A Systematic Review on Convulsion - Epidemiology to Pharmacotherapy

D. Kamble Rahul *, N. Rodge Kishor, Shaikh Haidarali and N. Khatal Pravin

Department of Pharmacology, Padm. Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India.

ABSTRACT
Epilepsy is a chronic disorder characterized by recurrent seizure. The molecular mechanism of epileptic seizure and how drug act on the neuronal membrane help to further development of new drug. In this review, we discuss the following stimulation devices, Vagal Nerve Stimulation (VNS), Intracranial or Deep Brain Stimulation (DBS), Repetitive Transcranial Magnetic Stimulation (rTMS). The principle of seizure (Epilepsy) management should be individualized and the selection of treatments should aim to control symptoms as well as to prevent other complications.

INTRODUCTION
Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures. Epileptic seizures result from abnormal, excessive or hypersynchronous neuronal activity in the brain. About 50 million people worldwide have epilepsy, and nearly 90% of epilepsy occurs in developing countries. Epilepsy (excluding febrile convulsion) is very common and can affect all ages (Hauser et al., 1993). All seizures are caused by abnormal electrical disturbances in the brain. Partial (focal) seizures occur when this electrical activity remains in a limited area of the brain. The seizures may sometimes turn into generalized seizures, which affect the whole brain. This is called secondary generalization. An epidemiological study suggests a prevalence of 6.8/1000 in the U.S.A (Hauser et al., 1991). According to several publications this can estimate to 70% of the people with epilepsies, with a high prevalence of about 0.8% in children below the age of seven years (Lord Cohen et al., 1998). Around 75-80% of epileptic patients may be provided with adequate seizure control with the help of conventional antiepileptic drugs (Czuczwar, S.J et al., 2001). An imbalance between the excitatory and inhibitory neurotransmitters is responsible for seizures. In the CNS, COX-2 is mainly present in glutamatergic neurons particularly within the hippocampus and cerebral cortex, the areas that demonstrate prominent role in the onset of seizures (Choi et al. 2009). However, results of previous studies about the role of COX-2 in the genesis and maintenance of convulsion are controversial; cell membrane excitability and long term synaptic plasticity in the hippocampus (Chen et al. 2002), suggesting that COX-2 may play a critical role in convulsive states, for instance both proconvulsant and anticonvulsant role for COX-2 has been reported in kainic acid-induced seizure (Kelley et al., 1999, Kim et al., 2008). Generalized epilepsy is a chronic disorder characterized by recurrent seizures which can increase the content of reactive oxygen species (ROS) generation in the brain. (Sudha, et al., 2001) Brain is susceptible to free radical damage, considering the large lipid content of myelin sheaths and the high rate of brain oxidative metabolism. (Choi et al., 1993) Thus, it appears that free radicals may be responsible for the development of convulsions. Many patients (20 - 30%) however, have seizures that are not adequately managed by the established antiepileptic drugs (AEDs) (Richens et al., 1993), making traditional herbs and herbalists very useful and indispensable especially in underdeveloped countries of Africa (Osuntokun et al., 1987; Shorvon et al., 1988). The therapeutic failure in 20-25% of patients has stimulated intensive research on novel antiepileptic drugs.
Thus a need arises for new agents and new therapies for the management of epilepsy with greater efficacy, negligible or reduced side effects and devoid of unfavourable drug interactions unlike most AEDs in the market today (Triamble et al., 1990). For patients with drug-resistant epilepsy in whom surgical therapy has been excluded, alternative therapies are critically needed. The aim of this work was a short overview of the current literature, epidemiology, pharmacotherapy and recent trends in treatment of epilepsy.

