Review Article

Recent Advancement in the Treatment and Diagnosis of Epilepsy

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ABSTRACT

Epilepsy is a long term disorder of the brain that occurs due to excessive temporary neuronal discharges resulting in uncontrolled, recurrent seizure of motor, psychological & sensory failure, however, it about never influences with Intelligence. There is a number of the drug being used in the treatment of epilepsy have several serious adverse effects such as hyperactivity in children, motor & systemic adverse effects and many CNS side effects. The research for the perfect antiepileptic compound with more selective activity and lower toxicity continues to be an area of intensive investigation in medicinal chemistry. To provide better treatment the newer antiepileptic drugs such as Brivaracetam, Eslicarbazepine acetate, Perampanel, Ezogabine/retigabine, etc are investigated with lesser adverse effect in comparison to older drugs. Different Non-pharmacological therapy is also identified for the treatment of epilepsy like Gamma-knife surgery, sub-threshold stimulation, stereotactic radiosurgery, minimally invasive surgery, external nerve stimulation various diets includes ketogenic diet, Atkins diet & modifies Atkins diet. Along with this treatment of epilepsy with herbal drugs as adjuvant seems to be more beneficial and is gaining more popularity because of lesser side effects.

Keywords: Traditional antiepileptic drugs, newer antiepileptic drugs, non-pharmacological treatment, herbal medicine.

INTRODUCTION

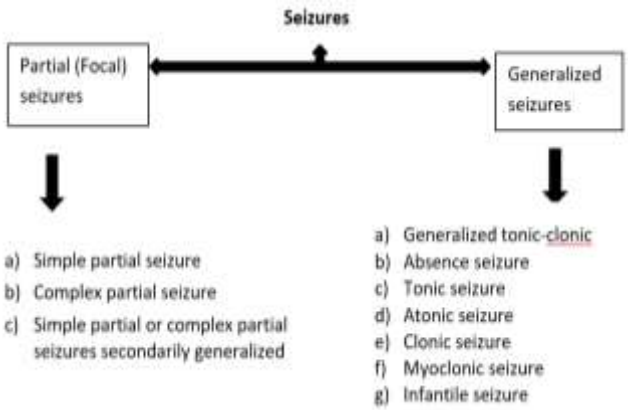
Epilepsy is a disorder of brain globally more than 40 forms of epilepsy have been identified. It is a long term CNS disorder distinguish by temporary, recurrent seizure of motor, psychological & sensory failure, while it about never influence with brainpower (Intelligence).[1] The term 'Epilepsy' based on the Greek Word 'Epilambaein' (meaning 'to seize') was first given by Hippocrates. The seizure called Epileptic seizures it is unusual, unexpected, uncontrolled, quick and local release of Grey matter.[2, 3] Headache is 1st & epilepsy is 2nd familiar neurological condition, specified by recurrent seizures of cerebral origin. 50 million people in the world and an approximate 6 to10 million people in India has experience epilepsy. It is of worry that treatment of this disease is often minimal in developing nations & European region.[4, 5] Epilepsy is both a medical diagnosis and asocial label because people with epilepsy face numerous psychosocial challenges (stress, social disgrace, trouble in driving, joblessness) that can adversely affected quality of life. Seizure are unexpected, temporary, and unlimited incident of brain dysfunction, develop atypical electrical discharge in cerebral neuronal cells, related with delayed depolarization of cerebral neurons result in motor, sensory or behavioral changes. Symptoms that are produced which are controlled by neuronal firing such as, if

- Motor cortex are included, a person might suffer from generalized convulsion or irregular movements.
- Seizures rising from occipital or parietal lobe involve visual, auditory, and olfactory hallucinations.[3]

Seizures may

- Remain localized (focal epilepsy)
- Spread (generalized epilepsy)

Types of Seizures:[6]



Antiepileptic drug (Anticonvulsant)

These are the drug which selectively depress the CNS (Central nervous system) and mainly used to prevent & control epilepsy. The drug should totally reduce seizures in desired doses without causing sedation or any undesired CNS toxicity.[3]

Epidemiology

Epilepsy knows no geographical, racial or social boundaries. Approx. 60 million individuals in this whole World suffer from Epilepsy. It affects both male & female and initiate at any age at any age, but mostly diagnosed in infancy, childhood, adolescence and old age. The prevalence in developed countries is about 0.5% (0.4%-1%)

and in developing countries it is five time higher. The incidence in developed countries after infancy annual incidence is about 20-70/100000 & in developing countries the incidence is double approx. 100/100000. The having a single seizure risk for life time is about 5%.[4]

