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**Title:** Neuroprotective Mechanisms of Valproic Acid in Epilepsy: An Update Review of Preclinical and Clinical Studies

**Running Title**: Therapeutic Effect of Valproic Acid

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**Abstract**

Epilepsy is a chronic neurological disease caused by anomalous neuronal action that displays as persistent, irrational, frequent seizures with frothing at the mouth, leading to a significant global health burden. Valproic acid (VPA) is a widely prescribed antiepileptic drug (AED) that has demonstrated efficacy in treating various types of seizures. Besides its anticonvulsant properties, emerging evidence proposes that VPA employs neuroprotective efficacy, possibly improving the progression of epilepsy and mitigating its related neurological damage. It represents a drug of choice in children and adults with epilepsy, with either general or focal seizures. This review highlights the signalling pathways modulated by VPA with a translational purpose, preclinical and clinical studies investigating the neuroprotective mechanisms supporting VPA's neuroprotective role in epilepsy, and identifies the areas for future research.

**Keywords:** Valproic acid, epilepsy, neuroprotection, mechanisms of action, preclinical studies, clinical studies

## 1. Introduction

Epilepsy is one of the most prevalent and burdensome neurological disorders, affecting people of all ages worldwide. It increases the risk of premature death by up to three times compared to the general population (Feigin et al., 2025). Clinically, it is characterized by recurrent, unprovoked seizures caused by abnormally high or synchronous neuronal activity in the brain. These seizures may be accompanied by loss of consciousness and, in some cases, impaired bladder and bowel control (Begley et al., 2022).

The term epilepsy originates from the Greek word epilambanein, which means "to seize, take hold of, or attack." The condition often presents with dramatic symptoms such as frothing at the mouth and convulsions. Globally, epilepsy affects more than 70 million people, with a higher incidence, prevalence, and mortality observed in low-income countries. The disease often exhibits a bimodal age distribution in these regions (Thijis et al., 2019). Alarmingly, nearly 90% of individuals with epilepsy in low-income nations do not receive adequate treatment, primarily due to stigma, cultural beliefs, limited drug availability, and systemic healthcare barriers (Trinka et al., 2019).

Epilepsy imposes a significant psychological, physical, mental, and financial burden on patients, families, healthcare systems, and societies at large (Ostendirf and Gedela, 2017). Among the various forms of epilepsy, temporal lobe epilepsy (TLE) is the most prevalent and one of the most pharmacoresistant subtypes. TLE is pathologically characterized by neuronal loss, reactive gliosis in the hippocampus, amygdala, and entorhinal cortex (Rashid et al., 2021).

The pathophysiology of epilepsy is complex and multifactorial, including genetic predispositions, neurotransmitter imbalances, ion channel dysfunction, and aberrant neuronal excitability. Additionally, inflammation, oxidative stress, and immunological reactions play significant roles in both the onset and progression of the disease (Brodie and Sills, 2011). More

than 30 antiepileptic drugs (AEDs) have been developed, targeting mechanisms such as modulation of voltage-gated ion channels, enhancement of GABAergic transmission, and inhibition of excitatory glutamate receptors (Li et al., 2023).

This review aims to provide an updated and comprehensive analysis of the mechanisms of action of valproic acid (VPA), with particular focus on its neuroprotective properties. VPA not only enhances GABAergic transmission but also inhibits histone deacetylases (HDACs), contributing to its broader neuroprotective and potentially anti-epileptogenic effects. We explore recent research that highlights VPA's potential as a disease-modifying agent, particularly in high-risk populations such as patients with post-traumatic brain injury. By shifting the perspective from symptomatic treatment to long-term disease modification, this review positions VPA as a unique therapeutic candidate in the ongoing effort to prevent epileptogenesis and improve patient outcomes.

## 2. Valproic acid

VPA (also known as valproate) is a widely used antiepileptic drug and a fatty acid derivative (Lopez-Munoz et al., 2012). It was originally employed as an organic solvent in industrial and pharmaceutical applications for almost a century (Beckner,1979). VPA (chemically known as 2-n-propylpentanoic acid) has since become a cornerstone in the treatment of various seizure disorders.

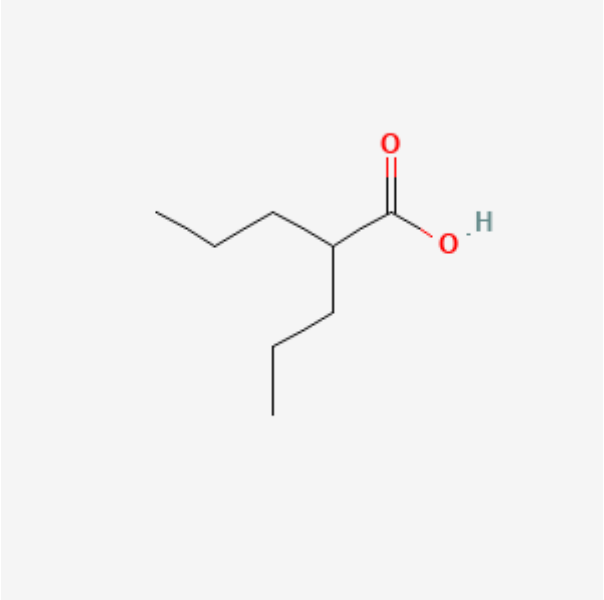


**Figure 1: Molecular structure of valproic acid. Structure of valproic acid retrieved from PubChem (CID: 3121), National Center for Biotechnology Information (NCBI 2025).**