Incidence and Prevalence
The incidence of new onset epilepsy has been documented as 90 per 100,000 in people between 65 and 69 years of age, and increases to 150 per 100,000 in people older than 80 years (Ramsay et al, 2004). The prevalence rate of epilepsy at age 60 is 1%, and increases further with age (Hauser et al, 1991). In nursing home residents, the prevalence of epilepsy is greater than 5% (Schachter SC et al, 1998). Another factor that compounds further the real incidence and prevalence of epilepsy in the elderly is the increased difficulty on diagnosing seizures in this population. Different studies have also shown that almost 10% of all nursing home residents receive an antiepileptic drug (AED) for epilepsy or other indications .Phenytoin (PHT) accounts for 60% of all AEDs used in the nursing home population. As there are few clinical indications for PHT use other than epilepsy, these studies may suggest that the prevalence of epilepsy is at least 6% in nursing home residents (Lackner TE et al 1998). Epilepsy is one of the most common neurological disorders with reported prevalence of 6-8/100,000 incidence of 30-50/100,000 per year and cumulative incidence of 3%. It requires prolonged and sometimes life-long drug therapy (Kurtzke JF et al, 2002). There are considerable barriers for the diagnosis of seizures, particularly simple and complex partial seizures, due to their subtle semiology resulting in a substantial rate of under diagnosis, misdiagnosis, and delayed diagnosis (Rowan AJ et al, 2005). Taken together, it has been speculated that the true incidence and prevalence of unprovoked seizures in the elderly might be two or three times the documented rates (Rowan AJ et al, 2005).

PATHOPHYSIOLOGY OF CONVULSION

a) Mechanisms of Seizure Initiation and Propagation
Partial seizure activity can begin in a very discrete region of cortex and then spread to neighbouring regions, i.e., there is a seizure initiation phase and a seizure propagation phase. The initiation phase is characterized by two concurrent events in an aggregate of neurons: (1) high-frequency bursts of action potentials, and (2) hyper synchronization. The bursting activity is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca++), which leads to the opening of voltage-dependent sodium (Na+) channels, influx of Na+, and generation of repetitive action potentials. This is followed by a hyperpolarizing after potential mediated by γ-aminobutyric acid (GABA) receptors or potassium (K+) channels, depending on the cell type. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG.

b) Mechanisms of Epileptogenesis
Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyper excitable. An immature brain is more prone to seizures than is a mature brain because of multiple changes that occur during development. Epileptogenesis (i.e., generation of seizures) in an immature brain is influenced by the inhibitory and excitatory systems, ionic microenvironment, and degree of myelination. There is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs. Maturity of inhibitory systems is crucial for cessation of seizure activity in an immature brain. γ-Amino butyric acid (GABA) is the predominant inhibitory neurotransmitter in the brain. The GABA
receptor may select for chloride conductance (GABA_A) or potassium conductance (GABA_B) (Hevers W et al, 1998). In contrast to the inhibitory system, the excitatory system is overdeveloped. Glutamate is the major excitatory neurotransmitter in the brain, and several subtypes for the glutamate receptor exist, including N-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) (Platt SR et al 2000 & Young AB et al, 1990). Decreased expression of glutamate transporters and variation of subtypes can lead to increased seizure susceptibility and to a lower seizure threshold (Sanchez RM et al, 2001 & Furuta A et al, 1997). Differences in the ionic microenvironment that surrounds neurons and glial cells also contribute to epileptogenicity of the immature brain. The potassium is increased in the extracellular fluid of immature brains (Sanchez RM et al, 2001). In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events. Pathologic studies of the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of epileptogenesis are related to structural changes in neuronal networks. There is also evidence that, in response to the loss of neurons, there is reorganization or “sprouting” of surviving neurons in a way that affects the excitability of the network. Some of these changes can be seen in experimental models of prolonged electrical seizures or traumatic brain injury.

Molecular Level Changes in Epileptogenesis
The concept that neuronal loss after trauma is permanent has been challenged in the context of current knowledge. Combination of neuronal plasticity, axonal regrowth and from replacement by multiplying neuronal progenitor cells, neuronal recovery is takes place. Metabolism of dentate gyrus of the hippocampus produces neuronal stem cells (Dash PK et al, 2001) and migrates to the areas of injury. Neuronal plasticity involves the transfer of function of damaged neurons to intact neurons (Whishaw IQ et al, 2000) and involves both the re organisation of old synaptic connections and the establishment of new ones (Jones TA et al, 1999). The CA 3 neurons of the dentate gyrus3 of the hypothalamus have regenerative potential. There is a selective vulnerability of hippocampal neurons to neurotrauma1. Post traumatic epileptogenesis possibly has its origins in hippocampal region. The factors contributing to epileptogenesis include disturbances in the ionic milieu and neuronal synaptic changes.

