

## Research Article



## An Outlook to Non-Pharmacological and Novel Approaches to Combat the Uncurable Firing Disorder

Karthika Ramesh<sup>1</sup>, Krishnapriya M, Anupriya, Sreeja C. Nair\*

Amrita School of Pharmacy, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham, Amrita University, Kochi, Kerala, India.

\*Corresponding author's E-mail: [sreejacnair@aims.amrita.edu](mailto:sreejacnair@aims.amrita.edu)

Accepted on: 23-06-2016; Finalized on: 31-08-2016.

### ABSTRACT

Epilepsy, a serious neurological abnormality which exhibit neuronal misfiring and send out of incorrect signals as its major characters which ultimately lead to seizures. The etiological factors of seizures vary widely ranging from Hypoxia to brain tissues, infection or injury to brain tissues and also certain inborn defects, stress, consumption of illicit drugs, withdrawal of alcohol and the current therapy cannot completely cure epilepsy. Drug resistant epilepsy (also known as pharmaco resistant epilepsy) is a chronic, life threatening condition that affect the quality of life and ultimately lead to death of the patient. The concentration related peripheral side effects of antiepileptic medications remains a major challenge to the researchers. Prevention of epilepsy can be done in 60% of the cases by the use of AEDs but the Non-conventional therapy helps in symptomatic relief and seizure frequency reduction especially in case of refractory or drug resistant epilepsy. These treatments also play a role in preventing the toxicity problems of AEDs. This review mainly deals with the innovative strategies for the site specific therapeutic maintenance of drug in the epileptic foci and several methods to diagnose epilepsy.

**Keywords:** Seizures, epilepsy, adverse effects, Seizure foci, Therapeutic concentration.

### INTRODUCTION

Epilepsy is a disorder exhibited by neuron with repetitive seizures affecting central nervous system, unprovoked by a neurologic insult.

The prevalence of epilepsy is nearly one lakh per year and it is 0.5-1% (5x higher in developing countries) Fig 1.

Seizure disorder is also known as Epilepsy. The seizure is said to be a hyper excitability of a group of cortical abnormal neurons. Seizure is a electrical activity of brain which is a sudden surge which immensely affect the individuals behavioural and cognitive aspects.

Based on the area and number of lobes affected the seizure type also varies.<sup>1</sup> Epileptogenesis is a cascade of events that slowly transform normal neuronal network to over excitable one.

The factors that affect the pathophysiology of epilepsy can be broadly categorized to intrinsic and extrinsic.

The onset of symptoms can occur at any age group in any point if their life period. Epidemiological studies suggest that it ranks fourth position among the neurological diseases.

Females and children of age less than 4 months are more vulnerable to seizure attack than men. Symptoms of epilepsy get worsened beyond the mid 50s and get milder until about the age 10.

The risk factors and seizure trigger of epilepsy vary widely.

This should be carefully monitored as it requires immediate medical requisites.

Pathophysiology of epilepsy is very complex and it involves various underlying intrinsic and extrinsic mechanisms which was an eye opener to the discovery of AEDs. But now, there is evolution of dreadful pharmaco resistant epilepsy which is a serious concern.

There urging need to counteract this by using non pharmacological treatment and non conventional therapy is increasing day to day.<sup>2,3</sup>

### Symptoms

- \* Confused stage
- \* Rapid blinking of eyelids
- \* Repetitive and rapid jerking movements
- \* Unconsciousness or unawareness
- \* Psychological problems

### Immediate Medical Help Requisites

Difficulty in rousing at varying intervals

- \* Headache
- \* Pupillary constriction and dialation
- \* Blurred vision
- \* Nausea
- \* Pregnancy condition
- \* Patients with varying glucose level
- \* Head injury<sup>4,5</sup>



