# "A Comprehensive Review of Risk Factors, Etiology, and Pathophysiology of the Epilepsy and Current Treatment, Strategies for Advanced Treatment of Epilepsy with a Novel Approach"

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Abstract:

About 1% of people worldwide suffer from epilepsy, a chronic neurological condition characterized by prevalent unprovoked seizures brought on by aberrant neuronal hyperexcitability. Its etiology is complex and includes metabolic imbalances, traumatic injuries, infections (like neurocysticercosis), mutations in genes, and structural abnormalities in the brain (like tumors and hippocampus sclerosis). Antiepileptic drugs (AEDs) that target glutamatergic signaling, GABAergic inhibition, and ion channels are still first-line treatments; however, 30% of patients exhibit pharmacoresistance, illustrating the need for more sophisticated approaches. In refractory situations, neuromodulation (such as vagus nerve stimulation), ketogenic diets, and surgical excision are used. Novel therapeutics are being researched as a result of recent developments in pathophysiology research that have highlighted channels including ion channelopathies, neuroinflammatory cascades, and synaptic reorganization. Innovations include prodrug strategies for targeted activation, implantable devices for extending intraparenchymal drug release, and drug delivery systems enabled by nanotechnology (e.g., solid-lipid nanoparticles, intranasal formulations) that boost blood-brain barrier penetration. Treatment personalization is the goal of emerging strategies like genetic/epigenetic biomarkers and hyperosmolar BBB disruption. Drug-resistant epilepsy therapy continuing to present obstacles despite innovations, emphasizing the critical importance of merging precision medicine, multimodal therapy, and patient-specific biomarkers. With the goal to optimize seizure governance and the quality of life for the people who experience them, this review provides some of the current information on the risk factors, molecular mechanisms, therapeutic advancements, and future directions of epilepsy.

**Keywords**: Epilepsy, Seizures, Antiepileptic drugs (AEDs), Nanotechnology, Drug resistance, Precision medicine

## 1. Introduction of Epilepsy

Epilepsy (convulsion) is the 4th most commonly diagnosed type of neurological ailment, trailing Alzheimer's disease, stroke, and Parkinson's disease. The prevalence rate of epilepsy is 1 in 25 patients. The overall incidence of epilepsy in India is estimated to be 5.59 to 10 per 1,000 patients. Epilepsy is a chronic condition of the brain that arises from an imbalance between neurotransmitters, particularly GABAergic neurons (which facilitate neuronal inhibition) and glutamate (which promotes neuronal thrills). Moreover, increased conduction of Ca2+ and Na+ channels contributes to the illness. Epilepsy is a chronic neurological disorder marked by an ongoing risk for seizures, which are abrupt, aberrant electrical currents in the brain that disrupt its typical activity. From brief conscious lapses or small muscle twitches to severe, full-body convulsions, these seizures may occur in a variety of ways. Basically, epilepsy

results from an imbalance between excitatory and inhibitory nerve impulses in the brain, which leads to clusters of neurons firing excessively and in the wrong way.

Though it tends to manifest more frequently in early childhood or later stages of life, this disorder affects people of all ages. Inherited genetic mutations, traumatic brain traumas, cerebrovascular events like stroke, infections like encephalitis or meningitis, and developmental abnormalities in the structure of the brain are some of the many causes of epilepsy. However, in many cases, no apparent cause is identified; this condition is known as idiopathic epilepsy.

Both the type of seizure—whether focal, generalized, or involving both hemispheres of the brain, or having a hazy beginning point—and the underlying etiology have significance concerns in contemporary categories of epilepsy. A thorough patient history, a neurological evaluation, and confirming testing like magnetic resonance imaging (MRI) and electroencephalography (EEG) are usually used to make the diagnosis. The primary means of treatment is antiepileptic drugs, however in some situations, electrical brain stimulation therapies, ketogenic meals, or surgery may be advantageous.

Beyond its effects on therapeutic practice, epilepsy has significant social and emotional ramifications. People with epilepsy often face social isolation, stigma, and obstacles in their daily affairs, which underlines the value of a comprehensive treatment strategy that include social and psychological assistance. Even though science has made significant strides in understanding and treating epilepsy, plenty of individuals remain unable to achieve seizure independence, highlighting the critical need for ongoing improvements in therapeutic research and tailored treatment.

. (Stiles, 2010)

**2. Type of Epilepsy:** (sarmasr, 2020, p. 6)

**2.1 Focal-Tonic-Seizure**

Seizures are similar to (FAS) but loss of muscle tone for a long period, from seconds to minutes, such as Appearing or experiencing muscle tightness in a limb or the neck

**2.2 Focal-Clonic-Seizure**

"Rhythmic and sustained jerking of a muscle group, occurring in a consistent pattern or sequence.

**2.3 Focal-Epileptic-Spasm**

This type of epilepsy in children is which sudden, painful muscle contractions that are uncontrollable. Sudden, uncontrollable, and sometimes painful muscle contractions that typically occur in children. These may present as sudden torso bending and limb flexion or extension, often in clusters. They can be focal, generalized, or of unknown origin, typically diagnosed with video-EEG. In infants, they are called Infantile Spasms.

**2.4 Focal-Hyperkinetic-Seizure**

Seizures involving exaggerated, often muscle movements in such as frantic kicking, thrashing, or pedaling motions.

**2.5 Focal-Automatism-Seizure**

Often misdiagnosed and overlooked as a seizure, it involves repeated motor actions typically occurring under altered consciousness, sometimes followed by amnesia. These actions can include repeated speech, frequent repetition of words, loss of control of tongue, lip movements, rubbing, or wandering. This is commonly associated with focal impaired awareness seizures.

**2.6 Focal-Myoclonic-Seizure**

Similar to clonic seizures, but typically involving short, involuntary muscle jerks lasting only a few seconds or less, often affecting only one part of the body.

**2.7 Focal-Atonic-Seizure**

Seizures are characterized by a momentary hindrance or loss of muscle tone duration of this activity for a few seconds, affecting one side of the body or a single limb. Typically, awareness remains unaffected.

**2.8 Focal-Tonic-Seizure**

Seizures are similar to (FAS) but loss of muscle tone for a long period, from seconds to minutes, such as Appearing or experiencing muscle tightness in a limb or the neck.

**2.9 Focal-Clonic-Seizure**

"Rhythmic and sustained jerking of a muscle group, occurring in a consistent pattern or sequence.

**2.10 Focal-Epileptic-Spasm**

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**2.11 Focal-Hyperkinetic-Seizure**

Seizures involving exaggerated, often muscle movements in such as frantic kicking, thrashing, or pedaling motions.