Ionic changes in epileptogenesis
Membrane depolarization during neuronal electrical activity results in an extracellular accumulation of potassium. This potassium has to be removed from the extracellular region by the ionic pump as well as by glial cell uptake and spatial dispersal. Both these mechanisms fail in a post trauma setting. The well defined entity of post traumatic ATP depletion results in a failure of the ionic pump (Mautes AE et al, 2001). This causes change in neuronal excitability and membrane Potentials with loss of GABA function.

Shift of Neurons
According to electrical activity, there are two types of neuron spikers & bursters. Spikers are neurons that generate a single spike in response to a brief current. Bursters, on the other hand, generate a cluster of spikes riding the shoulder of slow membrane depolarization. Neurons with burster characteristics are predominantly found in the CA3 sub region of the hypothalamus. An increase in extracellular K+ has been shown to shift neurons from a spiker to a burster state (Golorai G et al, 2001).

The Excitotoxicity of Glutamate
Brian injury causes increase in glutamate levels, excessive activation of glutamate receptor leads to a magnesium resistant blockade and calcium ingress into the cell (Choi DW et al, 1985). Which underlies the basis for calcium second messenger effects on both neuronal plasticity in neurons and cell death? A high level of
intracellular calcium generates reactive oxygen species (Schwartzhain PA et al, 1998).

**Neuronal Sprouting**
Following trauma induced neuronal loss, restorative changes are triggered by Neurotrophic factors in the hippocampus. These processes include axonal sprouting, neo synaptic genesis and dentate gyrus (CA3) region proliferation of progenitor cells (Dixon CE et al, 1987). Mossy fibre axonal sprouting after neuronal loss is associated with attempts at functional reorganization. Disorganization in this neo synaptogenesis process results in epileptogenesis (Dudeh FE et al, 1994).

**The Phenomenon of Kindling - Is it relevant as an epileptogenic mechanism**
Repeated stimulation results in a progressive lowering of the seizure threshold. This phenomenon is called kindling. Kindling is propounded as the mechanism by which secondary seizure foci are established in long standing seizure disorders. However, the classic antiepileptic drugs are not anti epileptogenic i.e. they control post traumatic seizures, but do not prevent the establishment of seizure foci. Tetradoxin, a sodium channel blocker, has been used in the rat model successfully, to prevent epileptogenesis (Graber KD et al, 1999).

**Pharmacotherapies in Convulsion**
Epilepsy is a condition in which a person has recurrent seizures, so need of rapid expansion in knowledge of its neurological disabilities. Therapeutic options, both medical, surgical and non medical have been markedly improved over the past decades, resulting in better condition, activities of daily living, and quality of life for epileptic patients.

The principle of seizure (Epilepsy) management should be individualized and the selection of treatments should aim to control symptoms as well as to prevent other complications. Various pharmacologic and surgical options are available, including different formulations. There are number of drugs available for treatment of epilepsy in modern therapy. But the major disadvantages being faced are their chronic side effects.

**Conventional Drug Therapy**
Current antiepileptic drugs are thought to act mainly by two main mechanisms
1) Reducing electrical excitability of cell membranes, possibly through inhibition of sodium channel. Following drugs inhibit voltage gated sodium ion channel: Phenytoin sodium, Phenobarbitone, Carbamazepine, Lamotrigine, Valproate
2) Enhancing GABA-mediated synaptic inhibition. This may be achieved by an enhanced pre- or post- synaptic action of GABA. Following drugs enhance GABA synaptic transmission: Vigabatrin, Valproate, Gabapentin, Phenobarbitone.
Selection of drug in epilepsy
For partial epilepsy base drug is carbamazepine can be treated up to serum level of 10-12 mg/dl. For generalised epilepsy, valproate is main drug, with target dose is 20 mg/kg (Hermanns G et al, 1996). Add on option for partial seizure includes phenobar and clobazam from the older drugs and newer drugs like levetiracetam and topiramate are effective. pregabalin may also be emerging significant add on drug (Carreno M et al, 2007). Add on drugs for generalised seizure are zonisamide, levetiracetam and lamotrigine, but unfortunately lamotrigine and topiramate cannot be combined because of a risk of hyperammonemia. (Mandelbaum DE et al, 2005)

