Taylor & Francis
Taylor & Francis Group

Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Non-pharmacological treatments for pediatric refractory epilepsies

Eleonora Rotondo, Antonella Riva, Alessandro Graziosi, Noemi Pellegrino, Caterina Di Battista, Vincenzo Di Stefano & Pasquale Striano

To cite this article: Eleonora Rotondo, Antonella Riva, Alessandro Graziosi, Noemi Pellegrino, Caterina Di Battista, Vincenzo Di Stefano & Pasquale Striano (2022): Non-pharmacological treatments for pediatric refractory epilepsies, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2022.2057847

To link to this article: https://doi.org/10.1080/14737175.2022.2057847

Accepted author version posted online: 23 Mar 2022.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Neurotherapeutics*

DOI: 10.1080/14737175.2022.2057847

Non-pharmacological treatments for pediatric refractory epilepsies

Eleonora Rotondo[1], Antonella Riva[2,3], Alessandro Graziosi[4], Noemi Pellegrino[5], Caterina Di Battista[6], Vincenzo Di Stefano[7], Pasquale Striano[2,3*]

1) Division of Pediatrics and Neonatology, Ciri Hospital, ASL TO4, Ciri, Torino, Italy.
2) Paeditric Neurology and Muscular Disease Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy.
3) Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Università degli Studi di Genova, Genova, Italy.
4) Department of Neuroscience Imaging and Clinical Sciences, University G. D'Annunzio, Chieti, Italy.
5) Department of Neonatology, National Maternity Hospital, Dublin, Ireland.
6) Neonatal Intensive Care Unit, G. D'Annunzio University, Chieti, Italy.
7) Department of Biomedicine, Neuroscience and advanced Diagnostic (BIND), University of Palermo, Italy.

***Corresponding author:**

Pasquale Striano

Address: Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy, Paediatric Neurology and Muscular Disease Unit, IRCCS Istituto "G. Gaslini", Genova, Italy; Via Gaslini 5, 16148 Genova.

Email: strianop@gmail.com

Abstract

Introduction: Antiseizure medications (ASMs) are the primary treatment option for epilepsies of wide etiologies, however, about 10-20% of children do not gain sustained seizure control and in this

case, it is worth investigating "alternative" therapeutic approaches aside from ASMs. Nowadays, non-pharmacological strategies for epilepsy treatment encompass dietary interventions, neurostimulation-based techniques, and biobehavioral approaches.

Areas covered: A search on PubMed database was conducted. Experimental and clinical studies, as well as meta-analysis and structured reviews on the latest non-pharmacological treatments for drug-resistant epilepsy (DRE) in children, were included. Special attention is given to the efficacy and tolerability outcomes, trying to infer the role novel approaches may have in the future.

Expert opinion: The large heterogeneity of primary clinical outcomes and the unavoidable subjective response of each patient to treatments prevents Researchers from the identification of a single, reliable, approach to treat DRE. The understanding of fine pathophysiologic processes is giving the way to the use of alternative therapies, such as the well-known ketogenic diet, in a "personalized" view of treatment. The goal is to apply the non-pharmacological treatment most suitable for the patient's sake.

Keywords: Epilepsy; Ketogenic diet; Neurostimulation; Non-pharmacological; Pediatric epilepsy; Treatments.

Article highlights

- Drug-resistant epilepsy (DRE) affects up to 20% of children with epilepsy.
- The ketogenic diet (KD) may be effective in etiologically heterogeneous DRE.
- Neurostimulation-based approaches may be a palliative treatment option for highly DRE.
- Biobehavioral approaches or homeopathy may indeed be effective in some cases.

1. Introduction

Epilepsy is one of the most common and most disabling neurological illnesses and affects up to 0.5-1% of children ([1]). While antiseizure medications (ASMs) invariably retain the right of first-line treatment in epilepsies of wide etiologies, up to 20% of children ([2]) do not achieve sustained seizure control despite two trials of well-tolerated, appropriately chosen, and used ASMs. For these cases, the International League Against Epilepsy (ILAE) has proposed the term drug-resistant epilepsy (DRE) ([3]). In such cases, it becomes mandatory to explore 'alternative' therapeutic options aside from ASMs. Non-pharmacological treatments for epilepsy range from dietary interventions to biobehavioral approaches, with expanding fields such that of the *–biotics* sciences and neurostimulation. In this review, we aim to discuss the latest updates on the efficacy and tolerability outcomes of a wide range of non-pharmacological approaches in the treatment of DRE in children.

2. Methods

A systematic search on PubMed database was conducted. Both experimental and clinical studies, as well as meta-analysis and structured reviews on non-pharmacological treatments for DRE in children (WHO definition age 0 to 18 years), were included. Attention was paid to the updates on efficacy and tolerability outcomes. Searches covered the period up to December 2021. Only studies published in English were reviewed.

3. Dietary treatments

For centuries, fasting has been recognized as a treatment for epilepsy. As ketone bodies are molecules produced by the liver during gluconeogenesis, they have been pointed out as the key mediators involved in the anticonvulsant effect of fasting, paving the way to a ketogenic diet (KD) as a therapeutic diet in DRE ([4]). To achieve a state of ketosis, there are several types of ketogenic diet.

Potential mechanisms of the effectiveness of KD are generally centered around the roles of brain energy metabolism, neurotransmitters, ion channels, and oxidative stress ([5]). A high-fat diet, such as

a KD, may attenuate seizure frequency and severity by producing metabolic ketosis. A KD increases the ability of neurons to manage metabolic challenges in the brain, improving neuronal function under stressful conditions and enhancing seizure threshold. Increased ketone bodies may then regulate neuron membrane excitability by activating two-pore domain (K2P) potassium channels which can set a hyperpolarized resting potential of the cell membrane. Moreover, it has been observed that the KD can lead to glutamic acid decarboxylase upregulation which induces γ-aminobutyric acid (GABA) synthesis and could alter GABA transaminase activity that inhibits GABA degradation ([6,7]). Also, the KD increases norepinephrine, which has been shown to have powerful anticonvulsant properties ([5]).

3.1 Classical KD and related treatments

The classic KD is a 4:1 ratio-based diet, where fats account for the larger amount as compared to carbohydrates. Medium protein intake is also accomplished and may alter the previous ratio to a 3:1 in children, which need more proteins for their growth ([5,8]). As a non-pharmacological treatment, the KD is recommended for childhood DRE of different etiologies ([9]), and metabolic diseases such as glucose transporter type 1 (GLUT-1) ([10]), and pyruvate dehydrogenase complex (PDHC) deficiencies ([11,12,13]). Moreover, since 2009, super-refractory status epilepticus (SRSE) and febrile infection-related epilepsy syndromes (FIRES) have also been included. On the other hand, in seizures with a clear surgical focus, the KD is less useful as it may reduce seizure frequency but does not allow to gain seizure freedom ([8,14]). Besides the classic KD, some variants depending on the type and quantity of fats to carbohydrates are commonly used: the medium-chain triglyceride diet (MCT), the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT) ([8]).

The underlying mechanism of these diets always dwells on ketone body production ([15]), which are pointed out as the main mediators of the anticonvulsant effect ([4]). However, additional mechanisms have recently been highlighted, particularly those centered around the gut microbiota, which includes the bacterial species inhabiting the human gastrointestinal tract of which about 90% are

Firmicutes and *Bacteroidetes*, whereas the remaining are *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* ([16]). The KD acts by reducing the alfa-diversity and increasing the relative abundance of selected taxa, such as *Akkermansia muciniphila* and *Parabacteroides merdae* [8,17]). Hence, ketosis alone may not be sufficient to provide KD-mediated seizure control. All the mechanisms through which the KD may exerts its anticonvulsant effect are resumed in **Figure 1**, while its indications and contraindications are shown in **Table 1**.

3.2 KDs and DRE

The classic KD usually requires comprehensive baseline monitoring, including blood, renal, liver, and lipidic profiles, as well as urine checks ([14]). Hence, hospitalization should be performed in infants younger than 12 months to start a stepwise approach, which from a 1:1 ratio could be increased daily to 3:1 or 4:1 based on growth parameters and adverse events (particularly gastrointestinal and metabolic derangements) ([5,14]). Three months of KD usually provide seizure freedom in up to 55% of the cases, whilst seizure reduction reaches rates as high as 85% ([15,18]).

Nowadays, a growing pool of evidence is also focusing on applying the KD in neurodegenerative diseases with debilitating evolution and DRE, such are progressive myoclonus epilepsies (PMEs). The aim is to increase the number of seizure-free days, mainly impacting on the patients' quality of life (QoL) if not on the disease progression ([19]). Hence, the MAD, a less restrictive variant of the classical KD which does not require hospitalization to be started, provided up to a 40% improvement in the health-related quality of life (HRQL) in patients with PMEs on a three months-basis ([20]).

Overall, outcomes on seizure control overlap between different KDs ([5, 21, 22]) and the choice mainly resides on the patients' age, metabolic balance, adhesion to treatment, and specific needs. Less restrictive application of the KD will increase the possibilities of outpatient treatment, making it easily achievable ([22]).

Table 1. Indications and contraindications to the KD ([14, 23, 9, 13]).

