Treatment of Epilepsy: Background and Future Directions

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***Abstract*—**Epilepsy is a mystery even though it affects an estimated 50 million people worldwide. Its management is enigmatic and as such, is not curative, but rather aims to attain freedom from seizures without side-effects. However, an approach for the selection of the most effective drugs and doses for individual patients is lacking. Almost all of the antiepileptic drugs in current use are associated with adverse reactions, some of which are severe and life-threatening. A more comprehensive treatment strategy requires improved research on epilepsy. This is the key to developing a treatment plan focused on the individual needs of each patient. Pharmacogenetics can offer a novel line of attack in the treatment of epilepsy. The potential advantages of gene therapy in the management of epilepsy are manifold. It encompasses the principle of testing as to how genetic variation among individuals affects variation in drug response, efficacy, and potential adverse drug events. Pharmacogenomics is the investigation of relationships between patient genotype and responses to drug treatment. It holds the promise of selecting the right drug at the right dose for the right person. A conceptual framework that outlines the pharmacogenetic and pharmacogenomic aspects of epilepsy presented here. Future directions for research and the application of these technologies to the clinical practice of individualising treatment for epilepsy are also discussed. A combination of research strategies and prudent policies from government may lead to a better understanding of treatment effects and futuristic but realistic management in epilepsy.

***Keywords*—**Epilepsy, etiology, neurogenetics, pharmaco-genomics, pharmacogenetics.

I. Introduction

EPILEPSY is one of the oldest known brain disorders. The word "epilepsy" is derived from a Greek word meaning, "a condition of being overcome, seized, or attacked." It was mentioned more than 2,000 years ago and references to it can be found in ancient papyri and Vedic texts, the Bible, and the Koran [1][2]. Decades ago, the 'falling sickness' was believed to be caused by a demon or angel, and epilepsy became known as a 'demonic possession' or 'sacred disease' [3].

Russia's greatest novelist, Fyodor Mihailovich Dostoevsky (1821-1881), probably suffered from temporal lobe epilepsy (most likely left mesiotemporal) and partial epilepsy coexisting with idiopathic generalized epilepsy (petit-mal – grand-mal), with complex-partial and secondary generalized seizures, with a relatively benign course [4].

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A. Definition

There are some definitions in epilepsy phrases based on International League Against Epilepsy (ILAE) commission. The terminology includes: "epileptic disorder", "epilepsies", "epileptic seizure", and "epileptic syndrome".

Epilepsy is a brain disorder in which a person has repeated seizures (convulsions) over time. Seizures are episodes of disturbed brain activity that cause changes in attention or behavior [5]. Epileptic disorder is a chronic neurologic condition characterized by recurrent epileptic seizures. Epilepsies are those conditions involving chronic recurrent epileptic seizures that can be considered epileptic disorders. Epileptic seizure is manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurons in the brain [4]. An epileptic seizure can be defined clinically as an intermittent, stereotyped, disturbance of consciousness, behavior, emotion, motor function, or sensation that on clinical grounds is believed to result from cortical neuronal discharge [6]. Epileptic syndrome is an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together, including type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and, sometimes, prognosis [7].

Therefore, epilepsy can be defined as a condition in which seizures recur, usually spontaneously. Two major types of epilepsy are recognized, i.e.; epilepsy with focal and epilepsy with generalized seizures.

B. Classification

Epilepsy is an extremely extraordinary-heterogeneous disease with various syndromes and subtypes. The classification at **Table I** shows the wide variety of epilepsy [8].

Table II shows the classification of seizures. It makes use of both clinical and EEG information. Brain inflammation might contribute to the onset and perpetuation of seizures in a variety of epilepsies [9].

Seizures may also result from nonepileptic causes, as in cardiogenic seizures or psychogenic nonepileptic seizures. The cause of epileptic seizures is unknown in just under 70% of cases, whereas some neurologic etiology is identified in approximately 30% of patients [10].

TABLE I ILAE CLASSIFICATION OF EPILEPTIC SEIZURES [8]

I. Partial (focal) seizures
   A. Simple partial seizures (consciousness not impaired)
      1. With motor signs (including jacksonian, versive, and postural)
      2. With sensory symptoms (including visual, somato sensory, auditory, olfactory, gustatory, and vertiginous)
      3. With psychic symptoms (including dysphasia, dysmensic, hallucinatory, and affective changes)
      4. With autonomic symptoms (including epigastric sensation, pallor, flushing, pupillary changes)
   B. Complex partial seizures (consciousness impaired)
      1. Simple partial onset followed by impaired consciousness
      2. With impairment of consciousness at onset
      3. With automatisms
   C. Partial seizuers evolving to secondarily generalized seizures
II. Generalized seizures of nonfocal origin (convulsive or nonconvulsive)
   A. Absence seizures
      1. With impaired consciousness only
      2. With one or more of the following: atonic components, tonic components, automatisms, autonomic components
   B. Myoclonic seizures, myoclonic jerks (single or multiple)
   C. Tonic-clonic seizures (may include clonic-tonic-clonic seizures)
   D. Tonic seizures
   E. Atonic seizures
III. Unclassified epileptic seizures

ILAE: International League against Epilepsy

TABLE II ILAE **CLASSIFICATION OF SEIZURES** [6]

Partial seizures (seizures beginning locally)
   Simple (consciousness not impaired)
      With motor symptoms
      With somatosensory or special sensory symptoms
      With autonomic symptoms
      With psychic symptoms

   Complex (with impairment of consciousness):
      Beginning as simple partial seizures (progressing to complex seizure)
      Impairment of consciousness at onset
   Partial seizures becoming secondarily generalized

Generalized seizures:
   Absence seizures
      Typical (petit mal)
      Atypical
      Absence with special features
         Myoclonic absence
         Eyelid myoclonia
   Myoclonic seizures
      Myoclonic
      Myoclonic atonic
      Myoclonic tonic
   Clonic seizures
   Tonic seizures
   Tonic-clonic seizures (in any combination)
   Atonic seizures

Examples of the application of the five-axis syndrome-oriented system would appear as follows: [11]

- Axis 1 (ictal semiology): generalized tonic-clonic seizure
- Axis 2 (underlying mechanism of seizure types): generalized tonic-clonic seizures
- Axis 3 (epilepsy syndrome): epilepsy with generalized tonic-clonic seizures on awakening
- Axis 4 (etiology): genetic causes
- Axis 5 (impairment): based upon the revised International Classification of Functioning, Disability and Health rating (http://www.who.int/icidh).

