ISSN 2349-7823

International Journal of Recent Research in Life Sciences (IJRRLS)
Vol. 2, Issue 3, pp: (32-44), Month: July 2015 - September 2015, Available at: www.paperpublications.org

A Review on the Treatments of Epilepsy

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Abstract: **Epilepsy is a serious and common chronic neurological disorder characterized by recurrent seizures, which are caused by abnormal synchronized neuronal disorders. It is a relatively common condition (up to 2% of the population) which can affect anyone at any age. Epilepsy can be controlled in a number of ways. The most common way to treat epilepsy is with anti-epileptic drugs. These AEDs can control but not cure epilepsy. Surgery can also be a possible treatment. Curative epilepsy surgery can only be performed in patients in whom the epileptogenic focus can be localized and does not overlap with eloquent brain areas. In the other patients with bilateral or multiple epileptogenic foci, with epilepsy onset in eloquent areas, or with no identifiable epileptogenic focus, treatments such as ketogenic diet, vagus nerve stimulation can be offered. VNS is an available procedure of which the mechanism of action is not understood, but with established efficacy for refractory epilepsy and low incidence of side-effects. The ketogenic diet is a high-fat, moderate protein, low carbohydrate diet used to treat intractable epilepsy, primary in the pediatric population. Hippocampal Deep Brain Stimulation has been used to treat patients with refractory epilepsy. Complementary and Alternative Medicine for epilepsy such as apuncture, aromatherapy, yoga etc may be used for lessening seizures, for alleviating related symptoms and for reducing side effects. Gene therapy aims to utilize viral and non-viral vectors in the delivery of DNA to target areas for the treatment of patients before their disease progresses. Gene therapy has delivered promising results in animal trials and pre-clinical settings and can be used for neurological disorders such as epilepsy.**

Keywords: **Anti-epileptic drugs, Apuncture, Aromatherapy, Epilepsy, Gene therapy, Hippocampal deepbrain stimulation, Ketogenic diet, Vagus nerve stimulation, Yoga.**

I. INTRODUCTION

Seizures may be partial when the abnormal electrical activity occurs in one specific area of the brain, or generalized, where the whole brain becomes involved. Partial seizures may be simple or complex. Some seizures may start as partial then become generalized. There are several types of generalized seizures- absence, atonic, tonic, myoclonic, tonic-clonic. Accurate diagnosis of the type of seizure is important in determining which medication is most likely to be effective, and for prognosis and lifestyle advice. The purpose of this article is to provide a review of the therapies that can be used to treat epilepsy. Many drugs are available to treat epilepsy, several of which have been recently released. Although generic drugs are safely used for most medications, anticonvulsants are one category which should be recommended with caution. Some older drugs which have been used to treat epilepsy for years are sodium valproate, phenytoin, clonazepum etc. and some newer drugs used to treat epilepsy include lamotrigine, topiramate and others. The ketogenic diet was first introduced into epilepsy therapy in the 1930s, but still rather surprisingly remains the subject of active research. The medical use of the ketogenic diet emerged as a strategy to mimic the biochemical effects of fasting or starvation. This diet can induce ketosis in a much more acceptable form and without restrictions on calories, fluids, proteins or need for a fast. The patients need to follow the diet strictly for it to be successful. It is a high fat and low carbohydrate diet, which is sometimes difficult for children to stick to. Some people's epilepsy is caused by a specific structural problem in part or parts of the brain. This may have resulted from some form of head injury, occurring either at birth or in later life or from celebral infection. It is also possible that the brain did not develop properly or there is some form of scarring, lesion or a birth mark on the brain which the person was born with. Epilepsy surgery which means removing the abnormal or

ISSN 2349-7823

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damaged part of the brain may help some of these. This is major brain surgery and is not undertaken lightly. Over 70% of people who have epilepsy surgery become completely seizure free. Despite the advent of new pharmacological treatments and high success rates of many surgical treatments for epilepsy, a substantial number of patients either do not become seizure-free or they experience major adverse effects or both. Neurostimulation-based treatments have gained considerable interest in the last decade. VNS is an alternative treatment for patients with medically refractory epilepsy, who are unsuitable candidates for conventional epilepsy surgery, or who have had such surgery without optical outcome. Hippocampal DBS has yielded a significant decrease of seizure counts and interictal EEG abnormalities during long-term follow-up. Alternative or complementary medical therapies have always been popular in epilepsy. These include mind-body medicines such as yoga; biomedical medicines such as herbal remedies, dietary supplements, homeopathy and others.

II. VARIOUS FORMS OF TREATMENTS

2.1. Antiepileptic Medication:

The overall goal of antiepileptic medication is to prevent seizures and avoid untoward side effects with a regimen that is convenient and easy to follow. People with epilepsy usually initiate treatment with one epileptic drug at the time of diagnosis, but 30% of patients will be refractory to this medication.