INDICATIONS	CONTRAINDICATIONS
Drug-Resistant Epilepsies: • Ohtahara syndrome • Infantile spasms (West syndrome) • Lennox-Gastaut syndrome • Dravet syndrome • Doose syndrome (Epilepsy with myoclonic-atonic seizures) • Myoclonic absence epilepsy • Absence seizures • Focal epilepsies- NLF and LF • SRSE • FIRES *Metabolic diseases*: • GLUT-1 deficiency • PDHC deficiency optional • Mitochondrial diseases • Pyruvate dehydrogenase deficiency • Complex I mitochondrial disorders	*Absolute contraindications:* • Fatty acid oxidation defects ▪ Primary carnitine deficiency ▪ Carnitine palmitoyltransferase I or II deficiency ▪ Carnitine translocase deficiency ▪ Medium-chain acyl dehydrogenase deficiency ▪ Long-chain acyl dehydrogenase deficiency ▪ Short-chain acyl dehydrogenase deficiency ▪ Long-chain 3-hydroxyacyl-CoA deficiency ▪ Medium-chain 3-hydroxyacyl-CoA deficiency • Pyruvate carboxylase deficiency • Porphyria • Prolonged QT syndrome *Relative contraindications:* • Inability to maintain adequate nutrition • Surgical focus identified by neuroimaging and video EEG monitoring • Non-compliant parent/caregiver • Growth retardation • Severe gastrointestinal reflux • Familial hypercholesterolemia

Legend: NLF= non lesional focal; LF= lesional focal; SRSE= super-refractory status epilepticus; FIRES= febrile infection-related epilepsy syndromes.

3.3 Medium-chain triglyceride diet

As an ‘alternative' to the classical KD, the medium-chain triglyceride (MCT) diet can be provided in an oil supplement which provides a major source for fats ([9]). These medium-chain triglycerides

yield more ketones, are more efficiently absorbed, and are carried directly to the liver. As a result, less total fat is needed in the diet and more protein and carbohydrates can be allowed.

The traditional MCT diet derives 60% of the energy from medium-chain triglycerides ([24]). However, in some children, there is the need to reduce this energetic contribution to 30-50% to minimize gastrointestinal symptoms (GI), and this requires using long-chain fats as a residual source of energy. Currently, a randomized controlled trial (RCT) found no difference in the efficacy and tolerability outcomes between the classical KD and the MCT diet in 145 children with intractable epilepsy ([25]). Differences in the mean percentage of baseline seizures between the two groups were evaluated at 3, 6, and 12 months. This study showed classical and MCT ketogenic diet protocols to be comparable in efficacy and tolerability.

3.4 Low glycemic index treatment

An even less restrictive KD is the low glycemic index diet, which restricts carbohydrates to 40-60 grams/day, does not require reducing fluids and proteins, or strictly monitoring of fats and calories ([26]).

Similar to other KDs, most children assume significantly more fat on this regimen diet than they did before. The low-glycemic-index treatment consists of more liberal total carbohydrate intake but is restricted to foods that produce relatively little increase in blood glucose ([27]). This diet treatment is based on a ratio of 0.6:1 of fat to carbohydrates and protein, containing 60% fats, 30% protein, and 10% carbohydrates with a low glycemic index ([28]).

This diet has an antiepileptic efficacy comparable to KD with fewer side effects ([29]). The type of carbohydrates is important in the low glycemic index diet, which only allows low glycemic indices (<50) carbohydrates; these carbohydrates include strawberries and whole-grain bread whereas potatoes, white bread, and most citrus fruits are to be avoided ([30]). The LGIT is theorized to reduce postprandial glycemia, resulting in more stable blood glucose concentrations. This diet alters the metabolism by favouring the use of fat as the main source of energy but does not lead to an increase

in ketone body production comparable to that of the other models. In patients on this diet, there is nearly no serum ketosis noted ([30]).

3.5 Modified KD

The modified KD uses a 1:1 ketogenic ratio (lower than normal), but still requires close monitoring of the intake of fats, proteins, and carbohydrates using a gram scale ([31]). This dietary regimen induces ketosis by encouraging a high fat and low carbohydrate intake, but without the requirement to limit protein, fluid, or energy intakes, in contrast to other KD ([32]). In the energy balance of this diet, approximately 75% of calories stored derive from fats, 20% from proteins, and 5% from carbohydrates. The advantage of this 'modified' diet is that comprehensive baseline monitoring is not required, hence it could also be started at home.

3.6 Modified Atkins diet

The modified Atkins diet (MAD) is a less restrictive variant of the classic KD, which has shown anyway similar benefits on seizures control. The MAD is specifically designed to mimic some aspects of the classic KD but allows more proteins, fluids, and calories to be taken. This less restrictive diet has been used successfully in both children and adults with DRE who are unable to follow the classic ketogenic diet ([33]).

A study conducted on adult patients by Atkin's foundation showed that approximately 65% of the patients had a 50% reduction in the number of seizures. A comparable study conducted in Korea reported similar findings, with a 50% reduction of seizures in 43% of patients and > 90% decrease in the frequency of seizures in about 36% of patients ([33, 34]).

In a randomized trial, 102 children aged between 2 and 14 years (mean, 5 years) with DRE (mean of three or more previously tested ASMs) were randomized to receive either the MAD or no dietary intervention for up to three months ([35]). Four out of the 50 patients early discontinued the diet due to frequent chest infections in two cases, and due to hyperammonemic encephalopathy and family

preference in one case each. In the intention-to-treat analysis, the MAD was associated with a decrease in mean seizure frequency and 26 patients experiencing >50% reduction in seizure frequency. Five children (10%) became seizure-free, while no children in the control arm did show such a result. Hence, these results show the efficacy outcomes for the MAD are similar to those reported for the classic KD.

4. Role of *pre-*, *pro-*, and *post-biotics*

As stated in paragraph **2.1** one of the possible pathophysiological mechanisms underlying diet efficacy on seizure control may derive from the close interaction with gut microbial profile (8, 17). Hence, attempts have been made to directly "*shape*" our gut commensal bacteria to achieve seizure reduction. Currently, the microbiota can be modulated through the use of nutritional strategies, the so-called biotics family: *prebiotics*; *probiotics*; and *postbiotics* ([36, 37]).

5. Brain stimulation in DRE

Neuromodulation, or neurostimulation (NS), is a palliative treatment option for many patients suffering from medically intractable seizures and who are not eligible for resective surgery.

NS-based treatments consist either of peripheral nerve stimulation, such as vagus nerve stimulation (VNS), or transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) ([38, 39]). The mechanisms of action of neuromodulation over epilepsy control are poorly understood and acknowledged as multifaceted and multifarious. The possible mechanisms of action and the current evidence for the use of NS to treat DRE are described in **Table 2**.

Table 2. Proposed mechanisms of action of neurostimulation.

Mechanism of action of NS
Increasing after-discharge thresholds with subsequent seizure decrease and reduce regional cerebral

blood supply in the stimulated area
Suppression of thalamic and cortical spike-wave and synchronous firing
Enhance GABAergic system by increasing receptor and neurotransmitter level and decrease levels of excitatory neurotransmitters like aspartate
Inhibitory effects on neurons due to high extracellular potassium accumulation (increasing hyperpolarization) and tonic inactivation of sodium channels (prohibiting initiation of action potential) and consequently seizure activation and propagation

First, NS techniques should be divided into "*invasive*" when they refer to devices that require a surgical procedure to be implanted and "*non-invasive"* when they do not. Moreover, NS techniques can be distinguished into those who provide continuous stimulation (*open-loop*) and those which sense brain activity, thus delivering stimulation based upon detected events (*closed-loop*) ([40, 41]). The disadvantage of the *open-loop* devices is that they deliver current in a pre-defined manner (i.e reducing the overall seizure probability), while the *closed-loop* devices can modulate brain activity in precise conditions (i.e. aborting seizures real-time).

Table 3. shows primary non-invasive brain stimulation techniques for epilepsy treatment.

Table 3. Summary of the primary non-invasive brain stimulation techniques for epilepsy treatment.

Drug	**Invasive/non-invasive**	**Open/closed loop**	**Stimulation site**	**Level of evidence**
RNS	Invasive	Closed-loop	The generator is implanted intracranially	Low
DBS	Invasive	Open-loop	The generator is implanted into the subclavian region	Moderate

CSCS	Invasive/non-invasive	Open-loop	The generator is implanted into the subclavian region	Low
VNS	Invasive/non-invasive	Mostly open-loop [a]	The generator is implanted into the subclavear region	High
TMS	Non-invasive	Open-loop	A magnetic field is applied externally	Low
tDCS	Non-invasive	Open-loop	An electric current is applicated externally	Low
TNS	Non-invasive	Open-loop	Stimulation is delivered bilaterally with adhesive skin electrodes	Low

Legend: [a] modern device can sense a tachycardia, offering a closed-loop model of stimulation, CSCS= chronic subthreshold cortical stimulation; DBS= deep brain stimulation; tDCS= transcranial direct current stimulation; RNS= responsive neurostimulation; TMS= transcranial magnetic stimulation; TNS= trigeminal nerve stimulation; VNS= vagus nerve stimulation.

