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A COMPREHENSIVE REVIEW ON EPILEPSY: EPIDEMIOLOGY, NEUROCHEMICAL BASIS, STRUCTURAL CLASSIFICATION, AND ETIOLOGY

Ritu Sharma[1]*, Prashant Mahendrabhai Patel[2,3], Atish Waghmare[3]

[1]Research Scholar, Department of Pharmacology, Lord's International College of Pharmacy, Lord's University, Alwar, Rajasthan, India.
[2]Department of Pharmacology, Professor, Lord's International College of Pharmacy, Lord's University, Alwar, Rajasthan, India.
[3]Department of Pharmaceutical Chemistry, Associate Professor, Career Point University, Kota, Rajasthan, India.

***Corresponding Author: Ritu Sharma**

Research Scholar, Department of Pharmacology, Lord's International College of Pharmacy, Lord's University, Alwar, Rajasthan, India.

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ABSTRACT

Epilepsy is a chronic neurological disorder characterized by an ongoing tendency to have unprovoked seizures, which are caused by abnormal electrical activity in the brain's cortex. Beyond the seizures themselves, people living with epilepsy can also experience various deficits related to their neurobiology, cognition, psychology, and social life. Globally, this condition affects over 50 million individuals. Other neuromodulators, including serotonin, dopamine, and acetylcholine, are also known to influence an individual's seizure threshold. The 2017 ILAE (International League Against Epilepsy) classification system categorizes seizures as focal, generalized, or of unknown onset. In contrast, epilepsy itself is classified based on its etiology, which includes genetic, structural, metabolic, infectious, immunologic, or unknown origins. Clinically, epilepsy disorders range significantly, from uncomplicated focal seizures to highly complex disorders like Lennox-Gastaut and Dravet syndromes. Antiepileptic medications (AEDs) like valproate, carbamazepine, lamotrigine, and levetiracetam are commonly used in first-line therapy. However, alternative therapies such as the ketogenic diet, vagus nerve stimulation (VNS), and various surgical options are taken into consideration for the approximately 30-40% of individuals with drug-resistant epilepsy (DRE). In India, treatment faces significant obstacles, such as limited access to essential medications, a shortage of specialist neurologists, and persistent social stigma. Looking forward, advancements in genetics, precision pharmacology, and AI-driven diagnostics offer exciting potential for developing highly individualized epilepsy treatment strategies.

KEYWORDS: brain region, glutamate, gamma-aminobutyric acid (GABA), excitatory and inhibitory neurotransmitter, seizures, epilepsy.

INTRODUCTION AND BACKGROUND

Epilepsy is a chronic neurological disorder characterized by a persistent predisposition of the brain to generate unprovoked seizures resulting from abnormal and excessive neuronal activity.[1] According to the International League Against Epilepsy (ILAE), epilepsy is defined not only by recurrent seizures but also by the associated neurobiological, cognitive, psychological, and social consequences that significantly impair quality of life. It affects individuals of all age groups and remains one of the most common neurological disorders worldwide.[2]

From a public health perspective, epilepsy represents a major global health burden.[3] Worldwide, epilepsy affects millions of individuals globally, with a disproportionately higher prevalence in low- and middle-income countries due to factors such as perinatal brain

injury, central nervous system infections, traumatic brain injury, and limited access to healthcare services.[4] Epidemiological studies further indicate that the incidence of epilepsy is significantly higher in resource-poor regions, where diagnosis and treatment gaps remain substantial.[5]

In India, epilepsy continues to pose a significant neurological and socioeconomic challenge. It is estimated that approximately 1% of the Indian population is affected, corresponding to more than 10 million individuals nationwide.[6] Despite the availability of effective antiepileptic drugs, a large treatment gap persists, particularly in rural and underserved areas, due to an inadequate healthcare sector, social stigma, economic constraints, and an uneven distribution of trained neurologists. These factors contribute to delayed diagnosis, poor treatment adherence, and increased disease burden.[7]

