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CURRENT AWARENESS SERVICE

Anti-seizure medications: trials and tribulations continue

Anti-seizure medications (ASMs), the pivotal treatment of people of all ages with epilepsy are again under extreme scrutiny and particularly their safety profiles. The most obvious ASM in the witness stand (again) is sodium valproate (VPA).

The original 'nail in the coffin' for VPA has been further driven in with the most recent directive issued by the Medicines and Healthcare products Regulatory Agency (MHRA) (MHRA 2023). It has issued the following instruction (not a recommendation) that as from January 31, 2024:

> A. Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.
>
> B. At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes.

The inclusion of men in this instruction is because of reports that the use of VPA may be associated with a risk of likely reversible infertility and also concerns of testicular toxicity. However, there is no information on the magnitude of these risks. The consequence of this instruction is that it will become almost impossible to prescribe what is arguably the most effective ASM used to treat generalised seizures and epilepsy syndromes – particularly those that are genetic in origin. It will also result in many, possibly even most, general practitioners not considering the prescription of VPA because the process has become so difficult and bureaucratically prohibitive. The complete instruction can be read on the MHRA website (https://bit.ly/mhraValproate). Most doctors working through and on behalf of the Royal Colleges, the British Paediatric Neurology Association and charities including Epilepsy Action, expressed their concerns (again) as soon as the MHRA prepared the directive but in vain (again) as it has now been published. The BPNA, in association with the Royal College of Paediatrics and Child Health (RCPCH) published its response to the MHRA's instruction on 24 January 2024. This document is available on the RCPCH website at: https://bit.ly/rcpchValproate (accessed 14 February 2024).

Pre-natal exposure to topiramate has also received critical coverage on its adverse effects on infants'

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development and specifically attention deficit hyperactivity disorder (ADHD) [Dreier et al, 2023]. Although the FDA has responded to these new data, the MHRA has yet to pick this up and launch another potentially prohibitive approach to its prescription in women and girls of child-bearing potential. In part this relates to considerably less evidence of the effect of topiramate, when taken during pregnancy, on the child's development and the risk of autism. It may take many years to gather such evidence because topiramate is not a commonly prescribed ASM, in view of its already recognised relatively unclean safety profile, including its effects on appetite, cognition and mental health.

Very recently, levetiracetam and clobazam have come under the interrogating spotlight, but currently only by the Food and Drug Administration (FDA), the US equivalent of the MHRA. In November 2023, the FDA issued an alert for levetiracetam and clobazam, which will be followed by a strengthening of the labelling for these medications. This will be to introduce new warnings of a rare, but serious, hypersensitivity reaction, called the 'Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)'. This is a severe cutaneous adverse reaction, formerly known as multi-organ hypersensitivity. DRESS is characterised by a range of signs including widespread skin rash, fever, lymphadenopathy, elevated eosinophils and atypical lymphocytes, thrombocytopenia and inflammation of one or more organs (liver, kidneys, lungs and heart). Rarely, it can cause death, especially if not recognised and treated by immediate discontinuation of the suspect medication. The vast majority of cases manifest in the first four to six weeks of treatment with the causative medication. With levetiracetam, 32 cases (three in the US, 29 abroad) were identified through March 2023, all of whom were hospitalised and two died. With clobazam, 10 serious cases of DRESS (one in the US and nine abroad) were identified through July 2023. All 10 patients were hospitalised but there were no deaths. Up until these cases of DRESS, the prescribing information for both medications had included warnings about rare cases of two other severe cutaneous adverse reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

In the almost 21 years during which I prescribed oral or intravenous levetiracetam, I never saw a child aged <18 years who experienced DRESS, SJS or TEN. This included the three large randomised trials of more than 750 children who had used high-dose intravenous levetiracetam in the management of convulsive status epilepticus [Messahel et al, 2022]. Clearly, this does not mean that these three serious allergic skin and systemic conditions don't occur, but their incidence globally is very rare. It is important to emphasise that their incidence is almost certainly less than the serious skin reactions associated with carbamazepine, lamotrigine and phenytoin.

