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A Systematic Review on Etiology of Epilepsy and Recent Advances in Its Treatment

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ABSTRACT

Epilepsy is the commonest neurological problem after stroke and Alzheimer's disease. It is a chronic disorder identified by unprovoked recurrent seizures which occur due to sudden intense electrical impulse outburst in the brain. Epilepsy has a serious impact on the quality of life of the patients. There are several antiepileptic drugs which provide effective control in the majority of patients but in some refractory cases, patients who cannot tolerate these drugs require an alternative treatment for epilepsy. Various newer approaches have been evolved in the rational management of seizures which are based on the different mechanism of action and side effect profile. A great progress has been made in the treatment of epilepsy during the last few decades. This review focuses on the newer treatment modalities and possible beneficial effect of this regimen and limitations of such use.

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INTRODUCTION

Proper functioning of the brain requires distinct isolation of electrical signals and thus demands a far higher level of regulation. This complex function control begins at the level of the ion channel and is further maintained through the effects of these ion channels on the activity of highly organized neuronal networks. The basis of **seizure** is the abnormal function of ion channels and neural networks which result in rapid, synchronous, and uncontrolled spread of electrical activity**. Epilepsy** refers to the condition in which an individual has a tendency toward recurrent seizures. Seizure symptoms may vary according to the location of seizure activity and may include prominent motor symptoms and loss of consciousness (as seen in tonic-clonic seizures), paroxysmal alterations in non-motor functions (e.g., emotions, memory, language, insight)[1].

Two important elements in the central nervous system are normally involved in fine-tuning of neuronal signaling. They also function in preventing the repetitions and synchronous firing of a characteristic of a seizure. At the cellular level, a 'refractory period' induced by Na^+ channel inactivation and K^+ channel-mediated hyperpolarization prevents abnormal repetitive firing in neuronal cells. The biochemical properties of Na^+ and K^+ channels, under physiologic conditions, impose a limit on the frequency of firing, helping prevent the repetitive firing characteristics of many seizure types. Beyond the single-cell level, neural networks ensure specificity of neuronal signaling by restricting the effects of a given action potential to a defined area. In a simplified neural network, the firing neuron activates immediately neighboring neurons in addition to interneuron's that transmit inhibitory (GABA) signals to surrounding neurons. This contrast of local amplification and surrounding cell inhibition results in what is referred to as **surround inhibition**. For the normal function of the nervous system, surround inhibition is essential as this phenomenon not only amplifies local signals but also provides insulation and protection against synchronicity in the surrounding areas. Disruption of this intricate balance results in many seizure disorders[1, 2].

Epilepsy: A complex brain disorder

Epilepsy is a neurological disorder, sometimes chronic, condition with physical risks and psychological and socioeconomic consequences impairing quality of life[3]. It is characterized by recurrent epileptic seizures, unprovoked by any immediately identifiable cause. A seizure is a temporary change in behavior which results from a sudden and abnormal burst of electrical activity in the brain. If the electrical disturbance is limited to only one area of the brain, then the result is a partial seizure. Some seizures occur as a result of acute medical illness (diabetic during hypoglycemic episode) or an acute injury (head injury) and cease once the treatment of illness is done[4].

Clinical Aspects and Epidemiology

Clinical presentation and underlying neurological disorders tend to classify epilepsies which are very controversial. The affected part of brain, spread of epileptic discharges through brain, age of the individuals are the factors on which the clinical presentation depends[5,6]. The clinical diagnosis of epilepsy depends on the description of events that takes place before, during and after a seizure, given by the person. The methods used to investigate individuals with known and suspected epilepsy are Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT). Epilepsy diagnosis can be difficult as it requires seizure types, epilepsy syndrome, and underlying cause[7].

About 50 per 100,000 per annum are the incidences of epilepsy reported. In childhood, these incidences are high which decreases in adulthood and rises again in old age[8]. One of the epidemiological studies reports a Standardized Mortality Rate (SMR) of 2-4 for epilepsy. Sudden Unexpected Death in Epilepsy (SUDEP) occurs during chronic epilepsy is the main cause of excess mortality[8].