TABLE III THE ETIOLOGY OF EPILEPTIC SEIZURES [11],[14]

Age Group	Potential Causes
Newborns	1. Brain malformations 2. Lack of oxygen during birth 3. Low levels of blood sugar, blood calcium, blood, magnesium, or other electrolyte disturbances 4. Inborn errors of metabolism 5. Intracranial hemorrhage 6. Maternal drug use 7. Infection
Neonatal	1. Perinatal injury 2. Hypoxia 3. Hypoglycemia 4. Hypocalcemia 5. Pyridoxine deficiency 6. Intraventricular hemorrhage 7. Intraparenchymal hemorrhage 8. Subdural hemorrhage
Children	1. Perinatal injury 2. Developmental malformation 3. Febrile seizures 4. Stroke 5. Vascular malformations 6. Head injury 7. Infections 8. Brain tumors 9. Amino acid disorders 10. Urea cycle disorders 11. Gray matter storage diseases
Infants and Children	1. Fever (febrile seizures) 2. Infections 3. Brain tumor (rarely) 4. Mesial temporal (Ammon's horn) sclerosis [14]
Children and Adults	1. Congenital conditions (Down syndrome, Angelman syndrome, tuberous sclerosis and neurofibromatosis 2. Genetic factors 3. Head trauma 4. Progressive brain diseases (rare)
Middle years	1. Neoplasm (high risk)
Adults/Elderly	1. Trauma 2. Tumor 3. Substance abuse or drug withdrawal 4. Drug reactions (stimulants, antihistamines, tricyclics, phenothiazines, butyrophenones, certain antibiotics, aminophylline) 5. CNS infections 6. Stroke 7. Intracranial hemorrhage 8. Vascular malformations 9. Systemic/metabolic derangements 10. Alzheimer disease 11. Dementia (high risk for > 65 years) 12. Cerebrovascular disease (high risk for > 65 years)

Using the five-tiered patient-oriented classification, the above patient according to the 2001 ILAE proposal would be classified as follows: [12]

- Dimension 1 (epileptogenic zone): generalized (epilepsy with generalized tonic-clonic seizures on awakening)
- Dimension 2 (semiologic seizure classification): generalized tonic-clonic seizure
- Dimension 3 (etiology): unknown
- Dimension 4 (seizure frequency): persistent (one per year)
- Dimension 5 (related medical information): seizures triggered upon awakening

Etiology may be divided into epilepsies due to genetic and acquired causes and those due to a combination of both, which contribute to the predisposition of recurrent seizures.[11] Although many cases may be multifactorial, clinicians should decide the most appropriate predisposition or risk factor in order to establish diagnosis and determine the right treatment.

C. Etiology

The etiology of epileptic seizures differs across the lifespan and depends upon the age of seizure onset. The most common causes of epilepsy for each age group have been reported by the Epilepsy Foundation of America (2008) [13] and are listed in **TABLE III** [11],[14].

Mesial temporal (Ammon's horn) sclerosis is the most common single lesion to be found post mortem in the brains of chronic epileptics who die a natural death. Evidence shows that it usually arises in infancy, often as a result of a prolonged febrile convulsion, and that it then becomes a potent epileptogenic lesion [14].

The causes and prognoses of epilepsies in children are varied and, therefore, each child with epilepsy needs an individualized, multiaxial assessment of their epilepsy syndrome, and any additional morbidities [15].

D. Epidemiology

Epilepsy is a chronic disorder, or group of neurological disorders, in which the indispensable feature is recurrence of seizures that are caused by abnormal electrical discharges from the brain; typically unprovoked and usually unpredictable. Absence epilepsy involves seizures that cause a sudden loss of awareness. It is characterized by the periodic occurrence of spontaneous seizures and affecting about 0.5%-1% of the world's population [16],[17], approximately 1 in 130 people [18], or at least 50 million people worldwide [19]. It often starts in childhood or adolescence and appears to be a major cause of morbidity in elderly [20].

E. Incidence

The incidence of epilepsy is particularly high in Latin America and in several African countries. The overall incidence of epilepsy is generally taken to be about 50 cases per 100000 persons per year (range 40 to 70 per 100000/year) [21] in developed countries, higher incidence figures are generally found from studies in developing countries [22].

In developing countries, a range of 100 to 190 per 100000 per year has been given [21]. The incidence of epilepsy is high in childhood, decreases in young people and rises again in the elderly [23]. Epilepsy has a lifetime cumulative incidence approaching 1 in 25, thus representing one of the most common serious neurological disorders [18].

F. Prevalence

The overall prevalence of active epilepsy in 5550 persons aged 55-95 years in the Netherlands from 1991 to 1993 was 0.8%-0.9%. It increased with age from 0.7% for those aged 55-64 years to 1.2% for those aged 85-94 years. The increase with age was detected among men and women both [20]. Another report, its prevalence is usually regarded as between 5 and 10 cases per 1000 persons. The lifetime prevalence of seizures is between 2% and 5% [22]. In children with epilepsy, the prevalence of refractory epilepsy is variably reported as 9%-24% [24].

G. Prognosis

Prognostic factors may include demographic features, disease-specific indicators (i.e., seizure frequency, etiology of epilepsy) or comorbidity. The study of the prognosis of epilepsy is confounded by the diversity of underlying diagnoses [25].

Overall, between 70% and 80% of people developing epilepsy will go into long-term remission, usually within the first 5 years. Over two-thirds of patients enter long-term remission, and subsequent relapse is uncommon [22]. Generally, the 1-year remission rate is between 65% and 80% [26]. The prognosis is largely determined by the background etiology [22].

H. Recurrence

The recurrence of epilepsy is multifactorial. A wide variety of prognostic factors will influence the recurrence rates of epilepsy, such as: age, sex, seizures, etiology, history, and medication.

TABLE IV

Factors	Explanation	References
Age	Onset below 10 years or 16 years or over 65 years has been correlated with recurrence.	[27],[28],[29],[30]
Sex	Sex does not correlate with prognosis for early recurrence.	[31],[32]
Seizures	Partial seizures are associated with poorer outcome for recurrence. Nocturnal seizures and mixed seizure types have also shown higher recurrence rates.	[33],[34],[35]
Etiology	Congenital neurological deficits, head injury, remotes causes of epilepsy (i.e. tumours) predict higher rates of recurrence. Abnormal neurological examination has been correlated to recurrence.	[36],[37],[38],[39]
History	A family history of seizure disorders increases the risk of recurrence. The presence of an EEG abnormality is a risk factor for recurrence.	[40],[41]
Medication	A threefold increased risk of seizure recurrence in the untreated group by 2 years.	[30],[41],[42]

I. Remission

Remission of epilepsy is the seizure-free period experienced by a patient who has had one or more seizures. It is usually defined as being of 1-5 years' duration. Terminal remission is when the remission continues to the end of follow-up [42].

Several studies have shown that up to a quarter of children with early intractability (within the first 2 years of follow-up have a remission of at least 1 year at 5 years [43],[44]. The probability of being in a remission lasting for five years or more was 61% at 10 years and as high as 70% at 20years [6].