A responsive neurostimulation (RNS) device can deliver targeted stimulation to the putative site of onset of seizures through an intracranial pulse generator in a *closed-loop* fashion. Hence, cortical synchronization may be suppressed during seizures. Even though this is an invasive technique, DBS is considered safe, with a low rate of complications ([42, 43]), and it offers the advantage of tracking seizures over time ([44]). A similar approach is used for the *chronic subthreshold cortical stimulation* (CSCS), where a subthreshold stimulation is chronically delivered over time. Nowadays, only few single-centers studies on the CSCS are available; however, this technique appears to be promising in lowering seizure frequency ([45]). Overall RNS and DBS are more invasive than VNS.

5.1 Further neurostimulation techniques

The VNS is a technique directed to stimulate the peripheral vagus nerve as an adjunctive treatment for refractory focal-onset seizures both in the adult and pediatric populations ([46]). The VNS was

firstly approved by the Food and Drug Administration (FDA) in 1997, and then also in Europe by the European Medicines Agency (EMA) for patients with focal-onset or generalized seizures ([23]). The vagus nerve has afferent (80%) and efferent (20%) fibers. Notably, all the afferent fibers project to the *nucleus solitarius* in the medulla, while the efferent fibers project from the dorsal motor nucleus of the vagus nerve and nucleus ambiguous, that regulate the parasympathetic system. ([47]).

When a patient is eligible for the VNS, a pulse generator is implanted in the upper left of the chest, and a wire is threaded to stimulate the left vagus nerve at regular intervals through the positive and negative electrodes. The procedure, that can be performed either on an inpatient or outpatient regimen, consist of implantation and activation of the pulse generator to generate currents of specific frequency and duration suitable for an adult or pediatric patient. As previously stated, many pulse generators detect the heart rate through a closed-loop circuit system, and, additionally, each patient has a magnet that can be placed over the pulse generator to stop stimulation in the event of complications or adverse events (AEs). Conversely, passing the magnet over the battery does deliver a single, pre-programmed, stimulation ([46]).

Overall, the procedure is at low risk. The main AEs described in the literature are alteration of the voice, vocal paralysis, dyspnoea, cough, pain, headache, hoarseness, paraesthesia, and local infection. The VNS may also be compatible with magnetic resonance imaging ([48, 38]).

Recently, the EMA also approved a new non-invasive form of VNS called the transcutaneous-Vagus Nerve Stimulation (t-VNS). The t-VNS is based upon the unilateral, transcutaneous, stimulation of the auricular branch of the vagus nerve, through an external pulse generator and an external cable placed in the pinna [48, 49]. The t-VNS is a complementary treatment option aimed at reducing seizure frequency in children with refractory epilepsy. However, additional studies will be needed to further assess the efficacy of this non-invasive approach, which has the potential to be an optimal treatment strategy in a wide range of refractory epilepsies avoiding troublesome implantation procedures in children ([50]).

Both in-animal and in-human studies have shown that the stimulus provided by the VNS converges over the nucleus of the *tractus solitarius* (NTS) and the *locus coeruleus* (LC). Thus, the VNS increases the serotoninergic and noradrenalin responses, which seem to have antiepileptic effects ([44, 46]). Moreover, the VNS increases brain metabolism, especially in the thalamus, cerebellum, orbitofrontal cortex, hypothalamus, medulla, and limbic system; however, the precise mechanisms through which the VNS may reduce seizures is not yet known ([46,51]). VNS has been reported to reduce seizure rates by more than 50% in patients with refractory epilepsy ([52, 53, 54]). In the study by Elliot R. and colleagues, the efficacy of the VNS in patients with DRE was evaluated during a long clinical follow-up of over 10 years, concluding that changes in ASMs doses or stimulation parameters may have a synergistic power on seizure control ([55]). In summary, the VNS provides beneficial effects in patients with DRE; indeed, the VNS can be an adjunctive treatment option to improve the quality of life of patients, their memory, mood, and cognition ([56, 48]) and is approved down to age 4 years.

In addition, VNS is a useful and proven treatment option, tested especially in the pediatric population, to result in multiple beneficial effects such as improving quality of life, memory, mood, and cognition ([54, 55]).

Transcranial magnetic stimulation (TMS) can modulate cortical activity through the application of magnetic fields and is approved by the FDA for the treatment of major depression, and migraine; moreover, the TMS could be used for the pre-surgical mapping of the motor and language functions. Conversely, the evidence in epilepsy is still low ([57, 58]).

The *transcranial direct current stimulation* (tDCS) delivers a constant current to the brain throughout electrodes applied over the scalp. Of note, the cathodal stimulation is thought to decrease cortical excitability by stabilizing neuronal membranes, thus encouraging a possible application in epilepsy. However, the use of tDCS in epilepsy treatment is still rare and, consequently, evidence is scarce ([59, 60]).

Finally, the *trigeminal nerve stimulation* (TNS) has been investigated in randomized controlled studies on small cohorts of patients with epilepsy ([44]), but results are still controversial ([47, 61]).

In conclusion, neurostimulation techniques are generally effective and safe, nevertheless, high-quality evidence is still lacking, and studies are largely heterogeneous. Moreover, the available stimulation parameters are empiric and will need more accurate validations and standardizations in the next few years, possibly studying large case series. Finally, much effort will also be put into the identification of reliable response biomarkers to establish optimal stimulation paradigms.

Transcranial magnetic stimulation (TMS) is a neurophysiological procedure for noninvasive stimulation of the nervous system that involves the application of rapidly changing magnetic field to the superficial layers of the cerebral cortex, inducing local small electric currents ([62]). Cerebral cortex acts as a secondary coil in this situation ([63]) with the advantages of being focused and bypasses the impedance of skull and superficial tissues, so needing lesser stimulus strength ([62]). TMS can modulate cortical activity through the application of magnetic fields and is approved by the FDA for the treatment of major depression, migraine and obsessive-compulsive disorder in adults; moreover, the TMS could be used for the pre-surgical mapping of the motor and language functions. Conversely, the evidence in epilepsy is still low ([57, 58]).

Although a lot of recommendations for TMS usage in adults are available, this does not happen for the pediatric population. However, its minimal risk and good tolerability make it a feasible tool in pediatric research, and subsequently into therapy ([64, 65]). Literature about safety of TMS in children is scarce but available evidence suggests similar risks. Particularly, Zewdie E et al. described potentially serious adverse events in 1.2% and only two children had seizures possibly related to TMS ([66]).

A recent systematic review indicates beneficial effects of TMS in children and adolescents with neurodevelopmental disorders, reducing autism spectrum disorder symptoms, such as lethargy, that conventional treatments have failed to ameliorate ([67]).

Moreover, TMS can be a useful treatment for child and adolescent affected by major depression, not responding to at least one antidepressant ([68]).

Some studies suggest that TMS may have a beneficial effect in decreasing seizure frequency in patients with medically refractory epilepsy, without significant side effects. Moreover, it also seems that TMS in combination with EEG may be used to develop quantitative biomarkers of cortical hyperexcitability in patients with epilepsy. Furthermore, TMS is already Food and Drug Administration cleared for presurgical mapping of cortex, suggesting that this technique represents an important clinical item for preoperative functional evaluation ([69]). Recently, Schramm S et al. added that TMS could be a feasible and effective method for mapping the motor cortex in pediatric patients with epilepsy ([70]). Overall, TMS shows potential benefit for patients with epilepsy, but larger studies are needed, especially in paediatric population.

6. Complementary and alternative therapies

Among the non-pharmacological options for DRE treatment, complementary and integrative medicine (CIM), also known as complementary and alternative medicine (CAM), can be defined as a wide range of healing practices that cannot be classified as a part of conventional healthcare ([71, 72]). These "alternative" treatments should not be considered as substitutes of well-established antiepileptic medications, but as a complement of accepted, standardized, therapies, particularly among patients with medically intractable seizures ([73]). CIM has grown in popularity in the last decades and it is increasingly perceived by epileptics patients themselves and their caregivers/physicians as an adjunctive treatment option to conventional therapies ([74]). Different techniques may be embraced by the CIM, ranging from biofeedback and music therapy to botanical remedies, yoga, acupuncture, hypnosis, massage therapy, and so on. A complete list of the treatments that fall within the CIM is shown in **Table 4**.

6.1 Nutrients and hormones

Supporting elements of the pharmacological therapies are the various nutrients (e.g vitamins, oligo-elements, micro-and macro-nutrients), which are taken regularly with food. However, taking ASMs

may drop the plasma levels of such nutrients, leading to the need for supplementation. Additionally, hormones, particularly melatonin and progesterone, seem to play a pivotal role in reducing seizures ([75, 76]).

The main nutrients that could reduce seizure frequency are pyridoxine (vitamin B6), vitamin E, manganese, magnesium, biotin, folic acid, dimethylglycine, taurine, omega-3 fatty acids, and thiamine. The latter has been proved to be effective in improving the cognitive functions of patients with DRE as well. On the other hand, the supplementation with folic acid, vitamin B6, biotin, vitamin D, and L-carnitine helps to prevent or treat deficiencies resulting from the use of ASMs. Besides, Vitamin K1 is also recommended for women on antiepileptic therapy during the last trimester of pregnancy ([77, 78, 79, 80, 81, 76]).