TABLE 1: Important characteristics of antiepileptic medications

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Carbamazepine	Na+ channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, vertigo Non-Neurological: aplastic anaemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash*	Enzyme Substrate: CYP 3A4, 2C8 Enzyme Inducer: CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4 Enzyme Inhibitor: None	Yes
Clonazepam	Potentiate GABA receptor function	Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, lethargy Non-Neurological: anorexia	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Ethosuximide	T-type Ca2+ channel inhibition in thalamus	Absence	Neurological: ataxia, lethargy, headache Non-Neurological: gastrointestinal irritation, skin rash, bone marrow suppression	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes, Only Available in Generic
Felbamate	NMDA receptor antagonist and increase GABA availability	Partial Lennox-Gastaut	Neurological: insomnia, dizziness, sedation, headache Non-Neurological: aplastic anaemia, hepatic failure, weight loss, gastrointestinal irritation	Enzyme Substrate: CYP 2E1, 3A4 Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	No, but Patent Expired 9/26/09
Gabapentin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: sedation, dizziness, ataxia, fatigue Non-Neurological: gastrointestinal irritation, weight gain, oedema	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	Yes
Lacosamide	Na+ channel inhibition	Partial	Neurological: headache, dizziness, diplopia, ataxia, fatigue, tremor, somnolence,	Enzyme Substrate: CYP 2C19 Enzyme inducer:	No

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Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
			blurred vision Non-Neurological: Nausea, vomiting, diarrhoea	None Enzyme Inhibitor: CYP 2C19	
Lamotrigine	Decrease glutamate release	Partial Tonic-Clonic Atypical Absence Myoclonic Lennox-Gastaut	Neurological: dizziness, diplopia, sedation, ataxia, headache Non-Neurological: skin rash*	Enzyme Substrate: UGT1A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes
Levetiracetam	Synaptic vesicle release modulation	Partial	Neurological: sedation, fatigue, incoordination, psychosis Non-Neurological: anaemia, leucopenia	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	Yes
Oxcarbazepine	Na+ channel inhibition	Partial	Neurological: fatigue, ataxia, dizziness, diplopia Non-Neurological: aplastic anaemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash	Enzyme Substrate: CYP Enzyme Inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Phenobarbital	Potentiate GABA receptor function	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash, hepatotoxicity	Enzyme Substrate: CYP 2C9, 2C19, 2E1 Enzyme Inducer: CYP 1A2, 2A6, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes, Only Available in Generic
Phenytoin	Na+ and Ca2+ channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, confusion Non-Neurological: gingival hyperplasia, peripheral neuropathy, lymphadeonopathy, hirsutism, osteomalacia, hepatotoxicity, facial coarsening, skin rash*	Enzyme Substrate: CYP 2C9, 2C19, 3A4 Enzyme Inducer: CYP 2B6, 2C8, 2C9, 2C19, 3A4 and UDPGT Enzyme Inhibitor: None	Yes
Pregabalin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: ataxia, somnolence, dizziness, blurred vision, diplopia Non-Neurological: peripheral oedema, increased appetite	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	No
Primidone	Inhibition of neuronal firing	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash	Enzyme Substrate: None Enzyme inducer: CYP 1A2, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes
Rufinamide	Na+ channel inhibition	Lennox-Gastaut	Neurological: headache, dizziness, fatigue, somnolence, convulsion, diplopia, tremor, nystagmus Non-Neurological: nausea,	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor:	No

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Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
			vomiting, nasopharyngitis, blurred vision	None	
Tiagabine	Increase GABA availability	Partial Tonic-Clonic	Neurological: confusion, sedation, depression, speech problems, paresthesias, psychosis Non-Neurological: gastrointestinal irritation	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Topiramate	Na+ channel inhibition	Partial Tonic-Clonic Lennox-Gastaut	Neurological: psychomotor slowing, sedation, speech problems, fatigue, paresthesias Non-Neurological: kidney stones, glaucoma, weight loss, hypohydrosis	Enzyme Substrate: None Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Valproic Acid	T-type Ca++ channel inhibition in thalamus increase GABA availability	Partial Tonic-Clonic Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, tremor Non-Neurological: Hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, hyperammonemia	Enzyme Substrate: UGT 1A6, 1A9, 2B7, beta-oxidation Enzyme Inducer: CYP 2A6 Enzyme Inhibitor: CYP 2C9, 2C19, 2D6, 3A4	Yes
Vigabatrin	Analogue of GABA, inhibits GABA catabolism	Complex Partial	Neurological: headache, fatigue, drowsiness, dizziness, tremor, agitation, visual field defects, abnormal vision, diplopia Non-Neurological: nausea, vomiting, diarrhoea, weight gain, skin rash	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	No
Zonisamide	Na+ channel inhibition	Partial	Neurological: sedation, dizziness, confusion, headache, psychosis Non-Neurological: Anorexia, renal stones, hypohydrosis	Enzyme Substrate: CYP 2C19, 3A4 Enzyme Inducer: None Enzyme Inhibitor: None	Yes

2.2. Surgery:

Evaluation of persons for surgery is generally recommended only after focal seizures persist despite the person having tried at least two appropriately chosen and well-tolerated medications, or if there is an identifiable brain *lesion* (a dysfunctional part of the brain) believed to cause the seizures. When someone is considered to be a good candidate for surgery experts generally agree that it should be performed as early as possible.

Surgical evaluation takes into account the seizure type, the brain region involved, and the importance of the area of the brain where seizures originate (called the focus) for everyday behaviour. Prior to surgery, individuals with epilepsy are monitored intensively in order to pinpoint the exact location in the brain where seizures begin. Implanted electrodes may be used to record activity from the surface of the brain, which yields more detailed information than an external scalp EEG. Surgeons usually avoid operating in areas of the brain that are necessary for speech, movement, sensation, memory and thinking, or other important abilities. fMRI can be used to locate such "eloquent" brain areas involved in an individual.