The most recent alarm has come from a report that ASMs may be associated with an increased risk of Parkinson's disease (PD) and particularly if multiple ASMs are used simultaneously [Belete et al, 2023]. It remains unclear as to whether this is a real association or simply an epiphenomenon. The current evidence is very limited and, predictably, makes use of statistical methods. A US commentary on this issue raised important questions about the methodology of the studies that had reported these 'findings' as well as confounding factors. However, the commentator concluded the following:

> "So what judgment should the jury pass on these drugs? I do not believe that based on the evidence so far, there should be a concern for levetiracetam or lamotrigine causing PD. However, valproic acid's track record remains a concern and its teratogenic effects have already led to physicians avoiding this drug in women of childbearing age. Given this, we should try to collect further evidence to determine whether we are placing patients at risk by exposing them to valproic acid, and whether the changes are irreversible. A guilty verdict remains premature, but at least we have a lead suspect."

This really worries me, because it is implicating sodium valproate almost exclusively on its recent and current adverse safety profile rather than on specific evidence that it induces PD. In addition, PD is a movement disorder and it would seem irrational and prejudicial (biased) to say that valproate causes PD because of its teratogenic effects. In fact, some might call this a 'knight's move' association, as seen in a number of psychiatric disorders including paranoid schizophrenia. There again, this could reflect the increasing paranoid approach of clinicians and the public to the continuing use of VPA in the management of epilepsy.

The longer doctors and the MHRA (and FDA) monitor the day-to-day use of all ASMs and certainly well beyond their traditionally very brief (typically three to four months) randomised controlled trials, the more information will be gained on their efficacy and safety. It is clearly very important that adverse side-effects of ASMs continue to be identified and, as soon as possible, proven, before crying 'wolf' on them prematurely. As soon as it is clear that an adverse side effect is highly likely or definitely thought to be caused by the medication, this will need to be communicated with patients. As always, the use of any ASM should be on a benefit-to-risk basis. All discussions should be honest, based on the available scientific (not anecdotal) evidence and always involve the patient and family where the patient is young, vulnerable or has learning difficulties. With VPA, more data are required before this very effective ASM can be defined as a medication of 'last resort'. Some unanswered questions include:

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- How long before a pregnancy is planned should valproate be discontinued?

- Is there a trimester in pregnancy when the damaging effects of the medication are particularly high – or low?

- What is the minimum dose of valproate that can be used before and during pregnancy that is not associated with fetal teratogenicity and developmental and delay in children whose mothers took the medication during pregnancy?

These are really important questions because their answers may allow a more individually tailored approach to the use of VPA in all patients and particularly in women and girls of childbearing potential. The medical mantra is that 'each patient is unique'; how we manage them should use the same principle. The MHRA should stick to being gatekeepers in the use of ASMs and not gate crashers of medical practice.

Richard Appleton
Co-editor

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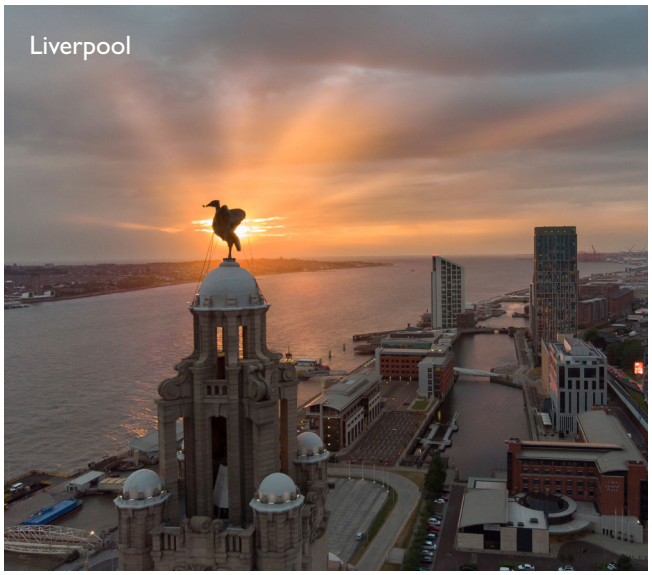
Forthcoming courses and conferences