J. Screening

The screening for epilepsy was taken from the World Health Organization (WHO) research protocol, i.e., (1) Have you ever lost consciousness? (2) Have you ever had episodes where you lost contact with your surroundings? (3) Have you ever had any shaking of your arms and legs which you could not control? [45]

Episodic memory impairment is a key feature of temporal lobe epilepsy (TLE). TLE is the most common form of focal epilepsy. Cognitive impairment is a major concern for patients as well as clinicians [46].

The EEG has great potential for investigating the presence or severity of epilepsy (epileptogenicity) and its development (epileptogenesis) in vivo and in vitro, owing to the capacity to utilize both macroelectrodes and microelectrodes, and to record normal and abnormal neuronal firing with excellent time resolution [47],[48]. Andrade-Valença et al., investigated the possibility of noninvasive detection of interictal high-frequency oscillations (HFOs) via scalp EEG recordings for more-precise delineation of the seizure-onset zone (SOZ) in patients with focal epilepsy [47]. Recording of HFOs with scalp electrodes was previously thought to be virtually impossible [48]. Investigation of HFOs is of great importance, since these oscillations can reveal fundamental mechanisms of epileptogenesis and epileptogenicity, and also have possible clinical value [49].

K. Prevention

There are a lot of ways to prevent epilepsy. Reduction in the incidence of stroke should be accompanied by a decline in head trauma mostly because of road traffic accidents may decrease the incidence of epilepsy. To prevent epilepsy in early life, we should reduce perinatal morbidity and improve genetic understanding of genetic disorders that is associated with epilepsy. A continuing counseling concerning provocative and underlying factors of epilepsy (such as: alcohol, drug abuse, etc) must be given to patients and their families [6]. Chronic epilepsy is very difficult to control and may best be prevented by more effective treatment at the onset of the disorder [50].

Suicide in epilepsy may occur during interictal dysphoric episodes with or without psychotic features or in a state of postictal depression. It can be prevented by psychopharmacologic treatment [51]. Sudden unexpected death in epilepsy is found to be associated with frequent generalized tonic-clonic seizures and greater ictal maximal heart rate, especially during nocturnal attacks. Thus, supervision at night is associated with a lower risk of occurrence [52].

L. Biomarker

Recent research has showed that tetranectin could be a candidate biological marker for epilepsy psy [53].

Tetranectin (TN) is a plasminogen kringle 4 binding protein and regulates fibrinolysis and proteolytic processes via binding to plasminogen [54],[55]. In brain tissue, TN is present in most neurons and myelinated fibers of the white matter in both the cerebrum and cerebellum and is located in cytoplasm. It is not expressed in glial cells [56],[57]. The concentration of TN in serum is approximately 10 mg/l [58]. The serum-TN concentrations of patients suffering from first-episode seizures were 3.77 mg/l to 9.03 mg/l. It is hypothesized that patients with lower serum-TN concentrations would progress to drug-refractory epilepsy [53].

Cerebrospinal fluid-tetranectin (CSF-TN) levels increased in epileptic patients while serum-TN levels decreased. Lower serum-CSF levels might be correlated with drug-resistance in epilepsy [53].

TABLE V DIFFERENTIAL DIAGNOSIS OF EPILEPSY [6]

1. Syncope:
1.1. Reflex syncope:
a) Postural
b) Psychogenic
c) Carotid sinus syncope
d) Micturition syncope
e) Valsalva
1.2. Cardiac syncope:
a) Dysrhythmias (heart block, tachycardias, etc)
b) Valvular disease (especially aortic stenosis)
c) Cardiomyopathies
d) Shunts
1.3. Perfusion failure:
a) Hypovolaemia
b) Syndrome of autonomic failure
2. Psychogenic attacks:
2.1. Pseudoseizures
2.2. Panic attacks
2.3. Hyperventilation
2.4. Night terrors
2.5. Breath holding
3. Transient ischaemic attacks (TIA)
4. Migraine
5. Narcolepsy
6. Hypoglycaemia

M. Differential Diagnosis

Epilepsy must be differentiated from other diseases and disorders. Syncope and pseudoseizures are most common fallibilities or pitfalls in the diagnosis of epilepsy. Both are common in young adults [6].

Seizure diagnosis is essentially clinical with no single, simple diagnostic test. Even in experienced hands the diagnosis is often incorrect, with psychogenic non-epileptic attack

disorder and convulsive syncope all too commonly misdiagnosed and mistreated as epilepsy [59].

Multiple diagnosis and multi-aspects that should be considered carefully before diagnosing epilepsy could be seen in **TABLE V**.

II. PATHOPHYSIOLOGY OF EPILEPSY: EPILEPTOGENESIS

Epileptogenesis is the process whereby, after an acute brain insult, pathological and pathophysiological alterations gradually occur in certain brain regions, leading to the expression of epilepsy [60]. The epileptogenic zone is the region from which the seizure discharges arise.

The epileptogenic zone refers to the region of cerebral cortex where localization-related epileptic seizures originate. Specific lesions such as mesial temporal sclerosis or foreign tissue lesions are referred to as anatomic or structural lesions. These focal anatomic lesions produce a surrounding primary epileptogenic zone, which in turn may produce distant epileptogenic zones, a condition referred to as secondary epileptogenesis [11].

There is some evidence in humans that epileptogenic foci in the mesial temporal regions may arise from epileptogenic neocortex surrounding distant primary structural lesions. This concept is still controversial because it has not been adequately demonstrated. FDA-approved anti-epileptic drugs (AEDs), such as levetiracetam have been tested using the kindling model without demonstrating efficacy in other more conventional models such as maximal electroshock and phenylenetetrazol models [61].

Temporal lobe structures, notably the hippocampus, the amygdala, and the piriform cortex are most susceptible to seizurogenic and epileptogenesis-triggering brain insults; accordingly, temporal lobe epilepsy (TLE) is the most common form of epilepsy [62].

Six steps lead from focal epileptogenesis to clinical epilepsy: (1) the generation of enhanced physiological responses, (2) paroxysmal depolarizing shift (PDS), which in turn lead to interictal spike appearance in EEG, (3) focus spread to perifocal neurones, (4) the utilisation or breakdown of control mechanisms with brain circuits that limit the propagation of seizure discharges via preferred routes of spread; (5) the appearance of secondary foci in regions synaptically linked to the primary focus, and (6) the emergence of clinical seizures [63]. Correlation between mechanisms of epileptogenesis and mechanisms of action of antiepileptic drugs (AEDs) can be seen in detail in **TABLE VI** [64]

Quinolinic acid is an endogenous ligand of the N-methyl-D-aspartate (NMDA) receptor which is elevated in the brain of some epileptic patients. A decrease in quinolinphosphoribosyltranspherase in the frontal and temporal cortex in epileptic human tissue, may lead to quinolinic acid accumulation with the corresponding amplification of some excitatory synapses, thus predisposing to epileptogenesis [65]-[67].