Currently, there are two indications for vitamin supplementation in epilepsy: i) replacement therapy in hereditary metabolic defects, such as pyridoxine-dependent seizures, biotinidase deficiency, and neonatal seizures reactive to folinic acid; ii) reduction of seizures frequency, through an unclear anticonvulsant effect on the inhibitory GABA and glutaminergic systems, with vitamin E, folic acid, and pyridoxine (vitamin B6) as the main nutrients implicated in this neuroprotective role ([75]).

Vitaminic supplementation as an adjunctive treatment in children with DRE has been studied in the literature; however, further studies are needed to assess the real role of vitamins in the treatment of epilepsy ([76]). On the other hand, with regards to hormones, it seems that melatonin decreases seizure frequency; notwithstanding, it has not been demonstrated yet whether this is due to a better quality of sleep or a neuroprotective effect ([82]). Whereas, adjunctive progesterone may be useful in women with catamenial epilepsy, a type of epilepsy closely linked to the cyclic hormonal changes of the menstrual cycle and, hence, causing cyclical relapses of seizures ([76]).

6.2 Complementary therapies and lifestyle

6.2.1 Regular lifestyle

A regular lifestyle is essential as adjuvant treatment for epilepsy in all age groups, especially in children. Indeed, exercise is recommended for children with epilepsy, as long as they are regularly

monitored. Physical activity holds a positive impact on the QoL and socialization of these patients rather than on seizures themselves. However, exercise is difficult for many children with epilepsy due to learning difficulties and physical restraints.

Currently, there are not enough studies strictly analyzing the effects of exercise over epilepsy ([83]), but a few cases of reflex seizures induced by physical activity are also reported ([84]). In conclusion, further assessments will be needed but the take-home message is to encourage physical activity in children with DRE, respecting their times and restrictions but encouraging socialization, and strictly avoiding specific tasks when they have been demonstrated to elicit seizures on several occasions.

Sleeping hygiene is another essential point to be addressed while acting for seizure reduction. Indeed, it has been shown that sleep deprivation is an important trigger for seizures, stimulating interictal discharges on the EEG and causing an increase in neuronal excitability ([85]). Consequently, children need to sleep regularly and constantly. The same educational behavior is appropriate during air travels when crossing time zones, as it is common for children and adolescents to experience the first generalized seizure during holidays, within 12-24 hours of arrival at destination. Particularly teenagers are at risk for epileptic seizures arising *de novo* or exacerbated by sleep deprivation; hence, in a teenager with a previous good control seizures, it is fundamental to inquire about the quality and hours of sleep before increasing or changing ASMs ([83]). Finally, during adolescence, excessive alcohol consumption may be a potential problem for patients with epilepsy, causing the occurrence of seizures within 48 hours of excessive consumption of alcohol. Moreover, alcohol may increase seizure frequency disrupting sleep and interacting with ASMs' pharmacodynamics and pharmacokinetics ([83]).

6.2 Psychological interventions

Psychological interventions may help in the treatment of epilepsy. To date, various psychological techniques are available to improve the QoL of epileptic patients. One of these interventions is the "relaxation technique", which has been effectively applied to children with epilepsy. In these

studies, patients learned to recognize the prodromal signs of seizures, concurrently starting to apply "relaxation techniques" ([83], [86]). Unfortunately, evidence-based studies are still too low to reach conclusive and reliable results and further work should be done. Nevertheless, it is certain that "relaxation techniques" such as sleep improvement can indirectly improve seizure control acting on pivotal sleep hygiene.

Another interesting psychological procedure is "adverse therapy". Basing on the principle of the operative conditioning state, seizures can be a behavior that one learns to avoid ([83]). Consequently, the chain of events occurring during a seizure can be altered by concurrently presenting a harmful stimulus. This technique became famous between the 1960s and 1970s, however, there is not enough scientific evidence to justify the use in clinical practice yet ([83]).

Another point is that the reduction of psychiatric diseases, such as anxiety, depression, and psychosis can also improve epilepsy. Psychiatric symptoms may be a constituting part of the patients' phenotypes, partnering epilepsy, or may depend on the use of ASMs and/or surgery. Hence, in severe cases, multidisciplinary work between pediatricians, psychiatrists, and psychologists is indeed appropriate ([87]).

Finally, *cognitive-behavioral therapy* (CBT) is another useful approach in epilepsy, given the huge emotional impact of seizures. Particularly, this technique aims to teach patients to cope with seizures in an attempt to recognize and control the symptoms. However, the CBT should be proposed to children older enough to understand the technique, and possibly shared with parents ([83]). To date, many studies have shown that psychological educational interventions can provide useful tools to improve patient's QoL and, consequently, also their adherence to ASMs. Specifically, it has been shown that the CBT is effective in managing stress, improves problem-solving, and reduces negative thinking when introduced into specific epilepsy programs; this is

largely evident in adolescents with epilepsy, where the CBT may improve mental health indices, social activities, and emotional well-being ([88]).

6.3 Other forms of mental-body technique

The practice of yoga aspires to achieve relaxation, reducing stress, which is a huge trigger for seizures. Yoga is built up of a set of exercises comprising breathing, postures and meditation techniques, which may restore the union between the body and the soul leading to stress relief. Nowadays, yoga has also been studied in patients with epilepsy concomitantly taking ASMs; indeed, it proved as a powerful adjunctive tool to decrease epileptic discharges, influencing the activation of the autonomic nervous system and, therefore, the electroencephalogram ([89], [90]). However, further studies will be needed to reach definitive conclusions as the lack of assessments' endpoints make particularly difficult to assess the beneficial effects of yoga in the pediatric population.

Other practices that aim to prevent stress-induced seizures through muscle relaxation are represented by meditation, aromatherapy, hypnosis, acupuncture, and massage therapy ([91]). Among the non-pharmacological treatments, hypnosis has been tried either alone or in combination with aromatherapy in adult patients with DRE ([86], [75]). Promising results have been showed particularly when both techniques were used together, with up to one-third of patients reaching seizure freedom for over 12 months. Unfortunately, this practice needs a long time to be properly applied to patients. On the other hand, hypnosis appeared to induce non-epileptic seizures in the pediatric population; hence, further studies are needed and evidence in the literature is still too low to propose these practices in the clinical management of patients ([75]).

6.4 Avoidance techniques

Reflex epilepsies are reproducibly and instantaneously triggered by a well-defined sensory or cognitive stimulus ([92]). The light stimulus is often the triggering element; however, there may be also other causes such as thinking, listening to specific types of pieces of music, eating, reading, soaking in hot water, playing chess, or even brushing hair ([84]).

A fundamental practice resides in the avoidance of all the triggering factors of seizures; indeed, children with epilepsy whose photosensitivity is documented by the EEG are advised to take measures to avoid seizures: i) sitting more than 2.5 meters from the television in a well-lit room; ii) using the remote control and approaching the television with one eye covered; iii) avoiding video games in a dark room or when mentally tired; iv) covering one eye when exposed to various visual stimuli ([75]).

6.5 Biofeedback techniques

Biofeedback is a non-invasive behavioral therapy based on the principle of operant conditioning. Providing direct feedback of covert physiological signals, subjects learn how to self-regulate, improving their volitional control over physiological processes of which they did not even have previously consciousness ([93, 34]). Diverse biofeedback methods have been explored from as early as the 1970s for the management of epilepsy ([94, 95]).

Neurofeedback, also known as EEG biofeedback, is a type of biofeedback therapy that aims to train individuals to regulate their brainwave patterns by providing them with real-time EEG data. Sterman and colleagues ([96]) conducted the first official research in this area focusing on the sensory-motor rhythm (SMR), an EEG rhythm recorded over the sensory-motor cortex with a frequency in the range of 12–20 Hz. Using the neurofeedback technique, patients learned how to change intentionally this component of the EEG to reduce the amount and frequency of seizure activity. Although acting over the SMR remains the most common neurofeedback training for epilepsy, a different method is based on the Slow Cortical Potentials (SCPs) which has recently

gained popularity. The SCPs reflect cortical excitability and some studies have demonstrated that training patients to control the amplitude of cortical potential changes can lead to a decrease in the rate of seizures ([95, 91, 73]). Overall, neurofeedback is considered a secure treatment; however, mild side effects such as fatigue, headache, and tiredness have also been described.

The use of neurofeedback in the pediatric population has been primarily studied in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and no RCTs have been conducted in pediatric epileptic populations. Current evidence suggests that neurofeedback could be effective in the treatment of pediatric epilepsy, but more studies are needed ([97]). Of note, promising results have been observed using skin conductance biofeedback, also known as Galvanic skin response (GSR) biofeedback, which aims to reduce the cortical excitability by increasing the level of peripheral sympathetic arousal ([98]). In this case, patients are trained to get positive visual feedback with lights and images on a screen after producing the 12-14 Hz activity ([75]); this training seems to reduce the cortical excitability through the modulation of the thalamocortical sensory flow and the activity of the ventromedial pre-frontal/ orbitofrontal cortexes, both functionally impaired in patients with epilepsy ([95]). However, this procedure requires nearly 30 minutes of training, multiple sessions a week for at least 3 months, and good skills of cooperation and concentration; hence, it is considered impractical for children who are too young or may have cognitive impairments ([75]). A recent systematic review has highlighted the potential value of the GSR biofeedback therapy, but it has concluded that larger-scale studies are required to definitively establish its utility ([95]).