Role of astrocytes calcium signaling in Epilepsy

Extracellular concentration of K^+ ions $[K^+]_0$ regulates the neuronal excitability in the brain network. Increased level of $[K^+]_0$ deriving from intense neuronal firing discharges tends , indeed to, depolarize neuronal cells which facilitate the development of epileptiform discharges. During hypersynchronous neuronal activities the peaks of 10-12 mM in the $[K^+]_0$ are reached that

characterized epileptic disorders and are proposed to play an important role in ictogenesis[9,10]. Several studies performed in both animal model and human epilepsy supports the fact that a defective K^+ buffering due to an altered expression of K^+ and aquaporin channels in astrocytes represents a possible cause of pathological neuronal hyperexcitability in the epileptic brain[11]. The role of astrocytes as modulators of epileptogenesis focused on the ability of astrocytes to buffer extracellular K^+ or neurotransmitters (released in excess during epileptic discharges). Ca^{2+}- dependent glutamate release astrocytes can directly excite groups of neighboring neurons and favors synchronized activities mediated by extrasynaptic N-methyl-D-aspartate (NMDA) receptor activation[12,13]. These observations show the role direct of Ca^{2+} dependent gliotransmission in the epileptiform activities generation.

The relevant information about the characterization of macroscopic network abnormalities in the epileptic brain was provided by the imaging studies. For the investigation of connectivity and organization of brain networks, the powerful tool is functional MRI. Resting state fMRI (RS-fMRI) employ fMRI, which investigates synchronous activity in the absence of an explicit task based on signal correlation, between the regions. Consistent pattern of spatially distinct, brain networks that show coherent signal fluctuations, were shown by RS-fMRI studies. These studies have been used in the identification of network abnormalities in much different pathology, including epilepsy and many brain disorders[14].

Development of New Antiepileptic Drugs

More than 20 compounds having potential antiepileptic activity are in various stages of clinical development and clinical trial results for many of these are already available[15]. New antiepileptic drugs can become successful only when it has at least one of the following properties[16].

- Greater efficacy than other drugs in the treatment of refractory epilepsies
- Ability to prevent or delay the onset of epilepsy (epileptogenesis), or at least modify its progression.
- Broad usefulness in non-epileptic CNS disorders
- Fewer adverse effects than available drugs
- Ease of use, such as rapid titration, linear pharmacokinetics
- Lack of drug interactions

- Longer half-life that enables once or twice daily doses
- Extended protection if a dose is missed

There is a significant need for the development of new antiepileptic drugs for many patients with intractable epilepsy. Antiepileptic drugs that have novel therapeutic targets are more efficacious, have better pharmacokinetic characteristics and have improved adverse effects profiles[17]. Table No. 1 lists the compounds having the potential to meet at least one of the above criteria.

Partial Generalized Seizures

A few randomized studies are available for the newer antiepileptic drugs, most of the epilepsies in this group respond to valproate. Chadwick *et al*., in a double-blind, placebo-controlled, parallel study found a tendency of gabapentin to reduce the frequency of generalized tonic-clonic seizures to a greater degree than placebo. No statistical significance has been achieved because of low dose of gabapentin (1200mg) [18]. In another study, a significant reduction in primary generalized tonic-clonic seizures (56.7% vs 9.0%) was observed with topiramate treatment group in a randomized, double-blind placebo-controlled trial[19].

Partial Seizures

In add-on randomized controlled trials for partial seizures, all newly marketed antiepileptic drugs were found to be efficacious. A direct comparison between newer with older antiepileptic drugs was done in few randomized studies and two newer antiepileptic drugs were compared with one another. Carbamazepine[20] was less efficacious than oxcarbazepine. Oxcarbazepine is as efficacious as phenytoin[21, 22] and valproate[23]. A comparison trial of lamotrigine and carbamazepine was done in adults[24, 25] and elderly[26], and it was found that lamotrigine was taken by a majority of patients because of fewer adverse effects, but no difference in efficacy.