**Risk Factors and Seizure Triggers (Fig 2 & Table 1)****Table 1:** Risk Factor and Seizure Triggers

Risk factors	Seizure Triggers
<ul style="list-style-type: none"> <li>• Small Babies with less body weight</li> <li>• Babies with seizures in the early stage</li> <li>• Babies with brain abnormalities</li> <li>• Cerebral haemorrhage</li> <li>• Impaired vascularisation in brain</li> <li>• CNS trauma/hypoxia</li> <li>• Lesions in brain</li> <li>• Brain Infections</li> <li>• Stroke</li> <li>• Genetical reasons</li> <li>• Functional disabilities</li> <li>• Convulsion after severe head injury</li> <li>• Past historical background Neuro degeneration in late stage of epilepsy</li> <li>• Neuronal imbalance</li> <li>• infantile spasm</li> <li>• Long episodes of seizures lasts for more than 30 mts</li> <li>• Narcotic drugs</li> <li>• Mild head injuries/unknown cause</li> </ul>	<ul style="list-style-type: none"> <li>• Skipping medicines</li> <li>• Insomnia</li> <li>• Sickness</li> <li>• Stress/strain</li> <li>• Chronic alcoholism or as a consequence of withdrawal syndromes</li> <li>• Mood elevating drugs</li> <li>• Any drug that antagonize the action of AED</li> <li>• Mal nutrition</li> <li>• Improper food habits</li> <li>• Hormonal imbalance</li> <li>• Photophobia</li> <li>• Specificity</li> </ul>

**Table 2:** Factors Leading to Epilepsy

Intrinsic Factors	Extrinsic Factors
<ul style="list-style-type: none"> <li>• The type, number and distribution of voltage gated channels</li> <li>• By Receptor chemical modification</li> <li>• Second-messenger systems activation - Binding of norepinephrine to its alpha receptor.</li> <li>• Modulating gene expression, as by RNA editing</li> </ul>	<ul style="list-style-type: none"> <li>• Variation in concentration of extracellular ion.</li> <li>• Remodeling of synaptic traffic signals.</li> <li>• Transmitter metabolism modulators.</li> </ul>

**Table 3:** Dietary Factors

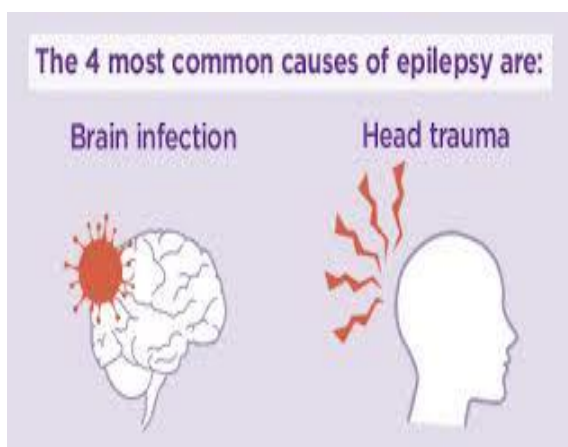
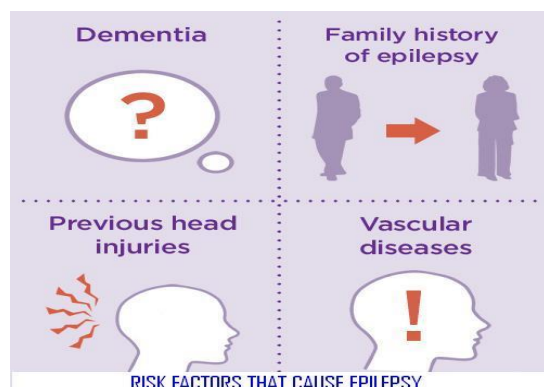
Dietary or Metabolic Factors
Reduction in blood glucose or blood insulin
Hypersensitivity reaction to various food items
Reaction to monosodium glutamate
Ketogenic diet
Atkins diet

**Table 4:** Non Pharmacological Treatments

Lifestyle changes	Psychological approach	Promotion of emotional well being	Physical therapies
<ul style="list-style-type: none"> <li>• Exercise</li> <li>• Sleep hygiene</li> <li>• Alcohol</li> </ul>	<ul style="list-style-type: none"> <li>• Avoidance</li> <li>• Relaxation techniques</li> <li>• Biofeedback</li> <li>• Aversive therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Yoga</li> <li>• Reduction in psychiatric co-morbidity</li> <li>• Meditation</li> </ul>	<ul style="list-style-type: none"> <li>• Acupuncture</li> </ul>

**Table 5:** Various Routes for Delivery of Anti-Epileptic Medications

Routes	Possible methods for direct delivery of AEDs to brain
Rectal	• CSF delivery
Skin	• Drug wafers
Nasal / Buccal	• Local perfusion
Inhaled	• Seizure-activated drugs
Direct delivery to CNS	• Liposome-microsomes
	• Cell transplants
	• Gene therapy

**Figure 1:** Causes of Epilepsy**Figure 2:** Risk Factors

### Pathophysiology of Epilepsy

Epileptic seizures generally arise because of hyper synchronous membrane excitability. Pathophysiological mechanisms of some forms of epilepsy are partially understood.