VPA exerts its antiepileptic effects primarily through modulation of neurotransmission, particularly by enhancing γ-aminobutyric acid (GABA) activity and reducing excitatory glutamatergic signaling (Braconnier et al., 2018). It can be used as monotherapy or as part of a polytherapy regimen, commonly in combination with other AEDs such as topiramate (TPM), carbamazepine, lamotrigine (LTG), and phenytoin (PHT) (LaBuzetta, 2010). Beyond epilepsy, VPA can be used in psychiatric settings to treat bipolar disorder during manic episodes, aggressive outbursts in children with attention-deficit/hyperactivity disorder (ADHD), and dystonia. It is occasionally combined with antipsychotic medications. Additionally, VPA is sometimes prescribed to prevent or treat migraine headaches (Mezghani, 2011).

Epilepsy imposes significant economic burdens on both individuals and healthcare systems. Annual healthcare costs for patients with epilepsy are higher than for non-epileptic controls, largely due to the cost of AEDs and the management of related comorbidities (Finsterer and Zarrouk, 2012).

Despite being a relatively older AED, VPA remains widely used due to its proven efficacy, cost-effectiveness, and favourable safety profile, particularly in elderly patients who are on multiple medications. VPA has a remarkable potential for drug-drug interactions but maintains a strong safety record in polymedicated populations. Currently, VPA is available in generic form, which is less expensive than the branded versions. Most formulations used for seizure management are considered bioequivalent (Verrotti et al., 2011). In addition to its antiepileptic properties, VPA has also shown anti-migraine, neuroprotective, and anti-manic effects in several studies (Gayam et al., 2018).

### 2.1 Mechanism of Valproic Acid Action

Although several theories have been proposed, the precise mechanisms of action of VPA (Figure 2) and its metabolites in neurological and psychiatric disorders remain incompletely understood. It is well known that succinic semialdehyde dehydrogenase (SSD) is inhibited by VPA and its pharmacologically active metabolites (Vanadia et al., 2013). This enzyme normally metabolizes succinic semialdehyde, a compound that functions as a GABA transaminase inhibitor. By inhibiting SSD, VPA increases GABA levels, enhancing GABAergic neurotransmission and reducing GABA degradation. Given that GABA is the primary inhibitory neurotransmitter in the central nervous system, this elevation leads to enhanced neuronal inhibition.

VPA also exerts direct inhibitory effects on voltage-gated sodium channels and indirectly suppresses cortical neuronal activity through its influence on GABAergic pathways. These actions may contribute to the suppression of neuronal excitability in the cerebral cortex (Muralidharan et al., 2020; Lunke et al., 2021).

Furthermore, the extracellular signal-regulated kinase (ERK) pathway may be affected by VPA and its active metabolites (Sakakibara et al., 2022). These effects are dependent on mitogen-

activated protein kinase (MEK) and lead to phosphorylation of ERK1/2. Subsequently, this pathway upregulates the expression of multiple downstream targets, including brain-derived neurotrophic factor (BDNF), involved in neuronal growth and plasticity; B-cell lymphoma/leukemia-2 (Bcl-2), an anti-apoptotic protein; and ELK-1, a transcription factor that increases expression of c-fos and growth cone-associated protein-43, both of which support neuronal plasticity (Begley et al., 2022). These effects account for the rise in neurogenesis and neurite outgrowth caused by VPA and its active metabolites. In addition, VPA enhances the expression of GABA receptors, further augmenting inhibitory GABAergic activity (Yamada et al., 2002).

Another mechanism involves the indirect, non-competitive inhibition of myo-inositol-1-phosphate synthetase, leading to depletion of inositol through reduced de novo synthesis of inositol monophosphatase (Shaltiel et al., 2007). This mechanism has implications for mood stabilization, as protein kinase C (PKC) is often dysregulated in the frontal cortex of patients with bipolar disorder (Watterson et al., 2002). VPA-mediated downregulation of PKC may be associated with its therapeutic effect in this condition (Watterson. Inhibition of the PKC pathway may contribute to migraine prophylaxis (Parikhet al., 2019).

Moreover, VPA lowers the availability of the PKC substrates, potentially altering synaptic remodeling by affecting the cytoskeleton (Traetta et al., 2021). VPA and its metabolites are also known to interfere with fatty acid metabolism, particularly by reducing the incorporation of fatty acid substrates into sterols and glycerolipids. This may alter the fluidity of the neuronal membrane and raise the action potential threshold (Rosenberg, 2007).