Pharmacoresistant Epilepsies

Pharmacoresistant epilepsy (also known as medically intractable or refractory epilepsy) defined by International League Against Epilepsy (ILAE) as the failure of a patient's seizures to respond to at least two antiepileptic medications that are appropriately chosen and used for an adequate time period. It is a chronic and lifelong problem often associated with significant disease-related costs (treatment and societal). Uncontrolled seizures in this type of epilepsy may have

debilitating psychosocial consequences and risk of injury and /or death. Patients may also experience feelings of depression / or anxiety[27]. Two double-blind, placebo-controlled crossover studies showed that lamotrigine was effective and well tolerated when used as an add on treatment in Pharmacoresistant generalized epilepsy[28, 29].

Rectal Diazepam Treatment for Epilepsy

Administration of rectal diazepam can be safe and effective treatment for acute repetitive or prolonged seizures. As serious respiratory depression was caused by intravenous diazepam, some studies show that rectal diazepam has found no instances of serious respiratory depression. The common side effect of rectal diazepam is sleepiness; other includes headache, dizziness, pain, poor coordination, nervousness, slowed speech, diarrhea, and rash. The incidence of side effects is greatest when more than one dose is given. Rectal diazepam is available in the form of rectal gel commonly prescribed in the form of Diastat. Diastat syringe of 2.5mg is also available; it can be stored at room temperature for 3 years[30, 31].

Surgical Options For Anti-Epileptic Drug Resistant Seizures

A total of 30% of patient's seizures cannot be fully controlled because of drug resistance. The new AEDs can reduce seizure frequency by 50% or more in 30% to 55% of patients with medically intractable seizures, but only 1 to 10 % will become free of seizures. Therefore, Vagus nerve stimulation or epileptic surgery is then considered.

Resective Surgery:

Vagus Nerve Stimulation Therapy for Epilepsy

This therapy was approved by the American Academy of Neurology (AAN) Board in 2013[32]. Vagus Nerve Stimulation (VNS) therapy helps in reducing the frequency and intensity of some seizures. A device, similar to a pacemaker is inserted under the skin on the left side the chest. An intermittent electrical signal to the brain was sent by vagal nerve stimulator which stimulates the left vagus nerve in the neck. The theory behind the working of VNS is that the stimulation alters nerve pathways that lead to a seizure. The vagus nerve is one of the cranial nerves which controls the muscles that are responsible for voice sounds, coughing and swallowing. The VNS system

battery operated, pulse generator and much looks like a pacemaker implanted under the skin of the chest[33,34].

Vagus nerve consists of large myelinated A and B fibers and smaller unmyelinated C fibers, ratio of A, B and C fibers are assumed to be the same for afferent and efferent fibers. The approximate currents required to stimulate A, B and C fibers in rat vagus nerve model is 10μA, 50μA and 325μA for A, B and C nerve fibers at 125 seconds. The diameter of the rat vagus nerve is 0.4mm which is 2.0 mm diameter in case of human vagus nerve. Therefore in case of humans the equivalent stimulation current is 25 times that of rat vagus stimulation. Activation of A fibers in rats at 125 seconds was 10μA, which correspond to 0.250 mA activation in humans using 25 multiplication factors. Table No. 2 shows currents required for the stimulation of vagus nerves in rat vagus nerve model and a close to the range of that clinically being used in humans[35].

