ADVANCEMENT IN EPILEPSY PHARMACOTHERAPY: AN INSIGHT ON PHARMACOPHORIC APPROACHES OF RECENT DRUGS

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Abstract

Epilepsy is the most general, extensive, and severe neurodegenerative disorder, yet we only have a minimal understanding of its pathogenesis and treatment rationale. This neurodegenerative disorder is affecting more than 50 million individuals globally. Initially, conventional medicines and simple salts like potassium bromide were employed as an antiepileptic medication candidate. Nowadays, a lot of anticonvulsant drugs have been discovered as first-generation, second-generation, and newer drugs and still, they are in development phases. The pharmacophore-based drug design process includes pharmacophore modeling and validation, pharmacophore-based virtual screening, virtual hits profiling, and lead identification with special reference to it. This comprehensive article reviews recently developed anticonvulsant derivatives on the basis of pharmacophoric approaches. A literature survey was performed using various search engines like
Google Scholar, Scopus, Sci Finder, ScienceDirect, Science gate, Scilit, PubMed, NINDS database of NIH, Bentham Sciences, and other online and print journals and scientific databases for the same. The presented review discusses such kinds of newer drugs that are in the market as well as in clinical trial phases. Detailed outcomes of pharmacophoric modeling have been discussed for newly derived derivatives like targets involved in Epilepsy, lead molecules etc. for the treatment of epilepsy. This exhaustive review will assist the researchers in further development of potential antiepileptic agents.

**Keywords:** Epilepsy, neurologic, derivatives, anticonvulsant, pharmacophore, clinical trial.

**Graphical Abstract**

Graphical Abstract: The graphical representation depicts the evolution of antiepileptic drug discovery, from the earliest medicine (KBr) to the most recent medications in clinical trials.

**Introduction:**
Epilepsy is a form of neurological disorder that affects more than 50 million people worldwide. An approximate 5,000,000 individuals are expected to have epilepsy per year worldwide [1,2]. In top-level salary countries, there are found to be 49 for every 100 000 individuals determined to have epilepsy every year [3]. In low-and center income countries, this figure can be as high as 139 for each 100 000[4,5]. This is likely because of the expanded danger of endemic conditions, for example, intestinal sickness or neurocysticercosis; the higher rate of street traffic wounds; birth-related wounds; and varieties in the clinical foundation, the accessibility of preventive wellbeing programs, and open consideration [6-8]. Nearly 80% of individuals with epilepsy live in low-and center income countries [9]. Epilepsy is a persistent non-communicable illness of the mind that influences individuals [10,11]. It is portrayed by repetitive seizures, which are brief episodes of compulsory development that may include a piece of the body [fractional]. or the whole body [summed up]. and joined by loss of awareness and control of inside or bladder work [12-14]. Seizure episodes are a consequence of unreasonable electrical releases in a gathering of synapses [15]. Various pieces of the cerebrum can be the site of such releases [16]. Seizures can differ from the briefest omissions of consideration or muscle bastards to serious and delayed spasms [17,18]. Seizures can likewise shift in recurrence, from under 1 every year to a few every day [19]. One seizure does not mean epilepsy [up to 10% of individuals worldwide have one seizure during their lifetime [20]. Epilepsy is characterized by having at least two unexpected convulsions [21]. Epilepsy is one of the world's most established perceived conditions, with put-down accounts going back to 4000 BC [22]. Dread, misconception, separation, and social shame have encircled epilepsy for quite a long time [23]. This disgrace proceeds in numerous countries today and can affect the personal satisfaction of individuals with the illness and their families [24].

Seizures can range from little lapses in judgment or muscular twitches to severe and delayed spasms [25]. Seizures can likewise shift in recurrence, from under 1 every year to a few every day [25]. One seizure does not mean epilepsy [up to 10% of individuals worldwide have one seizure during their lifetime [26-28]. Epilepsy is characterized by having at least two unexpected seizures [29]. Epilepsy is one of the world's most established perceived conditions, with put-down accounts going back to 4000 BC [30]. Dread, misconception, separation, and social shame have encircled epilepsy for quite a long time [31,32]. This disgrace proceeds in numerous
countries today and can affect the personal satisfaction of individuals with the illness and their families [33].