Symptoms of Epilepsy

Motor	Sensory	Automatic	Psychic
Twitching	Numbness	Lip smacking	Fear
Jerking	Tingling	Chewing	sadness
Rhythmic or semi-rhythmic uncontrolled movements	Pain	Swallowing	Elation Laughing

Other symptoms: Loss of tone, blackout, incontinence, and tongue biting, Staring or repetitive blinking, muscle spasms, Altered awareness, involuntary movement of arms and legs, visual hallucinations, emotional changes, impaired ability to connect usually, Individual may be unknowing seizure has happened.[1, 6]

Pathophysiology

At level of cortical plasma membrane, in a patients of epilepsy, some biochemical occurrence define the focus of epileptogenic, involving:

Nerve cell membrane instability

↓

Polarization irregularities such as unnecessary polarization, hypopolarization, or intervals in repolarization and allows the cell stimulation

↓

Oversensitive neurons with decreased thresholds for firing & firing extremely, linked to

↓

Increased excitatory transmitter activity such as Ach & Glutamate or reduced inhibitory activity such as GABA

↓

Causes instability of plasma membrane and decreased threshold for excitation

↓

Unnecessary polarization, hypo polarization permitting the cell activate naturally or by some ionic differences in instant chemical atmosphere of neurons. [6]

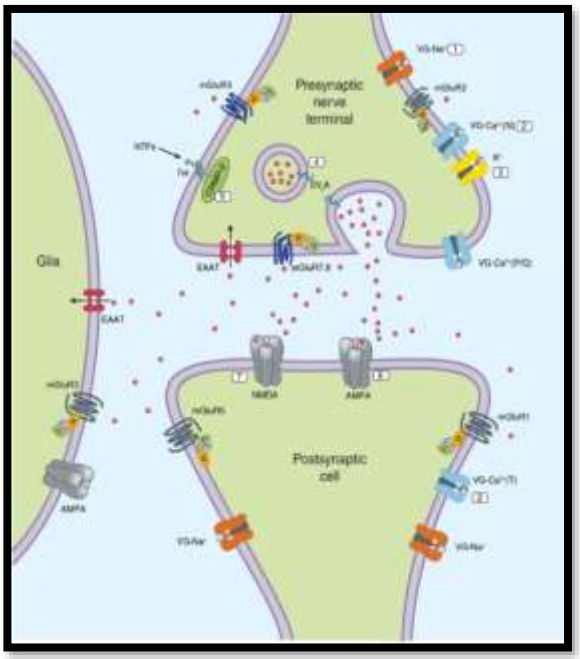
Mechanism of Action:

The aim of Anti-epileptic drugs is to prevent the unusual discharge of neurons instead to correct the principal cause. There are 3 principal action appear to be important:[1, 2]

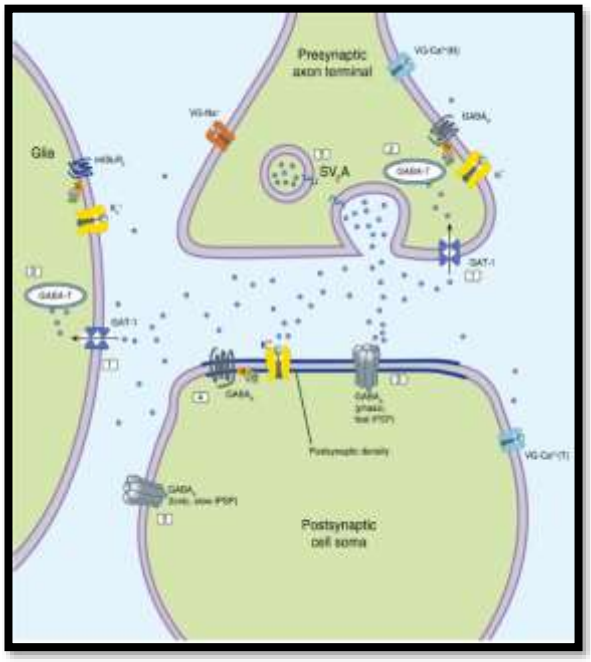
1. GABA action enhancement.
2. Function of sodium channel inhibit
3. Function of calcium channel inhibit.