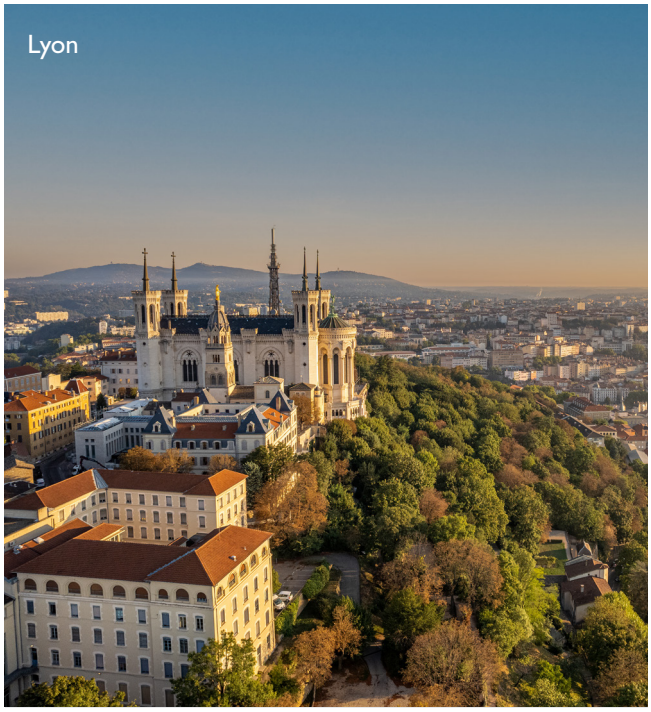
The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

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

June-July
29-2
10th Congress of the European Academy of Neurology
Helsinki, Finland
bit.ly/47LSi3L


Liverpool


Lyon

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

September 2024
19-22
14th International Summer School for Neuropathology and Epilepsy Surgery
Erlangen, Germany
bit.ly/3UCY0Wp

September 2024
23
ILAE British Branch Annual Scientific Meeting
Liverpool, UK
bit.ly/3Gjx8g0

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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**
Get in touch **learning@epilepsy.org.uk**

Ketogenic diets for epilepsy

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The editors are grateful to Dr Natasha Schoeler and Professor Helen Cross at UCL Great Ormond Street Institute of Child Health for writing a state-of-the-art review on the ketogenic diet.

Overview

Ketogenic diets or ketogenic diet therapy (KDT) are a group of high-fat, low-carbohydrate, adequate protein diets. They are the treatment of choice for the neuro-metabolic conditions glucose transporter type 1 deficiency syndrome (Glut1-DS) and pyruvate dehydrogenase complex deficiency (PDHD) and are used as a non-pharmacological treatment option for children, young people and adults with drug-resistant epilepsy (those who continue to have seizures despite having tried two or more anti-seizure medicines).

With KDT, the aim is to mimic the state of starvation on the body, promoting fat as the primary energy source through ketosis. KDT are different to low-carbohydrate diets, which include varying amounts of carbohydrate – and often more than 50g/day.

History of ketogenic diets for epilepsy

Reports of starvation associated with a reduction or cessation of seizures in people with epilepsy date as far back as Hippocrates. Centuries later in the Biblical Gospels, Mark (9.29, King James Version) described a boy with seizures, which only 'prayer and fasting' could cure.

In the early 1920s, Dr Wilder from the Mayo Clinic in the United States, proposed to mimic the state of starvation and produce ketosis with a high-fat, low-carbohydrate diet [Wilder, 1921]. This formed the basis of the classical ketogenic diet (KD).

The initial enthusiasm for KDT waned in the 1930s and 40s, in part following the discovery of diphenylhydantoin and then the advent of new, easy-to-administer anti-seizure medications (ASMs).

In the 1970s, in an attempt to make KDT more palatable, Peter Huttenlocher introduced the medium chain triglyceride (MCT) KD [Huttenlocher et al, 1971]. As MCTs are more ketogenic per calorie compared to long-chain fats, by including MCTs as part of KDT, larger amounts of protein and/or carbohydrate would be permitted.

KDT experienced a new lease of life in 1994, following NBC TV's Dateline report on Charlie Abrahams, who became seizure-free with KDT. A charity called The Charlie Foundation was formed by Charlie's father, the film director Jim Abrahams, helping to further publicise dietary treatment in the public and academic domains with the film, First Do No Harm, in 1997, and supporting the first multi-centre prospective study of the classical KD [Vining et al, 1998].

In the early 2000s, Dr Eric Kossoff from Johns Hopkins Hospital in the US published data on the use of the Atkin's diet as a treatment for epilepsy [Kossoff et al, 2003] and, later, on the development of a modified variant of KDT, the Modified Atkin's Diet (MAD) [Kossoff et al, 2006]. This was intended as a more liberal alternative to the classical KD. In 2005, the team from Massachusetts General Hospital published the results of a further KDT variant, the low glycaemic index treatment (LGIT), which aimed to minimise the increase in blood glucose following food consumption rather than producing ketones per se [Pfeifer et al, 2005].