Epilepsy comprises a heterogeneous group of disorders with diverse clinical and etiological characteristics. Contemporary classification systems categorize epilepsy based on seizure type, epilepsy type, etiology, and the involvement of specific brain regions.[8] The etiologies include structural, genetic, metabolic, immune, infectious, and unknown causes, reflecting the multifactorial nature of epileptogenesis.[9]

At the mechanistic level, epilepsy arises from complex alterations in neuronal excitability, synaptic transmission, and network synchronization.[10] A critical determinant of seizure generation is the imbalance between excitatory and inhibitory neurotransmission in the central nervous system.[11] Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter, acting through GABA A and B receptors to suppress neuronal firing; impairment of GABAergic signaling leads to hyperexcitable neural circuits and a reduced seizure threshold.[12] In contrast, glutamate serves as the major excitatory neurotransmitter and activates ionotropic receptors such as NMDA receptors and metabotropic glutamate receptors, which contribute to seizure initiation and propagation when dysregulated.[13]

In addition to neurotransmitter imbalance, abnormalities in voltage-gated ion channels, synaptic reorganization, neuroinflammation, and dysfunction of key brain regions, including the hippocampus, cortex, and thalamus, play a crucial role in seizure generation and the progression of epileptogenesis.[14] These molecular and cellular alterations are particularly important in the development of drug-resistant epilepsy.[15]

Antiepileptic drug therapy remains the primary treatment strategy for epilepsy, with a substantial proportion of patients achieving seizure control following early diagnosis and appropriate pharmacological intervention.[16] However, approximately one-third of patients develop drug-resistant epilepsy, requiring alternative approaches such as epilepsy surgery, neurostimulation, ketogenic diet therapy, and other non-pharmacological interventions.[17] Despite these advances, the limitations of current treatments highlight the urgent need for safer and more effective therapeutic strategies for epilepsy management.[18]

Epilepsy is a chronic neurological disorder that affects the central nervous system and is characterized by a persistent predisposition to generate unprovoked seizures due to abnormal electrical discharges in the brain.[19] Globally, epilepsy is one of the most common neurological disorders and represents a major cause of neurological morbidity and disability.[20] Epileptic seizures interfere with normal brain function and may result in impaired motor control, loss of consciousness, and autonomic disturbances such as loss of bladder or bowel control, thereby increasing the risk of injuries, fractures, and sudden unexpected death in epilepsy (SUDEP).[21]

1.1 The Global and Indian Burden

A disproportionately large burden of epilepsy is observed in low- and middle-income countries, where exposure to perinatal injury, central nervous system infections, and limited access to healthcare remains high.[22] Epidemiological studies indicate that the annual incidence of epilepsy in resource-poor regions ranges between 40 and 70 per 100,000 people, which is considerably higher than in high-income countries.[23] In India, epilepsy affects approximately 1% of the population, corresponding to more than 10 million individuals nationwide. Community-based studies report a prevalence ranging between 5.6 and 10 cases per 1,000 people.[24] Despite the availability of effective antiepileptic drugs, a substantial treatment gap persists. Both the World Health Organization and the Indian Epilepsy Society have highlighted that up to 90% of individuals with epilepsy in rural areas and about 22% in urban areas do not receive adequate treatment. This gap is largely driven by limited healthcare infrastructure, shortage of trained neurologists, social stigma, and poor awareness, all of which significantly compromise disease outcomes.[25]

Accurate epidemiological data are essential for guiding resource allocation, planning antiepileptic drug distribution, and developing public health policies aimed at reducing disease burden and stigma.[26]

1.2 The Importance of Early Intervention

More than 70% of individuals with epilepsy can achieve long-term seizure control when the condition is diagnosed early and treated appropriately with antiepileptic drugs.[27] Timely identification and management of seizures therefore play a critical role in preventing complications, reducing disability, and improving quality of life.[28] This review provides a comprehensive overview of epilepsy with a particular focus on the Indian context, including epidemiology,

clinical features, risk factors, and current management strategies, as well as future directions for improving epilepsy care.[29]