Some proposals:

- ✱ Excitatory glutamatergic synapses
- ✱ Excitatory amino acid neurotransmitter (glutamate, aspartate)
- ✱ Abnormal tissues — tumor, AVM, dead area
- ✱ Genetic factors (20%)

### Mechanisms of Seizure Origin at Cellular Level<sup>6-8</sup>

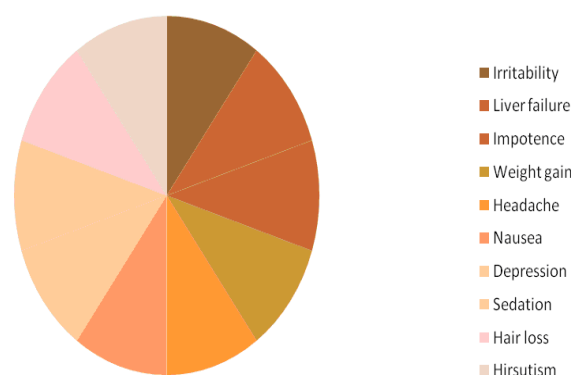
#### Experimental Models of Seizures and Epilepsy

##### Using Animal Models

- MES (maximal electroshock ) induced model
- Pentylentetrazole (PTZ) model
- Amygdala kindling model
- Post-status epilepticus model
- Threshold model
- Implant model
- Hydralazine induced model

#### Pharmaco Resistant Epilepsy

Characteristic epilepsy to which drugs are resistant. This is a chronic condition and treatment options are rare. Accounts a major portion of mortality due to epilepsy. Side effect of ARDs can be considered at this context, because increment in dosage to attain cure may have a large impact on patient's quality of life (Fig 3).

**Figure 3:** Side Effects of Antiepileptic Drugs

### Treatment Options

#### Non-medicated Therapy

##### Herbal Medicine and Homeopathy

- ◆ Less side effects
- ◆ Treat the underlying and thereby the symptoms

## Homeopathy

Here the active ingredient present in trace quantities are given after a series of dilutions.<sup>9-13</sup>

## Dietary Therapies

### Ketogenic Diet

Due to the calorie restrictions followed in this diet, nutritional deficiencies may occur. Fluid restrictions are also there. All these insists the mandatory supplementation with iron, calcium etc.<sup>14-16</sup>

### Atkins Diet

The amount of carbohydrates in the diet were limited to 10g/day. There the body utilize fat as the main source of energy. Since fat is considered as the fuel this is highly useful to obese individuals to control the body weight effectively. The success of the diet also lies in higher protein content, and its access to fluid or calorie usage. Further more the fasting is not mandatory at the beginning of the diet. Due to all these differences, it is applicable even to children.<sup>17,18</sup>

### Oligoantigenic Diet

It consist of variety of food but in small quantities. The diet is quite expensive and maintenance is difficult. Failure occur due food allergies. Cause significant reduction in seizures.<sup>19-21</sup>

## Vitamins in Epilepsy

### Main role:

- Helps to prevent side effects of AEDs
- Improvement in EEG
- Seizure frequency reduction
- symptomatic relief
- neurotransmitter resetting<sup>22-29</sup>

### Vitamin E

Tocopherol can correct the neurological imbalance of cortical neurotransmitters through its positive mediation by limiting the spread of uncontrolled neurological discharge.<sup>30</sup>

### Thiamine

This can be used to manage epilepsy that develops during the late stage of the life time. Long term diet devoid of Thiamine may lead to seizures in chronic drinkers and also in alcoholic non users with epilepsy; these seizures can be managed with supplementation of vitamin B1.<sup>31</sup>

### Pyridoxine (vitamin B6)

Vitamin B6 is very important to maintain the glutamate level in the brain. In the case B6 deficiency, chance of various developmental and mental disorders are high.

It is one of the important add on therapy to control seizure. Pyridoxine mediated epilepsy is an autosomal

recessive disease associated with refractory seizures in the early life stages.