The specific instrument of epilepsy is obscure, however, a little is thought about its cell and organization systems [34]. notwithstanding, it is obscure under which conditions the mind shifts into the action of a seizure with its exorbitant synchronization [35]. In epilepsy, the obstruction of excitatory neurons to fire during this period is diminished [36]. This may happen because of changes in particle channels or inhibitory neurons not working appropriately [37]. This at that point brings about a particular zone from which seizures may create, known as a "seizure center" [38-40]. Another system of epilepsy might be the up-guideline of excitatory circuits or down-guideline of inhibitory circuits following a physical issue to the cerebrum [41]. These auxiliary epilepsies happen through cycles known as epileptogenesis [42,43]. Disappointment of the blood–cerebrum hindrance may likewise be a causal component as it would permit substances in the blood to enter the mind [44]. There is proof that epileptic seizures are normally not an irregular occasion. Seizures are regularly welcomed by elements, for example, stress, liquor misuse, flashing lights, or an absence of rest, among others [45]. The term seizure limit is utilized to demonstrate the measure of boost important to achieve a seizure. The seizure limit is brought down in epilepsy [46]. In epileptic seizures, a gathering of neurons starts terminating in an unusual, unnecessary, and synchronized way [47]. These outcomes in an influx of depolarization known as a paroxysmal depolarizing shift [16]. Typically, after an excitatory neuron fires, it turns out to be more impervious to terminating for a while [48]. This is expected partially with the impact of inhibitory neurons, electrical changes inside the excitatory neuron, and the negative impacts of adenosine [49]. Central seizures start in one half of the globe of the mind while summed up seizures start in the two sides of the equator [50,51]. A few sorts of seizures may change cerebrum structure, while others seem to have little impact [52]. Gliosis, neuronal misfortune, and decay of explicit territories of the cerebrum are connected to epilepsy however it is hazy if epilepsy causes these progressions or if these progressions bring about epilepsy [53]. The sickness disturbs the movement of synapses called neurons, which regularly send messages as electrical motivations. A break in these motivations prompts seizures [54]. There is a wide range of sorts of epilepsy and various kinds of seizures. Quite possibly the most-contemplated synapses that assume a job in epilepsy are GABA, or gamma-aminobutyric
corrosive, which is an inhibitory synapse. [55]. Exploration of GABA has prompted drugs that modify the measure of this synapse in the mind or changes how the cerebrum reacts to it [56]. The presented review describes the note on epilepsy, the targets involved in epilepsy, and its inhibitors.

**Material and methods:**

This analysis includes all available randomized clinical trials and remarkable peer-reviewed analysis that explored features related to Epilepsy in developing economies to ensure a thorough examination of the works. On the following concepts involving Epilepsy in emergent markets, a systematic search of the literature was conducted using EMBASE, PubMed, and the Cochrane Review databases: Epidemiology, such as prevalence and incidence; economics, such as disease burden, productivity consequences, and other economic difficulties; drug consumption trends; treatment patterns; treatment guidelines; and unmet requirements.

**Pharmacophoric Model for Anticonvulsant Drugs:**

Pharmacophore models for the antiepileptic drug which have been recently developed are given below in figure 1. The pharmacophore model consists of the information about the binding capability of a drug to its specific target [57-58]. Such kinds of models cover the information about the binding affinity of the drug towards its receptors. Pharmacophoric models of antiepileptic drugs contain three central critical regions; a) hydrophobic domain, b) hydrogen bond D/A, c) electron acceptor [59-60].
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Section A - Research paper
Figure 1: Pharmacophoric features of recently developed antiepileptic derivatives

Targets for antiepileptic drugs

The regulation of excessive neuronal behavior with antiepileptic drugs [AEDs]. is done by raising the threshold of chemical and electrical stimuli of the neurons [61]. or by limiting the distribution of seizures emitted from their base [62,63]. In the pathophysiology of all causes of epilepsy, ion channels play an important part, rendering them clear targets for AEDs [64]. The possible molecular targets of AEDs have been established by current cellular neurophysiological and biochemical approaches and depicted in figure 2 [65]. Recent targets like Glu R5 kainite receptor, α2- δ subunits of voltage-activated Ca2+ ion channels,[66] L type voltage-gated Ca2+ ion channel, SV2A [synaptic vesicle protein]., T type voltage-gated Ca2+ channels, α subunit of voltage-gated Na+ channel[67], two inward rectifier [Kir]. transmembrane-helix channels, the Ca2+-activated K+ channels [KCa]., and the tandem-pore domain [K2P]. channels, [68]. Hyperpolarization-activated cyclic nucleotide- gated cation [HCN]. Channels [69], GAT-1 [GABA reuptake inhibitor], GABAA AND GABAB [γ-aminobutyric acid]. cation chloride contraseptors, AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor],[70]. NMDA [N-methyl-D-aspartate receptor]. [71]. some neurotropic receptor-like BDNF [Brain-derived neurotrophic factor]., TrKB [Tropomyosin receptor kinase B][72], FGF [basic fibroblast growth factor ][73], glutamate receptors[74], these are the all active site which are work as new targets for antiepileptic drugs [75].
Figure 2: This graphic depicts various targets that are accountable for the convulsions.