## 3. Prevalence of Active Epilepsy

In a study conducted in a developed country, data on the use of antiepileptic drugs among individuals with epilepsy revealed that 46% of patients had been seizure-free in the preceding year. About 33% experienced between one and 12 seizures annually, while the remaining patients had more than one seizure per month. Of these, 8% experienced over 50 seizures annually. The given data represent only a limited patients who have had a seizure attack. (Hart YM, 1995)

In contrast, a survey conducted in a developing country, where access to antiepileptic drugs was limited and only 15% of patients were receiving treatment, showed that 45% had fewer than 10 seizures before the survey, 14% had experienced between 10 and 100 seizures, and 26% reported having more than 100 seizures. (Placencia M, 1994)

## 4. Etiology of Epilepsy:

**4.1 Sex Differences**: Epidemiological studies indicate a moderately elevated incidence of epilepsy in males compared to females. While early hypotheses attributed this disparity to increased occurrences of cranial injuries in males, systematic analyses have refuted this association, given the low prevalence of post-traumatic epilepsy (2122). Notably, syncopal episodes and psychogenic non-epileptic seizures (PNES) exhibit a female predilection, heightening diagnostic challenges and misclassification risks in female populations. (Vecht, 2014)

**4.2 Neoplastic Associations**: Seizures manifest as the inaugural symptom in 25–30% of brain tumor cases, escalating to 40–60% during disease progression. Secondary generalized tonic-clonic seizures predominate, often preceded by undiagnosed focal seizures. Low-grade gliomas (LGGs) demonstrate a strong epileptogenic propensity, frequently presenting with isolated seizures for prolonged intervals. In contrast, high-grade gliomas exhibit reduced seizure incidence, likely due to their infiltrative and necrotic pathophysiology. Cortically proximate tumors, particularly in frontal and temporal regions, are strongly linked to ictogenesis. Genetic predispositions, including mutations linked to cortical developmental anomalies (e.g., tuberous sclerosis), further contribute to tumor-associated epileptogenesis. ( (Biton V. M., 1999)

**4.3 Genetic Contributions**: 40% of cases of generalized epilepsies are caused by channelopathies, which are mutations in ion channels such GABAA receptors and voltage-gated sodium channels (SCN1A, SCN2A). The pathogenesis of seizures is supported by these genetic abnormalities, which also influence treatment approaches like sodium channel blockers for conditions linked to SCN1A (e.g., Dravet syndrome).

**5. Risk Factors**

Epilepsy in adults is associated with diverse etiological factors, spanning genetic, structural, and environmental influences. Key predisposing elements include:

**5.1. Hereditary Influences**: Familial predisposition and genetic anomalies, such as mutations linked to syndromes like Dravet syndrome, heighten susceptibility to seizure disorders (o Berkovic, (2005).)

**5.2. Traumatic Brain Injury (TBI)**: The risk of developing post-traumatic epilepsy, which might appear years after an accident, is increased by severe cranial trauma, especially traumas that result in intracranial damage.(o Faust, 2006)

**5.3. Cerebrovascular Events Cerebrovascular Events**: Particularly in elderly individuals, ischemic or hemorrhagic strokes—which frequently result in brain scarring—are major causes of late-onset epilepsy. (o Vermiglio, 2007)

**5.4. Neuroinvasive Infections**: The risk of seizures can be raised due to pathogens that cause brain injury, such as meningitis, encephalitis, or parasite infestations (such neurocysticercosis). (o Sander, 2003)

**5.5. Congenital Malformations**: People with neurodevelopmental disorders, such as cerebral palsy and intellectual disabilities, are more likely to have epilepsy because of structural brain abnormalities. (Cilio, (2011))

**5.6. Perinatal Complications**: Obstetric complications are associated with long-term epileptogenesis, such as intrauterine growth restriction, preterm delivery, or newborn hypoxia.. (Dubeau, 2003)

**5.7. Substance Misuse**: Vulnerability may be increased by prolonged alcohol use, withdrawal symptoms, or illegal substance usage, which can lower seizure thresholds. (o Naylor, 2008)

**5.8. Pediatric Febrile Episodes**: Frequent occurrences may slightly increase the chance of epilepsy, even though the majority of juvenile febrile seizures end without any aftereffects. (o Hsieh, 2008)

**5.9. Neurodegenerative Pathologies**: Disorders like Alzheimer's disease are increasingly recognized as risk factors for seizure development in aging populations. (Hermann, 2006)

**5.10. Neuroendocrine Fluctuations**: In women, hormonal variations during menstruation, gestation, or menopause may modulate seizure frequency. (o Herzog, 2008)

Emerging evidence suggests potential associations between epilepsy and subcortical white matter abnormalities or psychiatric comorbidities (e.g., depression, schizophrenia), though these relationships remain understudied.

**6. Pathophysiology**

The primary causes of epilepsy are glutamatergic hyperactivity and GABAergic hypoactivity, which lead to a dysregulated excitatory-inhibitory balance. Preclinical models show that glutamate agonists (kainate, NMDA) or GABAA antagonists (pentylenetetrazol) can induce seizures. Pathological hypersynchrony is seen in a connection between interictal EEG spikes and paroxysmal depolarizing changes in neurons. Although necessary for regular processing, cortical laminar architecture promotes abnormal synchronization during ictogenesis.
Sixty percent of focal epilepsies have a variety of causes, including post-traumatic gliosis, vascular abnormalities, or cortical lesions. The prevalence of trauma-related epilepsy has gone up due to improved neurocritical care survival rates.

**Pathophysiological Mechanisms Underlying Epilepsy**

Recurrent, spontaneous seizures brought on by abnormally hypersynchronous neuronal discharges in the brain are the hallmark of epilepsy, a chronic neurological disorder. Multifactorial disturbances at the genetic, molecular, cellular, and network levels are the underlying mechanisms. An extensive synopsis of crucial routes may be seen below:

### 6.1. Dysregulation of Ion Channel Activity

### 6.1. Dysregulation of Ion Channel Activity

Ion channels, such as those for Na, K, Ca, and Cl, regulate the excitability of neurons.

Pathological hyperexcitability may be caused by inherited or acquired abnormalities in various channels:
Gain-of-function mutations in voltage-sensitive sodium channels (NaV) (e.g., SCN1A in Dravet syndrome) increase neuronal firing by prolonging the duration of action potentials.
Loss-of-function changes in potassium channels (KCNQ) reduce their ability to repolarize, which increases unchecked neuronal activity. T-Type Calcium Channels: Absence seizure phenotypes are caused by excessive activity in thalamocortical circuits.
Explain in detail in below **Figure 1**.(menezes, 2020)

### 6.2. Disrupted Excitatory-Inhibitory Equilibrium

**Glutamatergic Hyperactivation:** Prolonged depolarization and calcium overload brought on by excessive NMDA/AMPA receptor stimulation contribute to excitotoxic neuronal damage. This pathological process, depicted in **Figure 1**, highlights how excessive glutamate release and receptor overactivation lead to sustained calcium influx, mitochondrial dysfunction, and ultimately neuronal death.

**GABAergic Deficiency:** Homeostatic inhibition is disrupted by impaired inhibitory signaling brought on by interneuron loss or malfunctioning GABA receptors. As illustrated in **Figure 1**, the reduced GABAergic tone results in an imbalance between excitatory and inhibitory neurotransmission, promoting network hyperexcitability and increasing vulnerability to neurodegeneration.. (Rogawski M. L.–5., 2004)

### 6.3. Structural and Synaptic Pathological Alterations

Hippocampal Sclerosis: Reactive gliosis and neuronal degeneration in the hippocampus disrupt synaptic networks, which leads to temporal lobe epilepsy. Aberrant Axonal Sprouting: Self-reinforcing excitatory circuits are produced by mossy fiber rearrangement in the dentate gyrus. possessing inherent hyper-excitability. (Pitkänen, 2016)

Cortical Malformations: Developmental anomalies produce ectopic neuronal clusters

### 6.4. Pro-Inflammatory Cascade

Chronic neuroinflammation exacerbates epileptogenic susceptibility:

Inflammatory Mediators: Cytokines (e.g., IL-1β, TNF-α) potentiate excitatory signalling and suppress inhibitory tone.