Types of ketogenic diets

There are several different types of KDT, each with differing proportions of fat/carbohydrate/protein (Fig. 1). They are calculated and implemented in different ways.

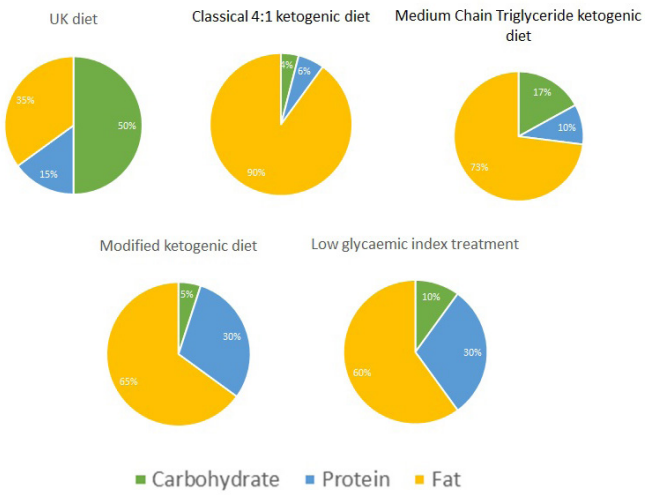

Figure 1: Approximate macronutrient composition of UK 'standard' diet and types of ketogenic diet therapy

The classical ketogenic diet (KD) works on a ratio of grams of fat to grams of protein and carbohydrate. Typically, the highest ratio used is 4:1 (4 grams of fat to every 1 gram of protein and carbohydrate combined), which provides almost 90% of total energy from fat. This type of KD is usually used for infants, individuals who are fed by gastrostomy tube, or those who benefit from a more structured approach to dietary management. Each meal, snack and feed is calculated to the individual's specific ratio and patients and their families must adhere to the recipe(s) provided.

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The MCT KD originally derived 60% of its calories from MCT oil [Huttenlocher et al, 1971]. A modified MCT KD was later developed, which was designed to minimise the gastrointestinal side effects of MCT. This included 30% of total calories from MCT oil and 41% from long-chain fats [Schwartz et al, 1989]. Currently, the total energy from MCT varies, but tends to be at least 30-40% from MCT. With the MCT KD, patients and families can make their own meals and snacks by 'mix and matching' options from 'choice lists'. These lists comprise measured amounts of food that provide specific amounts of fat, carbohydrate and/or protein. Sources of MCT can also be added to other types of KDT to boost ketosis and the production of ketone bodies.

With the MAD, fats are encouraged rather than specifically measured, carbohydrates are measured and protein is unlimited to aid compliance and reduce the burden of dietary implementation and education [Kossoff et al, 2006]. In the UK, individuals on the MAD also use a list of options. Sources of carbohydrate (predominantly fruit and vegetables) must be weighed, whereas household measures are generally used for fat sources, according to their individually set targets [Martin-McGill KJ et al, 2019]. Protein is not formally measured, but it is encouraged that individuals use normal portion sizes.

The LGIT allows up to approximately 50g carbohydrates per day, or around 60% of total energy, but only includes carbohydrates with a glycaemic index of <50 [Pfeifer et al, 2005]. Foods are not weighed, rather intake is based on portion sizes using choice lists.

KDT in practice

Individuals following KDT need not miss out. Meals can be very palatable (Fig. 2 and 3).

Figure 2: 'Strawberries, cream, chocolate and nuts' from Ketocooking: A Practical Guide to the Ketogenic Diet, by Judy Nation, J. Helen Cross, Ingrid E. Scheffer.

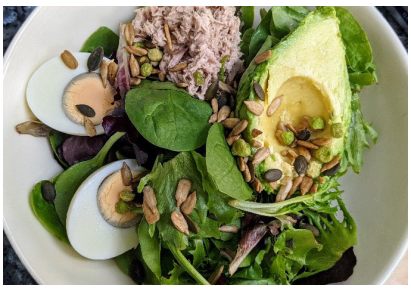

Figure 3: Avocado and egg salad with tuna mayo and seeds (photo courtesy of Victoria Whiteley)

A wide range of prescribable products are available, including milkshakes, cereal bars and puddings, which help to make KDT more palatable for those who feed orally and also expand the diversity of a patient's dietary intake. This facilitates compliance with the diet.