TABLE VI

	Mechanisms of epileptogenesis	**Mechanisms of actions of AEDs**
GABA	• Reduced GABA in microgyric cortex • Reduced benzodiazepine receptor binding in medial thalamic nucleus (*mesial temporal lobe epilepsy*) • Reduced benzodiazepine receptor density in CA1 region (*hippocampal sclerosis*) • Reduced GABA levels and GAD activity (*epileptic foci*) • Auto-antibodies to GAD (*Stiff-man syndrome*)	• Increased functional pool of GABA (*vigabatrin, tiagabine*) • Enhanced GABA-ergic inhibition (*benzodiazepines*) • GABA agonistic effects (*progabide*) • (Weaker) GABA-ergic properties (*phenobarbital, gabapentin, topiramate, valproate, zonisamide*)
Glu	• Upregulation of hippocampal ionotropic glutamate receptors (*temporal lobe epilepsy*) • Anti-gluR3 antibodies (*Rasmussen encephalitis*) • Increased plasma glutamate levels (*absence seizures*)	• Inhibition of glutamate release (*lamotrigine*) • Block of glycine site at NMDA receptor (*felbamate*)
Na^+	• Mutation voltage-gated Na^+ channel (*generalized epilepsy with febrile seizures*)	• Reduction of voltage-gated Na^+ currents (*carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate, zonisamide*)
K^+	• Mutation voltage-gated K^+ channel (*benign familial neonatal convulsions*)	• Reduction of T-type Ca^{2+} currents (*ethosuximide, valproate*)
Ca^{2+}	• Reduced ACh-mediated Ca flux (*nocturnal frontal lobe epilepsy*)	
	→ Increased membrane excitability	→ Decreased membrane excitability

Increases in postsynaptic glutamate receptors and decreases in gamma-aminobutyric acid (GABA) (A) receptors in microgyric cortex could promote epileptogenesis [68]. Changes in metabotropic glutamate receptor function may also play a key role in epileptogenesis [69]. Excessive glutamate release can underlie the resulting brain damage [70]. Thus, excessive glutamatergic activity is important in the induction of neuronal pathology that can lead to hyperexcitability and epilepsy.

Glutamate excitotoxicity is due to overstimulation of glutamate receptors producing excessive neuronal depolarization, which is accompanied by an overwhelming increase in free intracellular calcium, entering via glutamate channels and voltage gated calcium channels, as well as released from intracellular stores; the calcium-dependent signaling pathways that are subsequently activated lead to neuronal dysfunction and pathological alterations in morphology or death [70],[71].

Noradrenaline was increased in midbrain and brainstem whereas decreased levels of dopamine have been found in the nucleus caudatus [72] in the epileptic foci of epilepsy patients [73].

There are two mechanisms of interictal-ictal transition. A. Nonsynaptic mechanisms, i.e., (1) Alterations in the ionic

microenvironment, e.g., increased extracellular K^+, decreased extracellular Ca^{2+} (2) Decreases in size of extracellular space (3) Failure of ion transport : Na^+–K^+ pump or Cl–K^+ co-transport (4) Presynaptic terminal bursting, (5) Ephaptic interactions. What is this? B. Synaptic mechanisms, i.e., (1) Depression of GABA-ergic inhibition (2) NMDA receptor activation, voltage-dependent epilepsy (3) Frequency potentiation of epilepsy (4) Actions of modulators [74].

A. The role of amygdala and cytokine

The amygdala play a prominent role in the pathogenesis and the symptomatology of epilepsy. The basolateral nucleus of the amygdala (BLA) plays the most important role in the initiation and spread of seizures. It appears to be most susceptible to seizure generation [1],[76].

Magnetic resonance imaging has revealed that a common pathology of the amygdala in TLE is atrophy (reduced volume associated with neuronal loss), which can range from 10% to 57% volume reduction [77]. A correlation of amygdala atrophy with the chronicity of epilepsy has been found in some studies [78]. More severe amygdala atrophy may be associated with a history of prolonged febrile convulsions [79]. In many cases, amygdala damage is co-present with damage in other brain regions and particularly the hippocampus [80].

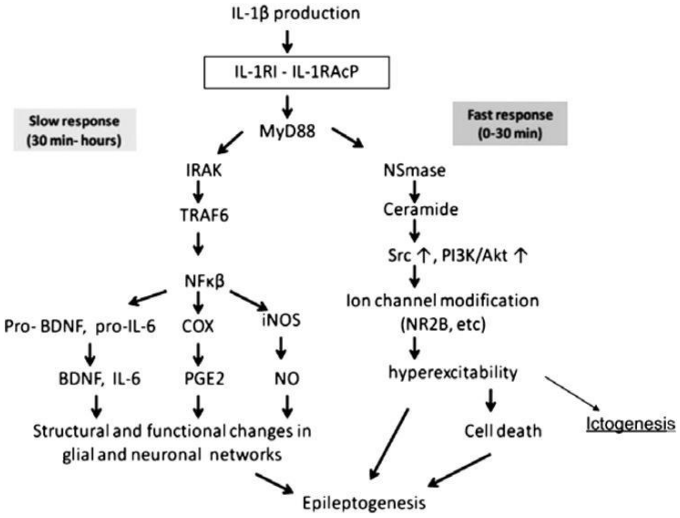

Figure 1 IL-1beta signaling in epilepsy

Elevated NMDA receptor activation may contribute to hippocampal hyperexcitability in epileptic patients. Hyperexpression of Glu6 (kainate) produces permanent change in hippocampal excitability which in turn may provoke epileptogenesis.

Most recently, experimental and clinical findings support a crucial role of inflammatory processes in the brain contributing to the etiopathogenesis of seizures and to the establishment of a chronic epileptic focus [83]. Prototypical inflammatory cytokines, such as IL-1beta, TNF-alpha and IL-6 have been shown to be overexpressed in experimental models of seizures in brain areas of seizure generation and propagation, prominently by glia and to a lesser extent by neurons. Cytokine receptors are also up regulated, and the related intracellular signaling is activated in both cell populations highlighting autocrine and paracrine actions of cytokines in the brain [84].

Alterations in distinct astrocyte membrane channels, receptors, transporters and phenotypic changes in activated microglial cells have been described in chronic epileptic tissue and they are possibly associated with the epileptic state characterized by recurrent spontaneous seizures [85]-[87].

Several reports show increased cytokines in serum and CSF in patients with epilepsy. For example, recent tonic–clonic seizures induce higher IL-6 levels and lower IL-1Ra-to-IL-1alpha ratio [88]. The analysis of human brain specimens from drug-refractory epileptic patients showed strong activation of the IL-1beta/IL-1R1 system in brain resident cells, such as in glia and neurons [89]. The finding that ongoing inflammatory events occur during epileptogenesis suggests that the activation of the IL-1beta system observed in human chronic epileptic tissue may precede the onset of epilepsy possibly playing an etiopathogenetic role [90].

Figure 1 shows IL-1beta signalling in epilepsy [85]. This is the cascade of events that explain the activation of IL-1beta following a precipitating event (eg. a primary brain insult), accounting for the role of IL-1beta in epileptogenesis and ictogenesis [85],[90].