Astrocytic Impairment: Defective glutamate clearance by astrocytes results in synaptic glutamate accumulation.

BBB Compromise: Extravasation of albumin activates pro-inflammatory TGF-β pathways in astrocytes.

(Vezzani, 2016)

### 6.5. Genetic and Epigenetic Contributions

Monogenic Disorders: Mutations in genes like *SCN1A*, *KCNT1*, and *DEPDC5* directly perturb neuronal excitability.

Epigenetic Dysregulation: Post-translational modifications (e.g., DNA methylation) alter expression of seizure-associated genes.

MicroRNA Imbalance: Dysregulated miRNAs (e.g., miR-134) influence synaptic remodelling and ion channel dynamics. (Thomas, 2020)

Integrated Model of Epileptogenesis

The transition to chronic epilepsy follows a **stepwise progression**:

1. Initiating Event

↓

(e.g., trauma, stroke, infection, genetic mutation)

↓

2. Hyperexcitable State

↓

(Ion channel dysfunction, neurotransmitter imbalance,

increased glutamate, decreased GABA)

↓

3. Network Reorganization

↓

(Synaptic rewiring, mossy fibre sprouting, glial cell activation neuroinflammation)

↓

[4. Persistent Epileptogenic Circuitry]

↓

(Stable structural and functional changes causing spontaneous recurrent seizures)

This cascade **lowers seizure thresholds**, enabling **spontaneous recurrent seizures**.

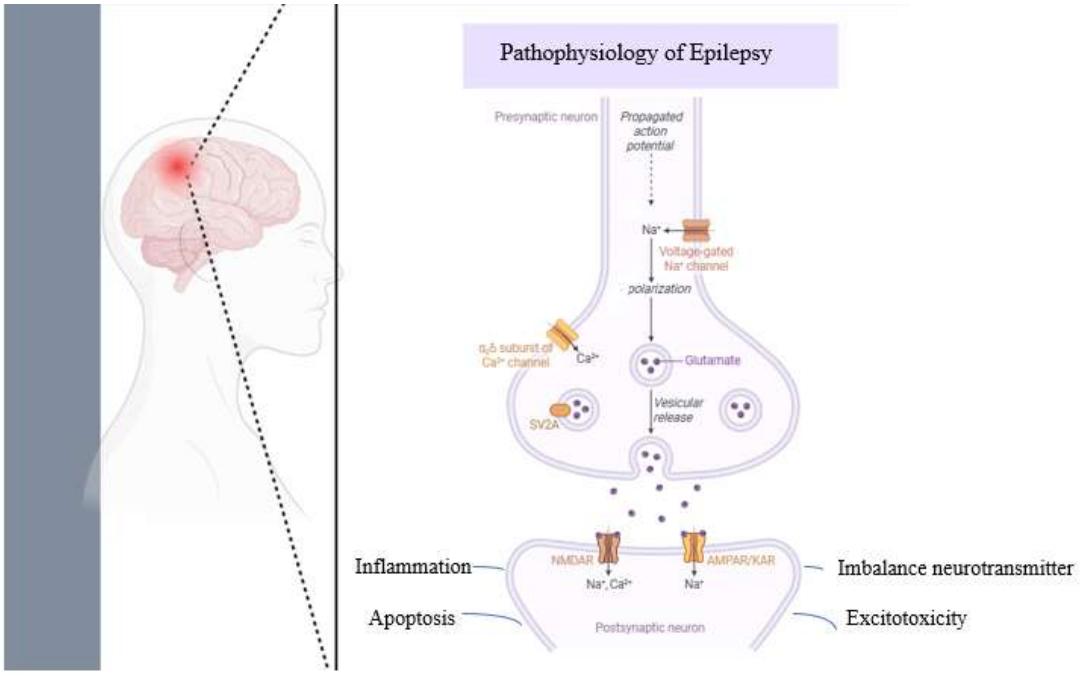


**Fig 2** Pathophysiology of epilepsy when the stimulation or conduction of Ca2+ and Na+, which can cause depolarization, excitation to glutamate hyper excitotoxicity, inflammation, and apoptosis.

(Figure generated by www.Biorender.com )

**7. Tumor-Linked Epilepsy: Underlying Mechanisms and Molecular Dynamics**

The method by which epileptic seizures in the setting of brain tumors develop is extremely complex and still poorly understood. Tumor cell type, anatomical location, genetic alterations, disruption of the blood-brain barrier, and the changed microenvironment surrounding the tumor mass are some of the interdependent factors that determine a tumor's epileptogenicity, or its capacity to cause seizures. Seizures are thought to be greatly influenced by changes in ionic gradients, oxygen deprivation in the surrounding brain tissue, and changes in neurotransmitter activity. (M.S. van Breemen, 2007) , (R. Rudà E. T., 2010) (M.F. Shamji, 2009)

One common observation in tumor-associated epilepsy is the elevated levels of the excitatory neurotransmitter glutamate in affected brain tissues. Increased cortical instability and neuronal excitability are thought to result from this excess. However, it is also believed that disturbances in inhibitory signaling, specifically involving gamma-aminobutyric acid (GABA), worsen this excitatory imbalance and further encourage seizure activity.. (M.F. Shamji, 2009) (R. Rudà A. P., 2015)

Commonly found in glioneuronal tumors, mutations such as BRAF V600E have been linked to poor seizure control following surgery, indicating that they may be the cause of long-term epileptic tendencies. Likewise, additional protein and genetic indicators have been linked to affecting seizure outcomes and risk.. (A.S. Prabowo, 2014)

For instance, high levels of Ki-67, a marker for cellular proliferation, are associated with diminished seizure control in low-grade glioma patients. The discovery of molecular biomarkers that influence tumor biology and their correlation with seizures has exploded in the last ten years. Among these, low-grade gliomas often carry mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2), which have been significantly linked with seizures at the time of initial presentation. IDH mutations have been strongly linked in a number of studies to an increased incidence of seizures, indicating a pro-epileptic effect. This connection is still debatable, though, as some extensive studies have not confirmed a clear correlation with other molecular changes such 1p/19q codeletion and p53 production of proteins.

On the other hand, seizure activity in glioma patients has been associated with unregulated levels of microRNA-128 and decreased expression of VLGR1, a major G-protein-coupled receptor (Y. Wang, 2015). Remarkably, research on anaplastic gliomas has shown that reduced expression of Ki-67. (Y. Yuan, 2016)

Amplification of the epidermal growth factor receptor (EGFR) in conjunction with seizures prior to surgery is linked to this condition.. (P. Yang, 2014)

**Brain Tumor-Related Epilepsy (BTRE)**

The process by which epileptic seizures arise from brain tumor formation is incredibly complex and poorly understood. Tumor cell type, anatomical location, genetic changes, disruption of the blood-brain barrier, and the altered microenvironment surrounding the tumor mass are some of the interrelated factors that affect a tumor's epileptogenicity, or ability to induce seizures. It is thought that fluctuations in ionic gradients, oxygen deprivation in the surrounding brain tissue, and alterations in neurotransmitter activity all have an important influence on the likelihood of epilepsy.