While surgery can significantly reduce or even halt seizures for many people, any kind of surgery involves some level of risk. Surgery for epilepsy does not always successfully reduce seizures and it can result in cognitive or personality changes as well as physical disability, even in people who are excellent candidates for it. Nonetheless, when medications fail, several studies have shown that surgery is much more likely to make someone seizure-free compared to attempts to

use other medications. Anyone thinking about surgery for epilepsy should be assessed at an epilepsy centre experienced in surgical techniques and should discuss with the epilepsy specialists the balance between the risks of surgery and desire to become seizure-free.

Even when surgery completely ends a person's seizures, it is important to continue taking antiseizure medication for some time. Doctors generally recommend continuing medication for at least two years after a successful operation to avoid recurrence of seizures.

Surgical procedures for treating epilepsy disorders include:

- Surgery to remove a seizure focus involves removing the defined area of the brain where seizures originate. It is the most common type of surgery for epilepsy, which doctors may refer to as a *lobectomy* or *lesionectomy*, and is appropriate only for focal seizures that originate in just one area of the brain. In general, people have a better chance of becoming seizure-free after surgery if they have a small, well-defined seizure focus. The most common type of lobectomy is a *temporal lobe resection*, which is performed for people with medial temporal lobe epilepsy. In such individuals one hippocampus (there are two, one on each side of the brain) is seen to be shrunken and scarred on an MRI scan.
- *Multiple subpial transection* may be performed when seizures originate in part of the brain that cannot be removed. It involves making a series of cuts that are designed to prevent seizures from spreading into other parts of the brain while leaving the person's normal abilities intact.
- *Corpus callosotomy*, or severing the network of neural connections between the right and left halves (*hemispheres*) of the brain, is done primarily in children with severe seizures that start in one half of the brain and spread to the other side. Corpus callosotomy can end drop attacks and other generalized seizures. However, the procedure does not stop seizures in the side of the brain where they originate, and these focal seizures may even worsen after surgery.
- *Hemispherectomy* and *hemispherotomy* involve removing half of the brain's cortex, or outer layer. These procedures are used predominantly in children who have seizures that do not respond to medication because of damage that involves only half the brain, as occurs with conditions such as Rasmussen's encephalitis. While this type of surgery is very excessive and is performed only when other therapies have failed, with intense rehabilitation, children can recover many abilities.

2.3. Vagus Nerve Stimulation:

The vagus nerve is the largest cranial nerve and comprises large myelinated A fibers and unmyelinated B fifers and unmyelinated C fibers. About (80-90) % of its fibers are afferent, encoding predominantly visceral sensory non-pain information, and emerge from or converge to four nuclei: the dorsal nucleus of the vagus nerve, the nucleus ambiguous, the solitary tract nucleus and the spinal trigeminal nucleus. Asymmetric heart interventions play an important role: the right vagus nerve is intimately associated with atriums and left nerve with ventricles, and owing to the fact of the atriums, left VNS is associated with arrhythmias.

a) Mechanism of action: Despite many studies, the exact mechanism by which VNS reduces seizure frequency is unknown, and many theories have been proposed. It is believed that VNS may modulate electrical stimuli to the nucleus tractus solitarius and the brainstem reticular formation. In this way, VNS may interrupt the synchronous electrical activity characteristic of seizures. Earlier research has attempted to characterize the mechanism of action of VNS by using EEGs, evoked potentials, cerebrospinal fluid (CSF) neurochemistry and functional imaging. CSF studies have shown in gamma-amino butyric acid (GABA) after 3-4 months of VNS treatment, but no significant decrease in glutamate, aspartate or 5-hydroxyindoleacetic acid (5-HIAA) levels after 3 to 9 months of VNS treatment. Non-responders had the greatest effect on neurotransmitter levels. Long-term VNS had no effect on interictal EEG background or epileptoform activity, and an effect on visual or auditory evoked potentials. Although the VNS mechanism of action is essentially unknown, a number of studies using functional imaging techniques, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET), have demonstrated widespread changes in blood flow and metabolism in several cortical and subcortical regions during short term VNS use. These widespread changes in blood flow and metabolism in various celebral structures have formed the foundation of hypotheses that attempt to explain the VNS effect.

ISSN 2349-7823

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b) VNS should be considered for patients with refractory epilepsy at any age in the following cases:

1. Patients who have failed to become seizure free following adequate trials whether as monotherapies or in combination of two tolerated and appropriately chosen and used first-generation AEDs (Phenobarbital, phenytoin, carbamezapine, valproic acid) plus another trial with second or third generation AED (oxcarbazepine, lamotrigine, topiramate, vigabatrin, clobazam);

2. Patients who have been previously evaluated at specialized secondary or tertiary-level epilepsy centres with the aim of diagnosis confirmation and exclusion of epilepsy surgery as a treatment option (owing to unacceptable neurologic deficits, high surgery risk or refusal of the patient to undergo epilepsy surgery);

3. Patients with ultra-refractory status epilepticus;

c) VNS therapy: VNS therapy is a type of treatment for epilepsy that involves a stimulator for pulse generation which is connected inside the body to the left vagus nerve in the neck. The stimulator sends regular, mild electrical stimulations to this nerve. The vagus nerve sends these regular stimulations into the brain. The aim is to help calm down the irregular electrical brain activity that leads to seizures.

d) The Stimulator: The stimulator is a bit like a heart pacemaker, it is implanted under the skin in the upper chest (under the left collar bone) during a small operation under general anaesthetic. Because of the size of the stimulator there will be a small lump where it lies and a small scar where it was put in. A lead connects the stimulator or in the chest to the left side of the neck. Because the electrodes are coiled around the nerve in the neck, there will be a small scar where they are inserted, usually in the fold of the neck. The stimulator is switched on within four weeks of it being implanted.