6.6 Music therapy

Another potential complementary treatment option for patients with DRE is represented by music therapy. The mechanisms through which music stimuli may act to improve epilepsy control are still poorly understood ([99]), however, a large number of trials and animal studies have focused on Mozart's music sonatas, and especially on Mozart's sonata for two pianos in D major K. 448 and K.

545, that seem to be effective in causing EEG changes, reducing the epileptiform discharges ([100, 101]). The so-called "Mozart effect" also appears to ameliorate the patients' quality of life, decreasing aggression and irritability, and improving mood and nighttime sleep. A similar effect has been observed with a song realized by a Greek musician, similar to Mozart's piece in melody and structure; conversely, no effects have been demonstrated with other famous musical compositions such as Beethoven's ones ([102]). The underlying effects of music therapy are uncertain; however, resonance mechanisms or the activation of mirror neurons may lead to a modulation of several neuronal networks which may ultimately exert an antiepileptic effect ([103, 104]). Furthermore, music has been shown to enhance the dopamine pathways and stimulate the parasympathetic nervous system ([105]) which can, in turn, reduce the propagation of epileptic discharges influencing thalamocortical projections.

Despite the lacking comprehension of the processes involved and the wide heterogeneity of the studies performed, a recent meta-analysis has shown a significant reduction in seizures and interictal epileptiform discharges frequencies after long-term music treatment, concluding that the "Mozart effect" should be considered as a safe and alternative treatment for patients with refractory epilepsy ([104]). Although further studies are needed, there is no doubt that the "Mozart effect" has great potential as an accessible and adjunctive therapy for epilepsy, particularly in younger patients.

6.7 Aromatherapy

Aromatherapy is an alternative/complementary treatment for stress-related symptoms featuring epilepsy. Several essential oils are known to have a calming and relaxing effect and may have a role in patients with epilepsy triggered by stress. The technique is based on massages with essential oils, diluted in a mild oil for external massage. The oils are absorbed through the skin, and their elements travel quickly to the CNS; probably a portion is absorbed through the olfactory system as well ([106]).

Different oils may have different chemical constituents and healthy properties ([106, 107]). For example, oil containing camphor, which has a pro-convulsing effect, should be avoided in patients with epilepsy. Commonly, a mixture of aromatic oils is used, which contains sage or rosemary, chamomile, lavender, rose, geranium, jasmine, and Ylang Ylang ([108]). The latter oil is distilled from the flowers of the tree Cananga odorata.

Aromatherapy is based on the most primitive of all the senses: the sense of smell. The smell is limited to the most primitive regions of the cerebral cortex, which are often highly epileptogenic, promoting the onset of seizures. Moreover, in many cases, seizures can manifest themselves with olfactory auras. ([109, 106]). Finally, it has been seen that aromatherapy, combined with hypnosis to enhance aroma conditioning, may furtherly increase the positive effects on seizure control ([106]).

6.10 Homeopathy

Homeopathy uses extremely dilute solutions of active agents to stimulate the immune defenses and normalize the homeostatic mechanisms. Several homeopathic medicines have been proposed for epilepsy treatment (**Table 3**) and even though case reports have proposed that they may be useful for seizures control, the inconsistency of the homeopathic compounds used and the lack of a close temporal relationship between treatment initiation and seizure resolution limits the strength evidence ([110]). This lack of scientific consistency militates against the recommendation of herbal medicines for the treatment of children with epilepsy by doctors practicing conventional medicine in Western countries ([75]).

Table 3. Proposed homeopathic medicines for epilepsy treatment.

Homeopathic medications used in stress induces seizure epilepsy
Calcarea carbonica
Bufo rana
Cuprum Metallicum
Oenanthe Crocata

Kali bromatum
Silicea
Nux vomica
Cicuta virosa
Sulphur
Hyoscyamus
Belladonna
Causticum

6.11 Phytotherapy and traditional Chinese medicine

Phytotherapy, i.e. herbal medicinal remedies, is used as a first-line remedy for a wide range of diseases in up to 80% of the World's population and is very popular among the Asian and Chinese populations ([75]).

To date, no RCTs have assessed whether herbal remedies may play a role in epilepsy treatment. However, two open-label studies published in the Chinese medical literature have reported some benefits of phytotherapy over DRE, with more than 75% reduction in seizure frequency in two-thirds of patients ([111, 75]). A multitude of botanicals/herbs, such as piper, ginkgo Biloba, radix ginseng, and turmeric, are generally considered safe, affordable and well-tolerated, and have been used for centuries to treat epilepsy ([112]). In that context, China has a significant tradition based on twenty-three different botanicals, all obtained from natural plants, that are usually mixed in different ways to create specific formulas ([112]). Despite this century-old tradition, the current scientific evidence mainly consists of animal models which suggest a potentiation of GABAergic activity as the mode of action of these remedies ([113]). As for the American hellebore, betony, blue cohosh, mugwort, pipsissewa, skullcap, and valerian, it is not known whether they may also have antiepileptic properties ([114, 115, 116]) and no scientific data on their clinical efficacy are currently available ([117, 115]).

Notably, all the interactions between herbs and drugs must be known for the correct management of epilepsy. Herbs can have different effects on the pharmacokinetics and pharmacodynamics of common ASMs ([118]), altering their effectiveness, and side effects, hence directly modifying seizures threshold ([118]). Unfortunately, without sufficient data on the efficacy, safety, and tolerability, it is difficult to recommend the use of herbal medicines for the treatment of epilepsy. Consequently, patients already taking herbs and supplements must report them to their doctor for possible interactions ([116]).

Traditional Chinese medicine (TCM) uses herbs taken from natural plants to treat the main problems of diseases. For example, gout (Uncaria rhynchophylla, UR), shitei-To, qingyangshen (QYS), ([119]), thianma (Gastrodia rhizoma), changpu (Acorus calamus), and dannanxing (Arisaema cum bile) have anticonvulsant properties and are used in the treatment of epilepsy ([120, 121]). The zheng tai instant powder is a medication used in the TCM and is indicated for the treatment of tonic-clonic seizures due to its effects on the CNS ([122]). Still, the lack of scientific studies on the topic prevents the recommendation of herbal remedies by Western doctors, particularly in children.

6.12 Acupuncture

Acupuncture is a procedure in which specific areas of the body, the so-called "meridian points", are pierced with thin needles for therapeutic purposes. Acupuncture is a common practice in the TCM, dating back over 2000 years ([123, 124]). Nowadays, modern forms of acupuncture such as electro-acupuncture, laser-acupuncture, and acupressure are practiced. Since acupuncture is a simple, inexpensive, and safe procedure, it has recently gained success in Western countries ([124]), and can be used for various neurological disorders as an alternative therapeutic approach to "conventional" medicine.

The principle of acupuncture is based on the regulation of the five elements (fire, earth, metal, water, and wood), of the yin and yang, Qi, blood, and body fluids ([124]). Briefly, the stimulation of

various meridian points corrects the dysregulation of the organic systems, reducing symptoms and restoring homeostasis ([125]). Responses to stimuli occur both locally ([126]) and remotely, through sensory neurons up to the CNS ([127]). Therefore, the result is the activation of pathways affecting various physiological systems in the central and peripheral nervous system ([128, 129, 130]).

Anecdotal reports and animal studies suggest that acupuncture may inhibit convulsions ([131]). It has been observed that electro-acupuncture can theoretically affect epilepsy by stimulating the inhibitory neurotransmitters ([131, 132]), such as serotonin, GABA, or opioid peptides. Even uncontrolled, case report limited, human studies have shown the beneficial effects of acupuncture on epilepsy control ([133, 134]). On the other hand, the effects of acupuncture on EEG recordings have been contradictory ([135, 136]) and it is therefore unclear whether the current data are sufficient to recommend acupuncture in the treatment of epilepsy. In conclusion, although there are currently Chinese studies showing a good reduction in seizure frequency when practicing acupuncture ([134]), there is no enough scientific evidence on this subject, particularly for the pediatric population. **Table 4** shows a list of complementary medicines.

Table 4. List of complementary and integrative medicine.

Natural products	Herbs, cannabinoids, vitamins, minerals, melatonin, antioxidants, and other dietary supplements
Spiritual/mind-body interventions	Biofeedback, music-therapy, cognitive behavioral therapy, educational intervention, yoga, meditation, aromatherapy, hypnosis, prayer, exorcism
Manipulative/body-based interventions	Exercise, sport, acupuncture, acupressure, cupping, massage, chiropractic care, reflexology
Alternative medical system	Traditional Chinese Medicine, acupuncture, phytotherapy, ayurvedic medicine, homeopathy

7. Conclusions

If a child with refractory epilepsy does not have a surgically remediable cause of epilepsy, dietary management should be an adjunctive strategy and the KD proved relatively successful. There can be adverse effects for all KD variations, such as short□term gastrointestinal□related disturbances and increased cholesterol but the creation of recommendations for use of KD in infants encourages safe and effective implementation of this treatment in children. Another promising therapeutic approach derives from the neuromodulation field; both VNS and DBS have proved effective, reducing seizures in patients not fully managed with pharmacotherapy. Recent studies suggest the feasibility, tolerability, safety, and efficacy of neurostimulation in the pediatric population, which are similar to the outcomes reported in the adult population. Consequently, when the dietary response is not effective, children and their parents/caregivers should be advised on the neuromodulation option.