Supporting the use of KDT in the UK are the charities: The Daisy Garland (www.thedaisygarland.org.uk) and Matthew's Friends (www.matthewsfriends.org), which have a wide range of ketogenic recipes available for review and use. They also provide pastoral support for patients and families. This includes online forums, 'starter kits' and published information (books and leaflets). Training courses are also provided for healthcare professionals.

Monitoring and side effects

Individuals who use KDT for epilepsy are closely monitored by a multi-disciplinary team at tertiary epilepsy centres, including specialist dietitians, doctors and, depending on the service structure, clinical nurse specialists and psychologists. Diet initiation is usually done in the community in the UK, except for those who are very clinically unstable, in emergency situations, and for children under two or three years of age (depending on the centre). Blood glucose levels are usually monitored twice daily for the first few weeks, together with blood or urine ketone levels for the first three months (and usually longer). This is to reduce the risk of hypoglycaemia or hyperketosis, although these rarely occur. Prospective studies of KDT reported rates of hypoglycaemia of only 1.8% and hyperketosis rates of 3.1% [Cai QY et al, 2017].

Side effects are predominantly gastrointestinal, especially during diet initiation. Constipation, diarrhoea or vomiting can occur in up to one third of individuals in the first month or two after starting a KDT. These are usually transient or managed with medication. Other short-term side effects that tend to be easily manageable include lethargy, irritability, increased rates of respiratory tract infections and exacerbation of gastro-oesophageal reflux.

Potential longer-term adverse side effects include renal stones (a reported incidence of 1.3-3.1%), osteopenia (1.2-14.7%), cardiomyopathy (0.8%), pancreatitis (0.1-0.8%) and bruising (0.3%) [Cai QY et al, 2017]. Adverse effects on lipid profiles have been reported in up to 14.7% of patients, although such effects have been shown to normalise over time and return to baseline after discontinuing KDT [Kapetanakis et al, 2014; Liu YM et al, 2013; Patel A et al, 2010]. A prospective study showed the cardiovascular safety of the MAD when used over 12 months in adults with epilepsy [Cervenka MC et al, 2016]. Biochemical monitoring of blood and urine occurs before the start of treatment and at follow-up appointments, which are usually at three, six, 12 and 24 months after starting a KDT. Monitoring is necessary to try to avoid any of the potential side effects and later nutritional deficiencies or identify them as soon as possible (Table 1).

Laboratory assessment prior to ketogenic diet initiation	Laboratory assessment during ketogenic diet treatment
Complete blood count with platelets	Complete blood count with platelets
Electrolytes to include serum bicarbonate, total protein, calcium	Electrolytes to include serum bicarbonate, total protein, calcium
Serum liver and kidney tests (including albumin, urea and creatinine)	Serum liver and kidney profile (including albumin, urea and creatinine)
Fasting lipid profile	Vitamin D level
Serum acylcarnitine profile	Fasting lipid profile
Vitamin D level	Free and total carnitine
Urinalysis	Urinalysis
Anti-seizure medication levels (if applicable)	Selenium level
Urine organic acids (if diagnosis unclear)	Anti-seizure medication levels (if applicable)
Serum amino acids (if diagnosis unclear)	Serum beta-hydroxybutyrate level *(Optional)*
	Urine calcium and creatinine *(Optional)*
	Zinc, copper levels *(Optional)*

Table 1: Laboratory assessments recommended in the pre-diet evaluation and follow-up assessments as outlined in international best practice guidelines 14.

Some centres also monitor risk of adversely impacted bone health (osteopaenia) with routine DEXA scans and renal ultrasound scans for renal stones. The latter is particularly important if the child or younger person is also taking topiramate or zonisamide. These ASMs are known to be associated with an increased risk of renal stones.

Growth and the nutritional adequacy of the diet are continually monitored by the specialist dietetic teams.

According to international best practice recommendations, children with epilepsy (excluding those with Glut1-DS) who respond to KDT stay on the diet for approximately two years before considering its discontinuation [Kossoff EH et al, 2018]. It is recommended that those with Glut1-DS remain on KDT for life.

