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A Review on Molecular Mechanism of Antiepileptic Drugs

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Abstract

This review paper delves into epilepsy and molecular mechanisms of selected AEDs (anti-epileptic drugs): CBZ (Carbamazepine), VPA (Valproate), PHT (Phenytoin), Topiramate (TPM), Lamotrigine (LTG), and Levetiracetam (LEV). Epilepsy is a neurological disorder categorized by recurrent seizures, which can affect the mental, psychological, and social well-being of an individual. Carbamazepine, an imino-dibenzyl derivative, acts by blocking voltage-gated sodium channels, modulating neuronal firing frequency, and inhibiting high-frequency firing. Phenytoin, a barbiturate derivative, inhibits collagenase activity and influences sodium and calcium fluxes. Valproate, a simple branched-chain fatty acid, exerts its effects on GABA and inhibitory neurotransmission, excitatory neurotransmission, monoamines, ion channels, and cerebral glucose metabolism. Topiramate, a broad-spectrum anti-epileptic drug, functions by blocking voltage-gated Ca2+ and Na+ channels, enhancing GABA-mediated neurotransmission, inhibiting glutamate-mediated neurotransmission, and inhibiting carbonic anhydrase isoenzymes. Lamotrigine, a phenyl-triazine compound that is chemically distinct from existing antiepileptic drugs (AEDs), inhibits voltage-gated sodium and calcium channels, thereby demonstrating antiseizure activity. Levetiracetam, another broad-spectrum AED, shows efficacy and tolerability superior to other AEDs, particularly in managing seizures and treating juvenile myoclonic epilepsy. It operates through a distinct mechanism by interacting with synaptic vesicle protein 2A (SV2A), setting it apart as a second-generation anticonvulsant. Therefore, understanding the molecular mechanisms of AEDs is essential for managing epilepsy effectively, improving seizure control, and enhancing living standards. This can also drive clinical advancements with the perspective of avoiding the adverse effects of AEDs. With a diverse range of AEDs available, there is hope for individuals having epilepsy to accomplish a satisfying quality of life.

Keywords: Molecular Mechanism AND (Antiepileptic Drugs OR Anticonvulsant Drugs OR AEDs) AND (Carbamazepine OR CBZ) AND (Phenytoin OR PHT) AND (Valporic acid OR Valproate OR VPA) AND (Topiramate OR TPM) AND (Lamotrigine OR LTG) AND (Levetiracetam OR LEV).

1. Introduction

Recurrent seizures characterize Epilepsy as a chronic neurological disorder, which impacts a substantial number of individuals globally. A seizure in epilepsy is a temporary manifestation which is triggered by unusual and heightened brain activity. This disorder is characterized by a persistent inclination to undergo such seizures over an extended period, accompanied by numerous neurological, mental, psychological, and social effects (1,2). Epilepsy is recognized as a widespread neurological disorder that impacts people of various ages, ethnic backgrounds, socioeconomic statuses, and geographical regions. It primarily

influences the brain and shows a consistent tendency to trigger seizures. These seizures manifest as repetitive alterations in behavior, providing insight into the neural mechanisms at the core of the condition (2,3). Epilepsy being a prevalent neurological disorder, is primarily treated with antiepileptic drugs (AEDs). The modern era of epilepsy treatment began with the initial usage of potassium bromide as an anticonvulsant by Sir Charles Locock in 1857. Early in the 20th century, drugs like phenobarbital, PHT, primidone, and ethosuximide were introduced as mainstays for treating epilepsy. Since the 1990s, the pharmaceutical landscape has seen the development of over 10 new types of AEDs, resulting in a current total of 28 such drugs actively used in clinical practice validated by the U.S. FDA (4,5,6). The first-generation AEDs, like valproate, phenobarbital, carbamazepine, primidone, ethosuximide, and PHT, were initially included in clinical practice due to their widespread utilization. These first-generation AEDs were categorized in the time frame of 1912 to 1978 (7,8,9). Most of the AEDs currently in use were developed and launched in 1990, and categorized as second and third-generation medications. The third-generation AEDs were released in 2008, while the second-generation AEDs were made available beginning in 1989 and distributed over 15 years. This group of medications includes Rufinamide, Eslicarbazepine acetate, Clobazam, Tiagabine hydrochloride, Ezogabine/Retigabine, Gabapentin, Oxcarbazepine, Felbamate, Zonisamide, Lacosamide, Pregabalin, Lamotrigine, Perampanel, Topiramate, Levetiracetam and Vigabatrin (8,9,10). Phenobarbital, which was identified in 1912 as one of the earliest substances for treating epilepsy, continues to be the oldest widely used antiepileptic medication. Over time, various AEDs have been created, but only a limited number have achieved widespread adoption. The predominant treatment for epilepsy involves just four medications; phenobarbital, phenytoin, carbamazepine, and valproic acid, which are estimated to be prescribed to most epilepsy patients (11). AEDs continue to be the most prescribed centrally active agents for managing epilepsy. Despite a limited understanding of the molecular actions of AEDs, recent research suggests that these drugs generally operate through multiple mechanisms. The therapeutic effectiveness of AEDs is influenced by the extent to which each mechanism contributes, which can differ depending on the particular medical condition being addressed. Earlier the treatment approach for epilepsy and other conditions involving AEDs did not rely on a mechanism-based strategy due to incomplete knowledge of how these drugs interact with underlying disease processes (9). Epilepsy treatment has indeed evolved over the years, and AEDs play a crucial role in managing seizures. Although noteworthy progress has been made in finding specific mechanisms, it is crucial to acknowledge the present limitations as well. The fundamental mechanism of AEDs involves the inhibition of voltage-dependent sodium channels. For example, CBZ (carbamazepine) as well as PHT primarily act by blocking voltage-dependent sodium channels (12,13).