III. Treatment and Management

There are several ways one can treat epilepsy, such as treatment with medications, surgery, stem cell, and gene therapy. In treating patients with epilepsy disorders, one is frequently faced with the decision of how long drug therapy should be continued. Permanent remissions of seizure of epilepsy are frequent in children and rare in adults. After a patient has remained seizure free on therapy for one and a half to three years, the drugs may gradually be withdrawn. The electroencephalogram is of some help in the decision about when drugs can safely be discontinued, but there is no dependable way to predict which patients will remain symptom free after medication is eliminated.

A. Pharmacologic Therapy

In the past two decades, nine new antiepileptic drugs have been marketed, making the choice of initial therapy complex. Antiepileptic drugs (AEDs) are classified as being either broad-spectrum or narrow-spectrum drugs with regard to efficacy against different seizure types and epilepsy syndromes. Broad-spectrum antiepileptic drugs are particularly useful because they are reasonable initial choices in most adult patients, regardless of the type of seizure or syndrome. These drugs include valproate, lamotrigine, topiramate, levetiracetam, and zonisamide. In contrast, narrow-spectrum drugs, which include carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine and pregabalin, should be restricted to patients who have localization-related (focal) epilepsy with partial and secondarily generalized seizures [91]. These drugs are less

effective than broad-spectrum agents in the idiopathic generalized epilepsy syndromes and they may even exacerbate some seizure types in these patients [92]. About half of patients in whom epilepsy is newly diagnosed become seizure-free while receiving the first antiepileptic drug. Failure of the first antiepileptic drug for reasons other than tolerability increases the likelihood of nonresponse to other drugs, but nearly two thirds of patients become seizure-free after receiving the second or third drug [93]. Further detailed explanation of AEDs could be seen in **TABLE VII**.

TABLE VII ANTIEPILEPTIC DRUGS (AEDS)

Antiepileptic Drugs (AEDs)	Indications	Side Effects and Explanation	References
Carbamazepine	Partial complex seizures, GTC, mixed SZ types.	Diplopia, dizziness, leucopenia, rash, SIADH. Efficacy as measured by seizure recurrence showed remacemide to be inferior to carbamazepine. Significant deterioration was seen on measures of information processing speed and attention after treatment with carbamazepine [95]. Efficacy as measured by seizure recurrence showed remacemide to be inferior to carbamazepine [96]. Significant deterioration was seen on measures of information processing speed and attention after treatment with carbamazepine [96].	[94], [95],[96]
Clobazam	broad spectrum antiepileptic, monotherapy for partial and selected epilepsies in childhood. intractable seizures [99] refractory epilepsy in children [100]	without much side effects [97]; drowsiness The cognitive and behavioural effects of clobazam appear to be similar to those of standard monotherapy [98]. Mood changes recorded included irritability, depression, and disinhibition [99]. Once started, clobazam should be tailed off with caution [99]. Severe behavior disorder in children like: aggressive agitation, self injurious behavior, insomnia, and incessant motor activity occurring between 10 and 55 days after initiation of drug therapy [100] A useful additional drug added to conventional anticonvulsant regimes [101]. A useful treatment for epilepsy as intermittent or short-term add-on therapy, but it should also be tried as long-term therapy in some situations, especially as add-on therapy for patients with refractory epilepsy, as add-on or monotherapy for patients with anxiety, or in some women in association with oral contraceptives [102].	[97],[98], [99],[100], [101],[102]
Clonazepam	Partial and generalized SZ (including absence and myoclonus). Lennox–Gastaut syndrome, neonatal SZ, infantile spasms and status epilepticus. (Adults and children)	Sedation (common and may be severe), cognitive effects, drowsiness, ataxia, personality and behavioural changes, hyperactivity, restlessness, aggressiveness, psychotic reaction, seizure exacerbations, hypersalivation, tone changes, leucopenia, withdrawal symptoms. Useful action especially in children. A broad spectrum of activity against the various types of epilepsy [104]. Hypersalivation and excessive bronchial secretion may be a problem in children and infants [104]. Although the mechanism of action of clonazepam has not yet been established, some investigators have been suggested that it involves enhancement of anti-anxiety effects, anticonvulsant effects on subclinical epilepsy, increase in 5-HT/monoamine synthesis or decrease in 5-HT receptor sensitivity mediated through the GABA system, and regulate in GABA activity [105]. Although reading epilepsy is usually refractory to anticonvulsant therapy, treatment with clonazepam resulted in complete control of the involuntary movements precipitated by reading [106]. Inhibition of seizure activity seems to be achieved already at low plasma levels of clonazepam. Plasma concentrations of clonazepam were determined 23 nmol/L, range = 11-41 nmol/L [107].	[103], [104],[105], [106],[107]
Ethosuximide	Absence, childhood absence epilepsy	Nausea, vomiting, rash, blood dyscrasias, increase frequency of grand mal seizures in mixed SZ types if used alone. The addition of ethosuximide to valproate can be helpful to those with myoclonic absences, where this combination appears more beneficial than either valproate or ethosuximide alone and in eyelid myoclonia with absences [108]. Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects [109]. Although ethosuximide, lamotrigine and valproate are commonly used to treat people with absence seizures we have insufficient evidence to show which drugs are best for treating seizures in children and adolescents with absence epilepsy [110].	[94],[108], [109],[110]
Gabapentin	Partial or secondarily generalized epilepsy. Adults and children (over age of 6 years)	Drowsiness, dizziness, seizure exacerbation, ataxia, headache, tremor, diplopia, nausea, vomiting, rhinitis.	[103]
Lamotrigine	Partial and generalized epilepsy. Also in Lennox–Gastaut syndrome and other	Rash (sometimes severe), headache, blood dyscrasia, ataxia, asthenia, diplopia, nausea, vomiting, dizziness, somnolence, insomnia, depression, psychosis,	[103],[108]