1. Neurochemical Basis of Epilepsy

Epilepsy arises from an imbalance between excitatory and inhibitory neurotransmission in the central nervous system. Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter and reduces neuronal excitability through GABA A and B receptors. Deficient GABAergic inhibition leads to hyperexcitable neuronal networks and a reduced seizure threshold. Glutamate is the main excitatory neurotransmitter and activates ionotropic receptors such as NMDA receptors and metabotropic glutamate receptors. Excess glutamatergic activity or impaired glutamate clearance contributes to excitotoxicity and promotes seizure initiation and propagation. Other neurotransmitters, including serotonin and dopamine, also modulate neuronal excitability and influence seizure susceptibility.[30]

In India, the large epilepsy treatment gap further worsens disease outcomes. This gap is attributed to inadequate healthcare sector, social stigma. Epidemiological data are therefore critical for optimizing antiepileptic drug supply, healthcare planning, and policy development to improve access to treatment and reduce stigma.[31]

2. Brain Regions Involved in Epilepsy

Epilepsy is characterized by abnormal, hypersynchronous neuronal discharges that primarily originate in the cerebral cortex, particularly in focal epilepsies. The temporal lobe, especially the hippocampus, is highly susceptible to excitotoxic injury and is the most common site of seizure onset in focal epilepsy. Frontal lobe epilepsy is also common and is often associated with complex motor and behavioral manifestations Electroencephalography plays a central role in epilepsy diagnosis and classification. Focal epilepsies are associated with localized epileptiform discharges, whereas generalized epilepsies show widespread spike-and-wave activity across both hemispheres. Subcortical structures, particularly the thalamus, are critical in the generation and synchronization of generalized seizures. Magnetic resonance imaging further aids in identifying structural abnormalities such as hippocampal sclerosis, tumors, and cortical dysplasia, thereby guiding diagnosis and treatment planning.[32]

3. ILAE Classification of Epilepsy

In the International League Against Epilepsy (ILAE) introduced an updated classification framework to improve the accuracy of epilepsy diagnosis and guide therapeutic decision-making. This system classifies epilepsy using a three-tiered approach based on seizure type, epilepsy type, and underlying etiology. The first step in classification is identification of the seizure type, which may be focal, generalized, or of unknown onset. Focal seizures originate within a localized region of one cerebral hemisphere and may present with either motor or non-motor features, with or without impairment of consciousness. Generalized seizures arise from networks involving both hemispheres at onset and include seizure types such as tonic-clonic, absence, and myoclonic seizures. Seizures of unknown onset are diagnosed when the initial site of seizure origin cannot be reliably determined.[33] The second stage of classification defines the epilepsy type, which is categorized as focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy, or epilepsy of unknown type. This determination is based on clinical seizure patterns, electroencephalographic findings, and neuroimaging results. The third component of the classification identifies the etiology of epilepsy, which may be structural, genetic, infectious, metabolic, immune-mediated, or unknown. Identifying the underlying cause plays a crucial role in selecting appropriate antiepileptic drug therapy and in identifying patients who may benefit from alternative interventions such as epilepsy surgery or immunotherapy. The ILAE framework also emphasizes the use of the term epilepsy syndrome when a consistent pattern of seizure types, age of onset, EEG features, and clinical characteristics is present. This structured classification system improves diagnostic precision, supports rational pharmacological and non-pharmacological treatment strategies, and facilitates effective communication among healthcare professionals involved in epilepsy care.[34]

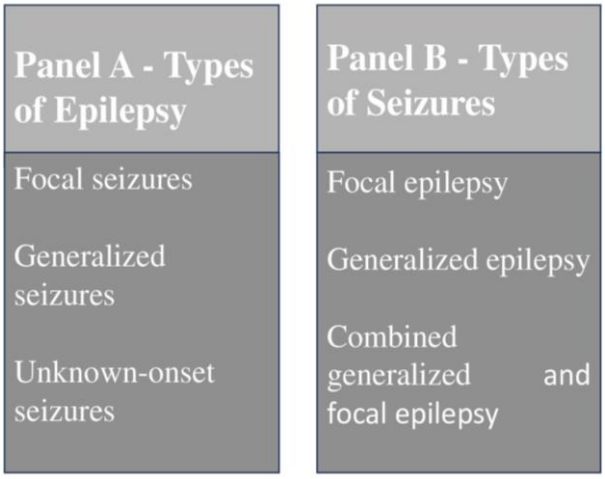

Figure 1: Classification of seizure and types of epilepsy.