VPA also directly inhibits microsomal long-chain fatty acyl-CoA synthetase in the brain in a non-competitive manner. This enzyme is crucial for the synthesis of arachidonyl-CoA, a substrate for the production of inflammatory prostaglandins. Reduced prostaglandin synthesis

may be another mechanism through which VPA contributes to migraine prevention, similar to the effect of non-steroidal anti-inflammatory drugs (NSAIDs) (Becker, 2015).

Lastly, VPA and its active metabolites directly inhibit histone deacetylases (HDACs). This inhibition leads to hyperacetylation of histone lysine residues, which promotes DNA unwinding and increased gene transcription. These genomic effects are diverse, with VPA affecting the expression of up to 461 genes, although the relationship between these changes and its therapeutic benefits is unclear (Sharma et al., 2006).

One proposed mechanism suggests that VPA may enhance the neuroprotective effects of histone hyperacetylation, particularly at the BDNF gene, leading to elevated BDNF expression following an epileptic seizure. This neuroprotective role is further supported by evidence linking hyperacetylation of histone H3 and decreased activity of glyceraldehyde-3-phosphate dehydrogenase, a pro-apoptotic enzyme (Bahna and Niles, 2018).

Overall, VPA influences several central nervous system pathways, resulting in a complex and multifaceted mechanism of action. Beyond its well-established anticonvulsant effects, increasing evidence suggests that VPA has neuroprotective effects.

Preclinical and clinical studies have explored these neuroprotective mechanisms in the context of epilepsy to better understand VPA's potential role in mitigating the long-term neurological consequences of the disease. To assess new compounds for seizure control, several animal models of epilepsy and seizures have been developed.

Among these, mice and rats are the most commonly used species. These models provide a vital platform to evaluate the *in vivo* efficacy and safety of novel compounds that demonstrate antiseizure potential *in vitro* (Yang et al., 2023).

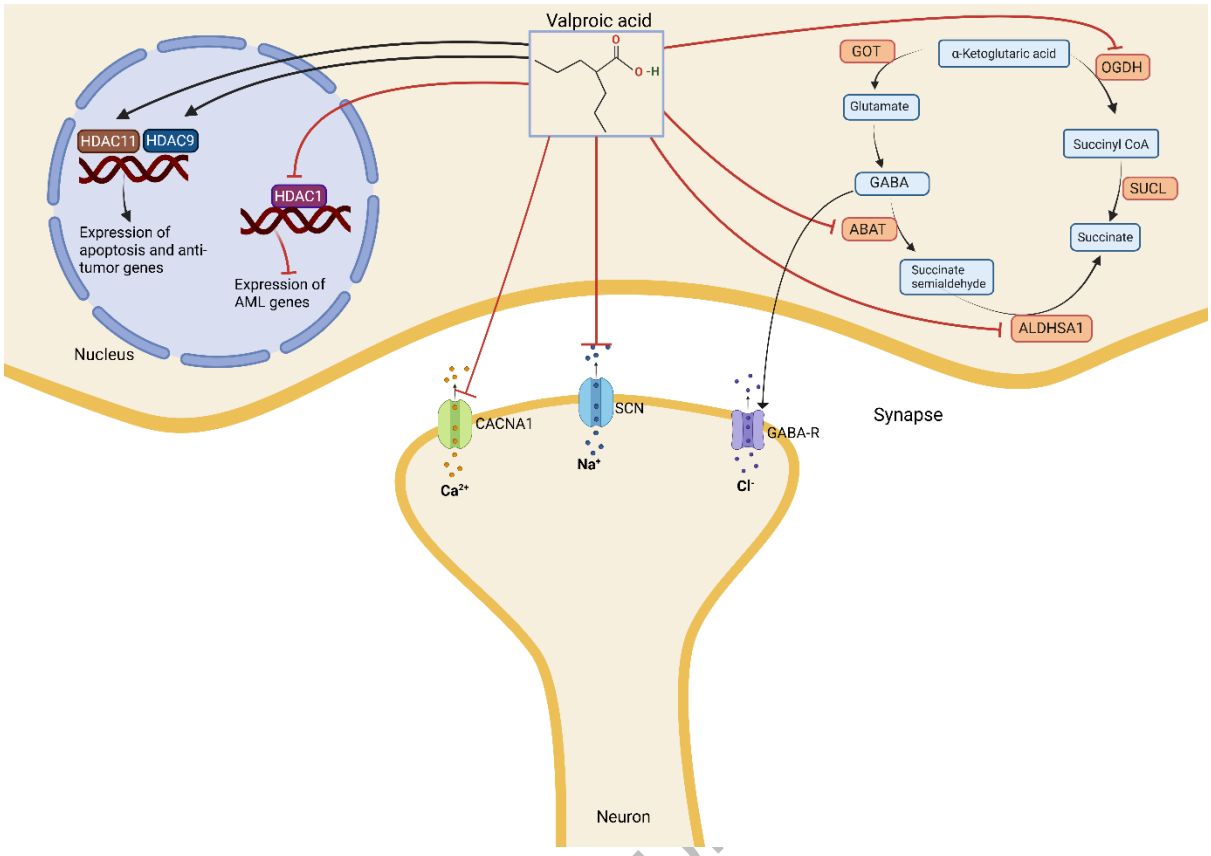


**Figure 2. Mechanism of action of Valproic acid Mechanism of action of Valproic acid (BioRender Content used under a publication license https://BioRender.com/5oyxiun)**

