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EPILEPSY: BRIDGING TRADITIONAL UNDERSTANDING AND CONTEMPORARY CLINICAL PRACTICE

Neha Jain*[1], Anuj Kumar[2], Sushmita Mishra[3], Dr. Ram Dayal[4]

*[1, 2, 3, 4] Sunder Deep Pharmacy College, Sunder Deep Group of Institutions, Ghaziabad 201015, India.

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Keywords	***Abstract***
Epilepsy, Seizures, Traditional Medicine, Antiepileptic Drugs, Neuromodulation, Integrative Therapy.	Epilepsy is a long-term neurological condition marked by repeated seizures that occur without any clear trigger, caused by irregular electrical impulses in the brain. Despite significant advances in neuroscience, the global burden of epilepsy remains high, particularly in low- and middle-income countries. This review seeks to present an in-depth understanding of epilepsy by combining age-old perspectives with current clinical knowledge and practices. It highlights historical perspectives on epilepsy, cultural beliefs, and ancient therapeutic approaches, while aligning them with current understanding of its etiology, classification, diagnostic criteria, and treatment modalities. Emphasis is placed on contemporary pharmacological therapies, surgical options, and emerging interventions such as neuromodulation and dietary therapies. In addition, the role of traditional and complementary medicine—including the use of herbal formulations and mind-body practices—is critically evaluated for their potential as adjuncts to conventional care. This integrative approach underscores the importance of a multidisciplinary perspective in improving patient outcomes, enhancing treatment adherence, and reducing stigma associated with epilepsy. The review concludes by identifying gaps in current practice and suggesting future research directions to bridge cultural beliefs with evidence-based medicine.

1. INTRODUCTION

Epilepsy affects approximately 50 million individuals globally, including an estimated 2 to 3 million in the United States, several million across Europe, and at least 40 million in developing countries.

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[4] The disorder significantly impacts not only those who suffer from it but also their families, often diminishing overall quality of life. Since the introduction of bromide in 1857 as the first antiseizure treatment, there has been remarkable progress in developing medications that reduce both the frequency and intensity of epileptic seizures.[5] These treatments are commonly known as antiepileptic drugs (AEDs); however, to avoid confusion with therapies that modify the disease process or address related comorbidities, the term "antiseizure drugs" is more appropriate and is used throughout this review.[6]

The discovery of newer antiseizure medications has largely resulted from systematic testing in a variety of preclinical seizure and epilepsy models, both in vivo and in vitro. The expanded availability of these medications has undoubtedly enhanced the management of epilepsy, with nearly two-thirds of patients achieving seizure control through pharmacological intervention. This success often leads to a marked improvement in life quality and a decreased risk of injury or death caused by uncontrolled seizures.[7]

However, around one-third of individuals with epilepsy still do not respond adequately to current treatments. For these patients, therapeutic progress has remained limited over recent decades. Moreover, existing drug screening methods have fallen short in predicting which medications might cause adverse effects that impact patients' well-being or prevent optimal dosing. Additional challenges include the potential for drug–drug interactions and concerns about teratogenicity, which can restrict treatment choices for women of reproductive age.[1,2]

- **Early life epilepsies**

There remains a significant gap in addressing early-onset epilepsies. Most preclinical research has traditionally relied on adult animal models, largely to avoid the complexities associated with ongoing brain development.[8] However, many forms of epilepsy actually begin during infancy or early childhood. By the time affected individuals reach adulthood, their brain structure and function may have been shaped by a combination of repeated seizures, long-term medication use, and associated health issues, which in turn influence the course of epileptogenesis. This raises concerns about how effectively treatments developed using adult models translate to younger patients. To improve therapeutic outcomes in pediatric epilepsy, there is a growing need to validate and incorporate early-life models of epileptogenesis, which may better reflect the age-specific mechanisms involved and lead to the discovery of more targeted and effective interventions.[8,9]

- **Seizures**

Seizures are primarily categorized into two main types: focal and generalized. Focal seizures originate in a specific region of the brain and may either remain confined to that area or extend to other parts. In contrast, generalized seizures are characterized by abnormal electrical discharges that affect both hemispheres of the brain from the onset.[9]

Approximately 60% of individuals with epilepsy experience focal seizures. These can manifest in a variety of ways—some may involve unusual sensations, emotional changes, or involuntary movements without affecting consciousness, while others may result in altered awareness or

complete loss of consciousness. The affected person may behave in a confused or repetitive manner, sometimes resembling a dreamlike state. Focal seizures are often named based on the lobe of the brain where they begin. For instance, temporal lobe epilepsy (TLE) originates in the temporal lobe, located on either side of the brain. TLE is one of the most prevalent forms of epilepsy involving focal seizures and is sometimes resistant to standard medical treatment.[9]

On the other hand, generalized seizures typically lead to a loss of consciousness and involve widespread disruption of electrical activity across large areas of the brain. These seizures often result in falls, muscle stiffness, or uncontrolled movements. There are several types of generalized seizures. Absence seizures, usually starting in childhood or adolescence, involve brief periods of staring or subtle muscle twitching. Tonic seizures cause the body's muscles to become rigid, while clonic seizures involve repetitive muscle jerking on both sides. Myoclonic seizures are marked by sudden, brief muscle jerks, usually in the arms, legs, or upper body. In atonic seizures, there is a sudden loss of muscle tone, often causing the person to collapse or drop their head abruptly. Tonic-clonic seizures combine both muscle stiffening and rhythmic jerking and typically include a loss of consciousness.[11]

