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EPILEPSY AND ANTIEPILEPTIC DRUGS - A COMPREHENSIVE REVIEW

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ABSTRACT

Epilepsy is one of the most common and disabling neurological disorders of the brain influencing approximately 50 million people around the world disorder affecting all groups of ages. There are nearly 125,000 new cases of epilepsy each year and about 30% of patients are less than 18 years old. Several epilepsy diagnosis and treatment advances have recently been introduced providing pharmacists with tremendous opportunities to help improve drug therapy for epilepsy and various advanced drugs each with specific health, effectiveness and cost requirements, are available for treating seizures. The aim is to reduce the frequency and severity of seizures while reducing damage to the brain and other tissues by treating epilepsy with drugs. A variety of biological factors, particularly the blood-brain barrier, have severely limited drug access to the brain and contributed to the use of drugs loaded into the nanoparticles. This review attempts to describe the classification of seizures, epidemiology and available diagnostic procedures and the antiepileptic drugs used to treat epilepsy.

Keywords: Epilepsy; Seizures; Treatment; Anti-Epileptic Drugs; Mechanisms; Nano drug delivery

INTRODUCTION

Epilepsy is one of the neurological disorder, described as repetitive (two or more) epileptic seizures resulting from sudden, excessive, abnormal synchronized neuronal discharges. The term "epilepsy" is acquired from the word “epilambanein”, which means “to be seized” or "to be overwhelmed by surprise". On the account of damaged brain cells a serious condition arises, called epilepsy, which is indicated by the frequent seizures **[1]**. It is a long-term phenomenon, although seizures can occur sporadically or often sometime during lifetime. The external signs of epilepsy are termed as seizures which differs according to the portion of the brain damaged and how far the condition has progressed. This variability probably reflects the many underlying causes of epilepsy and a number of epilepsy syndromes, in which the clinical and pathological symptoms are distinctive **[2]**. Seizures may occur from a family history or after a brain injury, but the cause for epilepsy is unrevealed. It is also found that the existence of the diseases like diabetes increases the risk of developing epilepsy by three folds **[3]**. The epilepsy is symptomatic when it is recognized after a specific incident like asphyxia, head injury or meningitis. It is considered to be a neurological cramp which includes excessive neuron activity **[4]**. There are no distinctions between race geography or society, It develops in both genders and at all ages mostly prevailed in men upto 56% according to a study **[5]**, particularly in children and elderly people **[6]**. In about one person per 103, it is affected. One of the first brain disorders that had been identified was epilepsy. More than 3,000 years ago it was recorded in ancient Babylon. Over the years, some superstitions and misconceptions have been resulted by the strange behavior that has been triggered by some seizures. Epilepsy prevalence, measured with DALYs, accounts for 1 percent of the total worldwide disease burden, excluding the people with epilepsy (PWE) in India experience epilepsy due to social stigma and loneliness **[7]**. It was estimated that about 7%-8% of the people have experienced epileptic seizure for once in their lives. Epileptic convulsions have not completely explained the basic mechanism. The International League for Epilepsy (ILAE) and other organizations have launched “Out of the Darkness” in order to improve public awareness, treatment and prevention of epilepsy **[8, 9]**.

CLASSIFICATION OF SEIZURES

An irregular, repetitive and hyper-synchronous discharge of the neurons into

your brain results in epileptic seizure. ILAE revised the classification of epileptic seizures in 1989 for the last time. This is important because the accurate detection of seizures and epilepsy is a key element for etiological diagnosis, appropriate treatment and precise prognosis **[10]**. The physiological characteristics of epilepsy and associated EEG findings are the basis of this method. The etiology or cell substrates are not taken into account. The seizures are mainly classified in to three categories: (i) Partial seizures (ii) Generalized seizures and (iii) Unclassified seizures. Revised version of the ILAE classification of epileptic seizures are represented in **Table 1 [11]**.