**8. Antiseizure Drug Mechanisms**

ASMs modulate neuronal excitability through:

**Sodium Channel Blockade:** As shown in **Figure 2**, drugs like **carbamazepine** and **lacosamide** suppress high-frequency neuronal firing by use-dependently inactivating voltage-gated sodium ($Na^+$) channels. This stabilization of the inactivated state reduces neuronal excitability and limits the propagation of epileptic discharges . (Ragstale D. S., 1998)

**Calcium Channel Modulation: Figure 2** also illustrates how **ethosuximide** selectively inhibits T-type calcium ($Ca^{2+}$) channels in thalamocortical circuits. This action disrupts abnormal oscillatory activity underlying absence seizures, effectively dampening the pathological rhythmic burst firing (Turner T. J., 1998)

**GABAergic Enhancement:** As depicted in **Figure 2**, enhancement of GABAergic transmission plays a crucial role in seizure suppression. **Tiagabine** increases GABA availability by inhibiting GABA transporter-1 (GAT-1), while **benzodiazepines** potentiate GABA_A receptor function, enhancing $Cl^-$ influx and promoting neuronal hyperpolarization.

**Glutamate Antagonism:** further demonstrates the mechanism of **perampanel**, a non-competitive AMPA receptor antagonist. By inhibiting AMPA-mediated excitatory postsynaptic currents, perampanel reduces synaptic excitation and prevents seizure spread.

**Emerging Targets – HCN and Kv7 Channels:** Lastly, **Figure 2** highlights emerging targets such as **HCN channels** and **Kv7.2/7.3 potassium channels**, which help maintain neuronal stability. Modulation of these channels leads to enhanced membrane hyperpolarization, reducing the likelihood of aberrant firing and offering new therapeutic avenues for precision epilepsy treatment.

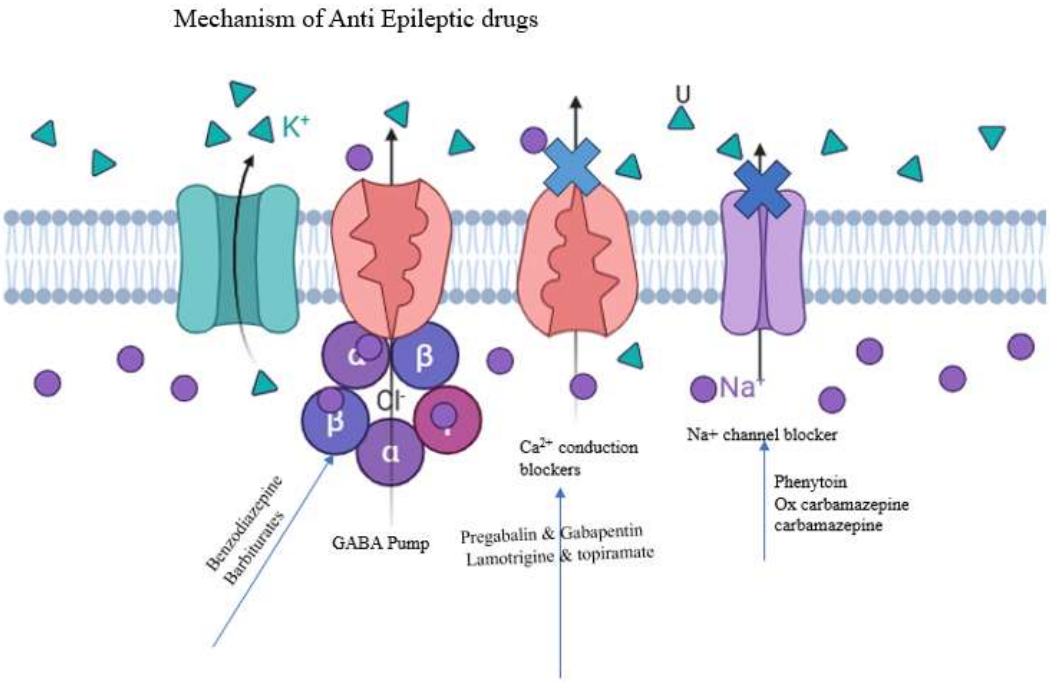


**Fig** 3 Antiepileptic drugs target various synaptic sites to control neuronal excitability. Levetiracetam modulates neurotransmitter release via SV2A binding. Benzodiazepines and barbiturates enhance GABAergic inhibition through GABAA_AA receptors. Sodium channel blockers like phenytoin, carbamazepine, and lamotrigine stabilize inactive sodium channels to reduce excitatory firing. Calcium channel modulators, such as ethosuximide and pregabalin, act on low- and high-voltage calcium channels. Many drugs exhibit multiple mechanisms, providing broad-spectrum seizure control**.** (Figure generated by www.Biorender.com )

Drug works by blocking voltage-gated sodium channels, which reduces the ability of neurons to fire repetitively. It's particularly effective in treating focal seizures and generalized tonic-clonic seizures. Despite its effectiveness, phenytoin has several drawbacks when used long term. These include side effects such as gingival overgrowth, excessive hair growth, loss of coordination, and bone weakening. It also poses a higher risk of drug interactions due to its strong effect on liver enzymes, and because of its narrow therapeutic range, regular blood level monitoring is necessary. (Parri H. R., 1998)

Oxcarbazepine, a related compound to carbamazepine, also acts by inhibiting sodium channels but tends to have fewer side effects and less potential for drug interactions. It's most commonly prescribed for focal seizures. Some of the more frequent side effects include dizziness, low sodium levels, tiredness, and headaches, although it's generally better tolerated than phenytoin. Due to its weaker liver enzyme induction, oxcarbazepine is often favored in combination therapy settings. (] McLean, 2005)

By laying out this kind of information, **Table 1** helps clinicians and researchers make informed decisions about seizure management, allowing treatment to be tailored to each patient's clinical profile while minimizing unwanted effects.

**Table 1** The table provides a detailed overview of antiepileptic drugs, outlining their mechanisms, common side effects, and primary uses. It helps clarify how these medications control seizures and aids in selecting suitable treatments based on seizure type and individual patient needs.

| Drug (Reference) | Applicable to which type of epilepsy | Mechanism of action | Side effect |
|---|---|---|---|
| Phenytoin<br><br>(Parri H. R., 1998) | • Focal (Partial) Seizures<br>• Generalized Tonic-Clonic Seizures<br>• Status Epilepticus | Phenytoin stabilizes neuronal activity by binding to inactive sodium channels, inhibiting their reactivation. This action prevents overactive firing during seizures, effectively reducing abnormal electrical activity in the brain. | • Bradycardia<br>• Teratogenicity<br>• Allergic reaction<br>• Cerebellar atrophy<br>• Gingival hyperplasia<br>• Nystagmus |
| Barbiturate Derivatives (Rogawski M. A.-5., 2004), (Painter, 1999) | • Status seizures<br>• Neonatal seizures<br>• Focal (Partial) Seizures:<br>• Generalized Tonic-Clonic Seizures (Grand Mal Seizures) | Barbiturates like phenobarbital enhance GABA activity by binding to GABA-A receptors, increasing chloride influx, hyperpolarizing neurons, and reducing excitability. This suppresses abnormal electrical activity, preventing seizures. | • Memory problem<br>• Mood swings<br>• Hypotension<br>• Respiratory suppression<br>• Confusion<br>• Lack of concentration |
| Benzodiazepine derivatives (Rudolph U, 1999). (Honoré, 1984) | • Status epilepticus<br>• Clobazam for LennoxGastaut syndrome or adjunct therapy in focal and generalized seizures. | Benzodiazepines enhance GABA activity by binding to GABA-A receptors, increasing chloride influx, hyperpolarizing neurons, and reducing excitability, thereby suppressing seizures | • Tolerance<br>• Dependence and withdrawal symptoms<br>• memory, concentration<br>• Sedation and fatigue<br>• Increased risk of falls (especially in elderly) |
| Carbamazepine Ox-carbamazepine | • Focal (partial) seizures | Carbamazepine and oxcarbazepine work by | • Hyponatremia)<br>• Osteoporosis |