2. Methods

A comprehensive search was carried out in the following databases: Google Scholar (https://scholar.google.com/), Science Direct (https://www.sciencedirect.com/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/). The reference sources were chosen based on the following keywords, either individually or in various combinations: “molecular mechanism”, “antiepileptic drugs”, “anticonvulsant drugs”, “AEDs”, “Carbamazepine”, “CBZ”, “Phenytoin”, “PHT”, “Valporic acid”, “Valproate”, “VPA”, “Topiramate”, TPM”, “Lamotrigine”, “LTG”, “Levetiracetam”, and “LEV”. A total of 43 reference sources, spanning from 1985 to January 2024, were utilized. The count of articles organized by their year of publication is provided below.: 1980, 1984, 1995, 1996, 1997 (2), 1999, 2000

(2), 2002, 2003, 2004, 2005 (3), 2007, 2008, 2009 (2), 2010, 2011 (2), 2013, 2014 (3), 2015 (3), 2016 (3), 2017, 2018 (2), 2019, 2020 (2), 2021, 2022 (3) and 2024.

3. Carbamazepine (CBZ)

Carbamazepine ($C_{15}H_{12}N_2O$) an iminodibenzyl derivative, has emerged as among the most commonly prescribed AEDs since its introduction in 1965. This tricyclic compound is chemically known as 5H-Dibenzo[b,f]azepine-5-carboxamide & shares structural similarity to the tricyclic antidepressants. Carbamazepine is effective in treating focal epilepsy, whether or not it is accompanied by Secondary GTCS (Generalized Tonic-Clonic Seizure) (14). The drug was discovered in Basel, Switzerland by Walter Schindler during the development of Imipramine in 1953. CBZ was originally introduced as a treatment for Trigeminal Neuralgia (previously known as Douloureux) in 1962 under the brand name Tegretol®. It subsequently gained acknowledgment as an antiepileptic and anticonvulsant in the UK beginning in 1965 and later obtained authorization for use in the U.S. in 1974. Although carbamazepine is primarily employed for the epilepsy treatment, it is also prescribed for other disorders, including schizophrenia, neuromyotonia disorder, Trigeminal Neuralgia, PTSD (Post-Traumatic Stress Disorder), phantom limb syndrome, paroxysmal extreme pain disorder, and borderline. It also functions both as an anticonvulsant and a mood-stabilizing medication (15). In general, carbamazepine stands out as the most efficient drug for treating partial seizures, although some of the newer AEDs have shown comparable effectiveness. Other AEDs are typically reserved for cases where carbamazepine proves ineffective due to adverse reactions or ineffectiveness (11,14,15).

3.1 Molecular Mechanism of Carbamazepine (CBZ)

Two proposals have been made regarding the mechanisms of action for carbamazepine:
1) Increasing sodium channel inactivation lowers high-frequency repeated action potential firing and 2) Block L-type Ca^{2+} channel (9,11,17). Carbamazepine (CBZ) exerts its effects on cortical neurons by suppressing the persistent and repetitive high-frequency firing. This is achieved by the blockage of voltage-gated sodium channels, likely depending on the frequency of neuronal firing. Carbamazepine primarily inhibits high-frequency firing but has little effect on low-frequency firing. Additionally, carbamazepine may impact neuronal firing by inhibiting L-type calcium channels and modulating neurotransmission (11,14). Carbamazepine reduces the frequency of high-frequency rhythmic action potentials, increases GABA (inhibitory neurotransmitter) levels, and decreases glutamate (excitatory neurotransmitter) levels. CBZ affects neuronal excitability and enhances inhibition by modifying the conductance of Na+, K+, or Ca++ ions, as well as by influencing GABA, glutamate, and other neurotransmitters associated with seizure activity. It binds to inactivated Na+ channels, slowing their recovery from inactivation, and reduces Ca++ entry into synaptic membranes, suppressing synaptic function. However, this reduction in synaptic potentiation occurs at supratherapeutic levels of CBZ. At elevated concentrations, CBZ inhibits catecholamine uptake and, due to its similarity to tricyclic antidepressants, blocks biogenic amine reuptake. Furthermore, CBZ interacts with A1 and A2 adenosine receptors, acting as an antagonist that may increase neuronal excitability by interfering with adenosine's inhibitory effects on neuronal activity and neurotransmitter release (15). Similar to other tricyclic compounds, CBZ demonstrates a mild anticholinergic effect, which contributes to some of the adverse reactions linked to its use (14).

3.2 Side-effects of Carbamazepine (CBZ)

Central nervous system-related adverse reactions are typically dose-dependent, appearing at the start of

treatment but are mostly reversible. Gradual dosage increases after initiation can help mitigate these reactions (14). When carbamazepine is administered in therapeutic doses, it can result in acute toxicity, impacting both the CNS and gastrointestinal system (16). Common adverse effects of carbamazepine include nausea, sedation, weight gain, diplopia, vomiting, ataxia, dizziness, blurred vision, loss of balance, and hyponatremia. (16,17). It also encompasses hypothyroidism, low white blood cell counts, and the exacerbation of GTCS in individuals who experience absence seizures. Additional considerations and drug-drug interactions (DDIs) related to carbamazepine include its induction of CYP1A2, 2B6, 2C9/19, and 3A4. This induction can increase the metabolism of estrogenic and progestogenic components in oral contraceptives (OCs), potentially diminishing their effectiveness in preventing pregnancy. In cases of liver dysfunction, it is important to monitor carbamazepine levels to ensure it remains at a safe and effective level (17). Severe skin reactions are important idiosyncratic side effects of carbamazepine, such as Toxic Epidermal Necrolysis & Stevens-Johnson Syndrome. These reactions occur in 1 to 6 cases per 10,000 people, primarily in Caucasian populations, with an increased risk in certain Asian countries linked to the HLA-B*1502 gene (16).