- **Symptomatic treatment**

- Antiseizure treatment: Antiseizure treatment refers to a type of therapy aimed at stopping seizures or reducing how often or how severe they occur, regardless of the root cause of epilepsy or whether the disease itself continues to progress. While the term may not have an exact equivalent in other languages, it helps distinguish these treatments from those that specifically aim to prevent the development or worsening of epilepsy (epileptogenesis).[15]
- Anticomorbidity treatment: Anticomorbidity treatment refers to therapeutic approaches that help manage or improve the associated health conditions often seen alongside epilepsy, such as cognitive impairments, mental health disorders, and cardiovascular complications.[15]

- **Improving Reproducibility of Preclinical Data**

Insights drawn from other neurological and non-neurological conditions have revealed a critical concern: the limited reproducibility of preclinical research, particularly when transitioning from academic investigations to industrial development and eventually to clinical trials. This issue has been notably emphasized in initiatives such as the Stroke Therapy Academic Industry Roundtable. The significant financial burden associated with drug development makes low reproducibility and poor translational value of preclinical data major barriers to further investment. Additionally, inconsistencies in experimental design often complicate the comparison of outcomes across different studies, further deterring progress in therapeutic innovation.[17]

Several underlying factors contribute to these challenges, among which methodological flaws in study design, execution, and data reporting are especially prominent. A meta-analysis examining preclinical research involving the SOD1 transgenic mouse model for amyotrophic lateral sclerosis highlighted several such issues. These included inadequate or absent blinding procedures, small sample sizes that reduce statistical power, initiation of interventions during presymptomatic phases—

limiting clinical applicability—and a tendency to publish only favorable results. Moreover, reliance on statistical significance without establishing clinical relevance, and failure to consider how preclinical findings translate to human conditions, all further undermine the reliability and impact of such studies.[18]

In response to growing concerns in the field of spinal cord research, the National Institute of Neurological Disorders and Stroke (NINDS) initiated a replication initiative, commissioning ten separate studies to reproduce previously reported preclinical findings. Unfortunately, most of these attempts were unsuccessful, with the original results proving difficult to replicate. Similarly, in the field of stroke research, efforts have been made to address issues related to data reliability. Specific guidelines and evaluation criteria have been introduced to help identify inconsistencies and improve the overall quality of research going forward.[19]

One such effort is reflected in the STAIR (Stroke Therapy Academic Industry Roundtable) recommendations, which stress the importance of several key elements in preclinical study design. These include proper sample size estimation, predefined inclusion and exclusion criteria, randomized group assignment, blinding during the study, and transparent reporting of any excluded subjects or conflicts of interest. The STAIR report proposed a set of essential standards that should be met before any experimental therapy is considered for clinical evaluation.[20]

However, even adherence to these rigorous guidelines does not always ensure clinical success. For example, the neuroprotective agent NXY-059, despite meeting STAIR criteria during its preclinical development, ultimately failed in a large-scale, randomized, multicenter clinical trial. This outcome highlights that while such guidelines may not guarantee effective translation from bench to bedside, they do provide a structured framework that can help identify the reasons behind discrepancies between preclinical and clinical outcomes—especially when studies are designed and executed in a consistent and methodical manner.[19]

- **Side effects**

The use of antiseizure medications is often linked with various side effects, many of which are neuropsychiatric in nature—such as fatigue, dizziness, imbalance, and irritability. These adverse effects can involve multiple organ systems and are sometimes subtle, making them easy to overlook. Therefore, clinicians should remain vigilant and monitor patients closely for any emerging symptoms.[22]

In women of reproductive age, the potential risk of birth defects should always be a key consideration when prescribing these medications. Among these, valproate poses a particularly high risk for causing congenital malformations and developmental issues in the fetus, and should be avoided whenever possible. It is equally important to discuss possible drug interactions with hormonal contraceptives. Some antiseizure drugs can reduce the effectiveness of oral contraceptives, potentially leading to unplanned pregnancies. Conversely, oral contraceptives can lower the blood levels of certain drugs like lamotrigine, increasing the chance of seizure recurrence.[23]

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Moreover, enzyme-inducing antiseizure medications can interfere with the effectiveness of other drugs, such as anticoagulants, and may also cause nutrient deficiencies (e.g., folic acid), hormonal imbalances, or issues related to bone health. Genetic screening—specifically for the HLA-B allele—should be considered before starting carbamazepine in individuals of Asian ancestry due to the elevated risk of severe skin reactions.[23]

Lastly, assessing patients for existing comorbidities can guide safer treatment choices—for example, avoiding medications that could worsen mood symptoms in individuals with underlying depression.[20]

- **Neuromodulation**

Neurostimulatory techniques are considered valuable palliative interventions for patients with epilepsy in cases where surgical treatment is not feasible or has not yielded successful outcomes. While randomized controlled trials have evaluated the effectiveness of neurostimulation devices in adults with epilepsy, the reported benefits may be somewhat inflated due to certain methodological limitations and biases inherent in these studies. These techniques work by delivering electrical impulses to targeted peripheral nerves or specific regions of the brain, aiming to disrupt or suppress the abnormal rhythmic activity that can lead to seizure initiation or spread.[25]

Stimulation can be administered either at predetermined intervals (open-loop systems) or in response to seizure activity (closed-loop systems). One commonly used method, vagus nerve stimulation (VNS), has been shown to reduce seizure frequency by 50% or more in approximately one-third of patients. In addition to seizure reduction, VNS has been associated with improvements in overall quality of life and a possible reduction in the risk of sudden unexpected death in epilepsy (SUDEP).[25]