## 3. Valproic acid, Oxidative Stress and Epilepsy

Oxidative stress plays a significant role in neuronal damage associated with seizures. Preclinical research in various experimental models of epilepsy has shown that VPA can mitigate oxidative stress and potentially reduce seizure-induced neuronal damage.

Oxidative stress arises when the body's antioxidant defense system, which includes both exogenous antioxidants derived from the diet and endogenous enzymes such as glutathione reductase (GR), catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), and reduced glutathione (GSH), is unable to neutralize the accumulation of reactive species (RS) generated by normal cellular metabolism or external insults (Yang et al., 2021; Checa et al., 2020).

An excess of reactive oxygen species (ROS) and nitric oxide (NO) can lead to lipid peroxidation and direct damage to proteins, including enzymes and membrane components. The molecules can react to form peroxynitrite, a potent reactive nitrogen species (RNS), which disrupts membrane integrity, cellular signaling, and neuronal function (Kovac et al., 2017).

Due to its high metabolic rate, elevated oxygen consumption, and abundance of polyunsaturated fatty acids, the brain is particularly susceptible to oxidative damage (Cobley et al., 2018). Among the cellular structures affected, the $Na^+/K^+$-ATPase (NKA) enzyme is especially vulnerable to oxidative stress and lipid peroxidation (McCoy et al., 2019). NKA is critical for maintaining ionic gradients, osmotic balance, and the electrical excitability of neurons (Farrell et al., 2017). Impaired NKA activity can lead to neuronal hyperexcitability, thereby facilitating seizure initiation and progression (De Freitas et al., 2010).

To counteract oxidative stress, antioxidant therapy has emerged as a promising strategy. This can involve dietary intake of natural antioxidants or supplementation with compounds known to enhance endogenous antioxidant defences (Forman and Zhang, 2021). Numerous studies suggest that antioxidant therapy offers neuroprotection in both clinical and preclinical models of neurological diseases (Lv et al., 2017; Haghnejad Azar et al., 2017; Wang et al., 2016; Taghizadeh et al., 2017).

Specifically, preclinical epilepsy models have shown that antioxidant treatment can reduce oxidative damage, thereby decreasing epileptogenic potential and possibly modifying disease progression (Essawy et al., 2022).

**4. Valproic acid, Neuroinflammation and Epilepsy**

As demonstrated by the occurrence of febrile seizures, inflammation has long been associated with epilepsy. This suggests that inflammatory processes may induce hyperexcitability in brain tissue. Although the primary pathophysiological agents have been identified, the results of

numerous studies attempting to elucidate this mechanism remain inconclusive. Pro-inflammatory cytokines (PICs), such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6), are secreted by microglia and astrocytes during neuroinflammatory responses. An overload of PICs in the central nervous system (CNS) leads to the disruption of the blood-brain barrier (BBB), facilitating the influx of additional inflammatory mediators from the systemic circulation (Soltani et al., 2022).

Over the past decade, clinical symptoms and neuropathological findings have underscored the crucial role of inflammation in epileptogenesis. Studies have shown that pro-inflammatory cytokines are among the most elevated molecules during this process. These cytokines enhance synaptic transmission via glutamate receptor-mediated pathways, thereby increasing neural excitability and lowering the seizure threshold (Gnatek et al., 2012). Consequently, the current study aimed to clarify the role of nuclear factor kappa B (NF-κB) and inflammatory mediators in LiCl- and pilocarpine-induced epilepsy. NF-kB is a redox-sensitive transcription factor that regulates the expression of pro-inflammatory mediators and is directly associated with neuronal excitability and gliosis in the hippocampus. Thus, it represents a potential therapeutic target in epilepsy management (Aronica et al., 2017).

The innate immune response is thought to be activated in epilepsy, resulting in elevated levels of inflammatory markers such as TNF-α, IL-1β, and IL-6. Previous studies reported that ischemic, epileptic, or excitotoxic injuries can initiate a proinflammatory cytokine storm, including these molecules (Ahmad et al., 2018). Neuroinflammation triggered by seizures can cause neuronal death in multiple brain regions, including the hippocampus. Severe inflammation is known to induce neurotoxicity and cellular damage. Experimental and clinical evidence indicated that inflammatory pathways, such as the nitric oxide (NO) pathway, play a significant role in the pathophysiology of epileptic seizures and associated brain lesions. NO, a gaseous neurotransmitter, is produced in the brain by NOS. Although NO is a relatively

unreactive free radical, it can combine with other radicals to form peroxynitrite, a highly cytotoxic compound capable of inducing cell death (Dzolji et al., 2015).