Figure 1. Classification of seizures and types of epilepsy. A. Types of seizures are classified as focal, generalized, and unknown-onset seizures. B. Types of epilepsy are classified into focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy, and epilepsy of unknown type according to the ILAE framework. Image credit: Ritu Sharma.

Epilepsy Types

Epilepsy is broadly classified into focal epilepsy and generalized epilepsy based on the region of the brain in which seizure activity originates. Generalized epilepsies arise from networks that involve both cerebral hemispheres at seizure onset and are typically associated with sudden loss of consciousness and symmetrical motor involvement. These seizures include absence seizures, myoclonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures, each reflecting different patterns of abnormal neuronal discharge. In contrast, focal epilepsies originate from a localized region within one cerebral hemisphere and may occur with preserved or impaired awareness. Focal seizures can be associated with motor, sensory, visual, or autonomic symptoms depending on the cortical area involved, and in some cases may evolve into generalized seizures. This anatomical classification is clinically important because it guides diagnostic evaluation and therapeutic decision-making.[35]

Epilepsy Syndromes

Epilepsy syndromes are clinically defined disorders characterized by a specific combination of seizure types, age of onset, electroencephalographic patterns, neuroimaging findings, and underlying etiological factors. These syndromes provide a framework for understanding the natural history of epilepsy and are essential for selecting appropriate therapeutic strategies. The International League Against Epilepsy (ILAE) recognizes epilepsy syndromes as a distinct level of diagnosis, particularly when a consistent pattern of clinical, electrophysiological, and imaging features is present.[36]

Epilepsy syndromes may occur across all age groups and include both genetic and acquired forms. In childhood, syndromes such as childhood absence epilepsy and developmental epileptic encephalopathies are commonly observed, whereas in adolescents and adults, conditions such as juvenile myoclonic epilepsy and temporal lobe epilepsy are more prevalent. These syndromes differ in seizure frequency, treatment response, and long-term prognosis, making accurate classification clinically important. Focal epilepsy syndromes, particularly temporal and frontal lobe epilepsies, are among the most frequently encountered in clinical practice. Temporal lobe epilepsy is often associated with hippocampal sclerosis and is a leading cause of drug-resistant epilepsy, while frontal lobe epilepsy commonly presents with prominent motor manifestations and brief, frequent seizures. Advances in neuroimaging and EEG techniques have significantly improved the identification of these syndromes and the selection of patients for surgical or targeted therapeutic interventions.[37]

Levels of Epilepsy

Epilepsy can be understood across multiple biological and clinical levels, reflecting the complexity of seizure generation and disease progression. At the molecular and cellular level, epilepsy arises from dysfunctions in ion channels, neurotransmitter receptors, and synaptic signaling pathways that regulate neuronal excitability. Alterations in GABAergic inhibition and glutamatergic excitation play a central role in creating hyperexcitable neuronal networks that predispose the brain to seizures. At the neural network level, abnormal synchronization and connectivity between groups of neurons lead to the propagation and maintenance of epileptic activity. Recurrent seizures induce long-term changes in synaptic plasticity and network organization, particularly within limbic and cortical circuits, which contribute to the development of chronic epilepsy and drug resistance.[38]

At the brain-system level, specific anatomical regions such as the hippocampus, cerebral cortex, and thalamus are critically involved in seizure initiation and spread. Structural and functional abnormalities in these regions, as observed through neuroimaging and electrophysiological studies, are strongly associated with focal and generalized epilepsies. Finally, at the clinical level, epilepsy manifests as recurrent seizures accompanied by cognitive, behavioral, and psychosocial impairments that significantly affect quality of life. Understanding epilepsy across these interconnected levels enables more accurate diagnosis and supports the development of targeted pharmacological and non-pharmacological treatment strategies.[39]