Recent advancements have led to devices capable of detecting physiological changes, such as a rise in heart rate related to seizures, allowing them to deliver additional pulses in real time, which may help in lessening the severity of seizures. Another approach, deep brain stimulation (DBS) targeting the thalamus, has demonstrated a reduction in seizure frequency by over 50% in nearly half of the treated patients and may also contribute to a lower risk of SUDEP.[24]

- **New diagnostic and treatment prospects**

One of the emerging advancements in epilepsy care is the development of wearable seizure detection devices that do not rely on EEG signals. These tools offer the potential to alert caregivers in real-time, particularly for seizures that might otherwise go unnoticed—especially during sleep. Accurate seizure detection can significantly improve recognition of nocturnal episodes, which are often under-reported. While current technology shows promise in reliably detecting convulsive seizures, the identification of non-convulsive seizure types remains inconsistent and less dependable.[26]

Such devices could play a vital role in enabling timely intervention, such as adjusting the patient's position or administering emergency medications, potentially helping to prevent severe complications like status epilepticus or sudden unexpected death in epilepsy (SUDEP). However, most of these devices have only been assessed in short-term clinical settings. Long-term studies

conducted in real-life, home environments are essential to determine their true value and usability in everyday care.[27]

In terms of surgical intervention, traditional craniotomy for epilepsy surgery carries the risk of damaging adjacent brain regions, which can negatively affect neurological and cognitive outcomes after surgery. To reduce such risks, newer and less invasive surgical methods are being explored. Techniques like stereotactic radiosurgery, radiofrequency thermocoagulation, and laser interstitial thermal therapy (LITT) focus on precisely targeting and ablating the epileptogenic zone using heat or radiation. These approaches have shown encouraging results in individuals with drug-resistant focal epilepsy.[28]

Despite these innovations, clinical trials have shown that procedures such as anterior temporal lobectomy still yield higher rates of seizure freedom compared to radiosurgery. LITT, however, has demonstrated quicker therapeutic effects and comparable success rates to traditional open surgeries, making it a viable alternative in selected cases. Magnetic resonance (MR)-guided focused ultrasound is another promising method currently under clinical investigation for its safety and seizure-suppressing potential.[29]

Since only a small proportion of patients are suitable candidates for epilepsy surgery, there remains a pressing need for novel and accessible treatment options. One area of interest is the gut microbiome, which may enhance the effectiveness of ketogenic dietary therapy. Adult patients are also increasingly seeking alternative and adjunct therapies, including the use of pharmaceutical-grade cannabidiol (CBD). While CBD has demonstrated effectiveness in treatment-resistant forms of epilepsy such as Dravet syndrome and Lennox-Gastaut syndrome, evidence supporting its broader use in other epilepsy types remains limited. Similarly, fenfluramine has shown beneficial effects in these specific syndromes.[30]

In patients with tuberous sclerosis complex, a condition marked by dysregulation of the mTOR pathway, the mTOR inhibitor everolimus has demonstrated a delayed but favorable impact on seizure control, suggesting the potential for disease-modifying therapy. Meanwhile, gene therapy approaches for epilepsy remain in the experimental stage. Current research is centered on strategies such as modulating neuropeptide expression, targeting microRNA pathways, and employing optogenetic methods to control neuronal activity through localized light stimulation, with the long-term goal of interrupting or preventing seizure onset.[35]

- **Epilepsy syndromes**

- **Electro clinical Syndromes with Age-Related Onset**
- **BFNE**

Benign Familial Neonatal Epilepsy (BFNE) is a genetic epilepsy syndrome that typically presents within the first week of a newborn's life. The seizures are usually focal in nature, either clonic or tonic, and may often be associated with episodes of apnea. These seizures generally subside on their own within a few days to weeks. Apart from the seizure episodes, the affected infants are otherwise healthy, and standard medical evaluations usually do not reveal any specific underlying cause. A key

factor in making the diagnosis is the presence of a family history involving similar neonatal or early infantile seizures that resolved without long-term issues.[2]

Most infants with BFNE have a favorable outcome; however, around 10% to 15% may continue to experience seizures beyond the neonatal stage, occasionally persisting into later childhood or adulthood. BFNE is notable for being the first epilepsy syndrome found to be associated with mutations in genes responsible for voltage-gated ion channels. Specifically, mutations have been identified in the KCNQ2 gene on chromosome 20q and the KCNQ3 gene on chromosome 8q. These genes code for subunits of potassium channels that are responsible for regulating the M-current, a type of neuronal current that is influenced by muscarinic receptors. The M-current plays a crucial role in maintaining the resting membrane potential of neurons. When this current is disrupted, it results in increased neuronal excitability, which can trigger seizures. Interestingly, although the genetic mutation persists throughout life, it remains unclear why the seizure activity typically appears only in the neonatal period and then resolves.[38]

- **WS**

West Syndrome (WS) is a distinct type of epilepsy that primarily affects infants and is defined by a characteristic triad: epileptic spasms, a specific EEG pattern known as hypsarrhythmia, and developmental delay or intellectual disability. The condition typically begins within the first year of life, most commonly between 4 to 6 months of age. The epileptic spasms observed in WS are brief and intense, lasting longer than myoclonic jerks but shorter than tonic seizures. These spasms frequently occur in series or clusters and may involve sudden nodding of the head, or abrupt flexion or extension of the arms, legs, and torso. They often take place during changes in the sleep-wake cycle, particularly upon waking.[39]