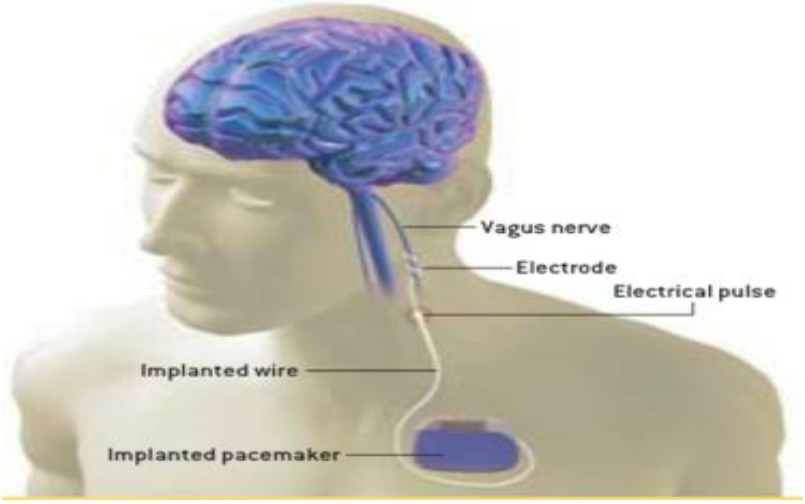

Fig.1: Vagus Nerve Stimulation

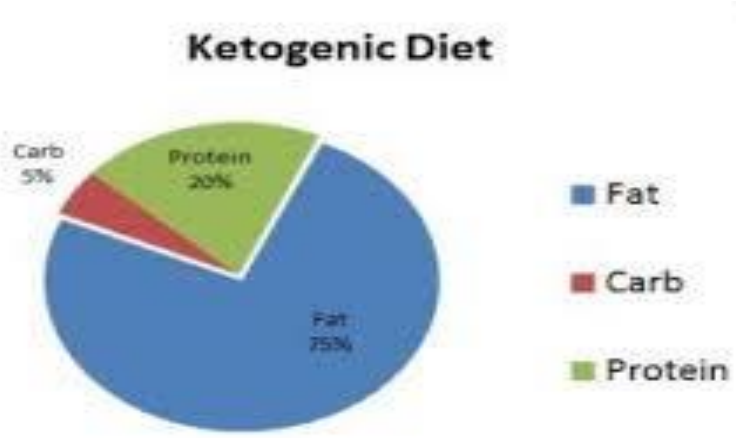

Fig.2: Ketogenic diet

ISSN 2349-7823

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2.4. Ketogenic diet:

The ketogenic diet includes about 75% fat, 20% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective. Initiation of the ketogenic diet is preceded by a 24- to 48-hour fast, with the patient being hospitalized. During the fast, the patient can drink water or sugar-free beverages and can eat unsweetened gelatin. Alternatively, Bergqvist et al have shown that a gradual initiation results in fewer adverse events and is overall better tolerated yet maintains the efficacy of the diet. Contraindications such as β-oxidation defects, liver disease, or metabolic disease interfering with glucose or ketone homeostasis must be excluded before initiation of the diet. Laboratory parameters of blood and urine glucose and ketones need to be monitored during fasting. The diet is introduced by starting with one-third of calories per meal, increasing to two-thirds of calories per meal and to the total amount of calories per meal every 24 hours. Patients are discharged when the total amount of calories per meal is reached and well tolerated, typically 2 to 3 days after initiation of the diet. Parents, patients, and caretakers are educated during admission about suitable food items, calculation, and preparation of ketogenic meals. If the diet is initiated without hospitalization, adequate facilities must be available to instruct families on meal preparation and monitoring techniques.

Meal plans are patient-tailored and can include heavy cream, bacon, eggs, tuna, shrimp, vegetables, mayonnaise, sausages, and other high-fat and low-carbohydrate products. Patients are not allowed starchy fruits or vegetables; breads, pasta, or grains; or sources of simple sugars.

Benefits and side effects: Patients on the diet become more alert and exhibit considerable improvements in attention, comprehension, activity levels, and endurance. Most of the side effects from the ketogenic diet are related to energy and nutrient deficiencies. Lack of protein, carbohydrates, and other nutrients can result in lack of weight gain and growth inhibition, especially at a young age. Inadequate calcium intake can further impair bone mineralization in children already at risk of osteopenia due to antiseizure therapy. Lack of fibre in the diet causes constipation. Acidosis is also commonly observed. Less common are kidney stones and hyperlipidemia. Adjustments to the diet (e.g. increased protein and polyunsaturated fat) can be made in children with high lipid concentrations. Serious adverse events include coma and obtundation. Rare side effects include cardiomyopathy, prolonged QT syndrome, vitamin and mineral deficiencies, pancreatitis, basal ganglia injury, and bruising. The long-term results of these side effects have not been adequately studied.

