) are expensive medications that can only be prescribed by paediatric neurologists with funding obtaining through the NHS Blueteq system.

First line - Sodium valproate

Sodium valproate is the first-line medication for DS as recommended by the National Institute for Health and Care Excellence (NICE) [NICE, 2022] and an international consensus opinion [Wirrell *et al*, 2022]. Although this is consistent with routine clinical practice, there is no randomised controlled trial data on the optimum first line ASM for DS [NICE, 2022]. In one retrospective study, sodium valproate monotherapy had a 48.4% responder rate (defined as over 50% seizure frequency reduction) [Dressler *et al*, 2015]. It has been suggested that sodium valproate may no longer be the first-line ASM in view of the fact that sodium valproate monotherapy is rarely sufficient to control seizures. This may potentially change in the future.

The adverse side effects of valproate are well-recognised. The most common are increased appetite and weight gain, behavioural difficulties (overactivity) and tremor (in high dose). Less common side-effects are encephalopathy, thrombocytopaenia, pancreatitis and hepatoxicity. [Arzimanoglou *et al*, 2018]. The hepatotoxicity may be fatal but is almost confined to those children with an early-onset (<3 years) and refractory epilepsy and with an underlying mitochondrial cytopathy.

Finally, there is the risk of teratogenicity and early speech impairment and autism in the children born to mothers who took the drug during pregnancy. Although it is unlikely that girls with DS will ever have children, there is the need to consider the valproate pregnancy prevention programme and the recent announcement from the Medicines and Healthcare products Regulatory Agency (MHRA). This is likely to indicate that two independent specialists will be required to agree that sodium valproate is the most appropriate ASM for any patient before it can be prescribed.

Add-on therapy: stiripentol and clobazam

Stiripentol with clobazam is the add-on suggested in the NICE guideline [NICE, 2022], similar to the recent international consensus guideline [Wirrell *et al*, 2022] placing it as 'step 2'. NICE guidelines state there should be is flexibility in adding stiripentol and clobazam one at a time to ensure positive effects of one drug are not missed and side effects are minimised. However, it could be argued that both should be added simultaneously to sodium valproate, although this will increase the risk and occurrence of adverse side-effects [NICE, 2022].

In the initial randomised controlled trial, Chiron *et al* demonstrated that 71% (15/21) of patients had seizure reduction by at least 50% compared to placebo when stiripentol was added to clobazam and valproate. A Cochrane review of two trials is also supportive of add-on stripentol therapy [Brigo *et al*, 2017]. Post-marketing surveillance data is also emerging. Two-year surveillance data from Japan showed a response rate of 43% (110/257) for convulsive seizures (36.5% if set at 75% responsive), 55% (58/105) for focal impaired awareness seizures (50.5% if 75% responsive) and 62% (56/90) for generalised myoclonic or atypical absence seizures (56.7% if 75% responsive) [Yamada *et al*, 2021].

Stiripentol increases the plasma concentrations of clobazam. Therefore, dose adjustments of clobazam should be considered as stiripentol is started and increased [Nickels and Wirrell, 2017].

Common adverse side effects of clobazam include fatigue, drowsiness, aggression, hyperkinesia, ataxia, hypersalivation and, bronchorrhoea. Less common side-effects include muscle weakness, psychosis and thrombocytopenia [Arzimanoglou *et al*, 2018]. Side effects for stiripentol can include decreased appetite (which can be severe), weight loss, somnolence, ataxia, hypotonia, dystonia, tremor, dysarthria and agitation [Strzelczyk and Schubert-Bast, 2022].

Second line – option 1: fenfluramine add on

NICE recommend fenfluramine for children over two years of age with seizures that are not controlled after two or more ASMs [NICE, 2022]. International consensus guidelines place fenfluramine alongside stiripentol and clobazam on 'step 2' [Wirrell *et al*, 2022]. However, there is stipulation in the NICE guidelines that for ongoing prescriptions of the drug, at least a 30% reduction in seizure frequency is required compared to the six-month period prior to starting treatment [NICE, 2022].

In a randomised double-blind placebo controlled trial, fenfluramine reduced mean monthly convulsive seizure

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frequency by 62.3% at 0.7mg/kg/day and 32.3% at 0.2mg/kg/day when used as an add on to either sodium valproate, clobazam, topiramate or levetiracetam [Lagae *et al*, 2019]. Importantly, the trial protocol stipulated that the recent use of siripentol or CBD was an exclusion criteria. When fenfluramine 0.4mg/kg/day was added to a regimen containing stiripentol with either valproate and/or clobazam in a separate multi-national phase 3 randomised controlled trial (RCT), mean monthly frequency of convulsive seizures wasreduced by 54% compared to placebo [Nabbout *et al*, 2020]. Meta-analysis data indicated that the mean convulsive seizure frequency was reduced by 45.3% with fenfluramine [Sharawat *et al*, 2021].

Longer-term data are now appearing for the use of adjunctive use of fenfluramine. Specchio *et al* followed up patients in Italy for a median of nine months, and found a 77.4% median reduction in convulsive seizures with 53% of patients showing a greater than 75% seizure reduction [2020]. More long-term data are still required [Gogou and Cross, 2021]. Some emerging data suggest that fenfluramine may improve cognitive functioning independent of seizure control [Bishop *et al*, 2023] and be linked with a reduction in the rates of sudden unexpected death in epilepsy (SUDEP) [Cross *et al*, 2021].

Adverse side-effects reported in trials included decreased appetite, weight loss, vomiting, diarrhoea, low blood sugar, fatigue, falls and fever. There were no reports of pulmonary hypertension or pulmonary valve regurgitation [Lagae *et al*, 2019; Nabbout *et al*, 2020], which had been reported in adults in whom the drug was used as an appetite-suppressant many decades ago.

An echocardiogram must be undertaken in all patients prior to the introduction of the drug use of fenfluramine to exclude any features of pulmonary regurgitation. The trial protocol also recommended that echocardiograms should be repeated every six months for the first two years of treatment and then annually whilst the patients remained on fenfluramine. This policy is now recommended as part of routine clinical practice (ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf).

Fenfluramine does interact with stiripentol and must be prescribed at a lower dose if the patient is already taking stiripentol.