4. Phenytoin (PHT)

Phenytoin ($C_{15}H_{12}N_2O_2$) a barbiturate derivative emerged as a promising Antiepileptic Drug (AED) due to its ability to effectively control seizures without causing sedation or significant side effects (18). Its chemical name is 5,5-diphenylimidazolidine-2,4-dione. PHT is most effective for treating focal epilepsy and Secondary Generalized Tonic-Clonic Seizure (GTCS) (14). PHT was initially synthesized in 1908 by Professor Heinrich Biltz in Germany as a barbiturate derivative. In 1923, organic chemists Dox and Thomas advanced its development at the Parke-Davis laboratories in Detroit, USA. Despite the lack of hypnotic activity observed by the latter, the compound was disregarded until it was reconsidered by Putnam and Merritt in 1936. The compound was officially introduced for clinical use as an anticonvulsant in 1938, marketed under the brand names Dilantin® in the United States and Epanutin® in Great Britain. This discovery, marking a crucial advancement in the history of drug development and epilepsy treatment, showcased one of the earliest rational approaches to drug discovery worldwide, employing an electroshock animal model of seizures (18,19). PHT's structure incorporates 2 phenyl rings at the position of C5, a hydantoin molecule, as well as it is this configuration that accounts for PHT's effectiveness as a non-sedative anticonvulsant (18). In 1936, an animal model for epilepsy was introduced by Putnam and Merritt, who utilized electro-convulsions in cats to systematically evaluate numerous barbiturate derivatives. They first demonstrated PHT’s strong anticonvulsant properties in these animal models and later confirmed its effectiveness in several patients. While their clinical findings were published, they chose not to file a patent for PHT's use in epilepsy, a decision that Putnam later regretted (19).

4.1 Molecular Mechanism of Phenytoin

Early discussions on PHT's mechanism of action focused solely on its anticonvulsant effects, ignoring other potential effects. The discovery of gingival hyperplasia as a side effect revealed PHT's multiple modes of action. This led to research in dermatology, where PHT was investigated for its potential to aid in treating ulcers, wound healing, epidermolysis bullosa, and various inflammatory skin conditions. In this context, it was found that PHT's mechanism of action involved inhibiting collagenase, a previously unrecognized molecular target. This characteristic clarified its therapeutic benefits in conditions associated with excessive collagen production, including epidermolysis bullosa and morphea (19,20). During the late 1970s and 1980s, sodium channels were recognized as targets because of PHT's anticonvulsant and

antiarrhythmic properties (21). The 1985 edition of Goodman and Gillman's, 'The Pharmacological Basis of Therapeutics', did not mention sodium channels in its discussion of PHT's mode of action. Instead, it linked PHT's mechanism to stabilizing neuronal membranes by affecting sodium and calcium fluxes, effects rarely observed at therapeutic concentrations, leaving the clinical mechanism unclear. Challenges in studying PHT included receptor-level concentrations and limited concentration-effect studies. Recent literature identifies PHT as a strong voltage-gated sodium channel blocker, but its micromolar affinity is generally considered insufficient for pharmaceutical development, which favours nanomolar-range affinities (19). While certain studies have investigated how PHT derivatives bind to specific receptors, like alpha-adrenergic receptors, comprehensive research on PHT's overall binding affinities to various channels and receptors is lacking. Existing research on PHT's binding affinities for specific targets has been sporadic in the literature, with new targets emerging over time. For instance, it was discovered in 2015 that PHT, at therapeutic levels, strongly binds to the estrogen alpha receptor. Although moderate-affinity binding sites in the brain have been identified within the micromolar range, they are poorly characterized and are not GABAergic (18,19,22).

4.2 Side-effects of Phenytoin

The primary adverse effects of PHT include hypersensitivity reactions encompassing conditions like Stevens-Johnson syndrome and Lyell's syndrome, dose-dependent symptoms like ataxia, drowsiness, and encephalopathy, and long-term issues such as gingival hyperplasia and hirsutism. It can also cause hematological and neurological problems like peripheral neuropathy and impact cognitive function, comparable to carbamazepine but better than phenobarbitone (14). Gingival hyperplasia, hypertrichosis, rash, lymphadenopathy, hepatotoxicity, pseudo-lymphoma, decreased platelets, osteoporosis, low WBC count, pancytopenia, low vitamin D, dysarthria, cognitive slowness, and porphyrogenic are some other side effects. Other considerations and drug-drug interactions (DDIs) with PHT include its contraindication for intramuscular administration and intravenous use in non-saline diluents or at rates exceeding 50 mg/min, due to risks of hypotension and bradyarrhythmia. PHT interacts differently with phenobarbital and valproate. Additionally, PHT metabolizes medications such as Topiramate, Carbamazepine, Lamotrigine, Felbamate, Oxcarbazepine, and others (17). PHT interferes with the cerebellar-vestibular system, which may cause signs of ataxia, vertigo, diplopia, and nystagmus. In some cases, patients may also suffer from drowsiness, mydriasis, lethargy, sedation, and encephalopathy. If the administration of PHT is suddenly halted, it renders the CNS vulnerable to the onset of hyperexcitability, with the most severe consequence being the occurrence of status epilepticus. It's worth noting that PHT is also a valuable therapeutic agent used in treating cardiac arrhythmias (18).