This review highlights the main neurobiochemical mechanisms:

a) Modulation of neurotransmitters: The major mechanisms proposed to explain the increased inhibition and/or decreased excitation that are induced by the KD involve the neurotransmitters GABA and glutamate. KBs act not only as energy sources but also contribute to reducing glucose consumption in the brain by modulating the activities of neurotransmitters .Changes in the levels of glutamate and GABA, which are the major excitatory and inhibitory neurotransmitters, respectively and their receptors have been proposed as the possible mechanisms of action of the KD . GABA is an intermediate of α-ketoglutarate, which is synthesized in the Krebs cycle (via glutamate) and converted into GABA by glutamate decarboxylase. Moreover, KBs inhibit glutamate decarboxylase and decreased levels stimulate the synthesis of GABA, thus contributing to seizure control.

b) Biogenic monoamines: The modulation of biogenic monoamine levels was proposed as a plausible mechanism for explaining the anticonvulsant effects of the KD. However, the specific mechanisms underlying such activities remain unclear.

c) Neuroprotective mechanisms: Many studies have shown that the epileptogenic state involves complex molecular pathways in which oxidative stress and mitochondrial dysfunction may exert important roles in neuronal programmed/controlled (apoptosis) or uncontrolled/passive (necrosis) cell death. Thus, investigators have given particular emphasis to the modulation of the mitochondrial biogenesis of neurons by the KD and caloric restriction, highlighting the neuroprotective role of the mitochondria as the primary key to the control of apoptosis and cell death .Mitochondria are intracellular organelles that primarily function in the production of cellular energy in the form of adenosine triphosphate (ATP). This nucleotide is produced by the mitochondrial respiratory chain through oxidative phosphorylation, which is performed by five multienzyme complexes (complexes I-V). The dysfunction of complex I may lead to decreased ATP production, which is commonly observed in neuronal diseases. In prolonged seizures, a temporary reduction in ATP levels can contribute to cell death.

ISSN 2349-7823

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d) Anticonvulsant mechanisms and ketone bodies: There are many hypotheses regarding the antiepileptic mechanisms of the KD. The early hypotheses regarding its activities were focused on the concepts of acidosis, dehydration and increased ketone concentrations. Other factors, such as γ-amino butyric acid (GABA) and glutamate, membrane potentials, ion channels, biogenic monoamines and neuroprotective activities (Figure 1), have been studied in experimental models (*in vivo* or *in vitro*).Energy metabolism in the brain involves distinct and complex pathways. Under physiological conditions, most precursors of KBs are long-chain fatty acids. They are released from adipose tissue in response to a decrease in blood glucose, such as that which occurs during fasting .Similar mechanisms are involved in the KD, during which long-chain fatty acids are metabolized in the liver and converted into KBs. These fatty acids are oxidized in the mitochondria, producing high levels of acetyl-CoA, which cannot be oxidized in the Krebs cycle. The excess acetyl-CoA is converted to acetoacetate and subsequently to acetone and β-hydroxybutyrate . The KBs cross the blood-brain barrier and are transported by monocarboxylic acid transporters to the brain interstitial space, the glia and the neurons. In these tissues, the KBs act as substrates in and respiratory chain, contributing to brain energy metabolism.