Second line – option 2: Cannabidiol (with clobazam)

There is only one cannabis-based medicine (cannabidiol [CBD], Epidyolex) licensed by the MHRA for use in children aged two years and above with DS. NICE have also stipulated that it should only be used if the child is already being treated with clobazam. NICE have stipulated that it should only be prescribed if two other ASMs have been unsuccessful in achieving reasonable seizure control in children with DS [NICE, 2019]. International consensus guidelines would currently place cannabidiol as 'step 3' of the therapeutic algorithm [Wirrell *et al*, 2022]. NICE guidance again stipulates that ongoing prescriptions can only be issued if the child has shown an at least 30% reduction in seizure frequency compared to the six months prior to starting treatment [NICE, 2019].

In RCTs, CBD in a dose of 20mg/kg/day reduced the median frequency of convulsive seizures per month by 22.8% compared to placebo [Devinsky *et al*, 2017] when used in conjunction with, on average, three standard ASMs (including clobazam, sodium valproate, stiripentol, levetiracetam or topiramate) and/or the ketogenic diet. Vagus nerve stimulation (VNS) was also one of the three included therapies. The GWPCARE2 study demonstrated that CBD reduced convulsive seizure frequency from baseline by 48.7% in the 10mg/kg/day dose and by 45.7% in the 20mg/kg/day dose when compared to placebo [Miller *et al*, 2020].

Interim longer-term data from these studies have shown that the median reduction in seizures at 144-156 weeks since starting CBD varies from 45 to 74% for convulsive seizures and 49% to 84% for all seizure types [Scheffer *et al*, 2021].

Common adverse side effects of CBD include decreased appetite, diarrhoea, impaired liver function tests, fatigue, somnolence or insomnia, rash and fever [Strzelczyk and Schubert-Bast, 2022]. There is a clear interaction between CBD and clobazam and their combined use increases the risk and incidence of somnolence, fatigue and impaired liver function; fortunately the latter is rarely clinically manifest.

Before treatment with CBD is initiated, liver function tests including AST and ALT should be checked. LFTs and AST should be re-checked at one month and three months, and then six monthly after starting CBD. There is also an increased risk of hepatotoxicity in CBD being co-prescribed with sodium valproate although its frequency is unknown. Thrombocytopaenia has been described in a third of patients receiving both medications concurrently [McNamara *et al*, 2020]. In our practice in Birmingham, we recommend the withdrawal of sodium valproate first before the introduction of CBD.

Further options

Step 3 – option 1: Ketogenic diet

The ketogenic diet is recommended when three or four ASMs have been used with unacceptable seizure control or significant adverse side-effects, or both [NICE, 2022]. This is 'step 4' in the recently-published international Dravet syndrome guidelines [Wirrell *et al*, 2022]. This approach is also consistent with international guidance on the use of the ketogenic diet in the management of the epilepsies [Kossoff *et al*, 2018]. A meta-analysis of seven studies that assessed the use of the ketogenic diet showed a greater than 50% seizure reduction in 63% of children with DS at three months, 60% at six months and 47% at

12 months [Wang *et al*, 2020]. Avoidant and restrictive food intake behaviours are seen in a significant proportion of children with DS, often with a significant worsening in their autism. Consequently, it is very likely that the diet will not be a realistic or feasible therapeutic option in many children.

Step 3 – option 2: Levetiracetam

The international Dravet syndrome guidelines place the use of levetiracetam lower than in the recent NICE guidelines and as 'step 5' [Wirrell *et al*, 2022]. Evidence on the use of levetiracetam in DS is limited. The study by Striano *et al* found that the addition of levetiracetam significantly reduced the median number of seizures per week from baseline for tonic-clonic seizures (from three to one), myoclonic (from 21 to three) and focal seizures (from 7.5 to three) after 18 weeks of treatment [2007]. A later study showed a responder rate of 30% (defined as a reduction in absolute seizure frequency), after three months of treatment [Dressler *et al*, 2015]. The most common adverse side-effects are behavioural changes (typically irritability or anger), nervousness and transient somnolence [Arzimanoglou *et al*, 2018].

Step 3 – option 3: Topiramate

Although topiramate was previously considered a first-line treatment alongside sodium valproate [NICE, 2012], topiramate has been placed much further down in the recent (2022) NICE and international guidelines [Wirrell *et al*, 2022]. Both guidance place topiramate alongside the ketogenic diet as 'step 4'. There are very limited trial data and most studies have been small. One small study showed a responder rate (seizure reduction by >50%) of 35% (7/20 patients) three months [Dressler *et al*, 2015]. In another study, after six months of treatment, data from 10 patients showed that one was seizure free, and six of the 10 showed a 75% reduction in seizures [Takahashi *et al*, 2010]. In 18 patients (six adults) with refractory seizures, 72% showed a >50% seizure reduction and 50% showedat leats a 75% seizure reduction[Nieto-Barrera *et al*, 2000].

The most common side effects include loss of appetite, weight loss, slurred speech, decreased concentration, word-finding difficulties and renal calculi [Arzimanoglou *et al*, 2018].

Step 4 - Potassium bromide

It is of interest that bromides, the most ancient of ASMs, are on 'step 5' of the international guideline on Dravet syndrome [Wirrell *et al*, 2022]. Potassium bromide is a drug that is more commonly used in Germany (second most common before CBD and fenfluramine became licensed [Schubert-Bast *et al*, 2019]) and in Japan but evidence for the efficacy of potassium bromide is very limited. It is very rarely used in the UK for any epilepsy, in part because of its potential serious toxicity.

Dressler *et al* in a very small series showed a 78% (7/9) responder rate (seizure frequency reduction by > 50%) at three months [2015]. Oguni *et al* reported that showed 36% (8/22 of patients) had 75% seizure reduction and 41% (9/22) had 50% seizure reduction after three months of treatment [1994]. Lotte *et al* reported a responder rate (a seizure reduction of >50%) of 81% (26/32 patients) and 47% (15/32 patients after one year of treatment. [2012]. Adverse side-effects are common and include loss of appetite, fatigue, sedation, cognitive slowing, tremor, ataxia, gastritis, acne and bromism [Strzelczyk and Schubert-Bast, 2022].

Vagus nerve stimulation (VNS)

Resective epilepsy surgery is very unlikely to represent a feasible option in the management of children with DS. Consequently, a palliative surgical procedure, specifically VNS, can be an additional therapeutic option as recommended by NICE [NICE, 2022]. VNS is on 'step 5' of the international guidelines on Dravet syndrome [Wirrell *et al*, 2022]. A meta-analysis of 15 studies involving 92 patients with DS suggested that 41% of patients showed at least a 50% reduction in total seizures [Hajtovic *et al*, 2022].