The hallmark EEG finding between seizures (interictal period) in WS is hypsarrhythmia. This appears as a chaotic, highly disorganized pattern characterized by high-voltage slow waves and spikes spread across various regions of the brain. During an actual spasm (ictal event), the EEG typically shows a generalized slow wave followed by a temporary reduction in background brain activity, a pattern referred to as the "electrodecremental response," which coincides with the physical manifestation of the spasm.[40]

In the majority of cases, WS is associated with an identifiable underlying cause. Common etiologies include birth-related complications like lack of oxygen (hypoxic-ischemic injury), bleeding within the brain (intracranial hemorrhage), infections affecting the central nervous system, congenital brain malformations, and certain metabolic disorders. One notable condition linked to a high occurrence of infantile spasms is Tuberous Sclerosis Complex (TSC), with studies indicating that nearly half of children with TSC develop this form of epilepsy.[41]

Management of WS typically involves hormonal therapy, with adrenocorticotropic hormone (ACTH) and corticosteroids being the mainstays of treatment. Although the exact mechanism through which ACTH controls seizures is unclear, it is thought to act through modulation of the hypothalamic-pituitary-adrenal axis or by directly influencing neuronal activity. In cases related to TSC, vigabatrin,

an inhibitor of the enzyme GABA transaminase, has shown significant effectiveness. For infants whose spasms are traced to localized brain abnormalities, such as cortical dysplasia, surgical removal of the affected brain region may provide benefit.[43]

Despite available treatments, WS is classified as an epileptic encephalopathy, indicating that the seizures themselves contribute to the progression of cognitive and neurological deficits. Prognosis is often guarded, with at least two-thirds of affected children developing long-term intellectual impairments. As children age, their seizures may evolve into different forms, such as those characteristic of Lennox–Gastaut syndrome, a severe type of epilepsy. Recent developments in animal models have offered new insights into the underlying mechanisms of infantile spasms, which may eventually lead to more targeted and effective therapies.[44]

- **Febrile Seizures Plus**

Children diagnosed with febrile seizures plus (FS+), previously referred to as generalized epilepsy with febrile seizures plus (GEFS+), tend to experience febrile seizures that continue beyond the typical age limit of around 5 years. Alongside prolonged febrile seizures, these children may also develop other types of afebrile seizures, such as generalized tonic-clonic (GTC), absence, or myoclonic seizures. This condition is distinct from simple febrile seizures, as it indicates a broader inherited tendency toward epilepsy. The clinical outcomes in FS+ vary from child to child—while some may eventually outgrow the seizures, others may continue to experience them. Research across different families has uncovered genetic abnormalities affecting neuronal sodium channels and GABA receptor function. Notably, many individuals with FS+ have been found to carry mutations in the alpha-1 subunit of the voltage-gated sodium channel gene.[47]

- **DS**

Dravet Syndrome (DS), formerly known as severe myoclonic epilepsy of infancy, is a rare and severe form of epilepsy that typically begins in the first 18 months of life. The first seizure usually presents during a fever and often appears as a hemiclonic seizure, affecting one side of the body. As the condition progresses, children develop various other seizure types and may experience a decline in developmental milestones.[48]

Seizures in DS are often resistant to conventional antiepileptic drugs. However, stiripentol has demonstrated some effectiveness in certain cases. Importantly, medications that block sodium channels should be avoided, as they may worsen symptoms. Genetic studies have shown that around 70% to 80% of individuals with DS carry mutations in the SCN1A gene. These mutations are mostly new (sporadic) and lead to a loss of function in sodium channels due to haploinsufficiency.[2]

The range of SCN1A mutations found in epilepsy varies in severity—from milder forms such as febrile seizures plus (FS+), often associated with missense mutations, to more severe forms like DS, which are usually linked to truncating mutations. Because SCN1A mutations are found in multiple epilepsy syndromes, they have become a major area of interest in neurological research.[2]

Experimental studies using SCN1A knockout mouse models have successfully mimicked many clinical aspects of DS. These studies suggest that the underlying problem may lie in dysfunctional

sodium channels in inhibitory cortical interneurons, leading to excessive activity in excitatory pyramidal neurons due to loss of inhibitory control. Multiple research groups are currently exploring strategies to counteract or correct the effects of SCN1A mutations.[2]

- **Lennox–Gastaut Syndrome**

Lennox–Gastaut Syndrome (LGS) is a severe form of epilepsy that typically begins between the ages of 1 and 6 years. It is considered an epileptic encephalopathy due to the presence of frequent, treatment-resistant seizures—sometimes occurring in the hundreds daily. The condition is marked by three core features: a slow spike-and-wave pattern on EEG (typically between 1.5 and 2.5 Hz), developmental or intellectual delay, and multiple types of seizures. Common seizure types include tonic seizures, generalized tonic-clonic (GTC) seizures, atypical absence seizures, atonic seizures (drop attacks), and myoclonic seizures.[2,50]

Tonic seizures, which involve prolonged muscle stiffening, occur most often during sleep. Atonic or drop seizures happen without warning, causing sudden loss of muscle tone and often leading to injuries, particularly to the face or head. Atypical absence seizures are also frequently seen in LGS and are characterized by a gradual onset and offset, during which the child may appear dazed or confused. These seizures often merge into each other, making it hard to determine when one ends and the next begins, especially since the child's awareness and responsiveness may not return between episodes. These prolonged seizure patterns are seen both during wakefulness and more commonly during sleep.[51]