5. Valproate (VPA)

Valproate ($C_8H_{15}O_2$) is an AED commonly used to treat various types of seizures. Valproate (2-propylpentanoate) is a saturated fatty acid anion with a branched chain, which is a conjugate base of valproic acid, making it structurally unrelated to any other AEDs. Known by its brand names, such as Depakote®, Depakene®, and divalproex sodium, valproate has emerged as a cornerstone in the management of epilepsy. Valproate is effective for partial seizures (with or without secondary generalization), myoclonic, absences, generalized tonic-clonic, and acutely in status epilepticus (23). In 1882, Valproic acid had been first synthesized, by Beverly S. as a valeric acid derivative, Burton extracted from the Valeriana officinalis (24). Valproate's journey in the field of epilepsy began when it was initially introduced for the therapy of manic episodes in bipolar disorder. However, its anticonvulsant properties

were discovered only in 1963 by Pierre Eymard in France, leading to its adoption as a primary therapy for epilepsy, in France in 1967, followed by the U.K. in 1972 and the U.S. in 1978 (25). Before its antiepileptic properties were discovered, valproic acid had been employed as an organic solvent. (14). Beyond epilepsy, valproate over the years has found utility as a mood stabilizer for bipolar disorder, migraine prophylaxis, and certain neuropsychiatric conditions due to its anti-manic properties. Uniquely, it has a broad antiepileptic spectrum (23). Valproate exerts effects by inhibiting HDAC (histone deacetylase), enabling specific modulation of gene expression. Growing evidence suggests that HDAC inhibitors may help treat CNS disorders. Valproate is particularly promising due to its ability to penetrate the brain, clinical availability, and extensive testing. Its efficacy in both adults and children makes it a versatile treatment option for a broad range of patients (25).

5.1 Molecular Mechanism of Valproate

Earlier, it was believed that the antiepileptic effects of VPA resulted from multiple actions in the central nervous system, given its broad effectiveness against various seizure types and status epilepticus (26). Despite valproate's extensive usage over numerous years, its exact mechanism for preventing epileptic seizures remains unclear. However, it is believed to work through various mechanisms, with one key action being the elevation of GABA levels, the brain's inhibitory neurotransmitter. Additionally, valproate may affect ion channels and block certain enzymes, contributing to its broad effectiveness against epilepsy (24, 25, 27).

5.1.1 Inhibition of voltage-gated sodium channels

VPA reduces neuronal activity and firing rate by inhibiting the influx of sodium ions into neurons. This impedes the generation and dissemination of anomalous electrical impulses that induce seizures (23, 27).

5.1.2 Inhibition of gamma-aminobutyric acid (GABA) transaminase

VPA suppress the GABA transaminase enzyme, that degrades GABA, the principal inhibitory neurotransmitter in the brain. This technique enhances neuronal inhibition and reduces susceptibility to seizures by elevating GABA activity and levels. VPA has been described to diminish neurogenic inflammation in neuropathic pain via GABA-A receptor-mediated regulation (23,27).

5.1.3 Enhancement of GABA synthesis

VPA enhances the expression and action of GAD (glutamic acid decarboxylase), the enzyme that converts glutamate into GABA, hence promoting GABA production. This leads to increased GABA action and levels. GABA has been synthesized from α-ketoglutarate via tricarboxylic acid cycle (TCA cycle) and then transformed into succinate semialdehyde. VPA inhibits succinate semialdehyde dehydrogenase and GABA transaminase, reducing GABA degradation and further elevating its levels (23,26,27).

5.1.4 Inhibition of HDACs

VPA inhibits HDAC enzymes, especially HDAC1, altering histone acetylation and influencing gene expression. These chromatin changes affect gene transcription related to neural plasticity, neurogenesis, synaptic transmission, inflammation, and neuroprotection. Such mechanisms may explain VPA's long-term effects on cognition, mood, neurodevelopment, and its potential anticancer and pro-apoptotic properties (25,27).

5.1.5 Modulation of calcium channels

VPA regulates T-type, L-type, and N-type Ca2+ channels, crucial for brain communication, neurotransmitter secretion, gene expression, and cellular viability. VPA’s effects on Ca^{2+} channels are complex, depending on factors like the channel's subtype, co-expression, location, and interactions with

other proteins. While some research implies that VPA enhances L-type calcium channels linked to neuronal plasticity and neuroprotection, others argue that it inhibits T-type Ca^{2+} channels involved in absences seizures. VPA may also affect N-type Ca^{2+} channels associated with migraine and neuropathic pain (23,27).

5.2 Side-effects of Valproate

Thrombocytopenia, hypothermia, coagulopathy, ataxia, alopecia, asthenia, constipation, depression, dizziness, diarrhea, diplopia, dyspnea, emotional instability, anxiety, rash, infection, nystagmus, insomnia, edema, pharyngitis, fever, sedation, abnormal thinking, tinnitus, tremor, and weight gain are among the common side effects of VPA. Hematological, neurological, and gastrointestinal issues are some of VPA's other side effects. (14, 17, 27). VPA has a broad range of adverse effects, particularly in certain patient groups, during polytherapy, and long-term use. Of particular concern is its potential to cause congenital malformations if used during pregnancy, necessitating careful risk-benefit evaluation in women of childbearing potential. Regular monitoring is essential to manage side effects, maintain therapeutic blood levels, and monitor liver function due to risks like hepatotoxicity and pancreatitis. VPA's hepatic metabolism and impact on drug-metabolizing enzymes require careful consideration of co-administered medications to prevent interactions. When combined with enzyme-inducing AEDs (e.g., PHT, phenobarbitone, carbamazepine), VPA doses may need a 30–50% increase, with potential dose reductions upon AED discontinuation (23,25,28). Other considerations and drug-drug interactions (DDI) of valporate; to ensure efficacy and safety of VPA, therapeutic drug monitoring (TDM) is recommended. VPA can prohibit metabolism or affect plasma protein binding (PB) of Clobazam, Diazepam, Ethosuximide, Lamotrigine, and Phenytoin. With rufinamide, start VPA at a lower dose. A combination of topiramate and VPA poses a risk of elevated ammonia levels and encephalopathy (17).