Personalised seizure plan for status epilepticus

Personalised seizure plans should have an emphasis on reducing triggers, such as management of fevers with anti-pyretics or the use of specialised filtered glasses where a reproducible photoparoxysmal response is demonstrated within a specific range. Routine childhood vaccinations are encouraged and not contraindicated.

Personalised seizure plans should also be in place because prolonged seizures, including status epilepticus (SE) are common in DS. The first benzodiazepine dose may be given earlier in the plan at three minutes rather than the usual five minutes for this reason [Wirrell *et al*, 2017]. It's advised for a second benzodiazepine dose to be given in hospital or by paramedics. The third step is with intravenous levetiracetam as recommended in the new Advanced Paediatric Life Support (APLS) guidelines in the UK [Bacon *et al*, 2023]. Phenytoin is a sodium channel-blocker and is contraindicated as an ASM in the long-term management of children with DS. It is also generally avoided in clinical practice in management of status epilepticus. A study of 99 patients with DS from Japan showed that intravenous phenytoin was less effective in terminating episodes of ongoing CSE (15-21% success) than intravenous barbiturates (75-100% success) or intravenous IV benzodiazepines (54-69% success) [Tanabe *et al*, 2008]. This would suggest that intravenous phenobarbital should be considered as the preferred first-line ASM in the treatment of benzodiazepine-resistant CSE in patients with DS.

If a child with DS is not receiving maintenance sodium valproate, then intravenous sodium valproate can be used within any personalised management plan for status epilepticus. In refractory CSE, intravenous midazolam infusions and thiopentone might be required [Tanabe *et al*, 2008].

It is recommended that the management of CSE be 'aggressive' to prevent or at least minimise the possibility

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of an hypoxic injury, fatal cerebral oedema, hippocampal sclerosis and the development of the rare hemiconvulsion-hemiplegia epilepsy (HHE) syndrome. These are all recognised complications of CSE in DS [Myers *et al*, 2017; Sakakibara *et al*, 2009].

Drugs to avoid

Sodium channel blockers should be avoided in DS as they can worsen seizures and also cognitive outcomes too. Example drugs to avoid as listed in the NICE guidelines include phenytoin, carbamazepine, oxcarbazepine, lacosamide, lamotrigine, gabapentin, pregabalin, vigabatrin and tiagabine [NICE, 2022].

Management of co-morbidities

Development, learning and behaviour

A child's development at seizure onset and in the first year of life is commonly reported to be normal. However, development typically slows or may subsequently regress leading to developmental impairment. After prolonged febrile status epilepticus, regression of skills has been reported [Wirrell *et al*, 2022]. A small proportion of children with DS may already show delayed development prior to seizure onset [Li *et al*, 2021].

Gross and fine motor skills

The average age of independent ambulation is typically delayed at 16 to 18 months. Ataxia may also become apparent by four to five years of age [Scheffer and Nabbout, 2019]. Some children may never achieve independent ambulation.

A crouched gait may develop from 12 years of age onwards. Pyramidal tract dysfunction manifest by slight spasticity [Rodda *et al*, 2012] and Parkinsonian features (without tremor) may be seen in early adulthood [Wirrell *et al*, 2022]; both may lead to a deterioration in an individual's gait [Selvarajah *et al*, 2022]. Fine motor development is also delayed [Verheyen *et al*, 2019] and particularly involving hand-eye coordination [Dravet and Guerrini, 2011].

Speech and language

Delayed speech and language is an almost universal feature in DS. Many of the more severely affected children never learn to speak and remain non-verbal [Wirrell *et al*, 2022].

Cognition

In a cohort of 152 DS patients above the age of three years, intellectual disability was mild in 17%, moderate in 30%, and severe or profound in 51% [Brunklaus *et al*, 2012]. Intellectual disability was reported in 95% in a large adolescent and adult group [Lagae, 2021]. Education in special schooling is nearly always required. Only a very small minority will be able to be educated within mainstream schooling and always with additional support.

Behaviour

Aggression, anger, dangerous behaviour and impulsivity are commonly reported by parents when children are aged three to 12 years. From adolescence, ritualised behaviour, compulsive and repetitive habits are reported [Postma *et al*, 2023]. The prevalence of features of autism spectrum disorder differed between physicians and caregivers when questioned through a Delphi survey. The international guidelines on Dravet syndrome emphasise that children should be formally assessed for ASD [Wirrell *et al*, 2022].

Sleep

Sleep impairment is a major concern for the parents (and siblings) of children with DS; some families describe this as being more important than frequent seizures. Approximately 75% of parents report nocturnal awakening which clearly has knock-on consequences during the day with increased seizures and difficult behaviour [Licheni *et al*, 2018; Van Nuland *et al*, 2021]. Sleep impairment will also adversely affect concentration and therefore learning. More recently, and perhaps not surprisingly, a Delphi study suggested that this is perhaps a bigger issue, with 90% of caregivers and 100% of physicians indicating nocturnal waking, insomnia, snoring and day-time sleepiness were significant issues [Wirrell *et al*, 2022]. The DREAMS study, a double-blind crossover randomised placebo-controlled trial with melatonin, did not show statistically significant differences in total sleep in 13 patients but caregivers reported clear differences [Myers *et al*, 2018]. This has translated into the potential use of melatonin and other drugs such as clonidine in guidelines on the management of children and young people with DS [Wirrell *et al*, 2022].

Dysautonomia

In a survey of the parents of 65 children with DS, dysautonomia was commonly reported. This included cardiac symptoms (bradycardia, tachycardia, arrhythmia) in 14%, respiratory problems (such as tachypnoea, bradypnoea, apnoea) in 23%, temperature regulation issues (cold hands and feet, flushing) in 55%, diaphoresis in 54%, constipation in 28% and other symptoms (pupillary changes, sialorrhoea) in 40% [Berg *et al*, 2021]. The recently-published international guidelines offered no specific treatment for symptoms of dysautonomia. [Wirrell *et al*, 2022].

Feeding difficulties

A caregiver survey undertaken in the UK found that that 92% of DS patients had a 'feeding issue' at a median age of three years [Clayton *et al*, 2023]. These included poor appetite and problems with chewing which often led to food-refusal and consequent weight loss [Dravet and Guerrini, 2011]. A possible contributing factor to these issues is the adverse side-effects of the ASMs which are commonly gastrointestinal, as described earlier. Dietician input is important and a feeding gastrostomy should be considered as and when appropriate [Clayton *et al*, 2023]. A feeding gastrostomy may also facilitate the administration of the ketogenic diet and specifically the medium chain triglyceride (MCT) type.