The symptomatic relief is possible with excessive dosage of pyridoxine but if no proper treatments given immediately non recoverable injury to neuron may happen.<sup>32,33</sup> By intravenous administration of B6 diagnostic aspects are fulfilled, leads to termination of seizure with very short duration of time.<sup>34</sup>

### Pyridoxal Phosphate

Mainly used to treat refractory epilepsy in children with unknown cause. Seizure can be of either generalized or partial form, symptomatic relief is possible with in 24 hours. It also plays a significant role in controlling the most dangerous absence seizures. EEG findings are a major substantiating evidence.<sup>35-37</sup>

### Vitamin D

With drugs such as phenytoin and phenobarbitone rate of production of liver enzymes that metabolize vitamin D which lead to Rickets and Osteomalacia. This can be controlled by vitamin D supplementation.<sup>38-40</sup>

### Folinic Acid

Infants are mostly prone to seizures triggered by folate deficiencies, which leads to life threatening syndromes and certain psychological issues. The main focus of treatment is to develop a corrective therapy for the defective mechanism of transport of folinic acid. This disorder is due to impaired folate transport across the BBB into the brain. The folic acid is administered in its active form to counteract the problems related to transport mechanism.<sup>41-43</sup>

### Biotin

It usually has drug interaction with anti epileptic drugs like phenytoin, carbamazepine and Phenobarbital and some drugs reduce its GI absorption. Consequences of Biotin deficiency leads to excessive oxidation of unsaturated fatty acids, catabolism of proteins and glucose production from non carbohydrate sources. Medical interventions can be applied to correct this disorder. It mainly affects children below 6 years of age.

## Other Supplements

### Omega-3 Fatty Acids

Engaged in seizure reduction.<sup>44</sup> But the role of essential fatty acids with variable pharmacological results were shown in some studies.

### Magnesium

Magnesium has good anticonvulsant action when given intravenously in experimental animals like dog, cat, rats etc. Magnesium plays a major role in seizure frequency reduction.<sup>45</sup> Severity of grandmal seizure is enhanced by decreased level of magnesium in plasma and cerebro spinal fluid. Oral route of magnesium administration proves a positive response in some EEG results.



## Manganese

In patients with trauma as a cause for epilepsy, manganese level in blood is higher. The development of seizure and deficiency is not categorised under malnutrition. The deficiency of manganese is a major contributing factor.<sup>46</sup> Presence of manganese in the diet may prevent seizure induced as a result of hydralazine. Several studies shows that the deficiency of mineral manganese increases the chance to seizure induced by electric shock. There is no relation with frequency of convulsion and the concentration of manganese in the body after AED therapy.

## Taurine

Used in patients with chronic refractory epilepsy. It modulates membrane excitability by suppressing calcium and other neurotransmitter release. It diminishes the release of mineral calcium from the mitochondria. Dose is 200 mg - 21 g per day. Some results showed remarkable decrease of frequency attack in case of epilepsy.<sup>47</sup>

## Dimethylglycine

Seizure frequency reduction is its major role. Dimethylglycine deficiency cause marked increase in reizes.<sup>48</sup>

## Epilepsy Surgery

Epilepsy surgery is an acceptable methods for controlling seizure attack and proved beneficial to the victims with pharmacoresistant epilepsy.<sup>49-50</sup>

Three main principles of epilepsy surgery:

- Incision of epileptic foci
- Interruption of seizure propagation nerve pathways.
- Introduction of implantation device.<sup>51</sup>

## Other Surgical Options

- Responsive neuro stimulation device (RNS)
- Lobe resection – high efficacy
- Multiple subpial transaction (MST)
- Corpus callosotomy
- Hemispherectomy
- Lesionectomy

## Vagus Nerve Stimulation

Drug resistant partial seizures are commonly treated using VNS. It is generally used as an adjuvant therapy in children more than 12 years and also in adults.<sup>52,53</sup>

It is a subcutaneously implanted device. Serious adverse events are rare. In situations where intracranial surgery is not applicable, VNS is considered.<sup>54</sup>

## Cortical Stimulation

The main principle is direct stimulation of cerebral cortex

by applying electrocardiography technique. Useful for patients refractory focal and bi temporal lobe epilepsy. Applicable when surgery is not possible. Shows marked reduction in seizure frequency and intensity.<sup>55-57</sup>

## Brain Neuronal Stimulation Strategies

### Deep Neuronal Stimulation to Brain

Symptomatic control of seizures preferably tremors is achieved by this surgery which focus only on damaged nerve cells. Measures of seizure severity and quality of life also improved over time.