External vagus stimulation: Two external vagus stimulation devices and 1 trigeminal nerve stimulator are being investigated in clinical studies. Stefan H, 2012 done pilot study in 10 patients. Application of electrical stimulation was given transcutaneously to the auricular branch of the vagus nerve (ABVN) to the left ear. Out of 10 patients, three patient left the study, five experienced an overall seizure reduction after 9 months of transcutaneous vagus nerve stimulation. Meaningful advances have been made in vagus nerve stimulation for epilepsy, during its first 25 years. More than 100,000 devices have been implanted and more than 70,000 patients have been treated. Efficacy continues to improve compared to pharmacotherapy[36]. Hoarseness and tingling or pain in the throat or neck is the common side effects of VNS. Other side effects are cough, headache, and ear pain. These side effects tend to diminish over time[33,34].

Multiple Subpial Transections

This procedure is applied to the patients with Landau-Kleffner Syndrome. It exploits the knowledge that functional cortical organizations is primarily vertical (columnar). The intracortical fibers are responsible for seizure spread and are horizontally oriented. In this technique a series of small parallel cortical slices 5 mm apart made perpendicular to the long axis of the gyrus to spare function and propagation is terminated. This procedure is used alone or in combination with resection in patients with seizures arising in or around the motor, sensory or language cortices[37].

Deep Brain Stimulation

Stimulation of deep brain structure made by various attempts reduces seizure frequency which includes the anterior thalamus, centromedian thalamic nucleus, the caudate nucleus, the posterior hypothalamus and the hippocampus[39].

Gamma Knife Surgery

Stereotactic delivery of a focused dose of a radiation to a single point within the brain. It is identified on magnetic resonance imaging (without causing significant radiation to adjacent tissues), long delay occurs before an optimal effect is seen (12-36 months). Reduced hospitalization, no craniotomy, lower risk of infection and bleeding are the benefits of this procedure. It is recently investigated in the treatment of hypothalamic hamartomas[39].

Responsive Neuro Stimulation Device

RNS is novel and implantable, first closed loop responsive brain stimulation system. It is an advanced technology designed to treat partial onset seizures by detecting specific type of electrical activity in the brain. RNS system responds by delivering imperceptible levels of electrical stimulation to normalize brain activity before an individual experiences seizures[40]. Vagus nerve stimulation[41], cerebellar or thalamic[42] is indirect modulatory stimulation therapies whereas RNS detects seizures directly. Implanted intracranial electrodes are placed near the patient's seizure focus or foci. The device delivers small bursts of electrical stimulation which reduces the frequency of seizures after detections thresholds are met. The detection and stimulation parameters of the implanted RNS neurotransmitters are programmed by the physicians.

On the basis of a pivotal study involving 191 patients having refractory focal epilepsy, the RNS device was recently approved by FDA[43]. RNS system safety and effectiveness in 187 patients after two years of treatment, was examined by Christianne Heck and colleagues, a newly published follow-up study[44]. These patients had high refractory epilepsy and from the study, it was found that previously 34% patients had tried VNS, 32% had undergone respective epilepsy surgery, 45% had one identified focus and 55% of the cohort had RNS for two seizure foci. After

two years of treatment, the efficacy of the device increased gradually, more than 50 % seizure reduction was observed and the median seizure reduction was 53% and 54%.

Stereotactic Laser Ablation

This technique is the combination of an image guided system using magnetic resonance imaging (MRI) with thermal ablation to localize high temperature, which is generated by the local absorption of laser energy to destroy the desired tissue. A 1-cm incision is made in the skull, the intracranial probe is inserted through the incision and MRI-guided probe to the target; visualization of thermal ablation can be done in real time[45]. This is a minimally invasive procedure, also called as laser-induced interstitial thermotherapy (LITT), laser interstitial thermal therapy, laser-induced thermotherapy, and interstitial laser therapy and laser ablation. Patients who are considered high-risk surgical candidates, laser thermal ablation may be an alternative to surgical resection for the treatment of focal lesional epilepsy.