Table 1: Outline of the International Classification of Epileptic Seizures

- **Partial Seizures (seizures with focal onset)**
  - **Simple partial seizures (consciousness not affected)**
    - **With motor signs**
    - **With somatosensory or special-sensory**
    - **With autonomic symptoms or signs**
    - **With psychic symptoms**
  - **Complex partial seizures (disabled consciousness)**
    - **Starting as simple partial seizures**
      - **Without automatisms**
      - **With automatisms**
      - **With impairment of consciousness at onset without automatisms**
  - **Partial seizures evolving into secondarily generalized seizures**
- **Generalized Seizures**
  - **Absence seizures and atypical absence seizures**
  - **Myoclonic seizures**
  - **Clonic seizures**
  - **Tonic seizures**
  - **Tonic-clonic seizures**
  - **Atonic seizures**
- **Unclassified Epileptic Seizures**
  - **Neonatal seizures**
  - **Infantile spasms**

Partial seizures: Partial seizures are most common type of seizures and are limited to specific cerebral regions, usually involving only a certain brain area initially and display clinical or EEG symptoms of a cerebral hemisphere. They are further grouped in to simple or complex and develops in to generalized seizures. When the seizure occurs as a partial seizure, it then extends over the whole brain, it is said secondarily generalized partial seizure. The epileptic cycle is usually limited to neocortical systems in simple convulsions and the limbic system and brainstem are excluded. The loss of consciousness is reported in complex partial seizures. Such seizures may also be expressed as changes in somatic feeling, vision, balance, autonomic system olfactory

changes, and hearing **[12]**. Such stimuli can cause a lot of discomfort to the patient.

Generalized Seizures: A complete loss of consciousness and an absence of aura characterizes the primary generalized seizures. They come about all of a sudden and unexpectedly and may harm themselves if the patients fall. Generalized convulsions are collectively triggered by both brain hemispheres **[13]**. Absence seizures commonly called as petit mal are defined by short span of consciousness without lack of postural function. Usually the seizure lasts for just seconds; the consciousness recovers as quickly as it had been lost **[14]**. General tonic clonic seizure is referred to as grandmal seizures. In the tonic stage where the person's arms and legs are tightened first and in the clonic phase, his or limbs and head begin to wrench. It can take minutes to hours to recover completely depending on the person **[15]**. Myoclonic seizures can cause body parts of an individual to twitch unexpectedly, his or her arm or leg. Atonic convulsions unexpectedly stiff a part or all of a person's body. Where their head may drop suddenly or fall down or even collapse entirely and fall down to the floor **[14]**.

Unclassified Seizures: Not all forms of seizure are partial or generalized, as it seems in neonates and child seizures. In addition, neuronal function variations and development in the developing brain are likely to lead to some of those seizures that occur in neonates and infants **[16]**.

ETIOLOGY

Seizures are caused by the change of normal excitement and inhibition equilibrium within the CNS and the dysfunction of the brain. As the different properties of the neuronal excitability can be controlled, it is not uncommon for this natural equilibrium to be disrupted in a wide range of ways **[17]**.

When the acute condition was too serious or not properly treated, convulsions would have been long and persistent, resulting in brain anoxia, accompanied by epilepsy **[18]**.

For children who otherwise are well, who are structurally disabled and who have genetic risk factors, seizures may be caused during high fever **[19]**.

Epilepsy may occur in older patients with Alzheimer's disease and stroke. Almost 50% of the risk of epilepsy is associated with a serious, deep traumatic brain injury.

Any region with an abnormative brain tissue (calcifications, cuts, or structural abnormalities) may be an area from which a "symptomatic epilepsy" - irregular neuronal activity takes place **[20]**.

Conditions that most likely cause seizures include syncope and transient ischemic

threats, some other probabilities include sudden fall of subarachnoid trauma, sleep disturbances, panic attacks and migraine disorders. As far many other idiopathic diseases such as diabetes are considered, the heritage form is complex, since many primary epilepsies are of hereditary origin **[21]**.

PATHOLOGY

Symptomatic epilepsy is related to definable brain injuries. Such lesions include areas of neuronal loss and gliosis (scars) or other tissue loss symptoms. The extent of these injuries is not fully known **[22]**. The initial CNS damage, such as trauma, stroke, or infection and the first seizure, takes months to years. The injury can reduce the seizure threshold in the area under seizure until there is a spontaneous seizure **[23]**. A bilateral neuron loss in the CA1 segment of a hippo-campus pyramidal cell layer extending into the adjoining areas of pyramidal and the underlying dentate gyrus is the most common histological finding in the brains of epileptic patients **[24]**.

In several immature seizure disorders, the most specific genetic factor is also identified: i) absence of epilepsy with spike and wave discharges three per second; and (ii) Benign Rolandic Epilepsy of Childhood [BREC] **[25]** Idiopathic epilepsy can be caused by affecting neurotransmitter receptor in ionic canals in a particular group of epileptic disorders. Other neurological disorders including cognitive impairment coexist with seizures in patients with symptomatic epilepsy. The goal is to classify different susceptibility genes, which are the origin of the most common forms of idiopathic epilepsy **[26]**.