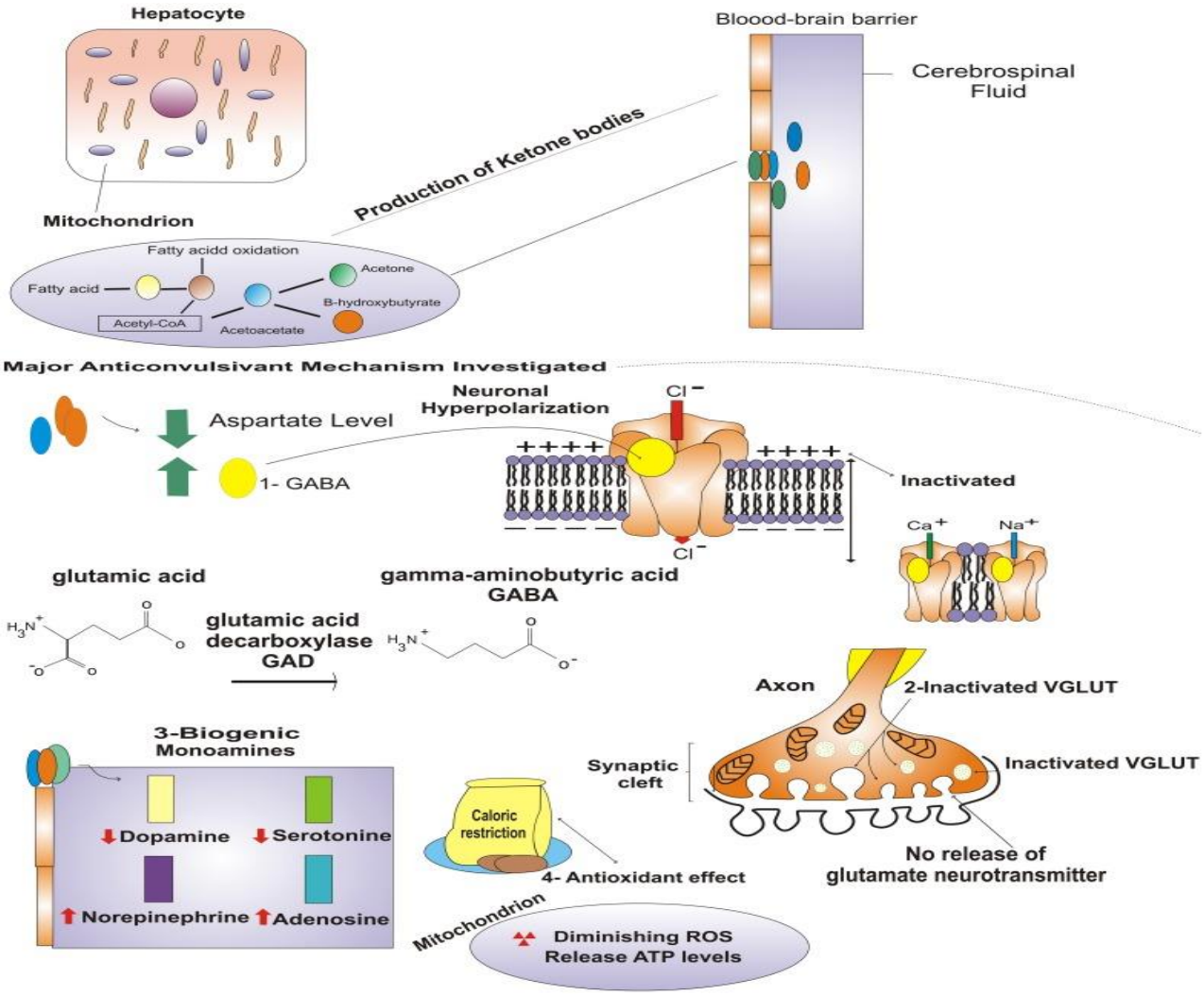

Fig.3: Production of ketone bodies and potential primary anticonvulsant mechanisms: (1) GABA neurotransmitter (neuronal hyperpolarisation and membrane channels; (2) inactivation of VGLUT and inhibition of glutamate neurotransmitter; (3) modified concentrations of biogenic monoamines; and (4) antioxidant mechanism of diminishing reactive oxygen species.

2.5. Complementary and Alternative Medicine:

The term "conventional medicine" refers to the methods and treatments most widely practised by Western health professionals today to diagnose and treat health conditions. These methods and treatments are based on scientific research. Their effectiveness is proven and their side effects are well known.

The term "complementary and alternative medicine" (CAM) refers to the use of treatment methods that are not yet approved by conventional Western medicine or proven by scientific research techniques. These may include physical treatments or procedures; herbal therapies, vitamins, and other substances; and even complete systems of medical theory and practice, such as traditional Chinese medicine and Ayurveda.

Strictly speaking, "alternative medicine" refers to using only the non-conventional treatment, whereas "complementary medicine" means using the non-conventional treatment in conjunction with conventional ones. However, the terms "complementary medicine" and "alternative medicine" are often used interchangeably. The terms "holistic" and "integrative" medicine can also be used to refer to patient-centred care that combines mainstream and complementary therapies.

CAM for epilepsy may be used for lessening seizures, for alleviating related symptoms, and for reducing side effects. Some complementary and alternative therapies for epilepsy are based on the principle that relaxation may reduce seizures. Others are based on the idea that the person with epilepsy has less of some vitamin or mineral in his body than is normal. Still others focus on avoiding certain types of food.

In cases of epilepsy, people may investigate CAM for various reasons:

- Conventional drugs, such as anti-epileptic drugs, may not be effective in controlling their child's seizures or if they are effective, the side effects may be intolerable.
- Parents may want to supplement the conventional treatment and improve the overall well-being of their child.
- Surgery may be too risky, not an option, or tried and failed.
- Their cultural beliefs may make the CAM a viable option.
- Parents may have heard of the CAM helping another child with a similar condition.

2.6. Deep Brain Stimulation of the Anterior Nucleus of the Thalamus:

Rationale: In 1937, James W. Papez described a circuit linking hippocampal output via the fornix and mammillary nuclei to ANT. Projections from ANT travel to the cingulum bundle and then around the wall of the lateral ventricle to the parahippocampal cortex, completing the circuit by returning to the hippocampus. Radiologic alterations have been noted in structures within the classic circuit of Papez in mesial temporal sclerosis, as well as other forms of epilepsy. Thus, it is conceivable that DBS of structures within this circuit may result in direct anterograde cortical stimulation. ANT is an appealing target because of its relatively small size and projections to limbic structures, ultimately affecting wide regions of neocortex. Further, it is not as deep or close to basal vascular structures as the mammillary nuclei. These anatomic connections and precursor ablative techniques have motivated investigation of ANT DBS for epilepsy. **Surgical procedure:** The patient is placed in a supine or semi-sitting position. After Mayfield fixation, sterile preparation of the unshaven head, and local infiltration with 1% Xylocaine 1:100,000 epinephrine, an incision is made overlying the coronal suture. A burr hole is placed, and the dura and pia are sharply incised and cauterized. A guide cannula is inserted and advanced deep into the brain to a point 10-mm from the desired target under direct fluoroscopic and Leksell frame guidance. Under local anaesthesia, monopolar single-unit recording electrode (Advanced Research Systems, Atlanta, GA, or FHC, Bowdoinham, ME) can be introduced to confirm anatomic depth for entry into thalamic tissue after traversing the lateral ventricle. No units are recorded while traversing the lateral ventricle. The electrode tip is advanced until recordings are first heard (ANT superficial surface), then until units cease (intralaminar region) and then recommence (dorsomedian nucleus of the thalamus). Extracellular action potentials are amplified with a GS3000 (Axon Instruments, Sunnyvale, CA) or Lead point (Medtronic, Minneapolis, MN) amplifier and simultaneously recorded using standard recording techniques (300–10,000 Hz), together with a descriptive voice channel. ANT neurons are identified based on (1) regional characteristics, (2) a firing rate previously described for human recordings, (3) and a characteristic burst firing pattern. After removing the single-unit recording electrode, a stimulation lead (Radionics Stimulation/ Lesioning Probe, Burlington, MA) is introduced to elicit the driving response suggestive of ANT placement with a stimulation frequency of 5 to 10 cycles/s, pulse width at 90-330 μs, pulse amplitude at 4-5 V, and total pulse durations between 3 and 10 s. ANT DBS has been associated with recruiting rhythms on cortical EEG in patients with the most pronounced seizure frequency reduction. These changes in EEG signal morphology, however, can be elicited from several other thalamic nuclei. Further,