Sudden unexpected death in epilepsy (SUDEP)

It is clear that children with epilepsy, and particularly those aged less than five years of age, have an increased risk of dying and specifically from epilepsy, including SUDEP. In a recently-published Swedish study of 55 children with DS, seven had died, three from SUDEP, one from an anoxic brain injury and three from pneumonia. The mean age at death was 4.7 years (range, 3.3-11 years) [Bjurulf *et al*, 2022). These findings are consistent with other studies showing a mortality rate of 3.7–17%, a SUDEP rate of 2.3–10% and a median age at death of 4.0–7.0 years [Cooper *et al*, 2016; Sakauchi *et al*, 2011; Skluzacek *et al*, 2011]. To date there have been no reports that have demonstrated a clear association between poor seizure control and SUDEP in individuals with DS; this should be an area of active clinical audit and research. Mortality and SUDEP in DS is an important but clearly sensitive and potentially very emotional issue that should be discussed openly and compassionately with families.

Conclusions and future perspectives

DS is one of the most common and important developmental and epileptic encephalopathies. Despite recent genetic and very recent pharmacological advances, the ultimate goals of long-term seizure freedom, normal intellectual development and life expectancy can still not be realistically achieved in DS patients – at least in their lifetime.

One new ASM being investigated in clinical trials is sotilcestat (NCT05163314), a selective inhibitor of cholesterol 24-hydroxylase [Hahn *et al*, 2022].

STK-001, an antisense oligonucleotide, was shown to restore Nav1.1 to normal levels. It led to reduction in mortality and seizures in a Dravet syndrome mouse model [Han *et al*, 2020]. It is currently undergoing human trials. Genome editing using CRISPR might provide opportunities to enhance NaV1.1 expression [Higurashi *et al*, 2022].

This article has outlined the current holistic treatment of children with DS based on recent evidence. Most of which is robust. It will be important to assess the long-term impacts of recently-licenced treatments such as CBD and fenfluramine on seizure control and cognitive and behavioural impairments. It is yet to be seen whether the now frequently quoted genetically-determined precision management of the epilepsies, including DS, comes to fruition. This is not at all straightforward. In the meantime it is important to ensure an early diagnosis of DS to allow appropriate treatment and also to recruit children (and adults) into RCTs of new therapies. Families are undoubtedly enthusiastic for their children to participate in these trials.

Other sources of information

Epilepsy Action (*epilepsy.org.uk*) and Dravet Syndrome UK (*dravet.org.uk*) are reliable sources of information that can be utilised to signpost parents to.

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References

Arzimanoglou A, O'Hare A, Johnston MV, Ouvrier RA, Aicardi J, editors. *Aicardi's diseases of the nervous system in childhood*. Fourth edition. London: Mac Keith Press; 2018.

Bacon M, Appleton R, Bangalore H, et al. Review of the new APLS guideline (2022): Management of the convulsing child. *Arch Dis Child Educ Pract Ed*. 2023; 2023: 43-48.

Berg AT, Coffman K, Gaebler-Spira D. Dysautonomia and functional impairment in rare developmental and epileptic encephalopathies: the other nervous system. *Dev Med Child Neurol* 2021;63:1433–40.

Bishop KI, Isquith PK, Gioia GA, Knupp KG, Scheffer IE, Nabbout R, *et al*. Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: A critical period for early neurodevelopment. *Epilepsy Behav* 2023;138:108994.

Bjurulf B, Reilly C, Sigurdsson GV, Thunström S, Kolbjer S, Hallböök T. Dravet syndrome in children-A population-based study. *Epilepsy Res*. 2022; 182: 106922.

Brigo F, Igwe SC, Bragazzi NL. Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy. *Cochrane Database Syst Rev* 2017.

Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain* 2012;135:2329–36.

Chiron C, Marchand M, Tran A, Rey E, d'Athis P, Vincent J, *et al*. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *The Lancet* 2000;356:1638–42.

Clayton L, Eldred C, Wilson G, Sisodiya S. Feeding difficulties and gastrostomy in Dravet syndrome: A UK-wide caregiver survey 2023. [online] Available at: *https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.15477*

Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. *Epilepsy Res* 2016;128:43–7.

Cross JH, Galer BS, Gil-Nagel A, Devinsky O, Ceulemans B, Lagae L, *et al*. Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome. *Seizure* 2021;93:154–9.

Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, *et al*.

Dr Yoshua Collins-Sawaragi, paediatric neurology grid trainee and Dr Amitav Parida, consultant paediatric neurologist. Birmingham Women's and Children's NHS Foundation Trust.

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med* 2017;376:2011–20.

Dravet C. The core Dravet syndrome phenotype: Core Dravet Syndrome. *Epilepsia* 2011;52:3–9.

Dravet C, Guerrini R. *Dravet syndrome*. Montrouge: J. Libbey Eurotext; 2011.

Dressler A, Trimmel-Schwahofer P, Reithofer E, Mühlebner A, Gröppel G, Reiter-Fink E, *et al*. Efficacy and tolerability of the ketogenic diet in Dravet syndrome – Comparison with various standard antiepileptic drug regimen. *Epilepsy Res* 2015;109:81–9.

National Institute for Health and Care Excellence (NICE). 2022. Epilepsies in children, young people and adults. [online] Available at: *https://www.nice.org.uk/guidance/ng217*.

Gogou M, Cross JH. Fenfluramine as antiseizure medication for epilepsy. *Dev Med Child Neurol* 2021;63:899–907.

Guerrini R, Striano P, Catarino C, Sisodiya SM. Neuroimaging and neuropathology of Dravet syndrome: Neuroimaging and Neuropathology of Dravet Syndrome. *Epilepsia* 2011;52:30–4.

Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, *et al*. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). *Epilepsia* 2022;63:2671–83.

Hajtovic S, LoPresti MA, Zhang L, Katlowitz KA, Kizek DJ, Lam S. The role of vagus nerve stimulation in genetic etiologies of drug-resistant epilepsy: a meta-analysis. *J Neurosurg Pediatr* 2022;29:667–80.

Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, *et al*. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. *Sci Transl Med* 2020;12:eaaz6100.

Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, *et al*. The spectrum of SCN1A-related infantile epileptic encephalopathies. *Brain* 2007;130:843–52.

Higurashi N, Broccoli V, Hirose S. Genetics and gene therapy in Dravet syndrome. *Epilepsy Behav* EB 2022;131:108043.

Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, *et al*. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open* 2018;3:175–92.

Lagae L. Dravet syndrome. *Curr Opin Neurol* 2021;34:213–8.

Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, *et al*. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2019;394:2243–54.

Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: An essential pre-requisite for precision medicine trials. *Epilepsia* 2021;62:2205–17.

Licheni SH, Mcmahon JM, Schneider AL, Davey MJ, Scheffer IE. Sleep problems in Dravet syndrome: a modifiable comorbidity. *Dev Med Child Neurol* 2018;60:192–8.

Lotte J, Haberlandt E, Neubauer B, Staudt M, Kluger GJ. Bromide in Patients with SCN1A-Mutations Manifesting as Dravet Syndrome. *Neuropediatrics* 2012;43:017–21.

Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, Zara F, *et al*. The genetics of Dravet syndrome: Genetics of Dravet Syndrome. *Epilepsia* 2011;52:24–9.

McNamara NA, Dang LT, Sturza J, Ziobro JM, Fedak Romanowski EM, Smith GC, *et al*. Thrombocytopenia in pediatric patients on concurrent cannabidiol and valproic acid. *Epilepsia* 2020;61:e85–9.

Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, *et al*. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. *JAMA Neurol* 2020;77:613.

Myers KA, Davey MJ, Ching M, Ellis C, Grinton BE, Roten A, *et al*. Randomized Controlled Trial of Melatonin for Sleep Disturbance in Dravet Syndrome: The DREAMS Study. *J Clin Sleep Med* 2018;14:1697–704.

Myers KA, McMahon JM, Mandelstam SA, Mackay MT, Kalnins RM, Leventer RJ, *et al*. Fatal Cerebral Edema With Status Epilepticus in Children With Dravet Syndrome: Report of 5 Cases. *Pediatrics* 2017;139:e20161933.

Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, *et al*. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. *JAMA Neurol* 2020;77:300.

National institute for Health and Care Excellence (NICE). 2022. Fenfluramine for treating seizures associated with Dravet syndrome. [online] Available at: *bit.ly/40b4dn5*.

National institute for Health and Care Excellence (NICE). 2019. Cannabidiol with clobazam for treating seizures associated with Dravet syndrome. [online] Available at: *bit.ly/3yJgQKh*.

National Institute for Health and Care Excellence (NICE). 2012. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. [online] Available at: *https://www.nice.org.uk/guidance/cg20*.

Nickels KC, Wirrell EC. Stiripentol in the Management of Epilepsy. *CNS Drugs* 2017;31:405–16.

Nieto-Barrera M, Candau R, Nieto-Jimenez M, Correa A, Ruiz del Portal L. Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 2000;9:590–4.

Oguni H, Hayashi K, Oguni M, Mukahira A, Uehara T, Fukuyama Y, *et al*. Treatment of Severe Myoclonic Epilepsy in Infants with Bromide and Its Borderline Variant. *Epilepsia* 1994;35:1140–5.

Postma A, Milota M, Jongmans MJ, Brilstra EH, Zinkstok JR. Challenging behavior in children and adolescents with Dravet syndrome: Exploring the lived experiences of parents. *Epilepsy Behav* 2023;138:108978.

Rodda JM, Scheffer IE, McMahon JM, Berkovic SF, Graham HK. Progressive Gait Deterioration in Adolescents With Dravet Syndrome. *Arch Neurol* 2012;69:873–8.

Sakakibara T, Nakagawa E, Saito Y, Sakuma H, Komaki H, Sugai K, *et al*. Hemiconvulsion-hemiplegia syndrome in a patient with severe myoclonic epilepsy in infancy. *Epilepsia* 2009;50:2158–62.

Sakauchi M, Oguni H, Kato I, Osawa M, Hirose S, Kaneko S, Takahashi Y, Takayama R, Fujiwara T. Retrospective multiinstitutional study of the prevalence of early death in Dravet syndrome. *Epilepsia* 2011; 52: 1144-9.

Scheffer IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, *et al*. Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial. *Epilepsia* 2021;62:2505–17.

Scheffer IE, Nabbout R. SCN1A-related phenotypes: Epilepsy and beyond. *Epilepsia* 2019;60.

Scheffer IE, Zhang Y-H, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? *Brain Dev* 2009;31:394–400.

Schubert-Bast S, Wolff M, Wiemer-Kruel A, von Spiczak S, Trollmann R, Reif PS, *et al*. Seizure management and prescription patterns of anticonvulsants in Dravet syndrome: A multicenter cohort study from Germany and review of literature. *Epilepsy Behav* 2019;98:88–95.

Selvarajah A, Gorodetsky C, Marques P, Zulfiqar Ali Q, Berg AT, Fasano A, *et al*. Progressive Worsening of Gait and Motor Abnormalities in Older Adults With Dravet Syndrome. *Neurology* 2022;98:e2204–10.

Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. *Lancet Lond Engl* 2004;363:1633–41.

Sharawat IK, Panda PK, Kasinathan A, Panda P, Dawman L, Joshi K. Efficacy and tolerability of fenfluramine in patients with Dravet syndrome: A systematic review and meta-analysis. *Seizure* 2021;85:119–26.

Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* 2011; 52: Supplement 2: 95-101.

Specchio N, Balestri M, Trivisano M, Japaridze N, Striano P, Carotenuto A, *et al*. Electroencephalographic Features in Dravet Syndrome: Five-Year Follow-Up Study in 22 Patients. *J Child Neurol* 2012;27:439–44.

Specchio N, Pietrafusa N, Doccini V, Trivisano M, Darra F, Ragona F, *et al*. Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. *Epilepsia* 2020;61:2405–14.

Steel D, Symonds JD, Zuberi SM, Brunklaus A. Dravet syndrome and its mimics: Beyond SCN1A. *Epilepsia* 2017;58:1807–16.

Striano P, Coppola A, Pezzella M, Ciampa C, Specchio N, Ragona F, *et al*. An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007;69:250–4.

Strzelczyk A, Schubert-Bast S. A Practical Guide to the Treatment of Dravet Syndrome with Anti-Seizure Medication. *CNS Drugs* 2022;36:217–37.

Sullivan J, Deighton AM, Vila MC, Szabo SM, Maru B, Gofshteyn JS, *et al*. The clinical, economic, and humanistic burden of Dravet syndrome – A systematic literature review. *Epilepsy Behav* 2022;130:108661.

Symonds JD, Elliott KS, Shetty J, Armstrong M, Brunklaus A, Cutcutache I, *et al*. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain* 2021;144:2879–91.

Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, *et al*. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain* 2019;142:2303–18.