Finally, CIM might represent a broad spectrum of adjunctive therapeutic strategies in epilepsy, but its effectiveness has yet to be fully determined. The current evidence is that most CIM can improve quality of life, but it does not reduce seizure frequency significantly. Longitudinal studies would be of great interest to better understand risks and potential benefits. As regards the other non-pharmacological therapeutic options, the current evidence is still insufficient and further research would be of benefit.

Another promising non-pharmacological therapeutic approach comes from the field of neuromodulation; both VNS and DBS have been shown to be effective, reducing seizures in patients not fully managed with pharmacotherapy. Recent studies suggest the feasibility, tolerability, safety, and efficacy of neurostimulation in the pediatric population, which are similar to the results reported in the adult population. In particular, VNS is widely used in the treatment of pediatric patients, with significant benefits and when diet is not effective, children and their parents/guardians should be counseled on the option of neuromodulation.

Our article is centred around the pediatric age (0-18 years per WHO definition), dealing with outcomes reported for this specific population. Although, the treatment strategies reported here would be applicable also in adulthood, with specific indications and contraindication as well as outcome measures worthy of separate discussion.

8. Expert opinion

Usually, epilepsy is treated with ASMs, and some DRE may be accessible to brain surgery. For patients not undergoing surgery for medical reasons or for personal choice, other treatment should be considered. Non-pharmacological and less invasive treatments have entered the "therapeutic cartridge" in the last few years. Yet, it is currently difficult to find objective and controlled data quantifying or documenting the effectiveness of these approaches given the large heterogeneity of primary clinical outcomes and the unavoidable subjective response of each patient to treatments. DRE occurs in 10-20% of children who have epilepsy and no single pathogenetic mechanism can be identified, potentially explaining these subjective, inter-patients, differences. The goal of the upcoming research is to identify the fine pathophysiologic processes giving patients drug-resistance and, hence, find for each patient the most suitable therapeutic strategy, avoiding wasting with ineffective options and directly skipping to the best, "personalized" treatment. In this view, literature about an altered gut-microbiota composition in patients with DRE is increasing. In clinical practice, it is already feasible to analyze the intestinal bacteria composition of patients with DRE with 16S rRNA or Shotgun Metagenomic profiling to eventually provide pre- or probiotics to directly impact the altered substrate. Further clinical and experimental data will be provided in the next few years, widening our perspective and possibilities of a routinely and real-life administration of currently straightforward approaches.

Funding

Declaration of interests

A Riva has received honoraria from Kolfarma s.r.l, Proveca Pharma Ltd., and PTC Therapeutics. P. Striano has served on a scientific advisory board for the Italian Agency of the Drug (AIFA); has received honoraria from GW pharma, Kolfarma s.r.l., Proveca Pharma Ltd, and Eisai Inc.; and has received research support from the Italian Ministry of Health and Fondazione San Paolo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (legge 232 del 2016).

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Aaberg, K. M. *et al.* Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics* **139**, (2017).

2. Aneja, S. & Jain, P. Refractory epilepsy in children. *Indian J. Pediatr.* **81**, 1063–1072 (2014).

3. Kwan, P. *et al.* Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **51**, 1069–1077 (2010).

4. WILDER & RM. The effects of ketonemia on the course of epilepsy. *Mayo Clin Proc* **2**, 307–308 (1921).

5. Barzegar, M. *et al.* Ketogenic diet: overview, types, and possible anti-seizure mechanisms.

Nutr. Neurosci. 1–10 (2019) doi:10.1080/1028415X.2019.1627769.

6. Cheng, C. M., Hicks, K., Wang, J., Eagles, D. A. & Bondy, C. A. Caloric restriction augments brain glutamic acid decarboxylase-65 and -67 expression. *J. Neurosci. Res.* **77**, 270–276 (2004).

7. Suzuki, Y. *et al.* Beta-hydroxybutyrate alters GABA-transaminase activity in cultured astrocytes. *Brain Res.* **1268**, 17–23 (2009).

8. deCampo, D. M. & Kossoff, E. H. Ketogenic dietary therapies for epilepsy and beyond. *Curr. Opin. Clin. Nutr. Metab. Care* **22**, 264–268 (2019).

9. Neal, E. G. *et al.* The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet. Neurol.* **7**, 500–506 (2008).

10. Sandu, C., Burloiu, C. M., Barca, D. G., Magureanu, S. A. & Craiu, D. C. Ketogenic Diet in Patients with GLUT1 Deficiency Syndrome. *Maedica* vol. 14 93–97 (2019).

11. Staretz-Chacham, O. *et al.* The Effects of a Ketogenic Diet on Patients with Dihydrolipoamide Dehydrogenase Deficiency. *Nutrients* **13**, (2021).

12. Inui, T. *et al.* Intravenous ketogenic diet therapy for neonatal-onset pyruvate dehydrogenase complex deficiency. *Brain & development* vol. 44 244–248 (2022).

13. Scholl-Bürgi, S. *et al.* Ketogenic diets in patients with inherited metabolic disorders. *J. Inherit. Metab. Dis.* **38**, 765–773 (2015).

14. van der Louw, E. *et al.* Ketogenic diet guidelines for infants with refractory epilepsy. *Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc.* **20**, 798–809 (2016).

15. Martin-McGill, K. J., Jackson, C. F., Bresnahan, R., Levy, R. G. & Cooper, P. N. Ketogenic diets for drug-resistant epilepsy. *Cochrane database Syst. Rev.* **11**, CD001903 (2018).

16. Iannone, L. F. *et al.* Microbiota-gut brain axis involvement in neuropsychiatric disorders. *Expert Rev. Neurother.* **19**, 1037–1050 (2019).

17. Olson, C. A. *et al.* The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. *Cell* **173**, 1728-1741.e13 (2018).

18. Sourbron, J. *et al.* Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. *Child's Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg.* **36**, 1099–1109 (2020).

19. Riva, A. *et al.* Emerging treatments for progressive myoclonus epilepsies. *Expert Rev. Neurother.* **20**, 341–350 (2020).

20. van Egmond, M. E. *et al.* The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. *Orphanet J. Rare Dis.* **12**, 45 (2017).

21. Liu, Y. C. Medium-chain triglyceride (MCT) ketogenic therapy. *Epilepsia* **49 Suppl 8**, 33–36 (2008).

22. Winesett, S. P., Bessone, S. K. & Kossoff, E. H. W. The ketogenic diet in pharmacoresistant childhood epilepsy. *Expert Rev. Neurother.* **15**, 621–628 (2015).

23. Sondhi, V. *et al.* Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy: A Randomized Clinical Trial. *JAMA Pediatr.* **174**, 944–951 (2020).

24. Kossoff, E. H. *et al.* Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia open* **3**, 175–192 (2018).

25. Neal, E. G. *et al.* A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* **50**, 1109–1117 (2009).

26. Cervenka, M. C. *et al.* E-mail management of the modified Atkins Diet for adults with epilepsy is feasible and effective. *Epilepsia* **53**, 728–732 (2012).

27. Pfeifer, H. H. & Thiele, E. A. Low-glycemic-index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy. *Neurology* **65**, 1810 LP – 1812 (2005).

28. D'Andrea Meira, I. *et al.* Ketogenic diet and epilepsy: What we know so far. *Front. Neurosci.* **13**, (2019).

29. Karimzadeh, P. *et al.* Low Glycemic Index Treatment in pediatric refractory epilepsy: The first Middle East report. *Seizure* **23**, 570–572 (2014).

30. Kennedy, R. L. & Khoo, E. Y. H. Health, Functional, and Therapeutic Implications of Obesity in Aging. in *Handbook of Models for Human Aging* 829–839 (Elsevier Inc., 2006). doi:10.1016/B978-012369391-4/50070-9.

31. Huttenlocher, P. R., Wilbourn, A. J. & Signore, J. M. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. *Neurology* **21**, 1097–1103 (1971).

32. Martin-McGill, K. J., Jenkinson, M. D., Tudur Smith, C. & Marson, A. G. The modified ketogenic diet for adults with refractory epilepsy: An evaluation of a set up service. *Seizure* **52**, 1–6 (2017).

33. Kossoff, E. H. & Dorward, J. L. The modified Atkins diet. *Epilepsia* **49 Suppl 8**, 37–41 (2008).

34. Alqahtani, F. *et al.* Non-pharmacological Interventions for Intractable Epilepsy. *Saudi Pharm. J.* **28**, 951–962 (2020).

35. Sharma, S., Sankhyan, N., Gulati, S. & Agarwala, A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. *Epilepsia* **54**, 481–486 (2013).

36. Żółkiewicz, J., Marzec, A., Ruszczyński, M. & Feleszko, W. Postbiotics-A Step Beyond Pre- and Probiotics. *Nutrients* **12**, (2020).