Evidence behind use of KDT for epilepsy

Before 2008, the only published data on the efficacy and safety of KDT was mainly based on uncontrolled small case series or anecdotes. In 2008, the first randomised controlled trial (RCT) of classical and MCT KDs to treat drug-resistant epilepsy was undertaken at Great Ormond Street Hospital for Children, London. Thirty-eight per cent of children aged between two and 16 years achieved ≥50% seizure reduction after three months of dietary treatment, compared to only 6% of controls [Neal EG et al, 2008]. No difference in effectiveness was found between the classical and MCT variants of the KD [Neal EG et al, 2009].

In the latest Cochrane review of KDT for epilepsy, data from the above RCT was combined with three other RCTs that investigated KDT in children compared to usual or standard care. They found that those on KDT were more than three times more likely to achieve seizure freedom, and almost six times more likely to achieve ≥50% reduction in seizure frequency three to four months after starting the diet [Martin-McGill KJ et al, 2020]. Two RCTs investigated the MAD for adults with epilepsy and showed that adults were five times more likely to achieve ≥50% reduction in seizures compared to usual (standard) care [Martin-McGill KJ et al, 2020]. However, no adult achieved seizure freedom. It should be noted that the evidence was described as of 'low certainty' or 'very low-certainty'. This was because of the limited number of studies available, all with small numbers of patients and a lack of clarity in methodology in some studies. Nine other RCTs were included in the Cochrane review, which compared different types or ratios of fat and carbohydrate contents in KDT.

There has since been a recently published RCT of the use of MAD in adults with epilepsy. This showed that, after six months, 26.2% of adults on the diet achieved >50% reduction in seizure frequency compared to 2.5% of controls [Manral M et al, 2023]. Quality of life also significantly improved in the MAD group compared to controls. The first RCT to assess KDT in infants with epilepsy compared to further ASMs was published in late 2023. Six to eight weeks after starting the KDT or a new ASM, the median number of seizures per day was similar in both the KD (5 [IQR 1–16]) and ASM groups (3 [IQR 2–11]; IRR 1·33, 95% CI 0·84–2·11) [Schoeler NE et al, 2023]. The proportion of infants who reported a serious adverse event was similar in both groups. The authors concluded that "a ketogenic diet could be a treatment option in infants whose seizures continue despite previously trying two anti-seizure medications".

In clinical practice, it is commonly stated that approximately 40-50% of children who start a KDT achieve at least a 50%

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reduction in seizure frequency and around 10-15% become seizure-free. These data are based predominantly on the first RCT of KDT in children with epilepsy [Neal EG et al, 2008] and prospective uncontrolled studies. Around 80% of children who achieve seizure freedom on a KDT maintain this response after discontinuing the diet [Martinez CC et al, 2007]. What is not known is the response after a KDT has been discontinued in those individuals who achieved a ≥50% reduction in seizure frequency but who never became seizure-free.

Additional benefits from the diet, such as increased alertness, concentration and developmental gains, are commonly cited in clinical practice but have not usually been assessed in a standardised, systematic way. One RCT has assessed this in children: those randomised to receive KDT were shown to be more active, more productive and less anxious than those receiving usual care [Iff D et al, 2016]. There may be a number of explanations for this reported benefit. These include the consequence of reduced seizure frequency (therefore allowing the child to function more 'normally'), a reduction in behavioural and cognitive adverse side-effects as one or more ASMs are withdrawn (if the KDT has shown clear effectiveness) or as a direct effect of ketones on cerebral functioning. Clearly, there may also be a placebo response with parents wanting to report that their child is generally better.

There are also reports of improvement in electroencephalographic (EEG) patterns in individuals on KDT. For example, a reduction in epileptiform discharges was reported after one month and maintained up to three months after commencing a KDT. However, the magnitude of reduction was highly variable among individuals [Kessler SK et al, 2011]. Children with 'substantial improvement' in spike-index (an often used, although crude measure of epileptiform activity) at one month were six times more likely than those without this improvement to achieve >50% seizure reduction at three months. Favourable longer-term improvements in the prevalence of epileptiform discharges and improved background activity have also been reported in children six months after starting KDT [Dressler A et al, 2010].