Another mechanisms involve -

1. Release of Glutamate inhibit and
2. Glutamate receptor block



Molecular targets for antiseizure drugs at the excitatory, glutamatergic synapse



Molecular targets for antiseizure drugs at the inhibitory, GABAergic synapse

Pharmacological treatment

Traditional Antiepileptic drugs[1, 2]

Drugs	Mechanism of action	Adverse effect
Phenobarbitone	Enhance g-amino butyric acid (GABA) inhibition	CNS adverse effects including sedation; hyperactivity in children
Primidone	metabolized to Phenobarbital which is the active compound	Inferior tolerability particularly in children.
Phenytoin	voltage gated sodium channels blockage	Several motor & systemic adverse effects; un-predictability because of non-linear elimination kinetics
Ethosuximide	Decrease of low threshold T-type calcium currents in thalamic neurons	Many CNS and systemic side effects
Benzodiazepines	Potentiation of $GABA_A$ mediated inhibition	Sedation, cognitive dysfunction, tolerance and withdrawal seizures
Carbamazepine	Voltage gated sodium channels blockage	Irregular toxicity; can aggravate absence & induction of enzyme; myoclonic seizures
Valproate	Precise mechanism unknown; multiple GABA-related actions	Weight gain, hepatotoxicity; teratogenicity
Lamotrigine	sodium channels blockade & to a reduced amount, calcium channels	Slow titration; occasionally severe Rash
Gabapentin	Structure is similar as GABA (gammaaminobutyric Acid) but its exact action in humans are not known	Modest efficacy

Newer antiepileptic drugs[7-11]

Drugs	Year of Approval	Mechanism of action	Adverse effect
Brivaracetam	February 2016	Synaptic vesicle affinity are high protein 2A ligand & at neuronal voltage gated sodium channels (VGSC) it shows inhibitory action.	headache, somnolence, dizziness, fatigue
Eslicarbazepine acetate	November 2013	Voltage gated sodium channels blockade	Somnolence, diplopia, abnormal coordination, blurred vision, vertigo and fatigue
Perampanel	October 2012	Selective and noncompetitive AMPA (2-amino, 3-*hydroxy*, 5 methyl, 4-isoxale propionic acid) antagonist.	dizziness, somnolence, memory impairment, abnormal coordination disturbance in attention
Ezogabine / retigabine	June 2011	potassium currents enhancement mediated by precise family of ion channels called KCNQ[11]	Urinary retention, Neuropsychiatric symptoms, like confusion & Hallucinations associated with psychotic states
Lecosamide	2008	Enhances slow inactivation of sodium channels	Dizziness, diplopia, PR prolongation
Stiripentol	2007	enhances central $GABA_A$ transmission[9]	Loss of appetite
Pregabalin	2005	Controls chemical transporter discharge by bind with α-2-delta sub-unit of voltage gated calcium channel	Dizziness, somnolence, weight gain
Rufinamide	2004	Sodium channels variation, specially, time spent time prolongation in the lethargic state of channel	Fatigue, anorexia, drowsiness, Serious seizures, status epilepticus, expansion of QT-interval
Zonisamide	2000	Multiple mechanisms Involving blockade of sodium and calcium channel (T type), potentiation of GABA, carbonic anhydrase inhibition	drowsiness, loss of appetite, atypical thinking, oligohydrosis, aplastic anemia, Stevens Johnson syndrome, renal calculi
Levetiracetam, topiramate	1999	Binds to synaptic vesicle 2A (SV2A) protein	vertigo, drowsiness, abnormal physical health, insomnia, problems related to behavior, depression Psychosis
Tiagabine	1998	Blocks the re-uptake of GABA in glial cells & neurons	tremor, atypical thinking, sweating, Rare psychosis, rare non-convulsive status epilepticus

Non-Pharmacological treatment[9, 12-14]

Epilepsy surgery techniques	Neurostimulation	Diet therapy
Focal resection	Vagul nerve stimulation	Ketogenic diet
Multiple Subpial Transection	Responsive Neurostimulation	Atkins Diet
Corpus Callosotomy	Investigational therapy	Modified atkins diet
Hemisphrectomy	Deep brain stimulation	Others with low glycemic index
Laser interstitial thermal therapy	Transcranial Magnetic Stimulation	
Functional hemisphrectomy	Electroconvulsive Therapy	