DIAGNOSTIC EVALUATION

Following one or more paroxysmal events involving an epileptic seizure, individuals must perform a detailed clinical evaluation and a multi-stage diagnostic procedure, including medical history evaluation, physical examination, EEG, and neuroimaging **[24]**. Biochemical parameters can also be estimated for the epileptic patients **[27]**. However, much research is carried out to develop an automated detection using machine learning and magnetic resonance spectroscopy **[28, 29]**. Evaluation of infants and young children is more important as dysmorphic and cutaneous disorders can identify a variety of cerebral disorders that are highly characteristic and due to which epilepsy is triggered **[30]**.

Family History: History is the key to identify epilepsy because the physical scanning is relatively undefined in most of the adults. The most significant aspect of all

in a patient with frequent epilepsy is a carefully considered medical history **[31]**.

EEG: In this process, the brain's electrical activity is detected amplified and recorded by a number of electrodes specifically placed on the head. During a seizure the EEG almost always displays irregular exudes. In the differentiation between partial and generalized seizures, it is often beneficial **[32]**.

Neuroimaging:

A collection of laboratory studies, like a complete blood count, blood chemical samples, liver and thyroid function scans, an EEG, and a brain examination are normally included in the initial medical assessment, preferably by magnetic resonance imaging (MRI) **[33]**. For the evaluation of a patient suffering from a seizure, computed tomography (CT) and MRIs are important additions to a clinical test and the EEG. The techniques of neuroimaging are especially susceptible to structural losses for the central nervous system **[31]**. In a patient with selective seizures, abnormal neurological findings or EEG focus discharges, MRI is more likely to show an abnormality **[34]**. Quantitative volume analysis with computer assistance for temporary lobes can detect asymmetries, which cannot be easily seen when analyzing the scan visually. CT is useful for hemorrhages, calcification or tumors in acute conditions. Blood Oxygen Level Dependence (BOLD) is used to monitor and find language and memory through functional MRI (fMRI). Positron emission tomography (PET) is used in a number of research facilities to classify areas of the brain that cause convulsions **[35]**.

MANAGEMENT AND TREATMENT

Management of epilepsy aims at eliminating or decreasing seizures, minimizing treatment effects, improving medical and neuropsychiatry comorbidity, and promoting excellent standard of life **[36]**. Usually neurologist prescribes medications to prevent seizure when epilepsy is diagnosed. Incase medications are failed, surgery, a special diet, complementary treatment, or stimulation of the vagus nerve could be tried. Treatment is designed to avoid further convulsions, prevent adverse effects **[37]**.

TREATMENT WITH ANTIEPILEPTIC DRUGS

Antiepileptic Drug Therapy:

The main therapeutic assistance of patients has four aims: to prevent seizures or to minimize their frequency to the greatest extent possible, to avoid adverse long-term therapeutic effects and to help patients maintain or restore psychosocial and technical habits and to maintain basic

lifestyles **[38]**. Only one drug should be given in beginning of the treatment. The drug choice is ideally dependent on the epileptic type and the type of seizure. A informed assessment of the probability of seizure reoccurrence and the adverse impacts of the drugs chosen should serve as basis for the choice for initiating AED treatment. For those who have to travel, continue to work or take care of family members, possible seizure can be distressing **[39]**.

Selection of Antiepileptic Therapy:

At present, AEDs not only fail to monitor seizures in some patients, but also often cause adverse effects that vary from minimum disability to death caused by aplastic anemia or hepatic insufficiency **[40]**. Many studies are carried out to include the natural antiepileptic agents like curcumin to reduce the dose of the anti epileptic synthetic derivatives like phenytoin and sodium valproate and were proved to be effective **[41]**. Total seizures management in up to 50% of patients is generally recognized and another 25% of patients significantly improve **[39]**. AED is classified into risk-assuming ones of relatively quantity and data insufficiency. This reinforces itself with an enhanced refusal of those who intake, the prescribed drugs of uncertain risk **[42]**. The latest data from the UK register of epilepsy indicate very clear dose-related effects with 5% risk with valproate exposure of 600 mg / daily to 11% at more than 1000 mg. With 2% of 200 mg, lamotrigine had a lesser steep curve, which increased by over 400 mg a day to 3.5 % . At 2% chance of risk with 500 mg of Carbamazepine daily and 3% risk for 500–1000 mg and 5% for 1000 mg **[43]**.