Takahashi H, Takahashi Y, Mine J, Mukaida S, Ikegami M, Ikeda H, *et al*. [Effectiveness of topiramate in eleven patients with Dravet syndrome]. *No Hattatsu Brain Dev* 2010;42:273–6.

Tanabe T, Awaya Y, Matsuishi T, Iyoda K, Nagai T, Kurihara M, *et al*. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome) – A nationwide questionnaire survey in Japan. *Brain Dev* 2008;30:629–35.

Van Nuland A, Ivanenko A, Meskis MA, Villas N, Knupp KG, Berg AT. Sleep in Dravet syndrome: A parent-driven survey. *Seizure* 2021;85:102–10.

Verheyen K, Verbecque E, Ceulemans B, Schoonjans A, Van De Walle P, Hallemans A. Motor development in children with Dravet syndrome. *Dev Med Child Neurol* 2019;61:950–6.

Dr Yoshua Collins-Sawaragi, paediatric neurology grid trainee and Dr Amitav Parida, consultant paediatric neurologist. Birmingham Women's and Children's NHS Foundation Trust.

Wang Y-Q, Fang Z-X, Zhang Y-W, Xie L-L, Jiang L. Efficacy of the ketogenic diet in patients with Dravet syndrome: A meta-analysis. *Seizure* 2020;81:36–42.

Wirrell EC, Hood V, Knupp KG, Meskis MA, Nabbout R, Scheffer IE, *et al*. International consensus on diagnosis and management of Dravet syndrome. *Epilepsia* 2022;63:1761–77.

Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, *et al*. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. *Pediatr Neurol* 2017;68:18-34.e3.

Yamada M, Suzuki K, Matsui D, Inoue Y, Ohtsuka Y. Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan. *Epilepsy Res* 2021;170:106535.

Young A, Tanenhaus A, Belle A, McLaughlin J, Li J, Lin W. 2019. A GABA-selective AAV vector upregulates endogenous SCN1A expression and reverses multiple phenotypes in a mouse model of Dravet syndrome.

Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, Riney K, *et al*. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia* 2022;63:1349–97.

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epilepsyspace.org.uk

The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

- Manage their epilepsy
- Feel less alone
- Increase their confidence
- Get the support they need

There's lots of epilepsy facts, tips and stories from young people sharing their experience.

The content is short and interactive. It's not all reading, there's video and young people can share their own quotes, stories and videos too.

It's been created with young people and reviewed by epilepsy nurses.

Take a look at:
epilepsyspace.org.uk

Leaflets about The Epilepsy Space to give to young people can be requested by emailing:
nurseorders@epilepsy.org.uk

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Information you can trust

Find out more
epilepsy.org.uk/trust

Recently published papers

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.

AMZICA F.
Impaired sleep homeostasis in children with epilepsy
Dev Med Child Neurol. 2023 Feb 27.
doi: 10.1111/dmcn.15547.

KULAWIAK J, Miller JA and Hovey SW.
Incidence of Medication-Related Problems Following Pediatric Epilepsy Admissions
Pediatr Neurol. 2023 Feb 3;142:10-15.
doi: 10.1016/j.pediatrneurol.2023.01.015.

YANG L, Ji J, Lu Q, Tang P, Jiang Y, Yang H and Tang W.
Caregivers' experiences in the management of children with epilepsy: A Systematic synthesis of qualitative studies
Seizure. 2023 Feb 8;106:117-128.
doi: 10.1016/j.seizure.2023.02.004.

ARONICA E, Specchio N, Luinenburg MJ and Curatolo P.
Epileptogenesis in tuberous sclerosis complex-related developmental and epileptic encephalopathy
Brain. 2023 Feb 20;awad048.
doi: 10.1093/brain/awad048.

MASTRANGELO M, Esposito D and Pisani F.
Sudden unexpected death in epilepsy: The need for age-specific evidence-based prevention
Dev Med Child Neurol. 2023 Feb 22.
doi: 10.1111/dmcn.15560.

WHITNEY R, Sharma S and Ramachandrannair R.
Sudden unexpected death in epilepsy in children
Dev Med Child Neurol. 2023 Feb 17.
doi: 10.1111/dmcn.15553.

CHEN J-S, Lamoureux A-A, Shlobin NA, Elkaim LM, Wang A, Ibrahim GM, Obaid S, Harroud A, Guadagno E, Dimentberg E, Bouthillier A, Bernhardt BC, Nguyen DK, Fallah A and Weil AG.
Magnetic Resonance-guided Laser Interstitial Thermal Therapy for Drug-Resistant Epilepsy: A Systematic Review and Individual Participant Data Meta-Analysis
Epilepsia. 2023 Feb 23.
doi: 10.1111/epi.17560.

WARSI NM, Wong SM, Gorodetsky C, Suresh H, Arski ON, Ebden M, Kerr EN, Smith ML, Yau I, Ochi A, Otsubo H, Sharma R, Jain P, Weiss S, Donner EJ, Snead OC and Ibrahim GM.
Which is more deleterious to cognitive performance? Interictal epileptiform discharges vs anti-seizure medication
Epilepsia. 2023 Feb 21.
doi: 10.1111/epi.17556.

JENSEN MP, Gammaitoni AR, Salem R, Wilkie D, Lothe A and Amtmann D.
Fenfluramine treatment for Dravet syndrome: Caregiver- and clinician-reported benefits on the quality of life of patients, caregivers, and families living in Germany, Spain, Italy, and the United Kingdom
Epilepsy Res. 2023 Feb;190:107091.
doi: 10.1016/j.eplepsyres.2023.107091.

NGUYEN MD, Nguyen TMT, Chi-Bao B, Giang H and Nguyen LTH.
Genotype and phenotype characteristics of West syndrome in 20 Vietnamese children: Two novel variants detected by next-generation sequencing
Epilepsy Res. 2023 Feb;190:107094.
doi: 10.1016/j.eplepsyres.2023.107094.

SAMIA P, Sahu JK, Ali A, Caraballo RH, Chan J, Coan AC, Fortini PS, Gwer S, Jocic-Jakubi B, Kissani N, Rivera Y, Sarfo FS, Singh MB, Trinka E, Yoo JY, Yu H-Y, Zelano J and Cross JH.
Telemedicine for Individuals with epilepsy: Recommendations from International League Against Epilepsy Telemedicine Task Force
Seizure. 2023 Feb 10;106:85-91.
doi: 10.1016/j.seizure.2023.02.005.