### Trans cranial Magnetic Stimulation

This could reduce frequency of seizures by suppressing excitability of cortex.

### Trigeminal Nerve Stimulation

Low frequency (120 Hz) electrical signal is applied to innervations of trigeminal nerve externally. TNS possess external electrodes with an external pulse generator. Mood elevation and reduction in seizure frequency is observed in patients with pharmaco resistant epilepsy.<sup>58-62</sup>

## Non Pharmacological Treatment of Epilepsy

### Rare Treatment Options for Epilepsy

Aroma combination therapies are usually recommended and the duration of treatment is usually more than 12 months.<sup>62-64</sup>

### Alerting Seizure using Dogs

It is one among the recent advances which mainly focuses on the seizure frequency reduction in patients suffering from pharmacoresistant epilepsy.

Statistical data support this statement. But no RCTs are available to prove this.<sup>65-66</sup>

## AED Delivery Routes

### Diagnosis<sup>67</sup>

### Strategy

- ✱ Taking history directly through patient
- ✱ Medical support
- ✱ Hospital data system

### History

- ✓ Event
- ✓ Previous medical history
- ✓ Drug and immunization history
- ✓ History from family and society

## CONCLUSION

Our nervous system is very complex and seizures may occur due to any problem related to it. When a normal nervous system cannot fulfil its nutritional requirements,





it can result in epilepsy. The causes of epilepsy can be unknown or in conjunction with a specific disease.

The management of toxicity problems of AEDs and pharmacoresistant epilepsy can be done by non pharmacological approaches and nonconventional AEDs. The success of psychological approaches where western medicines fail is considered as strong evidence.

To treat chronic conditions, complementary medicines are attributable nowadays.

The prevention of epilepsy is done by hormonal therapies, modifications in diet and also by treating nutritional deficiencies of CNS.

Diagnostic evaluation is also important and diagnostic technologies are really worthful.