6. Topiramate (TPM)

Topiramate ($C_{12}H_{21}NO_8S$) is a broad-spectrum AED which is efficient in managing epileptic seizures, either as a standalone treatment or in conjunction with other therapies, and for migraine prophylaxis (30). 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate is its chemical name, belonging to the sulfamate-substituted monosaccharides, and entered clinical use in 1995 (14). Topiramate is employed as an additional therapy for partial-onset seizures and primary GTCS, proving to be the most potent among the new AEDs for focal seizures. It is recommended for various seizure types in both adults and children, including difficult-to-treat epileptic encephalopathies like West and Lennox-Gastaut syndromes. Topiramate is approved for preventing migraines in adults and in some cases, in bipolar disorder, it may be utilized as a mood stabilizer (32). Researchers in Johnson & Johnson's pharmaceutical division first synthesized topiramate (TPM or TOPAMAX®) in 1979 as part of a study on fructose-1,6-diphosphate analogs to suppress fructose 1,6-bisphosphatase, thereby preventing gluconeogenesis and potentially act as antidiabetic agents. In late 1979, TPM was tested in the MES (maximal electroshock seizure) test in mice, which showed strong anticonvulsant activity. Subsequent research revealed TPM's long duration of action in mice and rats, with a clear distinction between doses that cause motor impairment and those that are effective as anticonvulsants. TPM’s potency, duration of action, and higher neuroprotective index led to its development as an antiepileptic drug (AED) (31). The initial focus was on sulfamate derivatives of fructose, as their unionized groups could mimic phosphate attachment to the enzyme, enhancing membrane permeability. Topiramate, an AED with a molecular weight of 339, is uniquely structured,

derived from the monosaccharide D-fructose, and possesses a sulfamate group (29,33). Its pharmacodynamic properties, including the essential sulfamate moiety, contribute to both its clinical benefits and observed adverse effects (30).

6.1 Molecular Mechanism of Topiramate

The precise mode of action of topiramate was not entirely understood, but it is thought to include several mechanisms that underlie the antiepileptic effect of TPM. The mechanisms encompass interaction with protein kinase phosphorylation sites, blocking of carbonic anhydrase isoenzymes, augmentation of the GABA-induced response, modulation of voltage-activated Ca2+ channels, along with blockade of voltage-dependent sodium channels and kainate-evoked currents (32, 33).

6.1.1. Voltage-Gated Sodium Channels Inhibition

Voltage-gated Na^{2+} channels have been necessary for the production & transmission of activity potentials in neurons, and topiramate seems to block them. It stabilizes neuronal membranes and lessens the abnormal electrical activity observed in disorders such as epilepsy by inhibiting these channels (31, 32).

6.1.2. Enhancement of GABAergic Activity

In the CNS, GABA is the main inhibitory neurotransmitter. Topiramate is thought to increase the activity of GABA at its receptors. This leads to increased inhibitory effects in the brain, helping to control seizures and reduce excitatory neurotransmission (31,32).

6.1.3. Antagonism of Glutamate Receptors

The primary excitatory neurotransmitter in the brain is glutamate. Certain glutamate receptors, like α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, may be antagonized (blocked) by topiramate. This modulation of glutamate neurotransmission contributes to drug's antiepileptic and neuroprotective effects (31,32).

6.1.4 Carbonic Anhydrase Inhibition

Topiramate inhibits the activity of carbonic anhydrase enzymes. This effect is not fully understood in the context of its antiepileptic action, but it is believed to contribute to the drug's efficacy. Carbonic anhydrase is an enzyme included in different physiological processes, such as acid-base balance (31,32).

6.1.5 Modulation of Voltage-Gated Calcium Channels

Additionally, the medication may alter voltage-gated calcium channels, which are involved in the release of neurotransmitters. Topiramate has antiepileptic and antimigraine properties because it influences calcium channel activity, which in turn influences the secretion of neurotransmitters in the synaptic cleft (31, 32).

6.2. Side effects of Topiramate

Common side effects of this medication include cognitive slowing, difficulty concentrating, tingling sensations (paresthesias), metabolic acidosis, and the formation of kidney stones due to their inhibitory action on carbonic anhydrase. Due to its weight loss association, topiramate is sometimes used off-label for this purpose. Its inhibitory effects on glutamate may cause CNS issues, such as acute cognitive impairment. Nervous system side effects, including tremor, ataxia, and dizziness, are more common than with a placebo, as noted in the TOPAMAX® U.S. Product Insert. Other frequently reported side effects include dry mouth, nausea, constipation, weight loss, speech and cognitive impairment, stomach discomfort, bad taste, and psychiatric effects like anxiety, irritability, depression, mental disorders, and anorexia. Starting with low doses (15–25 mg/day) and gradually increasing to a tolerable and effective

dose helps reduce many dose-related side effects (29,30,31,32,33). Topiramate may interact with other medications, potentially affecting their levels in the body. Individual tolerance to topiramate varies, with some individuals experiencing side effects that limit its use, while others tolerate it well. To minimize side effects, dosing is typically titrated gradually. The appropriate dosage depends on the specific condition being treated (14). Topiramate's drug-drug interactions (DDI) include decreased oral contraceptive (OC) efficacy at doses >200 mg/day—supplementation is advised. In renal failure, administer half (½) the dose after hemodialysis. Carbamazepine and Phenytoin reduce TPM levels. Combining TPM with carbonic anhydrase inhibitors (e.g., Acetazolamide, Zonisamide) increases the risk of kidney stones and metabolic acidosis (MA) (17).