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International Journal of Recent Research in Life Sciences (IJRRLS)
Vol. 2, Issue 3, pp: (32-44), Month: July 2015 - September 2015, Available at: www.paperpublications.org

a recent report demonstrated that these recruiting rhythms induced by low frequency ANT DBS may reflect mixed activation of both specific and nonspecific thalamocortical pathways, and thus may not serve as a physiologic verification of optimal localization. Once this lead is removed, the DBS lead is advanced to ANT, ensuring that all contacts of the lead are within thalamic parenchyma, and the cannula and lead stylet are withdrawn under fluoroscopy. The stimulation leads we use are Medtronic 3387 DBS Medtronic (Minneapolis, MN) depth electrodes with 4 platinum-iridium stimulation contacts 1.5 mm wide with 1.5 mm edge-to-edge separation, since ANT is relatively larger than other DBS targets. Another fluoroscopic image is performed to show that the electrode is secure. The lead is secured to a burr hole cap, and the skin incision is closed. The same sequence of steps is performed to place the contra lateral electrode. The stereotactic frame is removed.

Scalp EEG driving response to stimulation of the left-sided anterior nucleus of the thalamus at a frequency of 5 to 10 cycles/s, pulse width at 90-330 μs, pulse amplitude at 4-5 V, and total pulse durations between 3 and 10 s. We elect to place the internal pulse generator (IPG) at the same setting, but it can be placed at a later date. The head, neck, and infraclavicular regions are sterilized in preparation for placement of the IPG (model Itrel II, Soletra, or Kinetra; Medtronic) in a subclavicular pocket bilaterally. The scalp incision is reopened for connection of the lead to an extension wire (Medtronic 7495 Lead Extension, Medtronic, Minneapolis, MN), which is tunnelled subcutaneously to the IPG (s). **Postoperative management:** The site of placement of the DBS leads is confirmed postoperatively by MRI or CT after reversal and recovery from anaesthesia. Patients are discharged to home two days postoperatively, but multiple outpatient visits are usually necessary for optimization of stimulation parameters. Stimulators are turned on approximately 10 days postoperatively, and initial stimulation parameters are set at a frequency of 90-130 Hz, pulse width at 60-90 μs, and pulse amplitude at 4-5V, and adjusted over subsequent follow-up to maximize clinical benefit based on each individual response and minimize side effects, such as nystagmus, lethargy and anorexia.

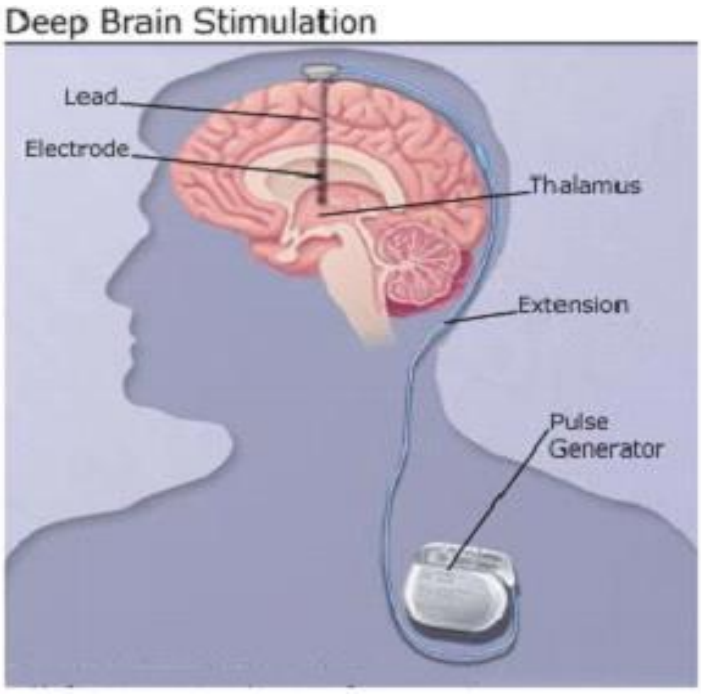

Fig.4: Deep Brain Stimulation

2.7. Gene Therapy For Epilepsy: Promising Results From An Epilepsy Research UK-Funded Study:

Neurons communicate with each other via chemical messengers known as neurotransmitters (NTs), and these can either be excitatory or inhibitory. An excitatory NT causes the communicating neuron to 'fire', whilst an inhibitory NT causes it to be inactive. The most common excitatory and inhibitory neurotransmitters in the brain are glutamate and GABA respectively, and a very fine balance between the two must be maintained for normal brain function to occur. Too much excitation (either because of an increase in glutamate or a decrease in GABA) can cause neurons to become hyperactive and seizures can result.