	generalized epilepsy syndromes. Adults and children over 2 years of age.	tremor, hypersensitivity reactions. Lamotrigine can be effective therapy for juvenile myoclonic epilepsy and eyelid myoclonia with absences when used alone and, in conjunction with other antiepileptic drugs (AED) (usually valproate) for early myoclonic encephalopathy, myoclonic-astatic epilepsy and particularly, epilepsy with myoclonic absences [108].	
Levetiracetam	Partial seizures with or without secondarily generalized seizures. Adults only.	Somnolence, asthenia, infection, dizziness, headache, irritability, aggression, behavioural and mood changes	[103]
Oxcarbazepine	Partial and secondarily generalized seizures. Adults and children	Somnolence, headache, dizziness, diplopia, ataxia, rash, hyponatraemia, weight gain, alopecia, nausea, gastrointestinal disturbance.	[103]
Phenobarbital	Anticonvulsant, sedative, hypnotic	Sedation, paradoxical excitement, hyperactivity, rash.	[94]
Phenytoin	Tonic-clonic SZs, psychomotor SZs, status epilepticus, prevention and treatment of SZs post-neurosurgery.	Nystagmus, ataxia, rash, gingival, hypertrophy, impaired cognition.	[94]
Pregabalin	Partial seizures with or without secondary generalization. Adults only	Somnolence, dizziness, ataxia, asthenia, weight gain, blurred vision, diplopia, tremor.	[103]
Primidone	Monotherapy or adjunctive in GTC, psychomotor SZs	Sedation, dizziness, ataxia, rash, paradoxical excitement.	[94]
Tiagabine	Partial and secondarily generalized seizures. Patients ≥ 12 years of age only	Dizziness, tiredness, nervousness, tremor, diarrhoea, nausea, headache, confusion, psychosis, flu-like symptoms, ataxia, depression, word-finding difficulties, encephalopathy, non-convulsive status epilepticus.	[103]
Topiramate	Partial and secondarily generalized seizures. Also for Lennox–Gastaut syndrome. Idiopathic generalized epilepsy. Adults and children over 2 years of age.	Dizziness, ataxia, headache, paraesthesia, tremor, somnolence, cognitive dysfunction, confusion, agitation, amnesia, depression, emotional lability, nausea, diarrhoea, diplopia, weight loss.	[103]
Valproate acid	Absence (petit mal), atypical absence, GTC, adjunctive for multiple SZ types.	Nausea, vomiting, tremor, thrombocytopenia, hepatic dysfunction, hair loss, weight gain. The treatment of first choice for benign myoclonic epilepsy in infants, myoclonic astatic epilepsy, epilepsy with myoclonic absences, eyelid myoclonia with absences, juvenile myoclonic epilepsy and progressive myoclonus epilepsy [98]. The risk of abortion was greater with use of valproate (8%) than with other drugs (from 1% with phenobarbital to 6% with lamotrigine). Doses of valproate below 700 mg/day were associated with a malformation rate in a similar range as that of carbamazepine 400–1000 mg/day, phenobarbital less than 150 mg/day, and lamotrigine of 300 mg/day or higher. The risk of major malformations increases with the prescribed dose of valproate, in general with greater risks at doses above 600–1500 mg/day [111].	[94],[98]
Vigabatrin	Partial and secondarily generalized epilepsy. West syndrome	Mood change, depression, psychosis, aggression, confusion, weight gain, insomnia, changes in muscle tone in children, tremor, diplopia, severe visual field constriction.	[103]
Zonisamide	Refractory partial epilepsy and generalized epilepsy (all types). Lennox–Gastaut syndrome. West syndrome. Progressive myoclonic epilepsy.	Somnolence, ataxia, dizziness, fatigue, nausea, vomiting, irritability, anorexia, impaired concentration, mental slowing, itching, diplopia, insomnia, abdominal pain, depression, skin rashes, hypersensitivity. Significant risk of renal calculi. Weight loss, oligohidrosis and risk of heat stroke. Zonisamide added to clonazepam and valproate or a barbiturate, can reduce the cascade of myoclonia in progressive myoclonus epilepsies for at least 2 years, but relapse may occur thereafter [108].	[103],[108]

GTC: generalized tonic clonic, SZ: seizure

B. Ketogenic Diet

The ketogenic diet was created by Wilder in 1921 at the Mayo Clinic in Rochester, Minnesota for children with refractory epilepsy. It restricted carbohydrates, protein, calories, and fluids while significantly increasing fat intake to comprise approximately 90% of calories. Within several years it became widely used for adults, as well as children [112]. The ketogenic diet, which is high fat and extremely low in carbohydrates, can help control seizures in some patients [113].

There are four different ketogenic diets available to choose from: the traditional 'classic' ketogenic diet, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD) and the low glycemic index treatment (LGIT). These alternative diets are better choices for many patients with epilepsy who are concerned about the difficulty in changing their lifestyle to adopt a ketogenic diet, including adolescents, adults, busy families with multiple children, and patients with very high baseline carbohydrate intake (or fat aversion). The details of each diets could be seen in **TABLE VIII**.

TABLE VIII COMPARISON OF THE FOUR MAJOR KETOGENIC DIETS [114]

Component	Classic ketogenic (4:1)	MCT	Modified Atkins	LGIT
Carbohydrate (%)	8 (3%)	50 (20%)	10 (5%)	40 (27%)
Fat (g, % calories)	100 (90%)	78 (70%)	70 (70%)	60 (45%)
Protein (g, %)	17 (7%)	25 (10%)	60 (25%)	40 (28%)
MCT: medium chain triglyseride; LGIT: low glycemic index treatment				

Adenosine may play a role in the ketogenic diet's antiseizure effects [115]. Norepinephrine plays a key role in the ketogenic diet's anticonvulsant mechanism [116],[117].

A ketogenic diet can decrease morphological signs of mitochondrial damage and protect against conditions wherein mitochondrial DNA damage occurs [118]. Moreover, ketogenic diets also may exert a neuroprotective effect through antioxidant mechanisms mediated via the nuclear factor E2-related transcription factor [119].

Recently, the ketogenic diet is extensively indicated for: [120]-[124]

1. absence epilepsy
2. Alzheimer's disease
3. amyotrophic lateral sclerosis (ALS)
4. autism
5. brain tumors
6. children receiving only formula
7. children with Lennox–Gastaut syndrome
8. Dravet syndrome
9. hypothalamic hamartoma
10. hypoxic-ischemic encephalopathy
11. infantile spasms
12. migraine
13. myoclonic-astatic epilepsy
14. Parkinson disease
15. refractory status epilepticus
16. Rett syndrome
17. Sturge–Weber syndrome
18. traumatic brain injury
19. tuberous sclerosis complex

Providing the ketogenic diet within 7-10 days as a formula through a nasogastric tube to a patient in an intensive care unit (ICU) with status epilepticus is a very feasible option [125].

The clinicians and physicians should be aware of the side effects of giving the ketogenic diets. **TABLE IX** shows side effects and solution of the ketogenic diets: [126]-[128]

TABLE IX

Side effects	Solution
➢ hypercholesterolemia	✓ alternative diets (MAD, LGIT)
➢ mineral deficiencies	✓ avoiding a fasting protocol
➢ acidosis	✓ supplements (calcium, selenium, zinc, and vitamin D)
➢ constipation	✓ oral citrates (children with the ketogenic diet)
➢ weight loss	

C. Neurogenetics

Neurogenetics is synthesis between neurology and genetics studies and researches. The comprehensive understanding of epilepsy neurogenetics is the key to study, learn, and develop epilepsy pharmacogenetics and pharmacogenomics. **TABLE X** shows an example of the study of epilepsy neurogenetics.