LOPRESTI MA, Zhang L and Lam S.
Disparities in pediatric drug-resistant epilepsy care
Childs Nerv Syst. 2023 Feb 17.
doi: 10.1007/s00381-023-05854-y.

BURATTI S, Giacheri E, Palmieri A, Tibaldi J, Brisca G, Riva A, Striano P, Mancardi MM, Nobili L and Moscatelli A.
Ketamine as advanced second-line treatment in benzodiazepine-refractory convulsive status epilepticus in children
Epilepsia. 2023 Feb 15.
doi: 10.1111/epi.17550.

GETTINGS JV, Shafi S, Boyd J, Snead OC, Rutka J, Drake J, McCoy B, Jain P, Whitney R and Go C.
The Epilepsy Surgery Experience in Children With Infantile Epileptic Spasms Syndrome at a Tertiary Care Center in Canada
J Child Neurol. 2023 Feb 14;8830738231151993.
doi: 10.1177/08830738231151993.

ANWAR SAM, Elsakka EE, Khalil M, Ibrahim AAG, ElBeheiry A, Mohammed SF, Omar TEI and Amer YS.
Adapted Evidence-Based Clinical Practice Guidelines for Diagnosis and Treatment of Epilepsies in Children: A Tertiary Children's Hospital Update
Pediatr Neurol. 2023 Jan 7;141:87-92.
doi: 10.1016/j.pediatrneurol.2022.12.009.

DANG H, Khan AB, Gadgil N, Sharma H, Trandafir C, Malbari F and Weiner HL.
Behavioral Improvements Following Lesion Resection for Pediatric Epilepsy: Pediatric Psychosurgery?
Pediatr Neurosurg. 2023 Feb 14.
doi: 10.1159/000529683.

ALEDO-SERRANO A, Battaglia G, Blenkinsop S, Delanty N, Elbendary HM, Eyal

S, Guekht A, Gulcebi MI, Henshall DC, Hildebrand MS, Macrohon B, Madaan P, Mifsud J, Mills JD, Neill KH, Romagnolo A, Vezzani A and Sisodiya SM.
Taking action on climate change: Testimonials and position statement from the International League Against Epilepsy Climate Change Commission
Seizure. 2023 Feb 4;106:68-75.
doi: 10.1016/j.seizure.2023.02.003.

ARFAIE S, Amin P, Kwan ATH, Solgi A, Sarabi A, Hakak-Zargar B, Brunette-Clément T, Pushenko D, Mir-Moghtadaei K, Mashayekhi MS, Mofatteh M, Honarvar F, Ren LY, Noiseux-Lush C, Azizi Z, Pearl PL, Baldeweg T, Weil AG and Fallah A.
Long-term full-scale intelligent quotient outcomes following pediatric and childhood epilepsy surgery: A systematic review and meta-analysis
Seizure. 2023 Feb 1;106:58-67.
doi: 10.1016/j.seizure.2023.01.020.

KNIGHT R, Craig J, Irwin B, Wittkowski A and Bromley RL.
Adaptive behaviour in children exposed to topiramate in the womb: An observational cohort study
Seizure. 2023 Feb;105:56-64.
doi: 10.1016/j.seizure.2023.01.008.

YAMAMOTO Y, Ohta A, Usui N, Imai K, Kagawa Y and Takahashi Y.
Clinical value of therapeutic drug monitoring for levetiracetam in pediatric patients with epilepsy
Brain Dev. 2023 Feb 7;S0387-7604(**23**)00020-7.
doi: 10.1016/j.braindev.2023.01.007.

RUGGIERO SM, Xian J and Helbig I.
The current landscape of epilepsy genetics: where are we, and where are we going?
Curr Opin Neurol. 2023 Apr 1;36(**2**):86-94.
doi: 10.1097/WCO.0000000000001141.

MEDINA-PIZARRO M, Spencer DD and Damisah EC.
Recent advances in epilepsy surgery
Curr Opin Neurol. 2023 Apr 1;36(**2**):95-101.
doi: 10.1097/WCO.0000000000001134.

LYNCH M, Smith K and Riney K.
Clinical seizure semiology is subtle and identification of seizures by parents is unreliable in infants with tuberous sclerosis complex
Epilepsia. 2023 Feb;64(**2**):386-395.
doi: 10.1111/epi.17454.

WHITNEY R and Jain P.
Memantine: a novel treatment for children with developmental and epileptic encephalopathies
Brain. 2023 Mar 1;146(**3**):796-798.
doi: 10.1093/brain/awad018.

BONARDI CM, Furlanis GM, Toldo I, Guarrera B, Luisi C, Pettenazzo A, Nosadini M, Boniver C, Sartori S and Landi A.
Myoclonic super-refractory status epilepticus with favourable evolution in a teenager with FIRES: Is the association of vagus nerve stimulation and cannabidiol effective?
Brain Dev. 2023 Jan 30;S0387-7604(**23**)00004-9.
doi: 10.1016/j.braindev.2023.01.004.

NISSENKORN A, Kluger G, Schubert-Bast S, Bayat A, Bobylova M, Bonanni P, Ceulemans B, Coppola A, Di Bonaventura C, Feucht M, Fuchs A, Gröppel G, Heimer G, Herdt B, Kulikova S, Mukhin K, Nicassio S, Orsini A, Panagiotou M, Pringsheim M, Puest B, Pylaeva O, Ramantani G, Tsekoura M, Ricciardelli P, Sagie TL, Stark B, Striano P, van Baalen A, De Wachter M, Irelli EC, Cuccurullo C, von Stülpnagel C and Russo A.
Perampanel as precision therapy in rare genetic epilepsies
Epilepsia. 2023 Feb 2.
doi: 10.1111/epi.17530.

LEITNER DF, Lin Z, Sawaged Z, Kanshin E, Friedman D, Devore S, Ueberheide B, Chang JW, Mathern GW, Anink JJ, Aronica E, Wisniewski T and Devinsky O.
Brain molecular mechanisms in Rasmussen encephalitis
Epilepsia. 2023 Jan;64(**1**):218-230.
doi: 10.1111/epi.17457.

YOSSOFZAI O, Stone S, Madsen J, Moineddin R, Wang S, Ragheb J, Mohamed I, Bollo R, Clarke D, Perry MS, Weil AG, Raskin J, Pindrik J, Ahmed R, Lam S, Fallah A, Maniquis C, Andrade A, Ibrahim GM, Drake J, Rutka J, Tailor J, Mitsakakis N, Puka K and Widjaja E.
Seizure outcome of pediatric magnetic resonance-guided laser interstitial thermal therapy versus open surgery: A matched noninferiority cohort study
Epilepsia. 2023 Jan;64(**1**):114-126.
doi: 10.1111/epi.17451.