Children affected by LGS usually already have underlying neurological impairments. The causes of LGS are varied and often overlap with those of West Syndrome. These include perinatal brain injuries (such as hypoxia), malformations of brain development, and certain genetic or neurocutaneous conditions. While the brain damage in most LGS cases is static (non-progressive), in some rare instances, it may stem from degenerative diseases like neuronal ceroid lipofuscinosis.[54]

Managing seizures in LGS is particularly challenging because they are often resistant to standard anti-epileptic drugs (AEDs). Treatment is usually customized based on the type and frequency of seizures. Medications that may offer some relief include valproic acid, clonazepam, lamotrigine, topiramate, rufinamide, lacosamide, clobazam, and felbamate. Due to poor seizure control, patients are frequently prescribed multiple AEDs simultaneously, a strategy known as polytherapy. However, this approach can lead to side effects such as drowsiness, fatigue, unsteady movements, nausea, and other drug-related toxicities, often without achieving satisfactory seizure reduction.[55]

Unfortunately, the long-term outlook for children with LGS remains poor. While some seizure types—such as myoclonic, atonic, and atypical absence seizures—may reduce in frequency as the child grows, others, particularly generalized tonic-clonic and partial seizures, tend to become more prominent. In addition to the physical burden of frequent seizures, these children also face significant cognitive challenges, which often prevent them from achieving independence later in life.[55]

One of the major obstacles to understanding and treating LGS more effectively is the lack of reliable animal models for the disorder. Although some models have been developed that simulate atypical

absence seizures, more work is needed to create experimental systems that accurately reflect the complexity of LGS.[55]

- **Landau–Kleffner Syndrome**

Landau–Kleffner Syndrome (LKS), also referred to as acquired epileptic aphasia, is a rare neurological condition primarily affecting children. It is characterized by the sudden or gradual loss of language abilities in children who had previously developed normal speech and comprehension skills. This language regression is associated with seizure activity or abnormal electrical discharges in the brain, as seen on an electroencephalogram (EEG).[56]

Typically, LKS affects children who were previously developing normally, particularly in terms of language, and over time, these children begin to struggle with both understanding and expressing spoken language. In recent years, the clinical picture of LKS has broadened to include not only language regression but also behavioral disturbances and cognitive decline, with some cases presenting features similar to those observed in autism spectrum disorders (ASD). However, a distinguishing factor is that children with LKS often retain better social engagement compared to those with autism, making differential diagnosis complex.[58]

The exact cause of LKS remains unclear. Conventional imaging studies such as MRI or CT scans often fail to show abnormalities, although positron emission tomography (PET) scans have indicated dysfunction in both temporal lobes—regions crucial for language processing. This supports the idea that specific language centers in the brain are impaired in LKS.[58]

EEG findings in affected children commonly show spikes or spike-wave patterns, which may be localized to one or both temporal lobes or may appear as generalized abnormalities. These epileptiform discharges are thought to disrupt the brain's language functions. One theory suggests that these discharges directly impair language processing, while another proposes that both the EEG abnormalities and language difficulties arise from a shared underlying brain dysfunction.[69]

Although antiepileptic drugs (AEDs) such as valproic acid and benzodiazepines can effectively control the seizures, they often do not lead to improvement in language abilities or behavioral symptoms. The long-term outcome for children with LKS varies widely—some may experience full recovery during adolescence, while others may continue to struggle with aphasia and communication deficits into adulthood.[68]

- **Childhood Absence Epilepsy (CAE)**

Absence seizures are typically marked by a sudden lapse in awareness, often accompanied by a blank stare and reduced responsiveness. These types of seizures are commonly observed in several epilepsy syndromes, such as childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME). It's important to recognize that the term “absence” can refer both to the specific seizure type and to a broader epilepsy syndrome. CAE usually begins between the ages of 4 and 10 years. The seizures start suddenly and tend to last between 5 and 20 seconds. Once the seizure ends, the child resumes their previous activity or conversation without any confusion or delay. Due to their short duration

and lack of dramatic physical symptoms, these seizures can often go unnoticed or be mistaken for daydreaming or inattention.[70]

The number of absence seizures a person experiences can vary widely—from just a few per day to several hundred. Factors such as emotional stress or physical fatigue can make them occur more frequently. Despite the seizures, children with typical absence epilepsy usually have normal neurological function and intelligence. However, their academic performance may suffer if the seizures happen often, as they disrupt attention and concentration.[71]

Electroencephalogram (EEG) findings during absence seizures typically show a normal background pattern but are characterized by generalized 3-Hz spike-and-wave discharges during the seizure itself. This EEG pattern is considered a hallmark of genetic predisposition to absence epilepsy. In clinical practice, hyperventilation is often used to trigger and detect these seizures, helping in both diagnosis and treatment monitoring.[72]

At the physiological level, absence seizures are believed to result from disruptions in thalamocortical networks. Specifically, abnormal activity in thalamic relay neurons, caused by malfunctioning calcium channels, plays a key role. Medications like ethosuximide and valproic acid (VPA) are commonly used to treat these seizures, as both act by blocking low-threshold calcium currents in thalamic neurons. CAE and related genetic generalized epilepsies generally have complex hereditary patterns, with only a small percentage being linked to single-gene mutations. The outlook for children with CAE is generally favorable, with around 75% eventually outgrowing the seizures during adolescence.