With the growing body of evidence supporting the efficacy of KDT in treating epilepsy, national and international guidelines have been produced and are constantly under review. There is an updated international consensus statement on the clinical management of children with epilepsy on KDT. This includes advice on who is eligible for consideration of a KDT, the prevention and treatment of adverse side effects, and how to discontinue dietary treatment [Kossoff EH et al, 2018]. Specific guidance has also been published on the use of KDT in infants [Kessler SK et al 2011], adults [Dressler A et al, 2010] and those receiving parenteral nutrition [van der Louw E, et al 2016]. Guidelines are currently being developed for the use of a KDT in critical care settings.

KDT in the UK: the current picture

Ketogenic diet therapy is recommended in the recently published NICE guidelines for 'Epilepsies in children, young people and adults' [NG217] for people with drug-resistant epilepsy and specifically, "If other treatment options have been unsuccessful or are not appropriate" and for "Certain childhood-onset epilepsy syndromes".

According to a survey conducted in 2021-22 by the Ketogenic Dietitians Research Network (KDRN) there were 854 individuals with epilepsy who were receiving a KDT in the UK and Ireland. These were being managed by approximately 30 specialist centres (Fig. 4) [Whiteley et al., in submission] and usually on a shared-care basis with secondary care (district) hospitals. This represents an almost nine-fold increase compared to 2000, when 101 individuals were on KDT [Cervenka MC, et al 2021] and a 13% increase compared to 2017 [van der Louw E et al, 2020].

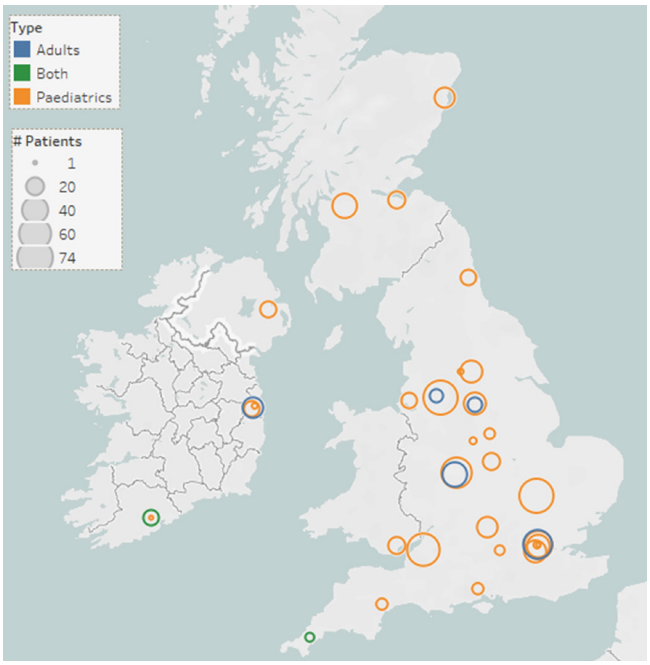

Figure 4: Map showing the ketogenic diet services in the UK and Ireland with comparative service size and patient age group, in 2022 [Whiteley et al., in submission; Ketogenic Dietitians Research Network]

A complex intervention, requiring intensive input from a multidisciplinary team, with growing services and patient numbers, has clear resource implications. The cost of implementing and maintaining KDT has been highlighted in the 2022 update of the NICE epilepsy guidelines. Although data are available from the Netherlands, it is not generalisable to UK practice due to differences in structures of healthcare funding and models of service delivery. The cost of KDT in the UK has been calculated as a first step towards a formal health economic analysis. The current estimate is that the average cost of implementing KDT over a period of two years is £13,130.59 (range, £8,078.67-£19,824.16), depending on the patient's age and complexity,

method of feeding (oral or gastrostomy) and the amount of prescribable products that are used [Whiteley et al, in preparation].

Conclusion

Ketogenic diet therapy is a well-established and now evidence-based, non-pharmacological treatment for epilepsy and a few neuro-metabolic disorders. Referrals and the number of individuals with epilepsy receiving KDT have increased dramatically over the past 20 years. In part this reflects the perennial fact that more, and newer, ASMs are not always beneficial, but also because accumulating evidence shows that the diet is effective and that its improved palatability has increased its compliance. However, it must be emphasised that KDT is not a 'natural' diet and therefore treatment option and all its variants have well-reported adverse side effects. Consequently, any KDT must be initiated, managed and monitored by an experienced clinical team within a tertiary epilepsy centre.

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Recently published papers

This section highlights recently published papers. There are many (often more than 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded.

We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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