I Monotherapy: The recommended primary treatment approach for epilepsy is antiepileptic drug monotherapy, as many patients can be treated with the first or second monotherapy successfully **[44]**. Most recent AEDs benefit from a more acceptable secured form and reduced adverse effects and drug interactions than their precursors. For certain patients like mothers, elderly and co-morbid patients, monotherapy is especially advisable **[45]**. Latest focal clinical trials show that monotherapy use of AEDs of second generation has approved. From the past decade, AED's like lamotrigine, felbamate, gabapentine of second generation drugs have became available **[46]** and the two new additional ("third generation") AEDs, lacosamide and rufinamide, have emerged in the apparently rising accumulation of AEDs. Monotherapy cannot work if the option of AED for a specific patient type is not optimal. In patients who

are not carefully assessed and advised by their doctors, monotherapy may fail **[47]**.

II. Combination therapy: Add-on treatment is taken into account if monotherapies failed to efficiently regulate seizures. Through confirming the unmanageable diagnosis and the operational procedure in clinicians with epilepsy, treatment with AED should become optimized **[48]**. Add-on treatment is taken into account if monotherapies failed to efficiently regulate seizures. Through confirming the unmanageable diagnosis and the operational procedure in clinicians with epilepsy, treatment with AED should become optimized. A main plus another drug with several mechanisms of action has been the most successful combination. In human beings, combinations of a sodium blocker and a drug with multiple operational mechanisms can have synergistic effects. Combinations of more than three medicines are not suggested **[49]**. The recommended total daily dosage of topiramate is 200 to 400 mg / day in two separated doses for adults with partial seizures of 17 years of age or older. For the first week, the titration will start at 25 mg. The dose must then be raised at intervals of 1-2 weeks per day to achieve an optimal clinical response through increments of 1-3 mg / kg **[50]**.

MECHANISM OF ACTION OF ANTI EPILEPTIC DRUGS

There are two important mechanisms through which AEDs act, they are:

- Reducing the release rate of neurons in the focus ("minimize initiation").
- Blocking the spread of excitation from the focus to other brain areas ("block spreading") **[51, 52]**.

These actions are caused by drug binding to one or more of the target brain molecules. Those objectives may include ion channels, neurotransmitters and metabolic enzymes for neurotransmitters. The overall effect is to alter the reactive effects of neurons and to reduce neuronal assemblies synchronization **[53]**.

AEDs can be categorized into many groups, depending on the mechanism of action.

- Blockage of voltage-gated sodium channels (Phenytoin, valproic acid, lamotrigine)
- Increase of GABA inhibition (Barbiturates , benzodiazepines)
- Blockage of T- type Calcium channels.
- Decreased glutamate excitation (Felbamate, gabapentin) **[54]**

ANTI EPILEPTIC DRUGS

Some of the approved Antiepileptic Drugs (AEDs) used for the treatment of various

types of epilepsy in the U.S. are listed in the **Table 2**. The drugs are used based on the occurrence of type of seizure.

Table 2: Approved Antiepileptic Drugs for the Treatment of Seizures in the U.S. [44]

Type of seizures	First line drugs	Alternative drugs
Primary generalized tonic clonic seizures	Valproic acid Lamotrigine Topiramate*	Zonisamide Phenytoin Carbamazepine Oxcarbazepine* Phenobarbital Primidone Felbamate
Absence seizures	Valproic acid Ethosuximide	Lamotrigine* Clonazepam
Partial Seizures	Carbamazepine Phenytoin Oxcarbazepine Valproic Acid	Gabapentin* Phenobarbital Primidone Felbamate Eslicarbazepine Vigabatrin* Lacosamide* Pregabalin Levetiracetam* Rufinamide*
Atypical Absence Myoclonic, and Atonic Seizures	Valproic acid Lamotrigine Topiramate	Clonazepam Felbamate

*New Antiepileptic Drugs

Valproic acid (Sodium valproate):

Sodium valproate is a wide range of AEDs with a particular value in idiopathic generalized epilepsy and effective throughout the entire range of seizures, used mainly for treating the generalized tonic clonic seizures in paediatric patients **[55]**. Valproate is named after the valproic acid which has been transformed to the form that functions in the body. The valproic acid dissociates in the gastrointestinal tract in to the valproate ion. In adults and teens, the starting dose of sodium valproate is 500 mg / day for 1 to 2 weeks, with increase in dose to 500 mg twice a day **[56]**. Sodium valproate was known to produce mild liver toxicity in epileptic children **[57]**.