2.3 Recently developed antiepileptic derivatives

2.3.1 Clobazam

In the treatment of epilepsy associated with Lennox-Gastaut syndrome, clobazam is used as adjunctive therapy. It was authorized in October of 2011 by the USFDA. Clobazam acts often by GABAA receptor positive allosteric modulation [76]. For acute seizures, Clobazam is safe and reliable. Clobazam is demethylated into its active metabolite N desmethylclobazam by cytochrome P450 CYP3A4 and CYP2C19 [norclobazam]. Since norclobazam itself is an anticonvulsant, an increase in its levels substantially enhances the duration of therapeutic effects by inhibiting CYP2C19 [77].
1.1.1 Stiripentol

An anti-epileptic drug Stiripentol is used in the treatment of refractory generalized tonic-clonic seizures in children with serious pediatric myoclonic epilepsy as adjunctive therapy of clobazam and valproate [78]. About 500 children in Japan have been successfully treated and new studies have been carried out. It increases GABAA central transmission [79].

1.1.2 Eslicarbazepine acetate

It was approved as a specific treating element in young humans having partial-onset seizures with or without secondary generalization by the EMA in 2009 and by the USFDA in November 2013 [80]. The weak activation of the voltage-gated Na+ channels is inhibited by ESL. ESL is quickly and completely metabolized into eslicarbazepine within 1-4 hours by hydrolytic first-pass metabolism [81]. ESL is quickly and completely metabolized into eslicarbazepine within 1-4 hours by hydrolytic first-pass metabolism [82].
2.3.4 Perampanel

Perampanel [PRP] has a broad anticonvulsant action continuum. It was authorized in July 2012 by the European Commission and in October 2012 by the USFDA [83]. PRP is a 2-amino, 3-hydroxy, 5-methyl, 4-isoxale propionic acid [AMPA] antagonist that is selective and non-competitive. Perampanel prevents the rise in intracellular Ca++ caused by AMPA and selectively prevents synaptic communication mediated by AMPA receptors, thus minimizing neuronal excitation [84].

2.4.5 Brivaracetam

Brivaracetam [BRV] is a novel synaptic vesicle protein 2A ligand with high affinity and exhibits inhibitory action at voltage-gated neuronal voltage channels [VGSC]. It is more potent faster in
action and has optimum SV2A occupancy [85]. The treatment of uncontrolled partial seizures in adults was recently approved by the USFDA in February 2016 [86].

2.4.6 Ezogabine

Ezogabine [EZG]. is also known as Retigabine, it is an ethyl ester carbamic acid, operates on the channels of potassium, GABA-A receptors, sodium, and calcium. It is a beneficial agent for the treatment of benign familial neonatal convulsions [BFNC]. caused by the lack of KCNQ2/KCNQEZG gene function mutations [87]. It was recently approved by the EMA in March 2011 and the USFDA in June 2011 as adjunctive therapy for partial-onset seizures [88,89].
2.5 Recent drugs available in the market for epilepsy:

For people with epilepsy, medicine is the most commonly recognized therapy. There are currently approximately twelve drugs. The majority of epilepsy disorders and, by far, most inherited conditions that cause seizures are treated with current medications satisfactorily. In case you're on the correct medication, you're probably going to have great control of your seizures. In any case, in case you're on some unacceptable medicines, you may continue having seizures - and you probably won't realize that there are better methodologies out there. Following table 1 contains the list of recent drugs used as therapeutic agent against epilepsy with their brief summary.

Table 1 presents a list of medications that the FDA has recently approved to treat seizures of any kind. The list also includes anti-seizure medicines that have newly been manufactured or discovered.