TABLE X THE STUDY OF EPILEPSY NEUROGENETICS

Diseases/Disorders	The Gene Symbols	Sum	References
Generalized myoclonic epilepsy, febrile seizures, absences	ALDH7A1, BRD2, CACNA1A, CACNA1H, CACNB4, CASR, CHRNA2, CHRNA4, CHRNB2, CLCN2, CSTB, EFHC1, EPM2A, GABRA1, GABRB3, GABRD, GABRG2, GPR98, GRIN2A, GRIN2B, KCNMA1, KCNQ2, KCNQ3, KCTD7, MBD5, ME2, NHLRC1, PCDH19, PRICKLE1, PRICKLE2, SCARB2, SCN1A, SCN1B, SCN2A, SCN9A, SLC2A1, TBC1D24.	37 genes	[129],[130]
Syndromic epilepsy	ARFGEF2, ARHGEF9, A2BP1, ASPA, ATP1A2, ATP2A2, ATP6V0A2, CACNA1A, CCDC88C, CLCNKA, CLCNKB, COH1, DLGAP2, GFAP, GLI3, GLRA1, GLRB, GPHN, KCNA1, KCNJ1, KCNJ10, KIAA1279, LAMA2, LBR, LGI1, MLC1, MLL2, NF1, NIPBL, PANK2, PI12, PIGV, PLA2G6, RAI1, SCN8A, SETBP1, SHH, SLC4A10, SLC6A5, SMC1A, SMC3, SYNGAP1, TBX1, TSC1, TSC2, VPS13A, ZEB2.	47 genes	[131]
Epileptic encephalopathies	ARHGEF9, ARX, CDKL5, CNTNAP2, FOXG1, GABRG2, GRIN2A, GRIN2B, MAPK10, MECP2, NRXN1, PCDH19, PNKP, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCN1A, SCN1B, SCN2A, SCN9A, SLC2A1, SLC25A22, SLC9A6, SPTAN1, STXBP1, TCF4, TREX1, UBE3A, ZEB2	30 genes	[132]
Epilepsy with mental retardation	ARHGEF9, ARX, ATP6AP2, ATRX, CASK, CDKL5, CUL4B, CXORF5, DCX, FGD1, GPC3, GRIA3, HSD17B10, JARID1C, OPHN1, PAK3, PHF6, PLP1, PQBP1, RAB39B, SLC9A6, SMC1A, SMS, SRPX2, SYP	25 genes	[133]
Joubert syndrome (brain malformations)	AHI1, ARL13B, CC2D2A, CEP290, CXORF5, INPP5E, NPHP1, RPGRIP1L, TMEM67, TMEM216	10 genes	[46],[130],[134]

IV. The Future of Epilepsy based on Pharmacogenetics and Pharmacogenomics Approach

A. Pharmacogenetics

Pharmacogenetics is the study of how an individual's genetics affects his or her response to drugs, combining traditional pharmaceutical sciences, such as biochemistry, with annotated knowledge of genes, proteins and single-nucleotide polymorphisms (SNPs) [136].

Pharmacogenetics aims to: [137]

1. Identify genetic variants that could explain variable response to AEDs (including drug resistance) and could potentially be used for treatment optimization in individual patients, resulting in a more targeted, more efficacious and less harmful treatment.
2. Aid development of new, more efficacious AEDs. As such, it could have important implications for the conduct of new AED trials.
3. Describe variation, either genetically or biochemically in a handful of proteins and genes.
4. Deliver a range of tests that could guide the clinician in his choice of treatment.

Ideally, pharmacogenetic studies should be conducted prospectively, i.e., patients should be genotyped before or at the time they start a specific drug, and then have their response studied over time and correlated to their genotype. Such studies are obviously more difficult to conduct than retrospective studies [138].

Moreover, recently several pharmaceutical companies have attempted to identify genetic variants that predict response to the drug ('efficacy pharmacogenetics') and genetic variants associated with toxicity ('safety pharmacogenetics') [139].

The potential advantages of epilepsy pharmacogenetics offer a revolutionary approach to clinical practice and the management of epilepsy. It can be used and developed as a tool during new drug trials and in the clinical setting as an effective treatment of epilepsy and as a guide to new AED development [136].

B. Pharmacogenomics

Pharmacogenomics is a more broad term that encompasses the influence of the wide range of tools of gene-based molecular science on pharmacology, including the strategy using the genetic association approach with new ways to design drugs and vaccines and also the goal of identifying genes that influence clinical response to drug treatment. Pharmacogenomic research has rapidly incorporated advances in biochemistry, molecular biology, cell biology, and genomics [140],[141].

Pharmacogenomic studies should consider non-genetic factors that can interact in influencing the phenotype. Pharmacogenomics will aid in understanding how genetics influence disease development, drug response, and contribute to discovery of new treatments [142].

Recent developments in genetic technology (including GWAS, Genome-wide association study) may facilitate the development of the best treatment for epilepsy. The effective crosscentre infrastructure of multinational collaboration will support and reinforce the developing platform and framework of epilepsy pharmacogenomics [143].

The roles of pharmacogenomics in clinical trials are: identification of variations in a large number of genes that affect drug action, stratification of patients in clinical trials according to genotype, reduction of the total number of patients required for clinical trials, reduction in drug development time by demonstrating efficacy in specific populations, prediction of drug-drug interactions, prediction of optimal doses of the drug in different patient populations, prediction of adverse reactions or therapeutic failures based on the genotype of the patient.[144] Moreover, steps in the application of pharmacogenomics in clinical trials are: [144]

1. Identification of the mechanism of action of drug
2. Identification of the target for drug action
3. Identification of the candidate gene
4. Clinical trials for relationship between candidate gene variants and efficacy/safety sequence
5. Controlled clinical trials on populations stratified by genotyping sequence

A conceptual framework that outlines the pharmacogenetic and pharmacogenomic aspects of epilepsy is proposed and summarized in **Table XI**.

Pharmacogenetics implies the study of a single gene whereas pharmacogenomics implies the study of many genes or entire genomes. Moreover, pharmacogenomics covers levels above that of DNA, such as mRNA or proteins, and thus relates more to drug development than does pharmacogenetics [156].

The main candidate gene categories in epilepsy pharmacogenetics are: genes affecting pharmacokinetics, e.g., drug transporter and drug-metabolizing enzyme-encoding genes, genes influencing pharmacodynamics, e.g., drug target-encoding genes, genetic factors relating to the epilepsy itself, and others, e.g., genes encoding immune factors implicated in idiosyncratic drug reactions [157].

Established genetic associations in epilepsy pharmacogenetics include cytochrome P450(CYP)2C9 alleles. doses and levels of the AED phenytoin. A functional polymorphisms in the voltage-gated neuronal sodium channel gene SCN1A, doses of phenytoin and carbamazepine, the human leukocyte antigen (HLA)-B*1502 allele and Stevens-Johnson syndrome on carbamazepine [158].

New technologies for comprehensive genomic analysis have already been applied. Therefore, a combination of research strategies may lead to a better understanding of treatment effects and management in epilepsy.