Gabapentin is a structural analogue of gamma- amino butyric acid (GABA) which does not interact with either GABA_A or GABA_B receptors, convert to GABA or GABA agonist nor does it inhibit GABA uptake or degeneration (French JA et al, 2004). It has been shown to be effective in complex partial seizures with or without secondary generalization and generalized tonic-clonic seizures.

Lamotrigine acts by inhibiting the release of excitatory amino acids such as glutamate through the modulation of sodium and calcium channels (Petroff OA et al, 1996). And lamotrigine is effective as an add-on or monotherapy for patients with partial seizures with or without secondary generalization, and in addition, in the treatment of absence, myoclonic seizures, and other seizure types associated with Lennox-Gastaut syndrome. (UK Gabapentin Study Group 1993).

Vigabatrin is a synthetic GABA derivative which causes irreversible inhibition of GABA transaminase thereby increasing the pool of the inhibitory neurotransmitter (UK Gabapentin Study Group 1990).

Topiramate is a sulfamate-substituted monosaccharide with carbonic anhydrase inhibitory properties. The mechanism of action as an antiepileptic drug is related to inhibition of GABA_A receptor mediated activities and its direct modulating effect is independent of carbonic anhydrase inhibition (Genton P et al., 2000). Other drugs used are Tiagabine, Levetiracetam, Zonisamide, Oxcarbazepine, Felbamate

Other new antiepileptic drugs in women, pregnancy and lactation Some of the new AEDs particularly Gabapentin, Topiramate, Vigabatrin and Levitiracetam have minimal protein binding properties and do not cause hepatic enzyme induction, and as such do not interact with oral contraceptive pills.

Recent Development in the Treatment & Management of Epilepsy
For patients with drug-resistant epilepsy in whom surgical therapy has been excluded, alternative therapies are critically needed.
Ketogenic diet
Ketogenic diet is a highly fat, low carbohydrate diet developed with the advent of effective anticonvulsants. The mechanism of action is unknown. The diet mimics aspects of starvation by forcing the body to burn fats rather than carbohydrates. Normally, the carbohydrates contained in food are converted into glucose, which is then transported around the body and is particularly important in fuelling brain function. However, if there is very little carbohydrate in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood, a state known as ketosis, leads to a reduction in the frequency of epileptic seizures. Chronic ketosis also modifies the tricarboxylic acid cycle to increase GABA synthesis in brain. In addition, reactive oxygen production is enhanced in brain tissue. These changes stabilize synaptic function and increase resistance to seizure generation throughout the brain. (Bough KJ et al, 2007)

The Ketogenic diet is not benign therapy, although the most of side effect are predictable and treatable. These include acidosis, weight loss, inadequate growth, and symptomatic nephrolithiasis (6%), hyperlipidemia, hypoglycaemia, hyperuricemia, GI symptoms and easy bruising. In small group of patients, the combined use of Ketogenic diet and vagal nerve stimulation appeared synergistic and yielded rapid benefits. (Hartman AL et al, 2007)