## REFERENCES

- Hauser WA, Seizure disorders: the changes with age, *Epilepsia*, 33, 1992, 6–14.
- Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2, 052, 922 and age-specific fertility rate of women with epilepsy, *The Lancet*, 352, 1998, 1790–3.
- Leppik IE, Birnbaum AK. Epilepsy in the elderly, *Ann New York Academic Science*, 1184, 2009, 208–24.
- Bradley PM, Lindsay B. Care delivery and self-management strategies for adults with epilepsy, *Cochrane Database of Systematic Reviews*, 1, 2008, CD006244.
- Sreeja C N, Anoop K R. Local Antimicrobial Delivery of Satranidazole Loaded Cross Linked Periodontal Chips using Bio Degradable Polymers. *Int J Pharm Pharm Sci*, 5(3), 2013, 839-847.
- Babb TL, Brown WJ. Pathological Findings in Epilepsy, 1987, 511–540.
- Ayala GF, Dichter M, Gumnit RJ, Matsumoto G, Spencer WA. Genesis of epileptic interictal spikes: New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paroxysms, *Brain Research*, 52, 1973, 1–17.
- Dichter MA. Emerging insights into mechanisms of epilepsy: Implications for new antiepileptic drug development, *Epilepsia*, 35, 1994, 51–57.
- Fisher RS. Animal models of the epilepsies, *Brain Research Reviews*, 14, 1989, 245–78.
- Berg AT, Kelly MM. Defining intractability: comparisons among published definitions, *Epilepsia*, 47, 2006, 431-6.
- Bautista RE, Glen ET. Seizure severity is associated with quality of life independent of seizure frequency *Epilepsy and Behaviour*, 16, 2009, 325-9.
- Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy *Neurology*, 55, 2000, 1780-4.
- Josefson D. Herbal stimulant causes US death, *BMJ*, 312, 1996, 1378-1379.
- Prasad A N, Stafstrom C F, Holmes G L. Alternative epilepsy therapies: the ketogenic diet, immunoglobulins, and steroids, *Epilepsia*, 37, 1996, 81–95.
- Kinsman SL, Vining EP, Quaskey SA. Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases, *Epilepsia*, 33, 1992, 1132-1136.
- Hemingway C, Freeman JM, Pillas DJ, Pyzik PL. The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively, *Pediatrics*, 108, 2001, 898-905.
- Atkins R C. Dr Atkins' new diet revolution, *Government Institutes*, 2002, 1.
- Kossoff EH, Krauss GL, Mc Grogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy, *Neurology*, 61, 2003, 1789-1791.
- Egger J, Carter C M, Soothill J F. Oligoantigenic diet treatment of children with epilepsy and migraine. *The Journal of Pediatrics*, 114, 1989, 51–58.
- Mavroudi A, Karatza E, Papastavrou T. Successful treatment of epilepsy and celiac disease with a gluten-free diet, *Pediatric Neurology*, 33, 2005, 292–295.
- Gupta R, Appleton R. Corticosteroids in the management of the paediatric epilepsies. *Archives of disease in childhood*, 90, 2005, 379–384.
- Lux A L, Edwards S W, Hancock E. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial, *Lancet*, 364, 2004, 1773–1778.
- Prasad A N, Stafstrom C F, Holmes G L. Alternative epilepsy therapies: the ketogenic diet, immunoglobulins, and steroids, *Epilepsia*, 37, 1996, 81–95.
- Leach J P, Chadwick D W, Miles J B. Improvement in adult-onset Rasmussen's encephalitis with long-term immunomodulatory therapy, *Neurology*, 52, 1999, 738–742.
- Razdan RK, Howes JF. Drugs related to tetrahydrocannabinol, *Medicinal Research Reviews*, 3, 1983, 119-46.
- Martin P, Consroe P. Cannabinoid induced behavioral convulsions in rabbits, *Science*, 194, 1976, 965.
- Phillips L, Appleton R E. Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment, *Developmental Medicinal Child Neurology*, 46, 2004, 771–775.
- Jones C, Huyton M, Hindley D. Melatonin and epilepsy, *Archives of disease of Childhood*, 90, 2005, 1203.
- Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures, *Neurology*, 45, 1995, 1660-1662.
- Ogunmekan AO, Hwang PA. A randomized, double blind, placebo-controlled, clinical trial of d-alpha-tocopherylacetate (vitamin E), as add-on therapy, for epilepsy in children, *Epilepsia*, 30, 1989, 84-89.
- Gascon G, Patterson B, Yearwood K, Slotnick H. N,N dimethylglycine and epilepsy, *Epilepsia*, 30, 1989, 90-93.
- Baxter P. Pyridoxine or pyridoxal phosphate for intractable seizures, *Archives Disease of Childhood*, 90, 2005, 441–442.
- Coursin DB. Convulsive seizures in infants with pyridoxine-deficient diet, *Journal of the American Medical Association*, 154, 1954, 406-408.
- Molony CJ, Parmelee AH. Convulsions in young infants as a result of pyridoxine (vitamin B6) deficiency, *Journal of the American Medical Association*, 154, 1954, 405-406.
- Crowell GF, Roach ES. Pyridoxine-dependent seizures. *American Family Physician*, 27, 1983, 183-187.
- Robins MM. Pyridoxine dependency convulsions in a newborn. *JAMA*, 195, 1966, 491-493.
- Mills PB, Surtees RA, Champion MP, Beesley CE, Dalton N, Scambler PJ, Heales SJ, Briddon A, Scheimberg I, Hoffmann GF, Zschocke J. Neonatal epileptic encephalopathy caused by