- **JME**

Juvenile Myoclonic Epilepsy (JME) is a well-defined epilepsy syndrome that typically emerges during adolescence. It is primarily characterized by myoclonic jerks or generalized tonic-clonic (GTC) seizures occurring in individuals who otherwise exhibit normal neurological and cognitive development. Myoclonic seizures often manifest as sudden, brief jerks that may cause a person to drop or involuntarily toss objects, particularly soon after waking in the morning. GTC seizures are reported in up to 90% of individuals with JME and are frequently the initial clinical presentation. In addition to these, approximately one-third of patients may also experience absence seizures.[65]

Factors such as lack of sleep, mental and physical fatigue, and alcohol intake are known to worsen seizure frequency in JME. Despite the seizure activity, neurological examinations and intellectual functioning in these individuals typically remain within normal limits.[67]

The condition is believed to have a multifactorial genetic basis. While some studies have suggested a potential link to a region on chromosome 6p, possibly inherited in a dominant pattern, the specific gene responsible has yet to be conclusively identified. Moreover, this genetic variant only explains a small number of cases.[67]

Electroencephalography (EEG) during the interictal phase often reveals distinctive high-frequency spike-and-wave discharges, generally within the 3.5 to 6 Hz range. These abnormalities can be triggered or amplified by photic stimulation.[66]

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Among antiepileptic drugs (AEDs), valproic acid remains the most effective treatment for JME. However, due to its potential side effects, especially in female patients, alternative broad-spectrum AEDs such as levetiracetam or lamotrigine are commonly preferred. As JME is typically a lifelong condition, long-term pharmacological management is usually necessary to maintain seizure control.[66]

- **Epilepsy Syndromes Caused by Structural/Metabolic/Autoimmune Causes**

Epilepsy syndromes, formerly known as "symptomatic localization-related epilepsies," are conditions where seizures originate from a specific area of the brain due to either a congenital defect or an acquired brain lesion. Common causes include brain tumors, scarring such as hippocampal sclerosis, cortical malformations, porencephalic cysts, or abnormalities in blood vessels. The nature of the seizures typically reflects the part of the brain that is affected—starting in one localized region and sometimes spreading to involve the entire brain. During the interictal period, EEG recordings often show abnormalities such as focal spikes, sharp wave activity, or localized slowing in the corresponding brain region. When findings from brain imaging, EEG data, and other evaluations like neuropsychological tests consistently point to the same area of seizure origin, surgical treatment may be considered as a potential option.[2]

- **Temporal Lobe Epilepsy**

Mesial temporal sclerosis (MTS) serves as a well-recognized example of a structural brain abnormality—specifically characterized by scarring of the hippocampus—that is commonly associated with difficult-to-control seizures. These seizures typically originate from the medial temporal lobe and may present with symptoms such as abnormal limb posturing, changes in awareness or responsiveness, and alterations in memory or behavior. As the condition progresses, seizure activity often extends beyond the hippocampus, contributing to the complexity of the clinical picture. In many cases, seizures become resistant to standard pharmacological treatment, and individuals frequently experience mood and behavioral disturbances as comorbid conditions.[69]

When a patient does not respond to at least two appropriately selected and adequately dosed antiepileptic medications, surgical evaluation becomes a recommended next step. Over the years, significant research has been carried out to uncover the underlying mechanisms involved in the onset and propagation of seizures in temporal lobe epilepsy. Contributing factors identified include reduced inhibitory neurotransmission via the GABAergic system, increased excitatory signaling due to axonal reorganization, and altered distribution and function of ion channels. Moreover, genetic predisposition may also influence the development and severity of the disorder.[68]

- **Childhood Hemispheric Epilepsy Syndromes**

Certain childhood epilepsy syndromes are known to involve only one cerebral hemisphere. One such condition is Rasmussen’s encephalitis, a rare and chronic inflammatory disease that typically affects a single hemisphere of the brain. It is characterized by a gradual onset of hemiparesis, treatment-resistant focal seizures—which may evolve into continuous seizure activity known as epilepsia partialis continua—and a progressive decline in cognitive abilities. Although the precise cause of

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Rasmussen's encephalitis remains uncertain, it is believed to have an autoimmune component. Some researchers suggest that a localized disruption of the blood–brain barrier may contribute to the disease's development. MRI imaging of affected individuals often reveals progressive shrinkage of one side of the brain's cortex.[70]

Another notable hemispheric disorder is Sturge–Weber syndrome (SWS), also referred to as encephalotrigeminal angiomatosis. This condition is marked by vascular malformations involving the brain, skin, and eyes—commonly affecting one hemisphere—and frequently leads to intractable seizures and hemiparesis. Recent studies have linked mutations in the GNAQ gene, which plays a role in blood vessel formation, to the development of SWS. In cases of severe, medication-resistant seizures associated with hemispheric syndromes like Rasmussen's encephalitis or SWS, some specialists advocate for early surgical intervention, such as hemispherectomy, as it may significantly improve long-term outcomes.[72]

- **Metabolic, Mitochondrial, and Autoimmune Epilepsies**

Epilepsies linked to metabolic, mitochondrial, or autoimmune causes are gaining increased recognition in recent years. Disruptions in the brain's energy production or utilization can disturb the balance between excitatory and inhibitory signals, ultimately leading to seizures. Moreover, the discovery of autoantibodies targeting various cellular proteins in patients with previously unexplained neurological decline has provided fresh insights into the diverse ways epilepsy may present itself.[73]