Upcoming treatment for Epilepsy

Scientists are studying several possible novel cures for epilepsy, involving:

Sub-threshold stimulation

Sub-threshold spurs in a part of your brain under a level i.e. physically observable, seems to recover seizure results personal satisfaction for certain individuals with seizures. This method might beneficial for individuals who suffer from seizures which start to a specific part of the brain which cannot remove due to it affects speech & CNS functions. Or it may be beneficial for those individuals who has low neuro-stimulation.[12]

Minimally invasive surgery

Novel invasive surgical methods, like Magnetic Resonance Imaging shown laser ablation, display capacity at decreasing seizures with rare risks in comparison to older open brain surgery for epilepsy.

Stereotactic radiosurgery

For certain kinds of epilepsy, stereotactic laser ablation or stereotactic radiosurgery might deliver actual treatment when an open system might be excessively dangerous. In this techniques, specialist direct radiation at particular part in the brain producing seizures to terminate that tissue in a work to improve the seizures.

External nerve stimulation device

It is very parallel to device called vagus nerve stimulation, for reducing the seizures frequency this gadget are very helpful because they excite particular nerves to decrease the seizures. But dissimilar to vagus nerve stimulation, this gadget damaged externally that's why no surgery to transplant the gadget are required.

Gamma knife surgery

This surgery is used to deliver a fixed amount of radiation to a specific point in brain, which are recognized on MRI. They are beneficial for patients because it involves decreased hospital stay, no craniotomy, & decrease the risk of bleeding & infection. Firstly, used for lesions which are deep inside the brain, its use was effectively prolonged to involve tumors and arterio-venous malformations. This surgery are presently being estimated for three conditions linked with epilepsy: vascular malformations, hypothalamic hamartomas linked with gelastic epilepsy, & mesial temporal lobe sclerosis linked with medial temporal lobe epilepsy.[9, 10]

Research progress in the diagnosis of epilepsy[12, 23]

The diagnosis of epilepsy is depending on precise older explanation of ictal episodes. The precise explanation beneficial for categorizing the type of seizure & epileptic syndrome. It also directs the doctor to starting the suitable Anti-epileptic drugs for epilepsy. In drug-resistant epilepsy, the explanation of semiology beneficial for lateralization & localization of the potential ictal beginning region. Different recording parameters are used like EEG, ictal single-photon emission positron computed tomography (SPECT), and positron emission tomography (PET) which are focused & accurate. We recently systematically evaluated the precision of home videos in evaluating the signs in epilepsy. India has the 2nd major ratio of cell phone operators, & this device never previously estimated for measuring epilepsy. The results of this study display that prevalent accessibility of cell phones, this is useful for rural region, and it can record seizures & categorize epilepsy precisely. In India this will very helpful for the management of epilepsy as well as for clinical studies.

Herbs used in the treatment of epilepsy[3, 15 -19]

S.no	Plant name	Scientific name	family	Part used	Uses
1	Jatamansi	*Nardostachys jatamansi*	Valerianaceae	Roots	epilepsy, hysteria, syncope, and mental weakness
2	Brahmi	*Bacopa monnieri*	Plantaginaceae	Leaves	asthma, epilepsy, insanity, and hoarseness
3	Dell- holl	*Ficus platyphylla*	Moraceae	Stem-bark	psychoses, depression, epilepsy, pain, and inflammation
4	Ashwagandha	*Withania somnifera*	solanaceae	Root	Depression, epilepsy, anti-cancer property, stress, anxiety
5	Him-champa	*Magnolia grandiflora*	Magnoliaceae)	Seeds	Rheumatism, epilepsy [20]
6	Bay laurel	*Laurus nobilis*	Lauraceae	Leaves	epilepsy, neuralgia, and Parkinsonism
7	Devil's claw	*Harpagophytum procumbens*	Pedaliaceae	Roots	*petit* and *grand mal* types of epilepsy
8	Himalayan Yew	*Taxus wallichiana*	Taxaceae	Leaves	herbal tea for indigestion and epilepsy
9	Jadwar	*Delphinium denudatum*	Ranunculaceae	Roots	Brain diseases
10	Skullcaps	*Scutellaria baicalensis*	Lamiaceae	Whole plant	Inflammation, anxiety, epilepsy
11	Satavari	*Asparagus Racemosus*	Asparagaceae	Root	depression and memory deficit
12	Liquorice	*Glycyrrhiza glabra*	Fabaceae	Root	CNS disorders
13	Water clover	*Marsileaquadrifolia*	Marsileaceae	leaves	Management of epilepsy
14	Sacred fig	*Ficusreligiosa*	Moraceae	Whole tree	management of epilepsy and associated behavioral comorbidities
15	Bel	*Aegle marmelos*	Rutaceae	Fruit	CNS disorders
16	Princess vine	*Cissus sicyoides*	Vitaceae	Aerial part	Epilepsy
17	Passion flower	*Passiflora*	Passifloraceae	Leaves & flower	Insomnia, epilepsy, hypertension
18	Damask rose	*Rosa domescana*	Rosaceae	Leaves	Reduce anxiety, depression, stress