37. Wegh, C. A. M., Geerlings, S. Y., Knol, J., Roeselers, G. & Belzer, C. Postbiotics and Their

Potential Applications in Early Life Nutrition and Beyond. *Int. J. Mol. Sci.* **20**, (2019).

38. Krishna, V., Sammartino, F., King, N. K. K., So, R. Q. Y. & Wennberg, R. Neuromodulation for Epilepsy. *Neurosurg. Clin. N. Am.* **27**, 123–131 (2016).

39. Fisher, R. S. & Velasco, A. L. Electrical brain stimulation for epilepsy. *Nat. Rev. Neurol.* **10**, 261–270 (2014).

40. Vassileva, A., van Blooijs, D., Leijten, F. & Huiskamp, G. Neocortical electrical stimulation for epilepsy: Closed-loop versus open-loop. *Epilepsy Res.* **141**, 95–101 (2018).

41. Boon, P., De Cock, E., Mertens, A. & Trinka, E. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. *Curr. Opin. Neurol.* **31**, 198–210 (2018).

42. Heck, C. N. *et al.* Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* **55**, 432–441 (2014).

43. Morrell, M. J. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* **77**, 1295–1304 (2011).

44. Starnes, K., Miller, K., Wong-Kisiel, L. & Lundstrom, B. N. A review of neurostimulation for epilepsy in pediatrics. *Brain Sci.* **9**, (2019).

45. Lundstrom, B. N. *et al.* Chronic Subthreshold Cortical Stimulation to Treat Focal Epilepsy. *JAMA Neurol.* **73**, 1370–1372 (2016).

46. Ben-menachem, E. Neurostimulation — Past , Present , and Beyond.

47. DeGiorgio, C. M. & Krahl, S. E. Neurostimulation for drug-resistant epilepsy. *Continuum (Minneap. Minn).* **19**, 743–755 (2013).

48. Bigelow, M. D. & Kouzani, A. Z. Neural stimulation systems for the control of refractory epilepsy: A review. *J. Neuroeng. Rehabil.* **16**, 1–17 (2019).

49. Clancy, M. J., Clarke, M. C., Connor, D. J., Cannon, M. & Cotter, D. R. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. *BMC Psychiatry* **14**, 75 (2014).

50. He, W. *et al.* Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. *Epilepsy Behav.* **28**, 343–346 (2013).

51. Lulic, D., Ahmadian, A., Baaj, A. A., Benbadis, S. R. & Vale, F. L. Vagus nerve stimulation. *Neurosurg. Focus* **27**, E5 (2009).

52. Kulju, T., Haapasalo, J., Lehtimäki, K., Rainesalo, S. & Peltola, J. Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. *Brain Behav.* **8**, 1–7 (2018).

53. Kuba, R. *et al.* Vagus nerve stimulation: longitudinal follow-up of patients treated for 5 years. *Seizure* **18**, 269–274 (2009).

54. Fisher, R. *et al.* Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* **51**, 899–908 (2010).

55. Elliott, R. E. *et al.* Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav.* **20**, 57–63 (2011).

56. Huf, R. L., Mamelak, A. & Kneedy-Cayem, K. Vagus nerve stimulation therapy: 2-year prospective open-label study of 40 subjects with refractory epilepsy and low IQ who are living in long-term care facilities. *Epilepsy Behav.* **6**, 417–423 (2005).

57. Braun, J. M. *et al.* Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: The HOME study. *Obesity (Silver Spring).* **24**, 231–237 (2016).

58. Fregni, F. *et al.* Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov. Disord.* **21**, 1693–1702 (2006).

59. Faria, P., Hallett, M. & Miranda, P. C. A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. *J.*

Neural Eng. **8**, (2011).

60. Auvichayapat, N. *et al.* Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. *Brain Stimul.* **6**, 696–700 (2013).

61. Gil-López, F. *et al.* External trigeminal nerve stimulation for drug resistant epilepsy: A randomized controlled trial. *Brain Stimul.* **13**, 1245–1253 (2020).

62. Chail, A., Saini, R. K., Bhat, P. S., Srivastava, K. & Chauhan, V. Transcranial magnetic stimulation: A review of its evolution and current applications. *Ind. Psychiatry J.* **27**, 172–180 (2018).

63. Horvath, J. C., Perez, J. M., Forrow, L., Fregni, F. & Pascual-Leone, A. Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns. *J. Med. Ethics* **37**, 137–143 (2011).

64. Rajapakse, T. & Kirton, A. NON-INVASIVE BRAIN STIMULATION IN CHILDREN: APPLICATIONS AND FUTURE DIRECTIONS. *Transl. Neurosci.* **4**, (2013).

65. Allen, C. H., Kluger, B. M. & Buard, I. Safety of Transcranial Magnetic Stimulation in Children: A Systematic Review of the Literature. *Pediatr. Neurol.* **68**, 3–17 (2017).

66. Zewdie, E. *et al.* Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. *Brain Stimul.* **13**, 565–575 (2020).

67. Masuda, F. *et al.* Clinical effectiveness of repetitive transcranial magnetic stimulation treatment in children and adolescents with neurodevelopmental disorders: A systematic review. *Autism* **23**, 1614–1629 (2019).

68. Majumder, P., Balan, S., Gupta, V., Wadhwa, R. & Perera, T. D. The Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depression Among Children and Adolescents: A Systematic Review. *Cureus* **13**, e14564 (2021).

69. VanHaerents, S., Chang, B. S., Rotenberg, A., Pascual-Leone, A. & Shafi, M. M. Noninvasive Brain Stimulation in Epilepsy. *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.* **37**, 118–130 (2020).

70. Schramm, S., Mehta, A., Auguste, K. I. & Tarapore, P. E. Navigated transcranial magnetic stimulation mapping of the motor cortex for preoperative diagnostics in pediatric epilepsy. *J. Neurosurg. Pediatr.* 1–8 (2021) doi:10.3171/2021.2.PEDS20901.

71. Zollman, C. & Vickers, A. What is complementary medicine? *BMJ* **319**, 693–696 (1999).

72. Asadi-Pooya, A. A. *et al.* Pediatric-onset psychogenic nonepileptic seizures: A retrospective international multicenter study. *Seizure* **71**, 56–59 (2019).

73. Sheth, R. D., Stafstrom, C. E. & Hsu, D. Nonpharmacological treatment options for epilepsy. *Semin. Pediatr. Neurol.* **12**, 106–113 (2005).

74. Farrukh, M. J., Makmor-Bakry, M., Hatah, E. & Tan, H. J. Use of complementary and alternative medicine and adherence to antiepileptic drug therapy among epilepsy patients: a systematic review. *Patient Prefer. Adherence* **12**, 2111–2121 (2018).

75. Kneen, R. & Appleton, R. E. Alternative approaches to conventional antiepileptic drugs in the management of paediatric epilepsy. *Arch. Dis. Child.* **91**, 936–941 (2006).

76. Gaby, A. R. Natural approaches to epilepsy. *Altern. Med. Rev.* **12**, 9–24 (2007).

77. Mock, D. M., Stadler, D. D., Stratton, S. L. & Mock, N. I. Biotin status assessed longitudinally in pregnant women. *J. Nutr.* **127**, 710–716 (1997).

78. Verrotti, A., Greco, R., Morgese, G. & Chiarelli, F. Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. *Int. J. Clin. Lab. Res.* **29**, 36–40 (1999).

79. Collins, N., Maher, J., Cole, M., Baker, M. & Callaghan, N. A prospective study to evaluate the dose of vitamin D required to correct low 25-hydroxyvitamin D levels, calcium, and

alkaline phosphatase in patients at risk of developing antiepileptic drug-induced osteomalacia. *Q. J. Med.* **78**, 113–122 (1991).

80. Grant, E. C. G. Epilepsy and manganese. *Lancet (London, England)* vol. 363 572 (2004).

81. Torres, O. A., Miller, V. S., Buist, N. M. & Hyland, K. Folinic acid-responsive neonatal seizures. *J. Child Neurol.* **14**, 529–532 (1999).

82. Sweis, D. THE USES OF MELATONIN. *Arch. Dis. Child. - Educ. & Pract. Ed.* **90**, ep74 LP-ep77 (2005).

83. Kneen, R. & Appleton, R. Alternative approaches to conventional antiepileptic drugs in the management of paediatric epilepsy. *Arch. Dis. Child.* **91**, 936–941 (2006).

84. Schmitt, B., Thun-Hohenstein, L., Vontobel, H. & Boltshauser, E. Seizures induced by physical exercise: report of two cases. *Neuropediatrics* **25**, 51–53 (1994).

85. Malow, B. A. Sleep Deprivation and Epilepsy. *Epilepsy Curr.* **4**, 193–195 (2004).

86. Ramaratnam, S., Baker, G. A. & Goldstein, L. H. Psychological treatments for epilepsy. *Cochrane database Syst. Rev.* CD002029 (2005) doi:10.1002/14651858.CD002029.pub2.

87. Kanner, A. M. Recognition of the various expressions of anxiety, psychosis, and aggression in epilepsy. *Epilepsia* **45**, 22–27 (2004).

88. Carbone, L., Plegue, M., Barnes, A. & Shellhaas, R. Improving the mental health of adolescents with epilepsy through a group cognitive behavioral therapy program. *Epilepsy Behav.* **39**, 130–134 (2014).