KNUPP KG, Scheffer IE, Ceulemans B, Sullivan J, Nickels KC, Lagae L, Guerrini R, Zuberi SM, Nabbout R, Riney K, Agarwal A, Lock M, Dai D, Farfel GM, Galer BS, Gammaitoni AR, Polega S, Davis R and Gil-Nagel A.
Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study
Epilepsia. 2023 Jan;64(**1**):139-151.
doi: 10.1111/epi.17431.

WIGGLESWORTH S, Neligan A, Dickson JM, Pullen A, Yelland E, Anjuman T and Reuber M.
The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data
Seizure. 2023 Feb;105:37-42.
doi: 10.1016/j.seizure.2023.01.003.

CARROLL JH, Cross JH, Hickson M, Williams E, Aldridge V and Collinson A.
A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): International parent and health professional consensus
Epilepsia. 2023 Jan 18.
doi: 10.1111/epi.17513.

ASHRAFZADEH F, Akhondian J, Hashemi N, Esmaeilzadeh M, Ghanaee A, Yavarzadeh H, Imannezhad S, Zand NS, Mirzadeh HS and Toosi MB.
Therapeutical impacts of transcranial direct current stimulation on drug-resistant epilepsy in pediatric patients: A double-blind parallel-group randomized clinical trial
Epilepsy Res. 2023 Feb;190:107074.
doi: 10.1016/j.eplepsyres.2022.107074.

ASADI-POOYA AA and Farazdaghi M.
Cluster analysis of a large dataset of patients with juvenile myoclonic epilepsy: Predicting response to treatment
Seizure. 2023 Feb;105:10-13.
doi: 10.1016/j.seizure.2023.01.006.

DHARAN AL, Bowden SC, Peterson A, Lai A, Seneviratne U, Dabscheck G, Nurse E, Loughman A, Parsons N and D'Souza WJ.
A cross-sectional investigation of cognition and epileptiform discharges in juvenile absence epilepsy
Epilepsia. 2023 Jan 10.
doi: 10.1111/epi.17505.

LU S, Champion H, Mills N, Simpson Z, Whiteley VJ and Schoeler NE.
Impact of ketogenic diet therapy on growth in children with epilepsy
Epilepsy Res. 2023 Feb;190:107076.
doi: 10.1016/j.eplepsyres.2023.107076.

RAVINDRA VM, Karas PJ, Lazaro TT, Coorg R, Awad A-W, Patino I, McClernon EE, Clarke D, Whitehead LC, Anderson A, Diaz-Medina G, Houck K, Katyayan A, Masters L, Nath A, Quach M, Riviello J, Seto ES, Sully K, Agurs L, Sen S, Handoko M, LoPresti M, Ali I, Curry DJ and Weiner HL.
Epilepsy Surgery in Young Children With Tuberous Sclerosis Complex: A Novel Hybrid Multimodal Surgical Approach
Neurosurgery. 2023 Feb 1;92(**2**):398-406.
doi: 10.1227/neu.0000000000002214.

RIIKONEN R.
Biochemical mechanisms in pathogenesis of infantile epileptic spasm syndrome
Seizure. 2023 Feb;105:1-9.
doi: 10.1016/j.seizure.2023.01.004.

MUTHIAH N, Joseph B, Varga G, Vodovotz L, Sharma N and Abel TJ.
Investigation of the effectiveness of vagus nerve stimulation for pediatric drug-resistant epilepsies secondary to nonaccidental trauma
Childs Nerv Syst. 2023 Jan 5.
doi: 10.1007/s00381-022-05817-9.

KOLASKI K.
Which antiepileptic drugs are safe and effective as monotherapy to treat focal and generalized seizures in adults and children? A Cochrane Review summary with commentary
Dev Med Child Neurol. 2023 Feb;65(2):158-161.
doi: 10.1111/dmcn.15473.

FERNÁNDEZ IS, Amengual-Gual M, Aguilar CB, Romeu A, Sheikh T, Torres A, Chao J, Jonas R, Gaínza-Lein M, Harini C and Douglass L.
Temporal trends in the cost and use of first-line treatments for infantile epileptic spasms syndrome
Epilepsia. 2023 Jan 4.
doi: 10.1111/epi.17498.

AUNGAROON G, Mehta A, Horn PS and Franz DN.
Stiripentol for Drug-Resistant Epilepsy Treatment in Tuberous Sclerosis Complex
Pediatr Neurol. 2023 Feb;139:86-92.
doi: 10.1016/j.pediatrneurol.2022.11.017.

MOTOBAYASHI M, Munakata S, Kitazawa N, Fushimi T, Murayama K and Inaba Y.
Partial Efficacy of Vigabatrin in an Infant With West Syndrome Due to Pyruvate Dehydrogenase Complex Deficiency: A Case Report
Pediatr Neurol. 2023 Jan;138:98-100.
doi: 10.1016/j.pediatrneurol.2022.10.012.

BÄTTIG L, Dünner C, Cserpan D, Rüegger A, Hagmann C, Schmitt B, Pisani F and Ramantani G.
Levetiracetam versus Phenobarbital for Neonatal Seizures: A Retrospective Cohort Study
Pediatr Neurol. 2023 Jan;138:62-70.
doi: 10.1016/j.pediatrneurol.2022.10.004.

ARNESEN RA, Barbour KK, Wu A, Yozawitz EG, Nelson A, Wolf SM, McGoldrick PE, Basma N and Grinspan ZM.
Multicenter Assessment of Sturge-Weber Syndrome: A Retrospective Study of Variations in Care and Use of Natural History Data
Pediatr Neurol. 2023 Jan;138:8-16.
doi: 10.1016/j.pediatrneurol.2022.08.009.

DE MATOS MMF, Batista LA, Thomé U, Sakamoto AC, Santos MV, Machado HR, Wichert-Ana L and Hamad APA.
Reduction in anti-seizure medications use in pediatric patients with pharmacoresistant epilepsy submitted to surgical treatment
Childs Nerv Syst. 2022 Dec 29;1-8.
doi: 10.1007/s00381-022-05812-0.

POKE G, Stanley J, Scheffer IE and Sadleir LG.
Epidemiology of Developmental and Epileptic Encephalopathy and of Intellectual Disability and Epilepsy in Children
Neurology. 2022 Dec 29;10.1212/WNL.0000000000206758.
doi: 10.1212/WNL.0000000000206758.

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