| | | | |
|---|---|---|---|
| ( (] McLean, 2005) | • Generalized tonic-clonic seizures<br>• Trigeminal neuralgia (carbamazepine) | inhibiting voltage-gated sodium channels, which helps stabilize neuronal membranes, limit excessive electrical activity, and prevent the spread of seizures in the brain. | • Weight gain or metabolic changes<br>• rashes or hypersensitivity reactions |
| Gabapentin (Stefani, 1998) (Backonja, 1998) | • focal (partial) seizures with or without secondary generalization | Gabapentin modulates calcium channels by binding to the α2δ subunit, reducing excitatory neurotransmitter release and stabilizing neuronal activity, which helps control seizures and neuropathic pain. | • Fatigue<br>• Weight gain<br>• Peripheral edema<br>• Depression<br>• Memory loss |
| Zonisamide (,Kwan, S.&Y., Chuang, ., 2015) | • focal (partial) seizures<br>• generalized tonic-clonic seizure<br>• Lennox-Gastaut syndrome. | Zonisamide blocks sodium and T-type calcium channels, stabilizes neuronal membranes, and enhances GABA activity, reducing abnormal electrical activity in the brain. | • Kidney stones (due to carbonic anhydrase inhibition)<br>• Weight loss or anorexia<br>• Fatigue or drowsiness<br>• Peripheral neuropathy |
| Lamotrigine (Trevathan, 1998) | • Focal (partial) seizures<br>• Generalized tonic-clonic seizures<br>• Lennox-Gastaut syndrome<br>• Absence seizures (adjunctive) | Lamotrigine stabilizes neuronal membranes by inhibiting voltage-gated sodium channels, reducing glutamate release, and preventing abnormal electrical activity in the brain | • Stevens-Johnson syndrome)<br>• Dizziness or drowsiness<br>• Headache<br>• Insomnia or sleep disturbances |
| Vigabatrin (Gidal, 1999) | • Infantile Spasms (West syndrome)<br>• Refractory Focal Seizures (when other treatments fail) | Vigabatrin irreversibly inhibits GABA transaminase, increasing GABA levels in the brain, which suppresses neuronal excitability and prevents seizures. | • Vision Loss<br>• Peripheral Neuropathy<br>• Weight Gain<br>• Psychiatric Effects (depression, agitation) |
| Ethosuximide (Snead OC 3rd, 1982) | • Absence seizures (petit mal) | Ethosuximide reduces thalamocortical excitation by blocking T-type calcium channels, preventing | • Rarely, blood disorders (e.g., leukopenia<br>• Gastrointestinal issue<br>• Headache |

| | | | |
|---|---|---|---|
| | | abnormal electrical activity in absence seizures. | |
| Felbamate (Rho JM, 1994) | • Lennox-Gastaut syndrome<br>• refractory focal seizures | Felbamate modulates NMDA and AMPA receptors, inhibiting excitatory neurotransmission, and enhances GABA activity, reducing neuronal excitability and preventing seizures. | • Aplastic anemia<br>• Liverfailure<br>• (hepatotoxicity)<br>• Insomnia or sleep disturbances<br>• Weight loss or anorexia |
| Levetiracetam (Rigo JM, 2002) (Lynch BA, 2004) | • myoclonic seizures,<br>• partial/focal seizures and generalized tonic-clonic seizures. | Levetiracetam's precise mechanism remains unclear, but it attaches to SV2A (a protein on synaptic vesicles) in the brain, influencing neurotransmitter release. Unlike older seizure drugs, it doesn't directly target GABA or sodium channels. Its distinct approach helps control excessive neuron activity with minimal sedative effects | • Drowsiness, dizziness, weakness, irritability, mood changes (e.g., aggression or depression).<br>• Psychiatric symptoms (suicidal thoughts), severe rash, or blood abnormalities |
| Tiagabine (Suzdak, 1995) | • refractory focal seizures | Blocks GAT-1 (GABA transporter-1), increasing GABA levels by preventing its reuptake into neurons. | • Dizziness, fatigue, sedation<br>• Drowsiness, weakness<br>• Rare psychosis/suicidal thoughts |
| Lacosamide (Krauss, 2012) (Beyreuther, 2007) | • focal seizures<br>• generalized tonic-clonic seizures. | Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, stabilizing hyperexcitable neuronal membranes and reducing seizure activity | • Dizziness<br>• Fatigue<br>• Headache<br>• Blurred vision or double vision |

• Confusion
• **Non-conv**

**10. Advanced Anti-Epileptic Drugs Available in the Market**

**1 Valtoco® (Intranasal Diazepam Spray)**

**Developed by:** Neurelis, Inc.

**Regulatory Status:** Approved by the U.S. Food and Drug Administration (FDA) in January 2020

### 2 Pharmacological Action and Delivery Mechanism:

A new intranasal formulation of diazepam, a long-acting benzodiazepine, is called Valtoco®. It works by intensifying the inhibitory effect of gamma-aminobutyric acid (GABA) on the brain's GABA-A receptors. The hyperexcitable neural circuits that underlie seizure activity are effectively dampened by this modulation, which increases neuronal inhibition.

Valtoco's intranasal administration, which takes advantage of the nasal mucosa's rich vascularization and close proximity to the brain, sets it apart from conventional oral or rectal diazepam.

Valtoco avoids the slower gastrointestinal route and hepatic first-pass metabolism by delivering drugs directly and quickly to the central nervous system through the use of the olfactory and trigeminal neural pathways. This focused strategy promotes a quicker therapeutic onset, which is essential for quickly and successfully stopping seizure episodes.

### 3 Therapeutic Benefits:

User-Friendly Administration: Designed for non-clinical settings, Valtoco is easily administered by caregivers or patients without the need for intravenous or rectal delivery.

Discreet and Non-Invasive: Unlike rectal diazepam, this nasal spray offers a socially acceptable and convenient alternative, particularly beneficial for adolescents and adults in public or school settings.

Quick Seizure Control: The nasal route achieves systemic absorption within minutes, allowing timely intervention during acute repetitive seizures or seizure clusters.

### 4 Clinical Use and Indications:

Valtoco is indicated for patients aged six years and older who experience intermittent, stereotyped seizure clusters that differ from their routine seizure pattern. It is intended for acute rescue therapy, not for routine seizure management or chronic prevention.

(Neurelis, Inc. (2020). *Valtoco (diazepam nasal spray)*

**10.1. Targeted Therapeutics: A Forward-Looking Approach with Advanced Controlled Drug Delivery Systems (CDDS)**

A complex class of pharmaceutical techniques known as controlled drug delivery systems was created to maximize the movement, security, and timed release of active pharmaceutical ingredients (APIs) within the human body. The main goal is to increase therapeutic efficacy by guaranteeing that the medication is delivered precisely to the target location with a controlled and prolonged release profile that optimizes bioavailability and reduces systemic adverse effects.

Developments by Generation in CDDS:

**First-Generation (1G) Technologies:** To enable longer action and lower dose frequency, the early CDDS primarily concentrated on modifying drug release kinetics. These devices, which provided straightforward but efficient control over drug availability, mostly depended on diffusion-based techniques.