7. Lamotrigine (LTG)

Lamotrigine (LTG), an antiepileptic medication, was first introduced for adjunctive therapy of partial seizures in Europe in 1991 and later in the U.S. in 1994. The US FDA Advisory Committee approved LTG in March 1993 for marketing to address focal (partial) seizures and primary GTCS. In the US, further indications for LTG use in adult monotherapy and Lennox-Gastaut syndrome were approved in 1997 and 1998, respectively (35,36). Lamotrigine ($C_9H_7Cl_2N_5$) was originally synthesized in the 1970s at Wellcome Laboratories (Beckenham, London, UK) as an antifolate analog, lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine) demonstrated potent activity in animal seizure models, prompting its development as an advanced AED option for obstinate patients, offering improved safety and efficacy. This development marked one of the earliest attempts at rational AED development, stemming from observations that many existing AEDs were folic acid antagonists. Notably, despite its origin as an antifolate analog, lamotrigine exhibits minimal folic acid antagonism and maintains potent anticonvulsant activity. Chemically classified as a phenyltriazine, lamotrigine stands out for its distinct chemical structure among existing AEDs. During the development of lamotrigine, a link between the convulsant action of folate and glutamate was suggested, adding an interesting dimension to its pharmacological profile. However, lamotrigine itself does not significantly exhibit folic acid antagonism, distinguishing it from other AEDs developed during the same period (14,35,36).

7.1. Molecular Mechanism of Lamotrigine

By acting on voltage-sensitive Na^{2+} channels, LTG stabilizes presynaptic neuronal membranes as well as regulates the secretion of excitatory neurotransmitters including glutamate and aspartate. Laboratory studies using rat brain tissue have demonstrated LTG's ability to inhibit veratrine-induced release of these neurotransmitters, with lesser effects on GABA or acetylcholine release, and no impact on potassium-induced amino acid release, indicating its presynaptic action at voltage-sensitive sodium channels. Research on mouse nerve cells further suggests that LTG suppresses repetitive sodium-dependent action potentials, underscoring its straight impact on voltage-activated sodium channels. Additionally, LTG might inhibit N- ass well as P-type Ca^{2+}currents in cortical neurons (34). These findings contribute to our understanding of LTG's antiepileptic mechanisms at the synaptic level. Preclinical animal studies have highlighted LTG's broad spectrum of activity against several seizure types, including tonic-clonic seizures, focal seizures, absence seizures, as well as Juvenile Myoclonic Epilepsy. LTG successfully stopped hind limb extension in models like PTZ (pentylenetetrazol) infusion and repeated MES (maximal electroshock) induction in rats as well as mice, demonstrating its effectiveness against focal and tonic-clonic seizures. Higher LTG dosages, however, did not result in an increase in clonus latency in the PTZ test, indicating

that they are not very helpful in preventing absence seizures. However, LTG showed effectiveness in more predictive models of human absence seizures, including lethargic (lh/lh) mouse model and the photically induced after-discharge test in rats. Moreover, LTG reduced electrically induced cortical and hippocampal after-discharge duration in marmosets, rats, and dogs, further supporting its therapeutic potential against focal and dyscognitive seizures (35,36,37).

7.2. Side effects of Lamotrigine

Dizziness, diplopia, ataxia, headache, blurred vision, nausea, hypersensitivity skin rashes, somnolence, and vomiting, including severe responses like SJS (Stevens-Johnson syndrome) (10 percent rash incidence), are among the common side effects of lamotrigine. HLA-B polymorphisms, like HLA-B*15:02, are linked to a higher chance of SCAR (severe cutaneous adverse reactions), SJS or TEN, from lamotrigine, primarily in Asian (Han Chinese) populations ($P < 0.05$). Additionally, one research found that the HLA-B*15:02 allele had been present in 33.3percent of SJS/TEN cases caused by lamotrigine, contrasted to just 9.4percent of lamotrigine-tolerant controls ($P < 0.05$), but the sample size had been modest (38). Aseptic meningitis, dizziness, headache, diplopia, ataxia, nausea, vomiting, sluggishness, and sleeplessness have been reported at high doses. Additionally, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, and eight cases of hemophagocytic lymphohistiocytosis (HLH) have occurred since 1994. Lamotrigine has several drug-drug interactions (DDIs), including with rifampin, oral contraceptives (OCs), and enzyme-inducing antiepileptic drugs (EIAEDs) such as Carbamazepine, Phenobarbital, Phenytoin, Primidone, all of which can decrease LTG levels by over 40%. During pregnancy, LTG levels may decrease by 50-67% and Valporate inhibits LTG metabolism, increasing its concentration by more than two-fold (17).

8. Levetiracetam (LEV)

In 1999, the US FDA authorized LEV [(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide], which is a broad-spectrum anti-epileptic medication. The oral formulation of LEV had been accepted in 1999, by the U.S. FDA as an adjuvant therapy for myoclonic, focal-onset, as well as generalized-onset seizures. In 2000, the EMA (European Medicines Agency) accepted LEV as a monotherapy and adjunct treatment for focal-onset seizures as well as focal to bilateral tonic-clonic seizures, among other seizure types. An intravenous formulation has been approved in 2006 for those unable to take oral medication. Levetiracetam (LEV), a second-generation anticonvulsant, exhibits enhanced efficacy and tolerance relative to existing AEDs. By 2002, it reached a 200,000 patient-year usage milestone and became widely prescribed for partial and generalized epilepsy. LEV, which shares structural similarities with the nootropic drug piracetam, has shown potential in treating neuropathic pain and has been studied for anti-inflammatory and anti-hyperalgesic effects. Among its analogs, brivaracetam (BRIV) has reached the market. Beyond SV2A modulation, several molecular targets have been identified for LEV's effects. LEV has exhibited properties such as preventing seizures, protecting neurons, reducing inflammation, and acting as an antioxidant. Recently recognized as a multitarget drug, LEV addresses various needs in epilepsy and other conditions. It is currently a broad-spectrum pharmaceutical used to treat both focal-onset as well as generalized-onset seizures, either by itself or in combination with other drugs. LEV is effective in treating reflex seizures and juvenile myoclonic epilepsy due to its high and sustained efficacy (14,39,40,42,43).