3.2 Etiology of Epilepsy (Cause or origin of disease)

Epilepsy stems from various factors that cause persistent brain dysfunction, leading to recurrent seizures. The current consensus categorizes the main causes of epilepsy as follows.[40]

i. Genetic (Idiopathic) Epilepsy: These result from known or presumed genetic mutations affecting components like ion channels or neurotransmitter receptors that control neuronal excitability. There are no associated structural or metabolic irregularities. Genetic epilepsies often emerge in childhood and can be inherited or arise from de novo mutations.

ii. Structural Epilepsy: This is caused by identifiable brain lesions or anomalies that disrupt normal neural networks. Examples include cortical malformations (e.g., focal cortical dysplasia), traumatic brain injury, tumors, stroke, hippocampal sclerosis, and post-infection gliosis. These abnormalities promote hyperexcitability and seizure susceptibility.

iii. Metabolic Epilepsy: This involves the effects of genetic or acquired metabolic disorders that destabilize neural function. Causes include congenital errors (e.g., mitochondrial disorders, urea cycle defects), severe electrolyte imbalances, or vitamin deficiencies that can trigger seizures.

iv. Infectious Epilepsy: Infections of the central nervous system, such as neurocysticercosis, tuberculous

meningitis, or viral encephalitis, can induce acute seizures. They may lead to chronic epilepsy due to subsequent neuronal damage caused by inflammation.

v. Immune Mediated Epilepsy: Seizures arise from immune system malfunctions. This includes autoimmune diseases (like lupus, celiac disease) and neurological disorders like Rasmussen's encephalitis. In some patients, the immune system creates antibodies that attack crucial brain proteins (e.g., NMDA receptors or VGKC channels). These types of epilepsy may respond to immunotherapy (like corticosteroids or immunoglobulins) alongside standard antiepileptic drugs (AEDs).

vi. Cryptogenic Epilepsy: This term is used when professionals strongly suspect an underlying neurological cause, but current diagnostic methods (e.g., imaging) cannot identify it. It is most common in adults with focal seizures. Even with an unknown etiology, cryptogenic epilepsy is treated symptomatically using standard AEDs.

3.3 Pathophysiology

The core of epilepsy's pathophysiology is neuronal hyperexcitability and a widespread disruption of brain networks.[35] The kindling model helps explain how repeated, low-level stimuli can sensitize neural circuits, eventually causing the brain to generate spontaneous, unprovoked seizures.[36] At a molecular level, many hereditary epilepsies are caused by ion channel dysfunction, specifically mutations in sodium, potassium, and calcium channels, which directly alter how excitable is a neuron. The process of epileptogenesis where a normal brain becomes epileptic involves significant structural and functional network reconfiguration. This includes changes like synaptic remodeling and a persistent imbalance between inhibitory and excitatory signals.[41]

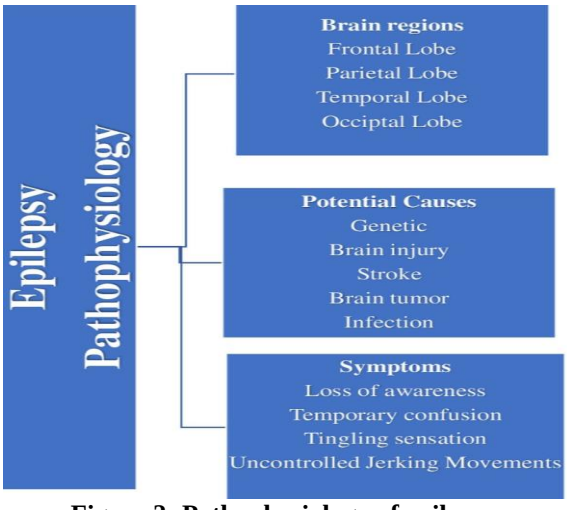

Figure 2: Pathophysiology of epilepsy.