Myeloperoxidase (MPO) is an inflammatory enzyme expressed in leukocytes and is the only peroxidase known to oxidize halides using hydrogen peroxide ($H_2O_2$) to generate hypohalous acids. This process contributes to the generation of RNS and ROS. Additionally, MPO also inhibits matrix metalloproteinase inhibitors, leading to BBB disruption, which is associated with seizure initiation and progression. VPA, a widely used AED, has demonstrated anti-inflammatory effects in several models of epilepsy and inflammation. Notably, VPA has been shown to decrease MPO activity (Mowafy et al., 2011). This anti-inflammatory action likely stems from VPA's ability to reduce pro-inflammatory cytokines and activate anti-inflammatory pathways. [Figure 3]



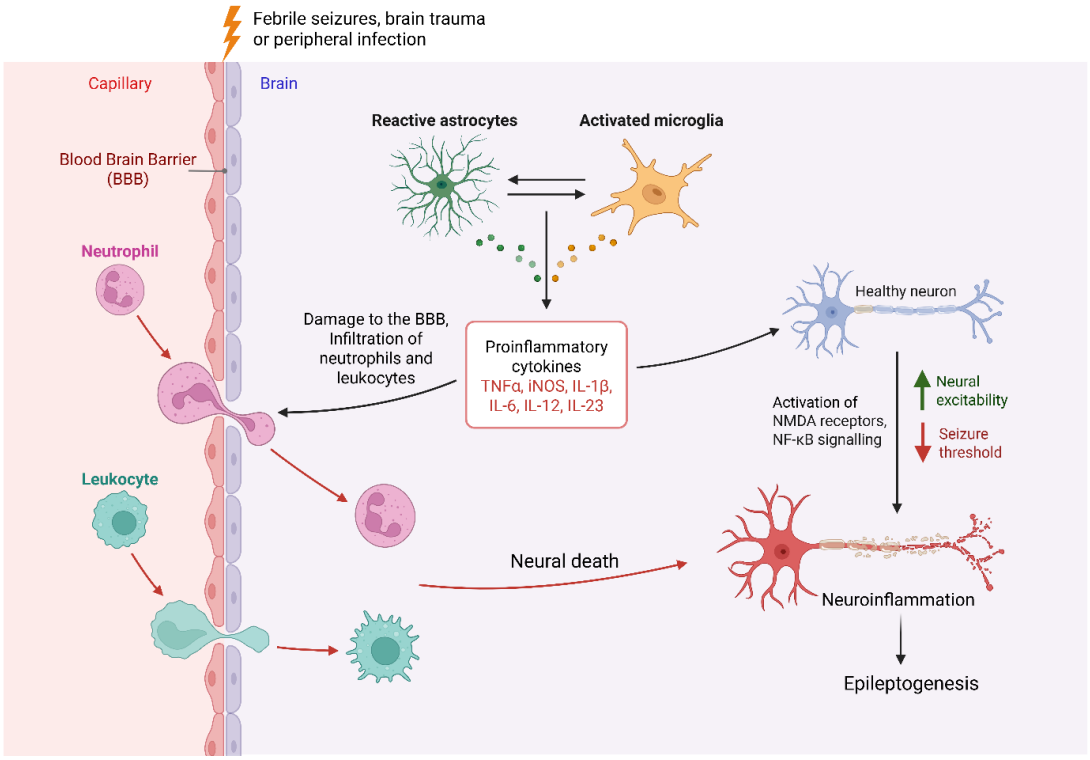


**Figure 3: Mechanism of Neuroinflammation of VPA in Epileptogenesis (BioRender Content used under a publication license https://BioRender.com/xiship1)**

Both acute seizure-induced injury and the development of chronic epilepsy are influenced by neuroinflammation. Preclinical studies have revealed that VPA exerts anti-inflammatory effects in the context of epilepsy. Specifically, VPA modulates the expression of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, which are implicated in neuronal damage and epileptogenesis (Ichiyama et al., 2000). Moreover, VPA has been shown to reduce microglial activation, the resident immune cells of the brain that are essential in orchestrating neuroinflammatory responses (Peng et al., 2015). It can inhibit microglial proliferation, migration, and the release of inflammatory mediators. In animal models of epilepsy, VPA treatment has been associated with enhanced neuronal survival, reduced expression of inflammatory markers, and attenuated neuroinflammation (Tribble et al., 2022).