Carbamazepine:

For focal seizures and general tonic-clonic seizures, carbamazepine, a tricyclic antidepressant is indicated. It is not successful and can be injurious for some individuals who have absences **[58]**. The low dose carbamazepine of about 100/200 mg daily should be taken as a potent auto inducer, which allows tolerance for its side effects on CNS. Carbamazepine seems to be functioning by decreasing the polysynaptic responses and obstruct post-tetanic potentiation. Carbamazepine can cause a

variety of unusual reactions, the most frequent being a skin rash, in up to 10% of people exposed to this disease **[59]**.

Phenytoin:

Phenytoin, because of its persistent toxicity and kinetic profile, is now a final alternative for focal and tonic-clonic seizures. The motor cortex seems to be the primary site of activity, where the drug prevents seizure development. Phenytoin is among a handful of therapeutic drugs that turn from first-line kinetics to saturation kinetics **[60]**. Phenytoin may help to stabilize the hyperexcitability threshold caused by excess stimulation or environmental changes that can reduce the membrane sodium gradient by promoting a sodium influence on the neurons. This behavior includes reducing post-tetanic potential at synapses. Use of an intravenous (IV) phenytoin is unacceptable in adults who require quick, steady-state serum levels. Phenytoin decreases the total activity of the tonic stage of tonic-clonic seizures at brainstem sites. Phenytoin is a target for medicines such as allopurinol, amiodarone, cimetidine because of their saturated metabolism **[61]**.

Phenobarbital:

Focal and tonic-clonic seizures have been treated by Phenobarbital but are rarely used in developing countries now a days due to their ability for neurotoxicity**.** A minimum dose of about 30 mg in adolescents and adults should be initiated to reduce sedation and can be gradually increased according to clinical criteria of dose 15-30 mg **[62]**.

Clonazepam:

A benzodiazepine derivative, Clonazepam is protective against absences, myoclonic jerks and tonic-clonical seizures but its usage is decreased due to its tolerance and sedation. Up to 30 per cent of patients in certain trials have shown a lack of activity commonly within three months. Benzodiazepines' antiseizure activity contributes primarily to their ability to improve Cl– conductance due to GABA enhancement. Some patients will respond correctly to this drug but almost 50% will intensify the attacks when it is withdrawn. The maximum recommended daily dose is 20 mg **[63]**.

Ethosuximide:

Ethosuximide is an antiseizure succinimide, which is classified as alpha-ethyl-alpha methyl-succinimide. This suppresses the 3-cycle (3-Hz) pick-and-wave paroxytic behavior linked with consciousness deficits, which are normal in the absence seizures. Clearly, impairment of the cortex and increase of the CNS threshold to invasive stimuli reduces the frequency of epileptic attacks **[64]**. Slow implementation is

susceptible to minimize gastrointestinal and CNS adverse effects. When other seizures coexist with absence epilepsy, ethosuximide can be provided in addition with other AEDs. The starting dose of 500 mg daily is practical with developmental raise of 1-2 g / day as required. Based on clinical necessity, the dosage can be increased every 2 to 4 weeks **[65]**.

DEVELOPING AGENTS

Eslicarbazepine Acetate: Derivative of carbamazepine, a new anticonvulsant CNS-active medicinal drug. For adults with refractive, partial initial convulsions, it is intended as a supplementary therapy. ESL has been linked to a significant reduction in seizure frequency in clinical trials in comparison with placebo in partial-accident epilepsy patients. As an adjunctive therapy for adult with partial seizures in March 2009, ESL was submitted for approval by FDA **[66]**. The New Drug Application (NDA) was licensed for approval and was formally reviewed by the FDA. ESL was given to patients with partial seizures once daily at dose levels of 400 mg, 800 mg or 1200 mg **[67]**.

Retigabine: A potassium-channel opener of the first level in neurons, retigabine as an adjunctive therapy is in final stage of development as a partial onset seizure. In October 2009,Valeant and GSK submitted an NDA for retigabine to the FDA. Specific adverse events (at a frequency above or equal to 5% and double that of placebo) in all completed trials to date were dizziness and fatigue, vertigo, tremor, abnormal coordination, respectively. The drug is currently under review by the FDA for approval **[68]**.

Other drugs: The treatment of Lennox – Gaustaut Syndrome is being studied with Clobazam and perampanel (E2007, Eisai), as potential intervention therapy for partially-accident seizure patients, is being developed. Fluorofelbamate, Valrocemide, Carisbamate, Licarbazepine are the some other newly developing drugs **[69]**.

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