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Recent Drugs</th>
<th>Chemical Structure</th>
<th>Mechanism of action</th>
<th>FDA</th>
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</table>

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<tr>
<th>No.</th>
<th><strong>Drug</strong></th>
<th><strong>Synonym</strong></th>
<th><strong>Formulated Form</strong></th>
<th><strong>Approved Date</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cannabidiol [CBD] [42]</td>
<td>Epidiolex</td>
<td>Oral Solution</td>
<td>31&lt;sup&gt;st&lt;/sup&gt; July 2020</td>
</tr>
<tr>
<td></td>
<td><strong>Synonym:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>Fenfluramine [43]</td>
<td>Fintepla</td>
<td>Oral Solution</td>
<td>26&lt;sup&gt;th&lt;/sup&gt; June 2020</td>
</tr>
<tr>
<td></td>
<td><strong>Synonym:</strong></td>
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</table>

There is evidence that CBD triggers serotonergic 5-HT1A and vanilloid TRPV1-2 receptors, antagonizes μ-opioid and alpha-1adrenergic receptors, inhibits synaptosomal noradrenaline absorption, dopamine, serotonin, and aminobutyric acid and anandamide cell uptake, works on Ca<sup>2+</sup> mitochondria stocks, blocks Ca<sup>2+</sup> low-voltage-activated [T-type] pathways, induces inhibitory glycine production.

Fenfluramine increases extracellular serotonin levels and serves as both a 5-HT2 serotonergic receptor agonist and an antagonist of the σ<sub>1</sub> receptor. These activities contribute to anti-epileptiform training and
Vigabatrin [44]

**Synonym:**
Sabril

**Formulated**
Form

**Supplemental drug**

| 3 | Vigabatrin [44] | By irreversible inhibition of GABA transaminase, Vigabatrin inhibits GABA metabolism [GABA-T]. Since vigabatrin is an irreversible gamma-aminobutyric acid transaminase [GABA-T] inhibitor, it is assumed that its span of action depends on the rate of re-synthesis of GABA-T rather than the rate of drug removal. | 24th Jan 2020 |

Cenobamate [45]

**Synonym:**
Xcopri

<p>| 4 | Cenobamate [45] | The cenobamate mechanism is unclear, but it modulates GABAA and inhibits the sodium | 21st Nov 2019 |</p>
<table>
<thead>
<tr>
<th>Formulated Form</th>
<th>channel voltage-gated.</th>
<th>5</th>
<th>Pregabalin [46]</th>
<th>In the central nervous system, it connects the alpha2 – delta subunit of presynaptic voltage – gated calcium channels</th>
<th>22nd July 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
<td>Synonym: NA</td>
<td></td>
<td></td>
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<tr>
<td>Formulated Form</td>
<td>First Generics</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>Nayzilam [47]</td>
<td>Midazolam is a central nervous system [CNS] depressant and short-acting benzodiazepines. Benzodiazepines improve the inhibitory action of the gamma-aminobutyric acid neurotransmitter amino acid [GABA].</td>
<td>17th May 2019</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Synonym: Midazolam</td>
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<tr>
<td>Formulated Form</td>
<td>Intranasal spray</td>
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<td>7</td>
<td><strong>Fycompa</strong> [47]</td>
<td>It is a potent glutamate receptor antagonist for alpha – amino – 3 – hydroxy – 5 – methyl – 4 – isoxazole propionic acid [AMPA], with the activity against epilepsy. While the mechanism of action by which perampanel exerts its antiepileptic activity has not been fully explained, 1st Sept 2018</td>
<td></td>
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<tr>
<td></td>
<td><strong>Synonym:</strong> Perampanel</td>
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<tr>
<td></td>
<td><strong>Formulated Form</strong> Oral Powder</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td><strong>Diacomit</strong> [48]</td>
<td>By raising the levels of the inhibitory neurotransmitters in the brain, it potentiates GABA transmission. Stiripentol is a positive allosteric modulator of GABA-A receptors in the brain that binds to a different site than the benzodiazepine binding site to maximize the opening length of the channel, 20th Oct 2018</td>
<td></td>
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<tr>
<td></td>
<td><strong>Synonym:</strong> Stiripentol</td>
<td></td>
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<tr>
<td></td>
<td><strong>Formulated Form</strong> Capsule/Oral Powder</td>
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<td></td>
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<td></td>
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<tr>
<td>9</td>
<td><strong>Briviact</strong> [49]</td>
<td>With high affinity, brivaracetam binds, 10th May 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Synonym: Brivaracetam
Formulated Form Oral Solution

SV2A. By modulating synaptic GABA release, SV2A is believed to play a role in epileptogenesis. Brivaracetam is thought to exert its anti-epileptogenic effects by its binding to SV2A.

10 Afinitor [50]

Inhibition of mammalian target of rapamycin activity results in inhibition of activation and proliferation of T lymphocytes associated with induction of antigens and cytokines [IL-2, IL-4, and IL-15] and inhibition of the development of antibodies.