8.1. Molecular Mechanism of Levetiracetam

A range of evidence points to SV2A modulation as the initial mode of action for LEV. Moreover, additional targets, including, AMPA (Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid) receptors, adenosine, serotonin noradrenaline, receptors, as well as pathways involved in blocking the neuromodulator action on GABA, Ca2+ N-type channels, and intracellular pH regulation, may also play significant roles in the drug's effects (40,41,42,43)

8.1.1. Synaptic Vesicle Protein 2A (SV2A)

SV2A, located in synaptic vesicle membranes, plays a crucial role in synaptic vesicle exocytosis and endocytosis. During exocytosis, SV2A interacts with residual Ca2+, as shown in SV2A/SV2B double knockout (DKO) neurons, which exhibit enhanced synaptic response and subsequent depression, reversible with EGTA, highlighting residual Ca2+'s role. SV2A facilitates vesicle priming, ensuring neurotransmitter release and the maintenance of the readily releasable pool (RRP), influencing SNARE complex formation. In endocytosis, SV2A regulates synaptotagmin (SYT-1) content, with Y46 mutations hindering SV2A-SYT-1 internalization, implicating SV2A in clathrin adaptor interactions and SYT-1 trafficking for Ca2+-stimulated fusion. Levetiracetam may affect SV2A by inhibiting vesicular priming, reducing RRP, or optimizing SV2A function. LEV could enhance SYT-1 modulation and trafficking, restoring normal protein levels in SV2A-overexpressing neurons. LEV interacts with SV2A during vesicle cycling and membrane diffusion. In vitro studies show LEV has membrane permeability despite low lipophilicity. Pharmacokinetic modeling estimates its BBB permeability at 0.015 mL/min/g, supported by PET studies in primates and rodents confirming brain penetration. LEV loading into vesicles reduces Excitatory Postsynaptic Currents, normalized upon unloading, indicating entry and exit during vesicle cycling. In CA1 hippocampal slices, LEV reduces EPSC amplitudes under high- (80 Hz) but not low-frequency (20 Hz) stimulation, demonstrating frequency-dependent effects on vesicular fusion and LEV entry. LEV crosses the Blood-Brain Barrier (BBB), enters brain parenchyma, and interacts with SV2A during vesicle recycling and endocytosis, released during exocytosis (40,42,43).

8.1.2. SV2A and the GABAergic System

All synaptic vesicles contain SV2A, which is strongly associated with the GABAergic system. In rats with the SV2A gene mutation (SV2AL174Q), decreased depolarization-evoked GABA release in the hippocampus and amygdala was observed, without affecting glutamate levels. In a pilocarpine-induced SE model, elevated SV2A expression in the hippocampus was linked to GABAergic, but not glutamatergic ones. SV2A KO and SV2A/SV2B DKO mice showed higher frequency sEPSCs and lower frequency and amplitude of sIPSCs in cultured hippocampal neurons. High SV2A and GABAergic neuron co-expression in the hippocampus and amygdala supports this. Systemic LEV administration decreased hyperalgesia by enhancing GABAergic neurotransmission, while local administration had no effect on the GABA system. The association between SV2A and the GABAergic system is key to understanding LEV's effects, warranting further research (40,42,43). LEV also inhibits Ca^{2+} N-type channels, counters the inhibitory effects of beta-carbolines and zinc on GABA and glycine currents, and reduces calcium release from intracellular stores. Additionally, LEV may hyperpolarize membrane potential by activating K^{+} channels and inhibiting Ca^{2+} influx into cells (41).

8.2. Side effects of Levetiracetam

A clogged nose or itchy throat, headaches, dizziness, hostility, irritability, agitation, and feeling ill (either nausea or vomiting) are some of the usual adverse effects of levetiracetam. These common side effects of

levetiracetam usually occur in 1 out of 10 people. The serious side effects of levetiracetam may include passing very little pee, fits or seizures getting worse, tiredness, confusion, having swollen legs, ankles, or feet (a probable sign of kidney problems), signs of serious mental changes, or signs of confusion, sleepiness, forgetfulness loss of memory, and abnormal behavior or uncontrolled movements. However, it should be mentioned that very few levetiracetam users experience severe side effects (40, 43). Other effects of LEV include restlessness, exhaustion, asthenia, light-headedness, infection, agitation, depression, psychotic symptoms (especially in children), ataxia, anemia, decrease in WBC, decrease in platelets, and elevated diastolic blood pressure in children under 4. Additional risks include suicidal thoughts and actions, SJS, TEN, angioedema, rhabdomyolysis, pancytopenia, and anaphylaxis. Additional factors and levetiracetam drug-drug interactions (DDI) include lowering the dosage in proportion to CrCl in cases of renal insufficiency. 50% is eliminated in 4 hours with hemodialysis (17).

9. Conclusion

The field of antiepileptic therapy and clinical studies in children faces specific challenges that necessitate individualized treatment approaches. Ongoing research is refining the role of AEDs, and exploring their mechanisms, potential indications, and strategies to minimize adverse effects. Healthcare professionals must possess a comprehensive understanding of AEDs pharmacology, clinical applications, and safety profiles for optimal management of epilepsy and related disorders.