**5. Valproic Acid, Apoptosis and Epilepsy**

Epilepsy is closely associated with apoptosis, particularly through mechanisms involving redox signaling. Prolonged epileptic seizures have been reported to aggravate brain damage by activating apoptotic signaling pathways. Mitochondrial permeabilization and the subsequent release of pro-apoptotic proteins in response to seizure-induced brain injury lead to the activation of executioner caspases, such as caspase-3, resulting in neuronal death and brain lesions (Rehman et al., 2015).

There is substantial evidence that oxidative stress and mitochondrial dysfunction are interrelated processes contributing to seizure-induced brain injury. Both factors play a crucial role in epileptogenesis by promoting apoptosis (Méndez-Armenta et al. 2014). Furthermore, as the primary site of ROS production, mitochondria are particularly susceptible to oxidative damage. Previous studies suggest that targeting oxidative stress, neuroinflammation, and mitochondrial dysfunction may provide a novel therapeutic strategy for preventing neuronal

death, mitigating epilepsy progression, and managing seizures (Engel and Henshall, 2009; Mao et al., 2009).

Apoptosis, or programmed cell death, is a key contributor to neuronal loss in epilepsy. Preclinical studies indicate that VPA can exert anti-apoptotic effects across various neuronal cell types. VPA has been shown to modulate the expression of both pro-apoptotic and anti-apoptotic proteins. Specifically, it can downregulate the expression of pro-apoptotic proteins like caspase-3 and Bax, while upregulating anti-apoptotic proteins like Bcl-2 (Li et al., 2017). VPA is also capable of suppressing caspase activation, crucial mediators of the apoptotic cascade, and inhibiting DNA fragmentation, a hallmark of apoptosis (Jürgensmeier et al., 1998).

In animal models of epilepsy, including those involving status epilepticus (SE) and other seizure-inducing paradigms, VPA treatment has been associated with decreased neuronal death, especially in vulnerable brain regions such as the hippocampus (Kuruba et al., 2008). VPA generally reduces neuronal apoptosis in epilepsy models, but some non-epilepsy cell systems show pro-apoptotic effects. Table 1 summarizes the effect of VPA on the preclinical apoptosis model.

**Table 1: VPA apoptosis effects on pre-clinical apoptosis model**

| Model | Effect of VPA on Apoptosis | Main Apoptosis Markers | Mechanism | References |
|---|---|---|---|---|
| Kainic acid rat epilepsy | Decreased neuronal apoptosis | Fewer TUNEL-positive cells, lower caspase-3 activity, lower Bax, and higher Bcl-2 | Enhanced PKC-dependent GABAAR γ2 Ser327 phosphorylation | Li et al., 2018 |
| KA or Mg2+-free neurons in vitro | Suppressed apoptosis and improved survival | CCK8 viability, PI/Annexin V staining | PKC inhibition abolished protection | Li et al., 2018 |
| PTZ seizure model | Reduced neuronal apoptosis | Lower apoptosis with lower GRP78 and CHOP | Inhibition of ER stress | Fu et al., 2019 |
| PTZ + VPA + 4-PBA | The combination further inhibited apoptosis markers | Lower caspase-3 and caspase-12 | Added ER-stress attenuation with 4-PBA | Rzayev et al., 2022 |
| Juvenile epileptic rats | Lower hippocampal neuronal apoptosis | TUNEL in the Hippocampus | Possible STXBP1-related effect | Guihai et al., 2025 |



## 6. Clinical Studies on the Neuroprotective Effects of VPA in Epilepsy

While preclinical studies provide strong evidence for the neuroprotective potential of VPA, clinical studies in humans with epilepsy have been more limited. However, some clinical evidence suggests that VPA may have neuroprotective effects in various conditions.

### 6.1 Clinical Efficacy of VPA in Epilepsy

While preclinical studies provide strong evidence for the neuroprotective potential of VPA, clinical investigations in humans with epilepsy have been more limited. Nevertheless, existing clinical data suggest that VPA may exert neuroprotective effects in several epileptic conditions.

VPA is one of the most effective and widely used AEDs, with a broad spectrum of action. Observational studies and randomized controlled trials have consistently demonstrated its efficacy in treating both focal and generalized seizures, as well as various epileptic syndromes, particularly in the pediatric population (Glauser et al., 2017). VPA's unique efficacy across nearly all seizure types distinguishes it from many other AEDs. However, its clinical effectiveness may vary depending on the specific subtype of epilepsy.

Numerous clinical studies, dating back to the late 1960s and early 1970s, have confirmed VPA's ability to lower the prevalence of both focal and generalized seizures. In patients with typical and atypical absence seizures, both in childhood and adulthood, many clinical trials have repeatedly shown that VPA achieves seizure control comparable to other AEDs (Maheshwari et al., 1992; Villarreal et al., 1978; Braathen et al., 1988; Davis et al., 1994).