CONCLUSION

During the past decade, great progress has been seen in the treatment of epilepsy. New anticonvulsant drugs and an innovative neurostimulation device were marketed almost every year. Randomized controlled trials are the essential evidence to judge the efficacy of the treatment. Despite the introduction many new anticonvulsant drugs, the understanding of the mechanism of certain seizure types is essential as the efficacy of many drugs is only partially explained by their known molecular profiles. As there is no cure for epilepsy, but epilepsy medicines can control seizures. Several compounds having antiepileptic activity are currently being tested. Some of the compounds have novel chemical structure whereas some are derivatives of antiepileptic drugs which are designed to be more efficacious and better tolerated. Surgery or implanted devices (such as vagus nerve stimulators, RNS) are used when medicines are not working. Apart from surgery laser thermal ablation technique is minimally invasive procedure and an alternative to surgical resections.

Table No. 1 New antiepileptic compounds with their Key structural or pharmacological features (modified from Perucca *et al.*, 2007; Patsalos, 2015); AMPA=α-amino-2,3-dihydro-5-methyl-3-oxo-4 isoxazole propionic acid; FDA=US Food and Drug Administration; MAO-B=monoamine oxidase B; SV2A=synaptic vesicle 2A protein.

Compounds	Structural analogue	Pharmacological feature	Stages of clinical development	Use
Brivaracetam	Levetiracetam analogue and Synaptic Vesicle 2A ligand	Additional sodium channel-blocking properties	In phase III development	Refractory epilepsy
Carisbamate	Carbamate derivative	-	Completing phase III development	Refractory partial epilepsy
Eslicarbazepine acetate	An oxcarbazepine derivative	-	Completing phase III development	Refractory partial epilepsy
Fluorofelbamate	Felbamate derivative	-	Completing phase I studies	-
Ganaxolone	A neurosteroid	Acts as modulator of GABAA-mediated transmission	In phase II development	Refractory partial epilepsy
Huperzine A	An alkaloid approved in China for Alzheimer's disease	-	Undergoing initial assessment in epilepsy	
Lacosamide	Methoxypropionamide derivative	-	Completing phase III development	Refractory partial epilepsy and neuropathic
Licarbazepine	Monohydroxy derivative of oxcarbazepine	-		Developed as a racemate for bipolar disorder
Losigamone	β methoxy-butenolide	-	Phase III clinical trial	Refractory partial epilepsy

Retigabine		A selective opener of KCNQ2/3 and KCNQ3/5 channels	Phase III development	Refractory partial epilepsy
Rufi namide	Novel triazole derivative	A sodium channel-blocker		Under assessment by the FDA as adjunctive treatment for the syndrome and for refractory partial seizures
Seletracetam	A levetiracetam analogue		Currently in phase II	
Safi namide		A sodium channel blocker and MAO-B inhibitor	Currently in phase III development	Focused mainly on Parkinson's disease
Stiripentol		A metabolic inhibitor		As adjunctive therapy to clobazam and valproic acid in severe myoclonic epilepsy in infancy
Talampanel		A non-competitive AMPA receptor antagonist	Completed phase II studies	Refractory partial seizures
Parempanel		-		
Tonabersat	A carabersat analogue		Phase IIa assessment	Migraine prophylaxis
Valnoctamide	A metabolically stable constitutional isomer of valpromide (the primary amide of valproic acid)	Undergoing phase II assessment		Bipolar disorder as a racemate
Valrocemide	A derivative of		Phase II development	Refractory epilepsy

(SPD-493)	valproic acid			with potential additional CNS indications

Table No. 2 Stimulation Current vs Pulse Duration in Rat Vagus Nerve Model and Human Vagus Nerve. (Modified from Woodbury and W.J. 1990)

Stimulation duration	**A fiber**		**B fibre**		**C fibre**	
	Rat	Human	Rat	Human	Rat	Human
125µ seconds	10µA	0.250mA	50 µA	1.250mA	325 µA	8.125mA
250µ seconds	5µA	0.0125mA	25 µA	0.625mA	200 µA	5.000mA
500µ seconds	5µA	0.0125mA	10 µA	0.250mA	125 µA	3.125mA

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