- mutations in the PNPO gene encoding pyridox (am) ine 5'-phosphate oxidase, *Human molecular genetics*, 14, 2005, 1077-86.
38. Krause KH, Berlitz P, Bonjour JP. Impaired biotin status in anticonvulsant therapy, *Annals of Neurology*, 12, 1982, 485-486.
  39. Krause KH, Berlitz P, Bonjour JP. Vitamin status in patients on chronic anticonvulsant therapy, *Journal international de vitaminologie et de nutrition*, 52, 1982, 375-385.
  40. Bouillon R, Reynaert J, Claes JH. The effect of anticonvulsant therapy on serum levels of 25-hydroxy-vitamin D, calcium, and parathyroid hormone, *The Journal of Clinical Endocrinology & Metabolism*, 41, 1975, 1130-1135.
  41. Torres OA, Miller VS, Buist N, Hyland K. Folinic acid-responsive neonatal seizure, *Journal of Child Neurology*, 14, 1999, 529-532.
  42. Ramaekers V, Rothenberg S, Sequeira JM. Auto antibodies to folate receptors in the cerebral folate deficiency syndrome, *New England Journal of Medicine*, 352, 2005, 1985-1991.
  43. Torres O A, Miller V S, Buist N M. Folinic acid-responsive neonatal seizures, *Journal of Child Neurology*, 14, 1999, 529–532.
  44. Vaddadi KS, Gilleard CJ, Mindham RH, Butler R. A controlled trial of prostaglandin E1 precursor in chronic neuroleptic resistant schizophrenic patients, *Psychopharmacology (Berl)*, 88, 1986, 362-367.
  45. Arnold JD, Oldfield RK, Pollard AC, Silink M. Primary hypomagnesaemia: case report, *Journal of Pediatrics and child Health*, 19, 1983, 45-46.
  46. Hurley LS, Woolley DE, Rosenthal F, Timiras PS. Influence of manganese on susceptibility of rats to convulsions, *American Journal of Physiology-Legacy Content*, 204, 1963, 493-496.
  47. Kuriyama K, Muramatsu M, Nakagawa K, Kakita K. A modulating role of taurine on release of acetylcholine and norepinephrine from neuronal tissues. *The Japanese Journal of Pharmacology*, 28, 1978, 259-68.
  48. Haidukewych D, Rodin EA. N,N-dimethylglycine shows no anticonvulsant potential, *Annals of Neurology*, 15, 1984, 405.
  49. Sperling MR, O'Connor MJ, Saykin AJ, Plummer C. Temporal lobectomy for refractory epilepsy, *JAMA*, 276, 1996, 470-475.
  50. Engel J Jr, Wiebe S, French J. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons, *Neurology*, 60, 2003, 538.
  51. Wiebe S, Blume WT, Girvin JP. A randomized, controlled trial of surgery for temporal-lobe epilepsy, *New England Journal of Medicine*, 345, 2001, 311-318.
  52. George R, Sonnen A, Upton A, Salinsky M, Ristanovic R, Bergen D, Mirza W, Rosenfeld W, Nari-Toku D, Manon-Espaillet R, Barolat G. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*, 45, 1995, 224-30.
  53. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *The Journal of Pediatrics*, 134, 1999, 563-566.
  54. Kuba R, Brázdil M, Novák Z. Effect of vagal nerve stimulation on patients with bitemporal epilepsy, *European Journal of Neurology*, 10, 2003, 91-94.
  55. Cohen-Gadol AA, Britton JW, Wetjen NM. Neurostimulation therapy for epilepsy: current modalities and future directions, *In Mayo Clinic Proceedings*, 78, 2003, 238-248.
  56. Osorio I, Frei MG, Sunderam S. Automated seizure abatement in humans using electrical stimulation, *Annals of Neurology*, 57, 2005, 258-268.
  57. Tellez-Zenteno JF, McLachlan RS, Parrent A. Hippocampal electrical stimulation in mesial temporal lobe epilepsy, *Neurology*, 66, 2006, 1490-1494.
  58. Fisher RS. Therapeutic devices for epilepsy, *Annals of Neurology*, 71, 2012, 157-168.
  59. Fisher R, Salanova V, Witt T. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy, *Epilepsia*, 51, 2010, 899-908.
  60. Chen R, Classen J, Gerloff C. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, 48, 1997, 1398-403.
  61. Sun W, Fu W, Mao W, Wang D, Wang Y. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy, *Clinical EEG and neuroscience*, 242, 2011, 40-4.
  62. DeGiorgio CM, Soss J, Cook IA. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy, *Neurology*, 80, 2013, 786-791.
  63. Betts T. Use of aromatherapy (with or without hypnosis) in the treatment of intractable epilepsy - a two-year follow-up study, *Seizure*, 12, 2003, 534–538.
  64. Barry J J, Atzman O, Morrell M J. Discriminating between epileptic and nonepileptic events: the utility of hypnotic seizure induction, *Epilepsia*, 41, 200, 81–84.
  65. Kloster R, Larsson P G, Lossius R. The effect of acupuncture in chronic intractable epilepsy, *Seizure*, 8, 1999, 170–174.
  66. Stavem K, Kloster R, Rossberg E. Acupuncture in intractable epilepsy: lack of effect on health-related quality of life, *Seizure*, 94, 2006, 22–426.
  67. Strong V, Brown S, Huyton M. Effect of trained seizure alert dogs on frequency of tonic-clonic seizures., *Seizure*, 11, 2002, 402–405.

Source of Support: Nil, Conflict of Interest: None.