**Second-Generation (2G) Innovations**: This era introduced stimuli-responsive polymers, often referred to as "smart" materials, capable of reacting to external factors such as pH fluctuations, temperature changes, or enzymatic activity. These systems aimed to achieve zero-order release kinetics, maintaining a steady therapeutic level over extended periods. Additionally, depot formulations emerged, supporting long-term delivery from a single administration (Cano A, 2021)

**Third-Generation (3G) Developments**: The most recent CDDS approaches feature highly selective, biointeractive carriers that are engineered to overcome complex physiological barriers. These systems are designed using predictive in vitro models, offering enhanced precision, extended duration of action, and improved patient adherence. A major focus is placed on creating platforms that are minimally invasive, easy to administer, and capable of site-specific targeting.

Key Features of Effective CDDS Carriers:

To function optimally, a controlled delivery system must incorporate the following core attributes:

• Consistent and rate-controlled release of the therapeutic agent.

• Versatility in administration, whether through localized or systemic routes.
• Sustained retention within the body, enabling extended pharmacological effect.
• Precise localization, ensuring the active compound acts directly at the intended site
.

**Mechanistic Pathways of Drug Release**: According to Fick's principles, molecular diffusion normally controls the controlled release of pharmaceuticals from these systems. But other processes like surface desorption, polymer expansion (swelling), and matrix breakdown (erosion) are also crucial. The physicochemical properties of the medication, such as its aqueous solubility, are closely related to the release kinetics.

• Thermodynamic stability;
- Partition coefficient between hydrophilic and lipophilic phases;
- Molecular size and structure;
- ionization degree and pKa values

CDDS Platforms Driven by Nanotechnology in Contemporary Medicine:

By providing nanoscale carriers with better control and targeting capabilities, the incorporation of nanotechnology into drug delivery has completely transformed controlled systems. Among the most notable nanocarrier systems are:

(Patra JK, 2018) , (. Su S, 2018) , (Su S, 2020) (Jabir N, Tabrez S, Firoz CK, Zaidi S, 2015)

- **Liposomes** – spherical vesicles composed of lipid bilayers that effectively encapsulate both hydrophilic and lipophilic drugs.
- **Micelles** – nanosized colloidal carriers formed by self-assembling amphiphilic molecules, useful for poorly water-soluble drugs.
- **Polymeric nanoparticles** – biodegradable and biocompatible particles designed for prolonged, site-directed release.
- **Hydrogels** – hydrophilic polymer matrices capable of responding to environmental cues and releasing their payload accordingly.
- **Dendrimers** – highly branched synthetic polymers with modifiable surfaces that allow multi-drug loading.
- **Carbon nanotubes and graphene materials** – unique nanostructures with high surface area and drug-loading capabilities.
- **Quantum dots** – nanocrystals that combine diagnostic imaging and therapeutic delivery (theranostics).
- **Polyelectrolyte complexes** – systems based on electrostatic interactions, ideal for encapsulating labile biomolecules.

**Table 4.** Nanoparticle-Based Intranasal Delivery for Selected Antiepileptic Drugs

| Drug | Nanocarrier Type | Carrier Matrix | Administration Method | Key Outcomes |
|---|---|---|---|---|
| **Alprazolam** (Singh AP, 2012) | Solid-Lipid Nanoparticle (SLN) | Glyceryl monostearate | Intravenous (i.v.), Intranasal (i.n.) | Intranasal route resulted in elevated brain drug levels. Use of SLN enabled better absorption at reduced doses. |
| **Carbamazepine** (Nair R & 11:72, 2012) . | SLN, NLC, Polymeric NP | Phospholipon R80H, Lipid myristyl myristate, PLGA, thermoresponsive gels, chitosan | Oral (v.o.), i.n., i.v. | Anticonvulsant response enhanced by SLN with/without chitosan. Thermosensitive gels promoted nasal drug retention. 30× efficacy via PLGA route. |
| **Clonazepam** (Abbas H, 2018) | SLN and NLC | Glycerol monooleate, Glyceryl monostearate/behenate, Oleic acid | Not specified | Mucoadhesive nasal formulation showed effective seizure protection. NLC helped guard against chemically induced convulsions. |
| **Diazepam** (Bohrey S, 2016) | Polymeric Nanoparticle | Poly(lactic-co-glycolic acid) (PLGA) | Not specified | Successfully formulated nanoparticles capable of encapsulating diazepam for use as an antiepileptic agent. |
| **Lamotrigine** (Scioli Montoto S, 2021) | Nanostructured Lipid Carrier | Glyceryl monostearate, Oleic acid | Intranasal (i.n.), Oral (v.o.) | Intranasal delivery increased brain targeting and retention. Provided better protective outcomes at lower doses compared to oral intake. |
| **Oxcarbazepine** (Musumeci T, 2018) | Polymeric Nanoparticle | PLGA | Intranasal (i.n.) | Reduced dosage frequency while maintaining efficacy. Detected accumulation in brain tissue in experimental seizure models. |
| **Valproic Acid** (Eskandari S, 2011) | Lipid nanoparticle (NLC) | Cetylpalmitate. Soy lecithin Octyldodecano | i.p. i.n. | Intranasal delivery facilitated superior brain penetration, achieving elevated drug concentrations in central nervous tissues compared to other administration routes." |

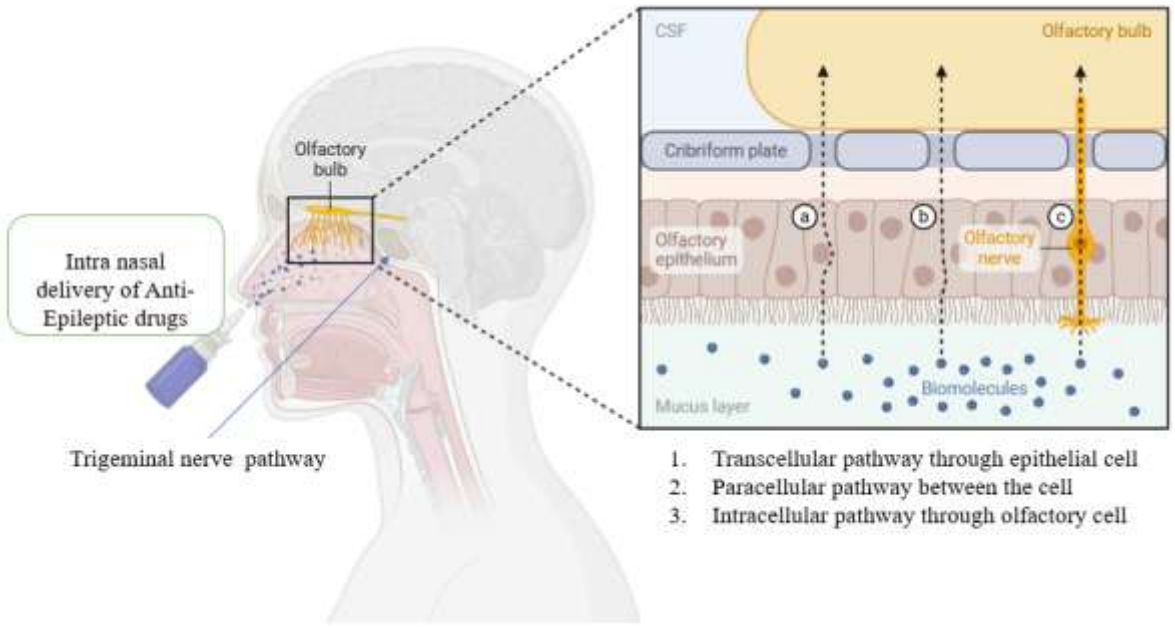


**Fig 4** The illustration depicts the intranasal route of drug delivery, showcasing the anatomical pathway from the nasal cavity to the brain. Upon administration, the formulation travels through the nasal passage, reaching the olfactory region, which provides a direct connection to the central nervous system (CNS). This pathway facilitates rapid and targeted delivery of therapeutics to the brain, bypassing the blood-brain barrier, and is particularly beneficial for treating neurological disorders (Figure generated by www.Biorender.com )