- **Neonatal Seizures**

Neonatal seizures, which occur within the first 30 days after birth or before 44 weeks of postconceptional age in preterm infants, form a distinct category due to their age-related features, diverse underlying causes, and unique neurological mechanisms. In many cases, seizures can be the earliest or even the sole indication of central nervous system (CNS) dysfunction in newborns, making timely identification and diagnosis extremely important.[74]

Neonatal seizures can be broadly categorized into four clinical types based on observable behavior: subtle, tonic, clonic (focal or multifocal), and myoclonic seizures. Subtle seizures are commonly seen in newborns with significant central nervous system injury and may present as repetitive movements involving the mouth, tongue, or face—such as sucking motions—or as bicycling-like leg movements or abnormal eye positioning. Tonic seizures in neonates typically involve sustained muscle stiffening, where the limbs may extend in a rigid posture intermittently. These seizures are usually linked to severe brain damage and are more frequently seen in premature infants.[75]

Clonic seizures are characterized by repetitive, rhythmic jerking of muscle groups. When these jerks are confined to one area, they are referred to as focal clonic seizures; when they appear in multiple areas and shift from one part of the body to another, they are termed multifocal clonic seizures. Focal seizures may be associated with localized brain injuries like perinatal stroke or structural abnormalities, but they can also result from widespread brain disturbances, including oxygen deprivation, metabolic issues, or infections.[76]

Jain Neha, Kumar Anuj, Mishra Sushmita, Dayal Ram (2025). *Epilepsy: Bridging Traditional Understanding and Contemporary Clinical Practice. International Journal of Multidisciplinary Research & Reviews, 4(2), 201-220.*

Due to the incomplete development of the neonatal brain—specifically, immature myelination and insufficient cortical connectivity—newborns are not capable of generating the generalized epileptiform activity typically seen in conditions like generalized tonic-clonic (GTC) or absence seizures. Therefore, such seizure types are not observed in this age group.[76]

Simultaneous video-EEG monitoring is a valuable tool in distinguishing between actual epileptic seizures, which show corresponding EEG changes, and behaviors that mimic seizures but do not have any EEG abnormalities. Among various seizure types, focal clonic seizures show the strongest association with observable EEG changes during the ictal phase. In contrast, some behaviors often assumed to be seizure-related—such as repetitive chewing or pedaling-like limb movements—frequently occur without any detectable EEG alterations, indicating that these actions may not be epileptic in origin. Subtle or tonic movements might instead reflect dysfunction of the brainstem or seizures that originate from deep brain regions, which cannot be easily captured by surface EEG recordings.[77]

Neonatal EEG typically does not point to a specific cause of neurological disturbance, but it can offer valuable insight into the extent and timing of central nervous system injury. In many cases, epileptic activity can be detected on EEG without any clear clinical symptoms, a phenomenon known as the “uncoupling” of electrical and physical seizure signs. When evaluating prognosis, particular attention is given to background EEG patterns and the presence of normal sleep–wake cycles. A more recent advancement, amplitude-integrated EEG (aEEG), enables continuous bedside monitoring using a simplified set of EEG channels. This method has shown considerable promise in identifying likely seizure activity in neonates.[78]

Identifying the underlying cause of neonatal seizures is essential, as it directly influences the choice of treatment and is strongly linked to the infant's prognosis. Seizures in newborns can result from a variety of factors, including oxygen deprivation (hypoxic-ischemic events), low levels of calcium, blood sugar, or sodium, as well as brain hemorrhage, infections, structural brain abnormalities, genetic conditions, metabolic disorders, and withdrawal from drugs. Among these, hypoxic-ischemic injury—most often occurring before birth—is recognized as the leading cause of seizures in neonates.[79]

The decision to initiate treatment in infants experiencing recurrent seizures depends on several key factors, including how often the seizures occur, their duration, any signs of autonomic dysfunction, the underlying cause, and EEG findings. If the seizures are short-lived and do not lead to autonomic disturbances, immediate treatment may not be necessary, or the infant may be managed with a short-acting benzodiazepine. However, in cases where seizures are frequent—particularly when they impact vital functions like breathing—immediate and aggressive treatment becomes essential.[81]

Phenobarbital has long been considered the first-line treatment for neonatal seizures; however, its effectiveness remains limited, with less than 50% of cases showing positive response. Although phenobarbital and phenytoin may sometimes control the visible signs of seizures, abnormal electrical activity in the brain often continues, a phenomenon known as "uncoupling." Drugs that act on

GABA receptors—such as barbiturates and benzodiazepines—might not work well in neonates, and in some instances, may even worsen seizures due to the excitatory nature of GABA in the immature brain. Current research is exploring the involvement of potassium-chloride cotransporters in the transition of GABA's effect from excitatory to inhibitory during brain development. Targeting these transporters with specific inhibitors holds potential as a new treatment approach. While newer antiepileptic drugs like levetiracetam have shown promise, there remains a critical need for the development of more reliable and effective therapies for managing seizures in newborns.[84]

- **Febrile Seizures**

Febrile seizures typically affect children between the ages of approximately 6 months to 5 years. Although the precise cause is not yet fully understood, these seizures are thought to reflect a temperature-sensitive reaction in the immature brain during early development. There is a strong familial tendency, with children in families with a history of febrile seizures being two to three times more likely to experience them compared to the general population. It is estimated that about 2% to 5% of children within the susceptible age group experience febrile seizures.[86]

Febrile seizures are broadly classified into two categories: simple and complex (or complicated).