Figure 2. Pathophysiology of epilepsy. The figure illustrates the major mechanisms involved in epileptogenesis, including imbalance between excitatory and inhibitory neurotransmitters, structural brain abnormalities, dysfunction of key brain regions, and abnormal neuronal network synchronization leading to recurrent seizures. Image credit: Ritu Sharma.

3.4 Clinical Features (Signs & Symptoms)

Epileptic seizures often begin with an aura, which signals the start of a focal seizure. Manifestations cover a range of motor signs (tonic/clonic movements), behavioral changes, and autonomic problems. After the seizure, postictal symptoms such as disorientation, lethargy, headache, and temporary neurological deficits are common. Clinicians rely on these characteristics for diagnosis.[41]

3.5 Management and Treatment

3.5.1 Pharmacological Interventions

Pharmacological intervention is primary, employing Anti-Seizure Medications (ASMs) such as sodium valproate, carbamazepine, and levetiracetam, among others, customized according to seizure type and etiology.[42][39]

3.5.3 Non-Pharmacological Strategies

Non-drug interventions offer critical support, particularly for resistant cases. The ketogenic diet (high fat, low carbohydrate) shows particular success in children with difficult-to-treat epilepsy. Epilepsy surgery, such as temporal lobectomy, can potentially cure certain focal epilepsies.[42] Furthermore, Vagus Nerve Stimulation (VNS) and behavioural therapy are valuable supplemental strategies.

4. Addressing Drug Resistance

These alternative treatments are vital for patients who do not respond adequately to standard drug therapies. Achieving optimal outcomes depends heavily on treatment adherence. Unfortunately, about 30% of people with epilepsy are unresponsive to conventional ASMs. Drug resistance often requires the use of alternative drugs or combination therapies. In these complex scenarios, a collaborative approach involving physicians, pharmacists, and mental health specialists is necessary to optimize care and improve the patient's quality of life.[43]

5. Challenges in Epilepsy Management in India

Long-term epilepsy management in India faces several major hurdles. Limited public awareness significantly delays recognition and timely access to medical care and treatment. This is severely amplified by social stigma, which discourages people from seeking help and worsens overall disease management. India also suffers from a vast treatment gap, worsened by economic constraints, the uneven distribution of qualified neurologists, and poor access to essential Anti-Epileptic Drugs (AEDs) (like phenytoin, carbamazepine, valproate, and levetiracetam), especially in rural and marginalized areas.[44]

To counter these issues, the government has launched public health strategies. These initiatives include awareness campaigns, community-level screening for early identification, and efforts to strengthen the primary healthcare system. The goal is to improve access to medication and promote treatment adherence, which is vital for effective seizure control. Since AEDs are central to treatment, guaranteeing their consistent supply, promoting judicious prescribing, and providing thorough patient education are essential to boost therapeutic efficacy and reduce pharmaco-resistance.[45]

6. Future Directions in Epilepsy Treatment

Recent innovative advancements are set to significantly change the epilepsy treatment paradigm. Genomics is key, as it helps identify genetic causes, which in turn guides the creation of personalized therapeutic strategies.[46]

The use of AI-based diagnostic methods will improve the speed and accuracy of finding and classifying seizures by analyzing complex EEG and clinical data. Furthermore, precision medicine focuses on studying molecular pathways unique to specific forms of epilepsy. The drug development pipeline continuously explores both innovative Anti-Seizure Medications (ASMs) and advanced non-pharmacological interventions.[47, 48]

CONCLUSIONS

Epilepsy is a complex disorder defined by diverse clinical presentations, neurochemical changes, and genetic factors. Timely diagnosis, personalized treatment, and comprehensive management are critical for significantly improving patient outcomes. Despite existing challenges, particularly resource limitations in regions like India, advancements in knowledge and technology offer real hope for better interventions and reduced stigma. Continued commitment to research, public health programs, and new therapies is essential to close the global treatment gap and enhance the quality of life for people living with epilepsy worldwide.

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Consent to Publish

Not applicable.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

Not applicable.

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