Intranasal drug delivery has emerged as a widely embraced approach for managing acute seizures, particularly in non-hospital environments, owing to its straightforward administration and proven efficacy. This method is increasingly utilized for both prescription and over-the-counter medications, providing a practical and accessible option for caregivers and patients. For example, preliminary studies highlight the effectiveness of nasal midazolam in controlling seizures at home, demonstrating its potential to reduce complications, fatalities, and strain on healthcare systems by decreasing hospital admissions and associated expenses.

The use of intranasal lorazepam for pediatric children who have protracted seizures is a striking example of this strategy in action, particularly in areas with limited access to healthcare resources. Clinical evaluations reveal that administering lorazepam via a nasal adapter (100 mcg/kg) resulted in seizure cessation within 10 minutes for 75% of cases. Notably, this method significantly reduced the reliance on additional rescue medications compared to conventional intramuscular paraldehyde.

The intranasal lorazepam formulation stands out as an optimal first-line treatment in primary healthcare settings due to its rapid onset of action, minimal cardiopulmonary side effects, sustained therapeutic impact, and cost-effectiveness. These attributes make it particularly valuable in resource-constrained areas, where accessibility, affordability, and ease of use are critical for improving patient outcomes and reducing healthcare burdens.

### 10.2. The Function of Prodrugs in Precision Drug Administration Through the Blood-Brain Barrier

Overview of Prodrugs

Prodrugs are pharmacologically inactive derivatives that have been purposefully designed to change a drug's physicochemical or pharmacokinetic characteristics in order to improve its performance. These compounds are changed chemically or enzymatically into the active therapeutic form after delivery, overcoming obstacles such systemic toxicity risks, low bioavailability, and poor aqueous solubility. (Rautio J, 2008)

Methods for Improving Penetration of the Blood-Brain Barrier (BBB) Increasing lipid solubility or using natural transport channels are common prodrug design strategies since the BBB selectively allows the passage of tiny, lipophilic compounds. Prodrugs

occasionally use disease-specific enzymatic triggers to selectively activate the brain, improving both safety and efficacy. (Rautio J, 2008) (Fechner J & 53., 2008)

**Illustrative Case Studies**

Design Method for DP-VPA (Valproic Acid Prodrug): By conjugating with lecithin, valproic acid enhances lipid affinity and promotes BBB permeability. Activation Site: Phospholipase A2, an enzyme that is elevated during seizures, breaks down the lecithin moiety at epileptic places releasing active valproic acid. Therapeutic Significance: This localized activation enhances seizure control and reduces systemic toxicity. However, potency might vary according on BBB integrity and enzymatic activity. (Bialer M & 43:, 2001).

**Design Method for Fosphenytoin (Phenytoin Prodrug)**

Safe intravenous or intramuscular delivery is made possible by the addition of a phosphate ester moiety, which increases water solubility.

Bioconversion: Alkaline phosphatases convert fosphenytoin to phenytoin, generating minimal byproducts such as phosphate and formaldehyde, which remain below toxic thresholds (Fechner J & 53., 2008) , (Knapp LE, 1998)

Clinical Application: This prodrug is widely used in acute seizure management, including status epilepticus, due to its fast action and reduced injection site irritation. Clinical outcomes demonstrated seizure control in approximately 94% of patients [66] (Knapp LE, 1998).

**Design Method for XP13512 (Gabapentin Prodrug):**

This prodrug, which was created as a carbamate ester, increases absorption by activating intestinal solute transporters such MCT1 and SMVT.

Bioconversion: Active gabapentin is released when it is broken down by endogenous esterases in the liver and stomach. Its oral bioavailability is increased by this route to about 84%, which is a considerable improvement over gabapentin's 25%. (Cundy KC, 2004), (Cundy, Annamalai T,, 2014)

Therapeutic Benefit: XP13512 provides better dosage proportionality, increased intestinal absorption, and more consistent pharmacokinetics.(Cundy KC, 2004) (Cundy, Annamalai T,, 2014)

Mechanistic Highlights

Lecithin conjugation in DP-VPA increases lipid membrane affinity, facilitating BBB penetration through lipophilicity-driven permeability.(Bialer M & 43:, 2001)

Enzymatic Targeting: Selective medication activation and low off-target effects are guaranteed by increased phospholipase activity at epileptic foci. (Bialer M & 43:, 2001), (Rautio J, 2008)

Transporter Exploitation: XP13512 benefits from intestinal transporters to bypass conventional absorption issues (Cundy KC, 2004).

**• Difficulties and Things to Think About**

Dependency on the biological context: Prodrug performance is impacted by variations in BBB integrity and enzyme expression.

Byproduct Management: Though some metabolic byproducts (e.g., formaldehyde) are generated, their concentrations are negligible and do not pose clinical toxicity risks (Fechner J & 53., 2008) , (Knapp LE)

Prodrugs offer a sophisticated approach to get around obstacles to drug distribution, especially in conditions affecting the central nervous system. Prodrugs make precise and efficient treatment possible by improving solubility, utilizing biological transporters, and ensuring targeted enzymatic activation. Their performance, however, necessitates a thorough comprehension of disease

pathophysiology and patient-specific factors, highlighting the significance of tailored prodrug design. (Rautio J, 2008), (Cundy KC, 2004)

**10.3 Blood-Brain Barrier Disruption by Hyperosmolar: Mechanisms, Treatment Prospects, and Limitations**

A hypertonic substance, such as 25% mannitol, is administered intraarterially to temporarily increase BBB permeability in a process known as hyperosmolar blood-brain barrier (BBB) disruption. By causing endothelial cells to osmotically shrink, this technique widens tight junctions and makes it easier for drugs to enter the brain.

(Haluska & Anthony, 2004) .

Human investigations have shown that the blood-brain barrier remains porous for about 40 minutes, with complete healing taking place within 8 hours. (Siegal et al., 2000)

This method was first utilized in neuro-oncology to increase the administration of chemotherapeutic medicines such as methotrexate and carboplatin to brain tumors. Research has shown a correlation between enhanced survival in primary CNS lymphoma and higher chemotherapy dosage intensity. (Kraemer et al., 2001)

Although osmotic BBB alteration has demonstrated benefits in oncology, concerns like neurotoxicity and edema, along with the requirement for exact drug administration timing, limit its wider use. (Kroll & Neuwelt, 1998)

Crucially, BBB disruption itself can cause seizures, making its application in epilepsy more challenging. According to clinical reports, 7% of cancer patients who had previously been seizure-free had seizures after the surgery; this incidence increases to 25% when chemotherapy is added (Marchi et al., 2007)

Preclinical studies in chronic epileptic rats further corroborate this risk, showing increased seizure frequency post-BBB disruption (Marchi et al., 2007)

Despite theoretical potential for improving antiepileptic drug delivery, the pro-convulsant effects of osmotic BBB opening make it unsuitable for epilepsy management.