A recent study (Glauser et al., 2013) showed that initial monotherapy with VPA resulted in effective seizure control, or even seizure freedom, without intolerable side effects in children with newly diagnosed or untreated absence seizures. While ethosuximide (ESM) and VPA carry a Level A recommendation as initial monotherapy in this population, lamotrigine (LTG) holds a Level C recommendation. In contrast, levetiracetam (LEV) cannot be recommended yet due to insufficient and conflicting evidence from a single phase III placebo-controlled trial (Hwang et al., 2012).

A recent systematic review aimed to evaluate the comparative efficacy of ESM, VPA, and LTG in treating absence seizures in children and adolescents, drawing from drug-versus-drug and placebo-controlled trials (Brigo and Igwe, 2017). Despite the relatively high prevalence of absence seizures in children, only eight randomized controlled trials (RCTs) were identified (Basu et al., 2017), seven of which included small sample sizes (20 and 48 participants), and only one trial involved a larger cohort (Glauser et al., 2013).

That larger trial was a parallel, double-blind, randomized study comparing ESM, LTG, and VPA in children with newly diagnosed absence epilepsy. It found that ESM or VPA produced significantly higher seizure-free rates than LTG. While LTG showed some efficacy over placebo, ESM was preferred over VPA due to its more favorable adverse effect profile. Nonetheless, when generalized tonic-clonic seizures co-occur with absence seizures, VPA is the preferred treatment (Glauser et al., 2013).

In 1982, Turnbull and colleagues (Turnbull et al., 1982) found that phenytoin (PHT) and VPA were effective in controlling primary generalized tonic-clonic (PGTC) seizures and focal seizures, though less so for the latter. Several studies confirmed these findings, showing that therapeutic doses of VPA achieved effective seizure control (Callaghan et al., 1985). The different clinical applications of valproic acid (VPA), along with the corresponding levels of evidence supporting its therapeutic use, are summarized in Table 2. The table highlights the available evidence and demonstrates that the strength of support varies among different applications.

In 1982, Turnbull and colleagues (Turnbull et al., 1982) found that phenytoin (PHT) and VPA were effective in controlling primary generalized tonic-clonic (PGTC) seizures and focal seizures, though less so for the latter. Several studies confirmed these findings, showing that therapeutic doses of VPA achieved effective seizure control (Marson et al., 2007).

**Table 2: Valproic Acid: Clinical Spectrum and Evidence**

| Aspect | Inference / Findings |
|---|---|
| **Spectrum of Efficacy** | VPA is a broad-spectrum AED effective against both focal and generalized seizures, with proven benefit across multiple epilepsy syndromes in children and adults [Glauser et al., 2013a]. |
| **Pediatric Use** | Strong efficacy in childhood absence seizures; both VPA and ethosuximide (ESM) hold a Level A recommendation as first-line monotherapy [Glauser et al., 2013b; Brigo and Igwe, 2017]. |
| **Comparison with Other AEDs** | VPA is superior to lamotrigine (LTG) in absence seizures. While ESM is preferred for pure absence epilepsy due to fewer side effects, VPA is favored when absence seizures coexist with generalized tonic–clonic seizures [Glauser et al., 2013b; Brigo and Igwe, 2017; Basu et al., 2017]. |
| **Monotherapy** | VPA monotherapy achieves seizure freedom without intolerable adverse effects in many newly diagnosed or untreated children with absence seizures [Glauser et al., 2013b]. |
| **Controlled Trials** | In a large RCT (n=453), VPA and ESM produced significantly higher seizure-free rates compared to LTG in childhood absence epilepsy [Glauser et al., 2013b; Basu et al., 2017]. |
| **Generalized Tonic–Clonic Seizures (PGTC)** | VPA shows robust efficacy in controlling PGTC seizures, supported by early studies (Turnbull et al., 1982) and subsequent confirmatory trials [Turnbull et al., 1982; Callaghan et al., 1985]. |
| **Complex Partial Seizures (CPS) and SGTC** | VPA demonstrates comparable efficacy to carbamazepine (CBZ) in adults with CPS and secondarily generalized tonic–clonic seizures [Mattson et al., 1992]. |
| **SANAD Study Conclusion** | The SANAD trial (UK) identified VPA as the preferred first-line therapy for idiopathic generalized and unclassified epilepsy, outperforming LTG and topiramate (TPM) in efficacy and tolerability [Marson et al., 2007]. |
| **Status Epilepticus (SE)** | Intravenous VPA is effective for both convulsive and non-convulsive SE in infants and children, with fewer adverse effects compared to sedatives such as benzodiazepines [Maheshwari and Jeavons, 1975]. |
| **Refractory Focal Epilepsy** | VPA demonstrates efficacy in difficult-to-treat focal epilepsy, including cases resistant to other AEDs [Beydoun et al., 1997]. |
| **Photosensitivity-Associated Epilepsies** | VPA is considered first-line therapy for photic-induced seizures, with seizure freedom reported in up to 85% of patients [Covanis et al., 2004]. |
| **Rare Syndromes Treated** | VPA has demonstrated effectiveness in syndromes such as Dravet, Lennox–Gastaut, West syndrome, myoclonic epilepsy, and other photosensitivity-related epilepsies [Guerrini and Genton, 2004 ]. |
| **Non-Epileptic Indications** | Beyond epilepsy, VPA is FDA/EMA-approved for bipolar disorder and migraine prevention. Its epigenetic properties further support its investigation as a therapeutic candidate in cancer and Alzheimer's disease [Romoli et al., 2019]. |