19	Vriddhadara	*Argyreia speciosa*	Convolvulaceae	leaves	Anticonvulsants, antidepressant, analgesics
20	Barberry	*Berberis vulgaris*	Berberidaceae	Fruits	Blood pressure, cholera, cancer [21]
21	Hill glory bower	*Clerodendrum infortunatum*	Lamiaceae	leaves	Liver disorders, joint pain, skin diseases
22	Echium	*Echium amoenum*	Boraginaceae	flower	CNS disorders[22]
23	Punarnava	*Boerhavia diffusa*	Nyctaginaceae	Roots	Antoiconvulsant, analgesic, rheumatoid arthritis
24	Holy basil	*Oscimum sanctum*	Lamiaceae	leaves	Anxiety, stress, joint pain, anti-inflammatory
25	Pongame oiltree	*Pongamia pinnata*	Fabaceae	leaves	Herpes, rheumatism
26	Saussurea	*Saussurea lappa*	Asteraceae	Roots	Anti-inflammatory, angina, arthritis
27	Java citronella	*Cymbopogon winterianus*	Poaceae	leaves	Antidepressant, febrifuge, diuretic
28	Valerian	*Valeriana officinalis*	Caprifoliaceae	Roots	Anxiety, psychological stress, insomnia
29	Sacred tree	*Butea monosperma*	Fabaceae	flower	Management of epilepsy
30	Cancer bush	*Sutherlandia frutescens*	Fabaceae	shoot	Rheumatism, epilepsy, liver problems

New drugs in the pipeline for epilepsy[12, 24]

S.no	Drugs	Sponsor	Target	Condition	Clinical trial phase
1.	Muscimol	National Institute of Neurological Disorders and Stroke (NINDS)	$GABA_A$ receptor	Epilepsy	Phase 1
2.	BGG492 (Selurampanel)	Novartis Pharmaceuticals	AMPA/ kainate receptor antagonism	Refractory partial seizures	Phase 2
3.	Ganaxolone	Marinus Pharmaceuticals	Positive allosteric Modulator of $GABA_A$ receptors	Uncontrolled partial epilepsy; catamenial epilepsy	Phase 2
4.	Buspirone	NINDS	5-$HT1_A$ receptor partial agonist	Localized epilepsy	Phase 2
5.	Brivaracetam (ucb 34714)	UCB Inc.	a new high-affinity SV2A ligand	Epilepsy	Phase 3
6.	PRX-00023	NINDS	5-HT receptors	TLE; partial epilepsy	Phase 2
7.	RWJ-333369 (carisbamate)	SK Life Science	Not elucidated	Partial epilepsy	Phase 3
8.	CPP-115	Catalyst pharmaceuticals	a GABA transaminase inhibitor (vigabatrin derived)	Epilepsy spasms	Phase 2
9.	ICA-105665	Pfizer	an extremely selective opener of neuronal Kv7 (KCNQ) potassium channels	Epilepsy	Phase 2
10.	UCB0942 (Padsevonil)	UCB Inc.	a new pre- and post-synaptic inhibitor	Focal epilepsy	Phase 2
11.	VX-765 (Belnacasan)	Vertex	a selective inhibitor of inter leukin-converting enzyme	Epilepsy	Phase 3
12.	YKP3089	SK Life	That attribute a new mode of action	Partial epilepsy	Phase 3
13.	2-Deoxy-D-glucose	Neuro- GenomeX	a glucose analog and glycolytic inhibitor	Epilepsy, alzheimer's disease	Phase 3
14.	NAX 810-2	Neuro Adjuvants	a galanin receptor 1 (GALR1) and GALR2 agonist	Epilepsy	Phase 2
15.	Valnoctamide	Hebrew University	a valproic acid second-generation derivative	Mania, epilepsy, schizoaffective disorder	Phase 3
16.	Imepitoin	-	a low-affinity partial agonist at the benzodiazepine site of the GABA-A receptor	Epilepsy	Phase 3
17.	TRI476	Novartis Pharmaceuticals	modulation of Sodium channel	Sodium channel modulation	Phase 3