Electrical stimulation
In this review, we will discuss the following stimulation devices:
– Vagal Nerve Stimulation (VNS)
– Intracranial or Deep Brain Stimulation (DBS)
– Repetitive Transcranial Magnetic Stimulation (rTMS)

i) Vagal Nerve Stimulation (VNS)
Vagal nerve stimulation is the most widely used stimulation tool in the field of epilepsy (approximately 40,000 cases implanted so far). Tonic seizures were reduced by 88% and atypical absences by 81% in a study of 46 LGS-patients (Frost M et al, 2001). Despite the large number of patients stimulated with VNS so far, no particular profile of the “perfect” VNS-candidate has emerged. Moreover, no particular antiepileptic drug pairs optimally with VNS, leading to enhanced synergistic efficiency than either VNS or the drug alone (Te coma ES et al, 2006). The mechanisms of action of VNS have been recently reviewed, but still remain unclear. VNS shows effect mainly by alteration in release of nor-epinephrine from solitary tract, increase GABA activity to vagal stimulation, inhibits aberrant cortical activity by RAS. It is of note that VNS received the FDA approval for treatment-resistant major depression in July 2005. (Vonck K et al, 2001)

ii) Deep Brain Stimulation (DBS)
It is surgical treatment involving implementation of medical device called brain pacemaker. It sends electrical impulses to specific parts of brain. DBS electrode implemented in anterior nuclei of thalamus bilaterally using stereotatic technique. One of the first stimulation sites investigated for the treatment of epilepsy was the thalamus. Stimulation of the anterior nucleus of the thalamus has so far been tested in about 31 patients worldwide with multifocal epilepsy and symptomatic generalized seizures or partial complex (Hodaie M et al, 2001). These studies report that stimulation at a frequency between 90 and 200 Hz, produces a significant reduction of the seizure frequency (≥60%) in 16/31 of the patients. There is currently an ongoing multicenter study in the US, called the SANTE trial (Medtronic, Minneapolis, MN, USA; Clinical trials. gov NCT00101933). The stimulation of the centromedian nucleus of the thalamus, at a stimulation frequency ranging from 4 to 185 Hz, has been tested in 78 patients so far where it leads to a significant reduction in seizure frequency of generalized tonic-clonic seizures and of absences, but not of partial complex seizures. Other studies have indicated no reduction in seizure frequency (Osorio I et al, 2005). Stimulation of the centromedian nucleus of
the thalamus has also been investigated as a treatment of Lennox-Gastaut syndrome (Velasco AL et al, 2007). Overall, a seizure reduction of about 80% was achieved and 2 out of 13 patients became seizure-free. This is a promising result in this difficult-to-treat patient group, but needs to be verified in further studies.

Repetitive Transcranial Magnetic Stimulation (rTMS)
In rTMS use of magnet rather than electric current to bain reduced discomfort of the procedure and induction of weak electric current here by rapidly changing magnetic field. Small intracranial electrical currents are generated by a strong fluctuating extracranial magnetic field (Barker AT et al, 1985). rTMS has been applied with therapeutic attempts in several pathologies such as depression, pain, tinnitus and stroke, and also in epilepsy patients. Low frequency (<1 Hz) rTMS decreases the cortical excitability, outlasting the duration of the stimulation itself (Chen R et al, 1997). Inhibition of epileptic activity with rTMS is based on the notion that rTMS can achieve a reorganization of the cortical circuitry in humans leading to potentially therapeutic effects. The inhibitory effects of low frequency rTMS have been attributed to the trans-synaptic activation of GABAergic inhibitory interneurons to the recurrent inhibition of the targeted cortical neurons through axonal collaterals. As a lack of GABAergic surround inhibition is assumed to be involved in the spreading of local epileptic activity, the concept of inhibitory rTMS in epilepsy with focal seizure onset is convincing. (Pascual-Leone A et al, 1994).

CONCLUSION
New anticonvulsion drug are require for effective treatment, in a status epilepticus the new intravenous medication require. There are considerable gaps of knowledge about the pathophysiological responses of the aged brain. individual basis particularly when new agents are being marked suggests that further research is needed in epileptogenesis Its good effect on mood and behavior has now been described in several studies.

REFERENCES


32. Mandelbaum DE, Bunch M, Kugler SL, Venkatasubramanian A and Wollack JB. Broad-spectrum efficacy of zonisamide at 12


46. Tecoma ES and Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned? Epileps. and Behav. 2006;8:127-36.


48. Vonck K, De Herdt V and Boon P. Vagal nerve stimulation 1—15 year survey of an established treatment