TABLE XI EPILEPSY PHARMACOGENETICS AND PHARMACOGENOMICS

Anti Epileptic Drugs (AED)	**Drug transporters** [145][146]	**Metabolism and (Major) mechanism of action** [147]-[150]	**Main Target** [136],[151]
Carbamazepine	MDR1, MRP2	Epoxidation (CYP3A4>CYP1A2, CYP2C8), hydrolysis (mEH); glucuronidation (UGT2B7); inhibition of voltage-dependent sodium conductance; action on monoamine, acetylcholine, and NMDA receptors	VG Na^+ channels
Felbamate	MDR1	60% hydroxylation (CYP3A4, CYP2E1OCYP2C19); conjugation; 40% unchanged renal excretion; inhibition of NMDA receptor (glycine recognition site) and sodium-channel conductance	NMDA receptors
Gabapentin	MDR1, LNAA	> 95% unchanged renal excretion; elevates GABA concentrations in the occipital cortex of epileptic patients [152].	Binds to the alpha-2-delta subunit of the L-type VG calcium channel [153]
Lamotrigine	MDR1	Glucuronidation (UGT1A4); inhibition of voltage-dependent sodium conductance; block voltage-sensitive calcium channels; selectively target neurons that synthesizes glutamate and aspartate [154].	VG Na^+ channels
Pregabalin	LNAA	98% unchanged renal excretion; binds to alpha-2-delta subunit of the voltage-gated calcium channel, reduces release of glutamate and other excitatory neurotransmitters	VG $Ca2^+$ channel alpha-2-delta-subunit
Phenobarbital	MDR1	8–34% hydroxylation (CYP2C9, CYP2C19OCYP2E1); glucuronidation; N-glucosidation; epoxidation, hydrolysis (mEH); enhances activity of GABA-A receptor; depresses glutamate excitability, and affects sodium, potassium and calcium conductance	$GABA_A$ receptor
Phenytoin	MDR1, MRP2	Hydroxylation (~90% CYP2C9, ~10% CYP2C19), hydrolysis (mEH), or GSH and GST; glucuronidation; inhibition of voltage-dependent sodium channels	VG Na^+ channels
Topiramate	MDR1	80% unchanged renal excretion; 20% hydroxylation (CYP2C19) and glucuronidation; inhibition of voltage-gated sodium channels; potentiation of GABA-mediated inhibition at the GABA-A receptor; reduction of AMPA receptor activity; inhibition of high-voltage calcium channels; carbonic anhydrase activity	VG Na^+ channels
Valproate (sodium valproate)	MRP	beta-oxidation; glucuronidation; CYP2A6, CYP2C9, CYP2C19; effects on GABA and glutaminergic activity, calcium (T) conductance and potassium conductance; decreases brain concentrations of the excitatory amino acid aspartate without influencing those of glutamate or GABA; elevates brain GABA levels and potentiates GABA responses [155].	Blockade of neuronal sodium channels in a voltage-and frequency-dependent manner [150].

MDR1, multidrug-resistance protein 1; MRP, multidrug-resistance associated protein; LNAA, large neutral amino acid transporter. GSH,glutathione; GST,glutathione S-transferase; NMDA, N-methyl-D-aspartate; AMPA, aminohydroxymethylisozole propionic acid. GABA, gamma-aminobutyric acid. VG, voltage gated.

C. Future therapeutic directions

Clinical trials to develop new therapies of epilepsy diseases in the next few years will be very expensive. The development of medicine may make testing these new therapies more economical by allowing the selection of patients who are most likely to respond to a given treatment. Controlled clinical trials are required to use a comparator group, and trial designs range from using true placebo treatments to using comparisons or add on therapies as compared to the control groups receiving the current standard of care. Improving the ability to identify subsets of patients who are more likely to respond biologically to a given agent would allow a more robust comparison between a treatment and a control group, expose less patients inappropriately to a test treatment, as well as increase the efficiency and reduce the costs of clinical trials. Drugs with apparently equivalent efficacy in an entire population may show particular benefits in different subsets of these populations.

1) Stem Cell Therapy

Stem cell–based epileptic therapies have the potential to repair and even correct the defects related to brain human diseases. Although stem cell applications have moved forward in the clinical setting, progress is slow, and ethical challenges have yet to be definitively addressed. The goal of developing pluripotent cells that can transmute to organ-specific maturity at our direction and possibly cure many brain human diseases has yet to be attained [159].

With recent advances, however, gene correction involving stem cells is becoming closer. Although techniques for correcting genetic abnormalities have been available in the laboratory for years, the tools for manipulating the genome tend to leave traces of unwanted genetic material within the cell or within the genes themselves.

2) Gene Therapy

Gene therapy is a novel form of drug delivery that enlists the synthetic machinery of the patient's cells to produce a therapeutic agent. Using the body to treat its own disease overcomes the need to manufacture highly purified proteins. It also eliminates the need for repeated parenteral administration of proteins or drugs and reduces the difficulties of complying with exogenous-drug regimens. Applications of gene therapy are not limited to rare inherited diseases, but extend potentially to common acquired disorders, including epilepsy, brain disorder, cancer, heart disease, and the acquired immunodeficiency syndrome [160].

Gene therapy is likely to have broad implications for the future practice of medicine. An important aspect of gene-delivery systems is the ability to regulate the expression of the introduced gene. With the vectors that are now approved

for gene therapy, cells express the genes continuously. As a result, the production of the therapeutic protein cannot be modulated. In diseases such as epilepsy regulation of the new gene is critical . In most other diseases, gene regulation is desirable; indeed, constitutive expression of the introduced gene may be detrimental or even life-threatening. To overcome this problem, yeast-gene or bacterial-gene regulatory systems have been adapted for use in mammalian cells. These inducible systems appear advantageous because they affect the expression of introduced, but not resident genes. There is no toxicity and the gene-inducing agent can be administered orally.

In principle, these new regulatory systems allow genes to be turned on and off and the level of the therapeutic protein varied over time. The complex goal of regulating genes through the use of endogenous biologic signals is also being pursued, but will take time to reach the epileptic therapy. One preclinical trial belonging to gene therapy, involves use allatostatin receptor (AlstR)/ligand system to regulate inhibitory neuron to make synchrony of brain functions by electrophysiology, laser scanning photostimulation, and voltage-sensitive dye imaging methods. The AlstR approach represents an important advancement for genetic manipulation of neuronal activity that can be valuable for many basic applications. The AlstR system can also be potentially used in translational applications, in seizure control and epilepsy treatment as a molecular anticonvulsant with few side effects [161].

V. Summary

Epilepsy affects millions of peoples in the world. The disorder requires the participation of all parties, from families, physicians, researchers, and of course the government. A combination of research strategies and prudent policies from government may lead to a better understanding of treatment effects and realistic management of epilepsy.

Disclosure

The authors report no conflicts of interest in this work.

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