Electrical current in neurons is generated by the flow of ions, including potassium and chloride, through structures known as ion channels. Potassium ion channels include many subtypes and together they are one of the main regulators of neuronal excitability. A potassium channel known as Kv1.1 also controls the release of glutamate from neurons, and its malfunction has been linked to over-release of glutamate, an increase in brain excitability and epilepsy development. Chloride channels are usually inhibitory, and they act by allowing chloride ions to enter a neuron, making it more difficult for the neuron to fire. Loss of these channels has also been associated with certain types of epilepsy If a loss of/defect in chloride or potassium ion channel function is associated with epilepsy susceptibility, can an increase in their activity treat or even prevent epilepsy? In a recent study that was part-funded by Epilepsy Research UK, scientists at University College London (UCL) explored this question, using advanced genetic techniques involving viruses.

Viruses have special mechanisms by which they can incorporate their DNA into the cells they infect, and scientists can use them as vehicles (known as vectors) to transfer genes, e.g. ion channel genes, to cells. Provided that a gene is incorporated successfully into the host cell DNA, it can encode a protein (e.g. an ion channel) that functions normally. This technique can only be performed using certain types of virus that have been genetically modified to make them less harmful; however it is a very useful tool in examining gene and protein function.

The researchers at UCL wanted to find out if it was possible to stop seizures in rodent epilepsy models, very soon after they had begun, by increasing the number of chloride channels in their epileptic neurons. They chose to use a special type of chloride channel known as halorhodopsin, which is found in certain bacteria and is activated by a specific frequency of light. Halorhodopsin is encoded by a gene called NpHR.

After having induced epilepsy in the animals with a special toxin, and identified the seizure focus (the region in which seizures originate) in each using wireless EEG; the scientists injected the seizure focus of each animal with viral vectors containing NpHR. Seven to ten days later, they used optic fibres to deliver light of the appropriate frequency to the NpHR-treated neurons, in order to activate the halorhodposin channels that had formed. They found that seizure activity in all animals decreased dramatically upon channel activation.

The team then wanted to find out if seizures could be prevented from occurring in animals treated with toxin, by increasing the number of Kv1.1 channels in their neurons. In order to do this, they used a vector to deliver the human gene KCNA1, which encodes Kv1.1, to the animals' brains, and administered the epilepsy-inducing toxin at the same site, at the same time. They then monitored the animals both visually and via wireless EEG for seizure activity, and found that it was completed prevented in these animals.

Finally, the scientists explored whether or not an increase in Kv1.1 activity during well-established epilepsy could reverse (cure) it. Again, they induced epilepsy in a group of animals, and after a week they delivered KCNA1 to the neurons in their seizure foci. The team noticed that both the frequency of seizures experienced by the animals and the seizure activity in their brains gradually decreased, and stopped completely after four weeks.

These results (although early) are extremely promising, because they show that it is possible to prevent and even cure epilepsy in living mammals using KCNA1 and NpHR gene therapy. If this approach is validated in human trials, it could revolutionise the treatment of epilepsy. In the future, it might even be possible to incorporate NpHR therapy into a device that detects early seizure activity in neurons and inhibits it with light, before a clinical seizure develops. If combined with longer-term seizure suppression via KCNA1, a very effective treatment could result. It is still the case that a third of people with epilepsy do not respond to anti-epileptic drugs, and as epilepsy surgery is only feasible for a small proportion, these findings are very welcome.

III. CONCLUSION

In this review paper we get a brief idea of some of the types of epilepsy. The first type of treatment is the use of anti-epileptic drugs. Though this is the main type of treatment, these drugs can cause side effects for some people. With improved awareness of the benefits of surgery, improvements in neuroimaging to identify abnormal brain areas, and improved technologies for intervention, it is likely that surgery will be the option of choice for those patients who suffer the most from this disease. On the horizon, and presently an intense area of research, is the use of deep brain stimulation (DBS) to control seizures in patients who are not candidates for resective surgery. DBS, including responsive neurostimulation, is not yet FDA approved. With improved awareness and ongoing technological advances, surgery for epilepsy is now well established

and readily identified as the optimal therapy for many forms of intractable seizures. The ketogenic diet, being high in fat and low in carbohydrates, has been suggested to reduce seizure frequency. It is currently used mainly for children who continue to have seizures despite treatment with antiepileptic drugs. Recently there has been interest in less restrictive ketogenic diets including the Atkins diet and the use of these diets has extended into adult practice. There are few complications associated with vagus nerve stimulation. The implantation of the pulse generator is a surgical procedure and therefore involves many of the related risks. The most common complication during surgery is nausea and vomiting, which could result in stomach contents being inhaled into the lungs. Other less common complications include changes in heart rate, blood pressure, allergic reactions, and lack of oxygen. CAM is used when other treatments do not work straight away. There is no anxiety, depression, fatigue or side effects. Neuroactive peptides, adenosine, and γ-amino butyric acid, are agents that can be delivered by gene and cell therapy with potential utility in epilepsy therapy.

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