Carbamazepine, highly bound to plasma proteins, undergoes complete metabolism with the primary metabolite being CBZ-E (carbamazepine-epoxide). Self-induction of metabolism leads to a rise in clearance, shortened half-life, as well as the need for escalating daily dosages to maintain therapeutic levels. Severe liver dysfunction and cardiac failure can impact its pharmacokinetics. Because of its narrow therapeutic window, clinical management in epilepsy should emphasize therapeutic drug monitoring to mitigate variability in plasma drug concentrations.

PHT, classified as a broad-spectrum ion channel blocker, inhibits multiple sodium and calcium channels. Recent research suggests its anticonvulsant effect may stem from its impact on persistent Na+ current inactivation. Valproate, widely used but posing risks, requires careful consideration, especially in pregnant women. Regular monitoring and a thorough risk-benefit assessment are crucial. Topiramate, with multiple mechanisms of action, is effective in various neurological and psychiatric conditions but requires careful monitoring and personalized evaluation.

Lamotrigine's expanding clinical use reveals unique issues, while levetiracetam stands out as a distinctive anticonvulsant with mechanisms different from classical anticonvulsants, lacking affinity with their targets and operating through routes distinct from low-voltage-activated Ca^{2+} channel modulation, Na^{2+} channel modulation, as well as direct GABA facilitation.

New AEDS, with novel mechanisms, enhance effectiveness and reduce side effects. A broad understanding of these drugs, tailored to seizure types, is crucial for personalized epilepsy treatment. Medical evidence is paramount in guiding treatment, with expert opinion reserved for specific clinical scenarios. In summary, while AEDs remain a cornerstone of epilepsy treatment, a comprehensive approach that considers individual needs, safety, and efficacy is essential for optimal management.

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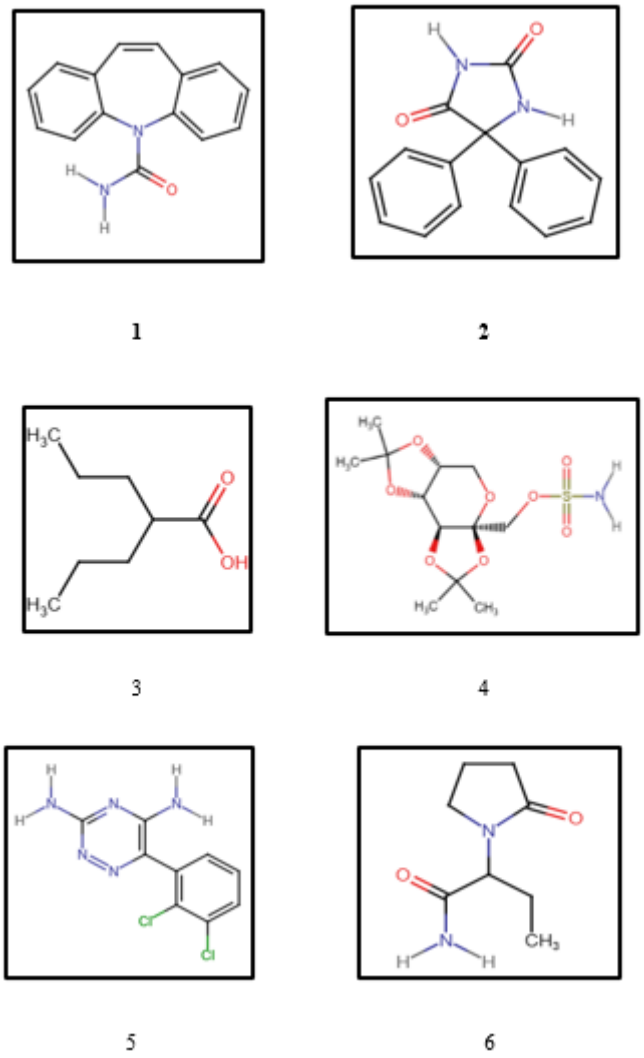

Figure 1: - The chemical structure of; 1). Carbamazepine (CBZ), a tricyclic compound, 2). Phenytoin (PHT), with 2 phenyl rings at C5 of hydantoin molecule, 3). valproate (VPA), a branched short-chain fatty acid, 4). Topiramate (TPM), 5). Lamotrigine (LTG) and 6). Levetiracetam (LEV).

Table 1. AED Clinical Characteristics (7,10,17)

AED	FDA Approved Seizure Type or Syndrome	Starting Dose	Half-Life	Range (mg/L)
Carbamazepine (CBZ)	Partial onset with secondary generalization	400 mg/day	12-35 h	4-12
Phenytoin (PHT)	Partial onset with secondary generalization	Adult: 300 mg/day Children: 5 mg/kg/day Intravenous: 15-20 mg/kg	8-42 h	10-20
Valproate (VPA)	Focal and "absence	250 mg/day 15 mg/kg/day	6-17 h	50-100
Topiramate (TPM)	Partial-onset seizures Primary generalized seizures Lennox-Gastaut Syndrome	Age 2-9: 25mg qPM Age 10+: 25mg BID	20-30 h	5-20
Lamotrigine (LTG)	Focal-onset seizures, primary generalized seizures & Multiple seizure types in Lennox-Gastaut Syndrome	25 mg/day or every 2nd day 50 mg/day with EIAEDs	Alone: 25-38h Enzyme inducer: 12-14h Enzyme inhibitor: 48h - 70h	2 - 20
Levetiracetam (LEV)	Myoclonic" seizures, Focal-onset seizures & Primary generalized seizures	1 - 5 months: 7mg/kg BID; 6 month - <16: 10mg/kg BID; Age 16 +: 500mg/day BID	6-8 h	12-46

Half-Life: Estimated time taken by a drug to reduce its amount or conc. in body by exactly one-half (50%); qPM: Every evening; BID: twice a day; EIAEDs: Enzyme-Inducing AEDs.

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