89. Shawahna, R., Hattab, S., Al-Shafei, R. & Tab'ouni, M. Prevalence and factors associated with depressive and anxiety symptoms among Palestinian medical students. *BMC Psychiatry* **20**, 244 (2020).

90. Panebianco, M., Sridharan, K. & Ramaratnam, S. Yoga for epilepsy. *Cochrane database Syst. Rev.* **10**, CD001524 (2017).

91. Saxena, V. S. & Nadkarni, V. V. Nonpharmacological treatment of epilepsy. *Ann. Indian Acad. Neurol.* **14**, 148–152 (2011).

92. Wolf, P. & Koepp, M. Reflex epilepsies. *Handb. Clin. Neurol. / Ed. by P.J. Vinken G.W. Bruyn* **107**, 257–276 (2012).

93. Yucha, C. B. & Montgomery, D. *Evidence-based practice in biofeedback and neurofeedback*. *Nursing* vol. 6656 (2008).

94. Rockstroh, B. *et al.* Cortical self-regulation in patients with epilepsies. *Epilepsy Res.* **14**, 63–72 (1993).

95. Nagai, Y. Biofeedback and epilepsy. *Curr. Neurol. Neurosci. Rep.* **11**, 443–450 (2011).

96. Sterman, M. B. Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clin. Electroencephalogr.* **31**, 45–55 (2000).

97. Nigro, S. E. The Efficacy of Neurofeedback for Pediatric Epilepsy. *Appl. Psychophysiol. Biofeedback* **44**, 285–290 (2019).

98. Micoulaud-Franchi, J. A., Lanteaume, L., Pallanca, O., Vion-Dury, J. & Bartolomei, F. [Biofeedback and drug-resistant epilepsy: back to an earlier treatment?]. *Rev. Neurol. (Paris).* **170**, 187–196 (2014).

99. Haut, S. R., Gursky, J. M. & Privitera, M. Behavioral interventions in epilepsy. *Curr. Opin. Neurol.* **32**, 227–236 (2019).

100. Brackney, D. E. & Brooks, J. L. Complementary and Alternative Medicine: The Mozart Effect on Childhood Epilepsy-A Systematic Review. *J. Sch. Nurs. Off. Publ. Natl. Assoc. Sch. Nurses* **34**, 28–37 (2018).

101. Coppola, G. *et al.* Mozart's music in children with drug-refractory epileptic encephalopathies: Comparison of two protocols. *Epilepsy Behav.* **78**, 100–103 (2018).

102. Grylls, E., Kinsky, M., Baggott, A., Wabnitz, C. & McLellan, A. Study of the Mozart effect

in children with epileptic electroencephalograms. *Seizure* **59**, 77–81 (2018).

103. Dawit, S. & Crepeau, A. Z. When Drugs Do Not Work: Alternatives to Antiseizure Medications. *Curr. Neurol. Neurosci. Rep.* **20**, 37 (2020).

104. Sesso, G. & Sicca, F. Safe and sound: Meta-analyzing the Mozart effect on epilepsy. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.* **131**, 1610–1620 (2020).

105. Liao, H., Jiang, G. & Wang, X. Music therapy as a non-pharmacological treatment for epilepsy. *Expert Rev. Neurother.* **15**, 993–1003 (2015).

106. Betts, T. Use of aromatherapy (with or without hypnosis) in the treatment of intractable epilepsy--a two-year follow-up study. *Seizure* **12**, 534–538 (2003).

107. Aromatherapy an A-Z. Patricia Davis. 1999. https://www.aromaweb.com/books/davis.asp.

108. Essential Oil Safety - 2nd Edition. https://www.elsevier.com/books/essential-oil-safety/tisserand/978-0-443-06241-4.

109. Carroll, B., Richardson, J. T. & Thompson, P. Olfactory information processing and temporal lobe epilepsy. *Brain Cogn.* **22**, 230–243 (1993).

110. Frye, R. E. *et al.* A review of traditional and novel treatments for seizures in autism spectrum disorder: Findings from a systematic review and expert panel. *Front. Public Heal.* **1**, 1–26 (2013).

111. Tyagi, A. & Delanty, N. Herbal Remedies, Dietary Supplements, and Seizures. *Epilepsia* **44**, 228–235 (2003).

112. Xiao, F., Yan, B., Chen, L. & Zhou, D. Review of the use of botanicals for epilepsy in complementary medical systems - Traditional Chinese Medicine. *Epilepsy and Behavior* vol. 52 281–289 (2015).

113. Manchishi, S. M. Recent Advances in Antiepileptic Herbal Medicine. *Curr. Neuropharmacol.* **16**, 79–83 (2018).

114. Pittler, M. H. & Ernst, E. Efficacy of kava extract for treating anxiety: Systematic review and meta-analysis. *J. Clin. Psychopharmacol.* **20**, 84–89 (2000).

115. Amabeoku, G. J., Leng, M. J. & Syce, J. A. Antimicrobial and anticonvulsant activities of Viscum capense. *J. Ethnopharmacol.* **61**, 237–241 (1998).

116. Pearl, P. L., Drillings, I. M. & Conry, J. A. Herbs in Epilepsy: Evidence for Efficacy, Toxicity, and Interactions. *Seminars in Pediatric Neurology* vol. 18 203–208 (2011).

117. Volz, H. P. & Kieser, M. Kava-kava extract WS 1490 versus placebo in anxiety disorders - A randomized placebo-controlled 25-week outpatient trial. *Pharmacopsychiatry* **30**, 1–5 (1997).

118. Spinella, M. Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects. *Epilepsy Behav.* **2**, 524–532 (2001).

119. Minami, M., Kinoshita, N., Kamoshida, Y., Tanimoto, H. & Tabata, T. brinker is a target of Dpp in Drosophila that negatively regulates Dpp- dependent genes. *Nature* **398**, 242–246 (1999).

120. Wang, Q. Advances in treatment of epilepsy with traditional Chinese medicine. *J. Tradit. Chinese Med. = Chung i tsa chih ying wen pan* **16**, 230–237 (1996).

121. *A TF Hung. Medical Bulletin. 2009*.

122. Neel, B. A. & Sargis, R. M. The paradox of progress: environmental disruption of metabolism and the diabetes epidemic. *Diabetes* **60**, 1838–1848 (2011).

123. Wu, J. N. A short history of acupuncture. *Journal of Alternative and Complementary Medicine* vol. 2 19–21 (1996).

124. Cheuk, D. K. L., Yeung, W. F., Chung, K. F. & Wong, V. Acupuncture for insomnia. *Cochrane Database of Systematic Reviews* (2007) doi:10.1002/14651858.CD005472.pub2.

125. Maciocia. The Foundations of Chinese Medicine - 1rd Edition.

https://www.elsevier.com/books/the-foundations-of-chinese-medicine/maciocia/978-0-7020-5216-3.

126. Jansen, G., Lundeberg, T., Kjartansson, J. & Samuelson, U. E. Acupuncture and sensory neuropeptides increase cutaneous blood flow in rats. *Neurosci. Lett.* **97**, 305–309 (1989).

127. Magnusson, M., Johansson, K. & Johansson, B. B. Sensory stimulation promotes normalization of postural control after stroke. *Stroke* **25**, 1176–1180 (1994).

128. Liu, Q. Effects of acupuncture on hemorheology, blood lipid content and nail fold microcirculation in multiple infarct dementia patients. *J. Tradit. Chinese Med. = Chung i tsa chih ying wen pan* **24**, 219–223 (2004).

129. Middlekauff, H. R., Shah, J. B., Yu, J. L. & Hui, K. Acupuncture effects on autonomic responses to cold pressor and handgrip exercise in healthy humans. *Clin. Auton. Res.* **14**, 113–118 (2004).

130. Sun, K. O., Chan, K. C., Lo, S. L. & Fong, D. Y. Acupuncture for frozen shoulder. *Hong Kong Med. J. = Xianggang yi xue za zhi* **7**, 381–391 (2001).

131. Liu, W., Bai, B., Song, C., Wang, S. & Shi, W. [The role of periaqueductal gray neurotensin in electroacupuncture analgesia]. *Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese J. Appl. Physiol.* **13**, 253–256 (1997).

132. Wu, D. Mechanism of acupuncture in suppressing epileptic seizures. *J. Tradit. Chinese Med. = Chung i tsa chih ying wen pan* **12**, 187–192 (1992).

133. Shi, Z. Y., Gong, B. T., Jia, Y. W. & Huo, Z. X. The efficacy of electro-acupuncture on 98 cases of epilepsy. *J. Tradit. Chinese Med. = Chung i tsa chih ying wen pan* **7**, 21–22 (1987).

134. Cheuk, D. K. L. & Wong, V. Acupuncture for epilepsy. *Cochrane Database of Systematic Reviews* vol. 2014 (2014).

135. Chen, K. Y., Chen, G. P. & Feng, X. Observation of immediate effect of acupuncture on

electroencephalograms in epileptic patients. *J. Tradit. Chinese Med. = Chung i tsa chih ying wen pan* **3**, 121–124 (1983).

136. Kloster, R. *et al.* The effect of acupuncture in chronic intractable epilepsy. *Seizure* **8**, 170–174 (1999).