- A simple febrile seizure is brief—lasting less than 15 minutes—generalized (involving the whole body), and does not reoccur within 24 hours.
- A complex febrile seizure may last longer than 15 minutes, show focal signs (such as movement limited to one side of the body or deviation of the eyes to one side), or happen more than once in a 24-hour period.

While simple febrile seizures typically do not require any specific treatment, most complex febrile seizures also resolve without needing intervention.

In terms of recurrence, a child who has had one simple febrile seizure has about a one-third (33%) chance of having another during a future illness with fever. If two such episodes have already occurred, the likelihood of a third episode increases to approximately 50%. Recurrence is more likely in children who had their first febrile seizure before turning 12 months old or those with a family history of such seizures.[87]

More serious concerns arise regarding the potential development of epilepsy, particularly afebrile seizures, later in life. Adults with temporal lobe epilepsy, especially cases linked to mesial temporal sclerosis, often have a history of prolonged febrile seizures in early childhood. However, for children who experience only simple febrile seizures, the long-term risk of developing epilepsy is only marginally higher than that of the general population—around 2%. In contrast, the risk can increase to around 9% in certain high-risk groups. These include children with preexisting neurological conditions (like developmental delay or cerebral palsy), a family history of epilepsy, or those who experienced complicated febrile seizures (prolonged, focal, or repeated within a short timeframe).[85]

Currently, large-scale studies such as the FEBSTAT project are ongoing, aiming to better understand the long-term effects of febrile status epilepticus using longitudinal clinical assessments and MRI

imaging. Additionally, experimental studies using animal models are essential to explore how high body temperatures and immune responses during fever impact the developing brain, potentially offering more clarity on the pathophysiology of febrile seizures.[86]

- **Nonepileptic Seizures (NES)**

Non-epileptic seizures (NES), also referred to as psychogenic seizures or pseudoseizures, are sudden episodes of altered movement or behavior that mimic epileptic seizures but do not show any corresponding changes on an EEG. Although these events are not caused by abnormal electrical activity in the brain, they can still be highly disruptive and are often linked to significant underlying psychological conditions.[89]

NES can present in a range of patterns. In many cases, the episodes resemble generalized tonic-clonic (GTC) seizures; however, a distinguishing feature is that the limbs on each side of the body may move out of sync, or out of phase, with each other. When GTC-like movements occur while the patient remains conscious, a nonepileptic origin is more likely. That said, caution is needed in diagnosis, as some seizure patterns once assumed to be psychogenic have since been confirmed to be epileptic.[90]

For instance, seizures that originate from the supplementary motor area (SMA) of the frontal lobe often involve bilateral motor activity but occur with preserved consciousness. These seizures tend to be shorter in duration, more repetitive in nature, and typically arise during sleep—differentiating them from NES. Likewise, seizures from the orbitofrontal cortex can involve intense emotional responses such as fear, loud vocalizations, nonrhythmic bilateral limb movements, and even complex behaviors like pelvic thrusting or sexual automatisms—symptoms that were historically misclassified as NES.[90]

These findings highlight the diagnostic challenges in distinguishing NES from epileptic seizures based solely on clinical features. Therefore, video-EEG monitoring remains a vital tool for accurate diagnosis. It is also important to note that in some individuals, both NES and epileptic seizures can occur concurrently, further complicating the clinical picture.[89]

2. CONCLUSION

To advance treatment options for individuals living with epilepsy, it is essential to improve how we evaluate preclinical models. This includes developing more reliable protocols, consistent methods for assessing outcomes, and refining experimental designs. The current commentary is not intended to serve as a final set of recommendations, but rather to offer a foundational framework upon which specific and practical guidelines can be built. These future guidelines could also serve a role in the research funding process, helping reviewers prioritize proposals that are more likely to yield clinically meaningful results.

One possible direction for future work involves creating a structured, tiered list of preclinical evidence that should ideally be met before advancing to formal clinical trials. A supplementary list could include optional but beneficial data that might enhance interpretation. Such a structure would make it possible to compare different antiepileptic therapies (AETs) based on their translational

potential, allowing each to be assigned a relative probability of clinical success based on its supporting preclinical evidence.

It would also be highly beneficial to conduct regular, systematic reviews of existing preclinical AET research. These reviews should focus on the suitability of the animal models used, the methods of behavioral assessment, and the overall study design. In addition, they should provide critical evaluations of the efficacy data related to specific seizure types or epilepsy syndromes. This process would ensure that the guidelines evolve in parallel with scientific and clinical advances. A collaborative initiative, similar to the Cochrane model, could be instrumental in achieving this goal. Importantly, there should be a platform for sharing both positive and negative findings, as both are vital to accurately assessing the potential of new treatments.

Epilepsy is a complex symptom cluster, often involving multiple risk factors and frequently linked to a genetic predisposition. It is not a single disease with a uniform cause. Recent developments in genomic research are beginning to reveal the intricate genetic patterns associated with different forms of epilepsy. Additionally, comorbid conditions are increasingly recognized not just as co-occurring problems but also as factors that may influence the cause and prognosis of epilepsy. Although antiepileptic drugs can successfully control seizures in a significant portion of patients, they generally do not impact the long-term progression of the condition. Epilepsy continues to impose a heavy burden on patients' quality of life, overall health, and life expectancy—particularly for those with drug-resistant forms of the disease.

For these individuals, surgical intervention remains the most effective approach for achieving long-term seizure freedom, although it is suitable only for a minority of patients. With ongoing progress in the understanding of epileptogenesis, along with advances in epigenetics and pharmacogenomics, the future holds promise for more targeted and durable treatment strategies.

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