10th April 2018

Synonym: Everolimus
Formulated Form Tablet/ Oral Suspension

Other marketed antiepileptic drugs include Carbamazepine, Zonisamide, Phenytoin, Oxcarbazepine, Valproate, Felbamate, Topiramate, Tiagabine, Phenobarbital, Benzodiazepine etc [96-99].

2.6 Antiepileptic drugs under clinical trials:

Clinical studies have raised a ray of hope for humanity. It has shown some benefit in research centre testing, patient testing, or testing with a small gathering of volunteers until
researchers discovered any new approach [100]. In larger meetings of people, clinical trials are then conducted to test whether another procedure works and is protected [101]. Recent drugs under clinical trial have been listed in table 2. Novel medicines cannot be sold in the United States until they had passed clinical trials [102]. Treatments that demonstrate viability during this examination may proceed to get endorsed for specific use in individuals.

Table 2 lists the medications that are currently being explored in clinical trials:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical Structure</th>
<th>Description</th>
<th>Associated Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA-105665</td>
<td></td>
<td>Activator of subtypes of KCNQ ion channels.</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Molecular Weight(g/mol)</td>
<td>325 g/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Padsevonil</td>
<td></td>
<td>Binds to all three isoforms of the SV2 protein with high affinity.</td>
<td>UCB Pharma, Monheim am Rhein, Germany and UCB Pharma, Brussels, Belgium</td>
</tr>
</tbody>
</table>
### Molecular Weight (g/mol)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Weight (g/mol)</th>
<th>Activity Description</th>
<th>Company/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>YKP-3089</td>
<td>267.67</td>
<td>Enhances galanin receptor neuro-transmission by preferential activation of GalR2 receptors.</td>
<td>SK Life Science Inc., Fair Lawn, NJ</td>
</tr>
<tr>
<td>Huperzine A</td>
<td>242.32</td>
<td>Increases [GABA]-ergic inhibition of abnormal CNS activity via presynaptic mechanisms, avoiding typical GABA axis side effects such as drowsiness and decreased cognition.</td>
<td>Insero Health, Inc., Miami, FLNRE1</td>
</tr>
</tbody>
</table>

The table above lists the molecular weight and activity of two compounds relevant to the research on epilepsy pharmacotherapy.

- **YKP-3089**: Enhances galanin receptor neuro-transmission by preferential activation of GalR2 receptors.
- **Huperzine A**: Increases [GABA]-ergic inhibition of abnormal CNS activity via presynaptic mechanisms, avoiding typical GABA axis side effects such as drowsiness and decreased cognition.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Researcher/Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRE1 [intranasal diazepam]</td>
<td>To assess the bioavailability and pharmacokinetics of diazepam after intranasal [nasal spray]</td>
<td>University of Minnesota Neurelis, Inc.</td>
</tr>
<tr>
<td>Ganaxolone</td>
<td>To determine the effectiveness, safety window and tolerance of adjunctive Ganaxolone therapy.</td>
<td>Marinus Pharmaceuticals</td>
</tr>
<tr>
<td>Valnoctamide</td>
<td>Valproate substitute of Valnoctamide having low B.M.H.C.</td>
<td>B.M.H.C. Stanley - Medical Research</td>
</tr>
</tbody>
</table>

**Molecular Weight (g/mol):**
- NRE1 [intranasal diazepam]: 281 g/mol
- Ganaxolone: 332.5 g/mol
- Valnoctamide: 332.5 g/mol
3 Conclusion:

Currently, the territory of antiepileptic drug advancement has grown very futuristic with empowering research openings. Around the globe, epilepsy has become one of the enormous problems threatening human societies. Researches worldwide have gained emotional estates across all zones of epilepsy to treat, forestall, and fix it. The current status of antiepileptic drugs, their research pattern, and the newer analogues under clinical trial are mentioned in this article. Researchers, scientists, and scientific reviewers are always linked with their work to gain exciting results for the benefit of society. This review article investigates an overview of antiepileptic medicines and the advancement of novel atoms that may one day serve as AEDs.

4 Consent for Publication: Consent for Publication is not applicable here in this article as it is a review article which does not contain study related to human/patients.

5 Funding: There is not any source of funding for this review article. The personal choice has written it of authors.

6 CONFLICT OF INTEREST: The authors declare no conflict of interest.

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8 IAEC Approval: Above study is not related to the use of animals.

9 LIST OF ABBREVIATIONS: AEDs= Antiepileptic drugs.

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