Novel approaches

COX-2 inhibitors as potential therapeutics in epilepsy

It is reported from various clinical studies that COX enzyme which are present in brain is rate limiting enzyme which catalase the conversion of arachidonic acid into prostaglandins are induced by seizures.[25]

Celecoxib a NSAID which is investigated to use in the management of pilocarpine induced epilepsy. It observed that reduces the frequency of seizures and duration but not much effective to reduce the number of rat that developed epilepsy. Perecoxib a second generation PTG-2 inhibitor & also a NSAID are investigated in pilocarpine induced SE. The result is not much effective in comparison to vehicle it only reduces the behavioral severity of seizures. It is reported from literature that COX-2 inhibitors have a potency for the treatment of resistant epilepsy by reducing the upregulation of P-glycoprotein which is a rate limiting step in penetration of AEDs in Blood brain barrier. It is well established that during seizures, P-glycoproteins were upregulated that reduces the efficacy of AED and its penetration in BBB.

Neurosteroids

Steroidal hormones & neurosteroids were reported to have anticonvulsant and pro-convulsant properties. During menstrual cycles, progesterone have anticonvulsant properties while estrogen have pro-convulsant properties. The level of estrogen increases before ovulation while the level of progesterone decreases prior menstrual bleeding make patient more prone for seizures. [11] Progesterone is converted into allopregnanolone. Allopregnanolone is a neurosteroid with anti-convulsant action and it binds to the GABA-A receptor and increase the inward flow of chloride and causes membrane hyperpolarization. Allopregnanolone is different from BZD and barbiturates because it also affects in BZD resistant therapy. Ganaxolone is a neurosteroidal analogue of allopreganolone and GABA-A receptor mediated anti-convulsant properties. Ganaxolone in dose of 150 mg/day reduces the weekly seizure frequency by 18%.[26, 27]

Pharmacogenomics

The recent therapeutics approaches used in the management of symptomatic seizure the modern scientist more likely to use biomarkers- based anticipation of epileptogenesis. Due to the complexity of disease, a single biomarkers is not much effective to predict epileptogenesis that's why a combination of approaches used to identify suitable biomarkers at different stages of epilepsy. Modern scientist also identified several key factors (i.e. biomarkers & mutations) to identify the risk associated in the development of disease. In the development of epilepsy, several changes occur which will further lead to epileptogenesis. These changes are immune responses, neuronal plasticity, cell survival and death. These changes were served as a new target for the identification, management and treatment of disease. The complex pathophysiology of disease transcription may use to target the biomarkers which are involved in the development of disease. Other biomarkers like blood biomarkers of brain injury. BBB damage inflammation epigenetic factor and microRNA require clinical validation. Genetic biomarker may also target to reduce the transfer of disease from parents to offspring's.[12]

For example, 10% patient with early onset absence early-onset epileptic patient may cause mutation in the glucose transporter gene SLCAI. These kinds of patient diagnosed by genetic sequencing and gene mapping and may be treated with ketogenic diet. Gene mapping may also help to reduce the risk of epilepsy by avoiding the unhealthy diet and gene mapping also help in the treatment of epilepsy by personalized medicine.[28]

CONCLUSION

Epilepsy is a serious brain disorder, available drugs which are used in the treatment of epilepsy have several serious side effects So many newer AEDs have been introduced in the last few years with improved pharmacokinetics and potentially novel mechanism of actions, different non-pharmacological therapy are also beneficial for treating epilepsy like several surgical techniques & diets, along with this treatment herbal drugs as adjuvant seems to be more beneficial & gaining more popularity because of lesser side effects. Results from clinical studies have shown different new drugs in pipeline & various novel approaches may also beneficial for treating epilepsy. Availability of these new treatments for epilepsy will further increase the treatment options and thus provide a significant benefit to patients who remain uncontrollable to existing therapy.

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