The 2007 SANAD (Standard and New Antiepileptic Drugs) trial, a large UK-based unblinded RCT, compared the effectiveness and tolerability of VPA, LTG, and TPM in patients with

generalized and unclassified epilepsy. Consistent with earlier research, SANAD concluded that VPA should remain the first-line treatment for idiopathic generalized epilepsy and unclassifiable seizures due to its superior efficacy and tolerability. LTG and TPM, in comparison, were less effective and less well tolerated (Mattson et al., 1992).

However, SANAD was later critiqued for its non-prescriptive dosing approach and lack of blinding, which may have influenced treatment retention outcomes. Still, the trial offered valuable insights into the long-term efficacy of VPA, which is especially important in chronic conditions like epilepsy.

In adults with complex partial seizures (CPS) or secondarily generalized tonic-clonic seizures (SGTC), a multicenter double-blind trial comparing VPA with carbamazepine (CBZ) found that both drugs had similar efficacy, although CBZ may offer slightly better control of CPS (Mattson et al. 1992). Nevertheless, VPA remains a strong candidate for first-line treatment in generalized-onset seizures and has also shown efficacy in managing refractory focal epilepsy (Beydoun et al., 1997).

More recently, intravenous (IV) VPA has been reported to be effective in treating both convulsive and non-convulsive SE, especially in young infants (Maheshwari and Jeavons, 1975). Unlike other sedative options, which may cause hypotension or respiratory depression, IV VPA provides a safer alternative. However, conclusions on its efficacy remain tentative in SE due to the limited number and quality of relevant studies. More high-quality RCTs are needed to evaluate VPA's role in SE compared to other AEDs.

VPA has also proven effective in rare and complex epilepsy syndromes, including myoclonic or myoclonic-astatic seizures, idiopathic generalized epilepsies, photosensitive generalized tonic-clonic seizures, West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome (Guerrini and Genton, 2004). For patients with high photosensitivity, VPA has been particularly

useful, with some evidence suggesting that 85% of patients achieve seizure freedom on VPA. It has been recommended that VPA is a first-line treatment for photosensitivity-associated epilepsies (Covanis et al., 2004).

Beyond epilepsy, VPA has garnered interest for its therapeutic potential in other neurological and psychiatric conditions, owing to its multiple mechanisms of action. It has been approved by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the migraine prophylaxis and treatment of bipolar disorder. Because of its epigenetic effects, VPA is also being investigated for potential roles in cancer therapy and Alzheimer's disease (Romoli et al., 2019).

## 7. Conclusion

Beyond its proven anticonvulsant effects, VPA exhibits a range of neuroprotective properties through its multifaceted mechanisms of action. Preclinical research has consistently demonstrated that VPA supports neurogenesis and synaptic plasticity and protects against oxidative stress, excitotoxicity, inflammation, and apoptosis across various epilepsy models. Although clinical evidence remains limited, emerging studies suggest potential neuroprotective effects of VPA in specific contexts, such as SE and the prevention of epileptogenesis following brain injury. Further well-designed, large-scale clinical trials are needed to fully elucidate and validate these effects in human populations, especially those with epilepsy.



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**Author Contributions:**

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**Abbreviation**

VPA- Valproic acid

AED- Anti epileptic drug

TLE- Temporal Lobe Epilepsy

HDAC- histone deacetylases

GABA- γ-aminobutyric acid

TPM- topiramate

LTG- lamotrigine

PHT- phenytoin

ADHD- attention-deficit/hyperactivity disorder

SSD- succinic semialdehyde dehydrogenase

ERK-extracellular signal-regulated kinase

MEK- mitogen-activated protein kinase

BDNF-brain-derived neurotrophic factor

Bcl-2- B-cell lymphoma/leukemia-2

PKC- protein kinase C

NSAIDs- non-steroidal anti-inflammatory drugs

BDNF-Brain-Derived Neurotrophic Factor

GR-glutathione reductase

CAT- catalase

GPx- glutathione peroxidase

SOD- superoxide dismutase

GSH- reduced glutathione

ROS- reactive oxygen species

NO- nitric oxide

RNS- reactive nitrogen species

NKA- $Na^+/K^+$-ATPase

PIC- Pro-inflammatory cytokines

IL-1β -interleukin-1β

TNF-α- Tumor necrosis factor-alpha

IL-6- interleukin-6

CNS- central nervous system

BBB- blood-brain barrier

NF-κB- nuclear factor kappa B

MPO- Myeloperoxidase

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