Critically, BBB disruption itself may provoke seizures, complicating its use in epilepsy. Clinical reports note seizures in 7% of previously seizure-free cancer patients undergoing the procedure, with incidence rising to 25% when combined with chemotherapy Preclinical studies in chronic epileptic rats further corroborate this risk, showing increased seizure frequency post-BBB disruption

Despite theoretical potential for improving antiepileptic drug delivery, the pro-convulsant effects of osmotic BBB opening make it unsuitable for epilepsy management.

**Key Citations Mapped to Claims:**

Mechanism and clinical application in oncology: [69] (Haluska & Anthony, 2004)[71] (Kraemer et al., 2001)

BBB permeability timeline: (Siegal et al., 2000)

Risks and limitations: (Kroll & Neuwelt, 1998)

Seizure induction in humans/animals: (Marchi et al., 2007).

**10.4. Intraparenchymal Delivery of Antiseizure Therapeutics: Mechanisms, Advantages, and Challenges Enhanced Efficacy of Focal Drug Delivery**

Delivering anticonvulsants directly into the brain parenchyma offers the distinct advantage of providing the medications to epileptogenic sites, which is much more targeted, efficient, and effective than traditional routes. For instance, in preclinical studies, local administration of adenosine 100 µg into cortical seizure foci resulted in a >50% reduction in both amplitude and frequency of

spikes within the first 45 minutes, whereas intraventricular administration resulted in only a transient reduction of frequency ((Yildirim & Marangoz, 2007)

This underscores the utility of precision-targeted interventions, where drugs engage hyperexcitable networks directly, minimizing off-target effects and systemic exposure. Key Advantages of Intracranial Drug Delivery Circumvention of Neurovascular Barriers Intraparenchymal strategies circumvent neurovascular barriers, achieving localized concentrations up to 100-fold higher than systemic delivery, which significantly reduces peripheral toxicity ((Tolmacheva & Van Luijtelaar, 2007)

**Long-Term Release via Implanted Technology**

With drug diffusion reaching several millimeters from the implant site, biodegradable polymer matrices including polyanhydrides and PLGA allow for sustained release for weeks to months. For example, throughout a 30-day period, carmustine-loaded disks maintained effective concentrations of up to 3 mm, whereas free drug injections degraded within 1 mm. ((Fung et al., 1996) Similarly, titania bio-ceramic reservoirs eluting valproic acid achieved seizure suppression for 5 months without detectable neuronal toxicity ((Lopez et al., 2007)

**Novel Agents Enabled by Local Delivery**

This platform allows delivery of pharmacologically potent molecules that are otherwise ineffective systemically due to poor BBB permeability. TRH-eluting implants, for example, delayed seizure progression in kindled rats for nearly 50 days, offering a promising modality for refractory epilepsy ((Kubek et al., 1998).

**Challenges and Limitations**

Restricted Diffusion Kinetics

Despite localized efficacy, intraparenchymal administered drugs often face restricted diffusion kinetics due to the dense extracellular matrix and interstitial architecture. For example, phenytoin-loaded polymer implants reduced spikes only in close proximity (within 3–5 mm) to the administration site ((Tamargo et al., 2002)

**Device Biocompatibility and Functional Longevity**

Non-degradable polymers risk chronic immune responses, while biodegradable implants may suffer early drug depletion. GABA-releasing matrices demonstrated efficacy for only 7 days due to neurotransmitter degradation ((Kokaia et al., 1994).

**Technical and Clinical Difficulties**

Stereotactic procedures are necessary for precise distribution in order to prevent iatrogenic harm.
In sustained-release systems, dose calibration is essential. For instance, valproate-titania composites needed a lot of preclinical calibration to strike a balance between safety and efficacy. ((Lopez et al., 2007) .

**Emerging Innovations**

**Microinvasive Neural Implants (MINI)**

It has been demonstrated that phenobarbital or valproate infused by micro-scale implants aimed at the temporal lobe can reduce focal seizures by 70% without affecting motor behavior ((Sawyer et al., 2006) .

**Hybrid Neuroprosthetics**

Real-time feedback-controlled drug release and electrophysiological seizure detection are now features of next-generation closed-loop systems. Adaptive seizure suppression has been demonstrated using subdural implants that release muscimol in response to cortical hyperactivity ((Fung et al., 1996).

Drug Penetration Enhanced by Nanoparticles PLGA nanoparticles have been used to improve distribution within thick parenchyma by extending diffusion radii by almost 200% compared to free drug equivalents . ((Saltzman & Olbricht, 2002)

## 11. Conclusion

Epilepsy is still a complicated neurological condition with a variety of causes, including brain structure defects and genetic alterations. Although many people may effectively control their seizures with standard antiepileptic medications, a sizable portion of patients continue to be drug-resistant, underscoring the need for more sophisticated treatments. Precision medicine, targeted drug administration, and new therapeutic modalities including intranasal and nanoparticle-based systems have all been made possible by an understanding of the underlying pathophysiological mechanisms, such as ion channel dysfunction, neurotransmitter imbalances, and neuroinflammation. Promising approaches to getting around the drawbacks of conventional treatments include prodrug design, nanotechnology, and intraparenchymal delivery devices. Going forward, improving clinical outcomes and raising the standard of living for people with epilepsy will require individualized treatment plans that incorporate pharmaceutical, surgical, and technology approaches that are catered to each patient's unique profile.

intraparenchymal administration of antiseizure medication allows for targeted, high-dose, and prolonged pharmacological manipulation of epileptic circuits, it represents an exciting method for treating drug-resistant epilepsy. However, addressing obstacles in implant engineering, diffusion dynamics, and biocompatibility will be essential for clinical translation. Adaptive, patient-specific neuromodulation in order that goes beyond limitations of systemic therapy may be possible by integration with real-time responsive technologies.

When it comes to delivering antiepileptic medications (AEDs), the intranasal route has shown great potential, especially in acute and emergency situations where traditional methods have major drawbacks. The oral route is unreliable during epileptic seizures because of weakened swallowing reflexes, and intravenous (IV) administration has limitations in its use in community or home settings since it requires trained healthcare staff and suitable clinical conditions. Despite being more widely available, intramuscular (IM) injections frequently have a delayed pharmacological response, which can jeopardize prompt seizure control.

When it concerns delivering antiepileptic medications (AEDs), the intranasal route has shown great potential, especially in acute and emergency situations where traditional methods have major drawbacks. The oral route is unreliable during epileptic seizures because of weakened swallowing reflexes, and intravenous (IV) administration has limitations in its use in community or home settings since it requires trained healthcare staff and suitable clinical conditions. Despite being more widely available, intramuscular (IM) injections frequently have a longer pharmacological response, which might compromise prompt seizure control.

The delivery of antiepileptic drugs (AED) via the intranasal route has demonstrated considerable promise, especially in acute and emergency scenarios where other routes have shortcomings. The oral route is compromised during epileptic events, as the swallowing reflex deteriorates; and intravenous (IV) delivery is limited in community or home settings by the necessity for qualified healthcare personnel and the need for correct clinical circumstances associated with its administration. Although intramuscular (IM) delivery routes are more broadly available, they often produce a delayed pharmacological response, which may impinge on seizure control.

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**Author contribution**

PK wrote the Primary draft of article, prepared the table and figures; VM to contributed in design and the revised the article; JS provided the overall guidance.

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