A Review of Structure–Activity Relationship, Mechanism of Action and Therapeutic Benefits of Selected Newer Antiepileptic Drugs

P. Keerthana[1],K. Kaviyarasan[2], B. Bhavani[3], J.S. Kanishka[4], T. Poovizhi[5]
[1, 2, 3, 4, 5]Dept of Pharmaceutical Chemistry
[1, 2, 3, 4, 5] G. P. pharmacy college, Jolarpettai Tirupattur Dist.

Abstract- *Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. Despite the availability of conventional antiepileptic drugs, treatment limitations such as adverse effects, drug resistance, and drug interactions have prompted the development of newer anticonvulsant agents. Recent advances in medicinal chemistry have led to the discovery of several effective antiepileptic drugs including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. These agents exhibit diverse mechanisms of action and improved safety profiles. This review summarizes the structure–activity relationship (SAR), mechanisms of action, and beneficial therapeutic effects of selected newer antiepileptic drugs. Understanding the relationship between chemical structure and pharmacological activity may facilitate the development of novel anticonvulsants with enhanced efficacy and reduced adverse effects.*

Keywords: Epilepsy, Antiepileptic Drugs, Anticonvulsants, Structure–Activity Relationship, Mechanism of Action, Gabapentin, Lamotrigine, Levetiracetam.

I. INTRODUCTION

Epilepsy is a neurological disorder in which a person has a tendency to experience recurrent, unprovoked seizures. Seizures occur because of sudden, abnormal electrical activity in the brain, which can temporarily affect movement, sensation, behaviour, awareness, or consciousness.[1]

Epilepsy can affect people of all ages and may result from various causes, including genetic factors, brain injuries, infections, stroke, developmental disorders, or sometimes an unknown cause. Not everyone who has a single seizure has epilepsy; the condition is generally diagnosed when a person has had two or more unprovoked seizures or has a high risk of recurrent seizures.[2]

Symptoms vary depending on the type of seizure. Some seizures involve brief staring spells, while others may cause muscle jerking, loss of awareness, or convulsions. Although epilepsy is a chronic condition, many people can control their seizures effectively with medications, lifestyle adjustments, or, in some cases, surgery and other specialized treatments.[3]

With proper diagnosis and management, most individuals with epilepsy can lead active, productive, and fulfilling lives. Epilepsy remains one of the most common neurological disorders worldwide and continues to be an important area of medical research and healthcare.[4]

Epilepsy is one of the most common neurological disorders affecting millions of people worldwide. It is characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. These seizures can vary widely in their presentation, ranging from brief episodes of staring and loss of awareness to severe convulsions involving the entire body. Epilepsy is not a single disease but rather a group of disorders with different causes, symptoms, and outcomes[5]

The brain functions through a complex network of neurons that communicate via electrical and chemical signals. When these signals become disrupted and excessive electrical discharges occur, a seizure may result. If a person experiences repeated seizures without an immediate provoking cause, the condition is generally classified as epilepsy.[6]

Epilepsy affects individuals of all ages, genders, races, and socioeconomic backgrounds.

Although it is often associated with dramatic convulsions, many seizures are subtle and may go unnoticed. The condition can have significant physical, psychological, social, and economic consequences if not properly managed. However, advances in medical science have made it possible

for many people with epilepsy to achieve good seizure control and maintain a high quality of life.[7]

Epilepsy is a common neurological disorder affecting about 1% of the world's population. Biomarkers are measurable indicators that help in the diagnosis, monitoring, and treatment of epilepsy. Reliable biomarkers can identify epileptogenicity (presence of epilepsy) and electrogenesis (development of epilepsy). They help improve diagnosis, select appropriate treatments, assist in presurgical evaluation, and support drug development. Recent advances in electrophysiology, neuroimaging, molecular biology, and genetics are contributing to the discovery of useful biomarkers for epilepsy. These biomarkers may improve patient care and treatment outcomes in the future.[8]

Temporal lobe epilepsy is a type of epilepsy that originates in the temporal lobe of the brain. Epileptic disorders can be idiopathic (genetic, with no brain damage) or symptomatic (caused by a brain lesion or injury). Symptomatic temporal lobe epilepsy includes mesial temporal lobe epilepsy (MTLE), which is associated with hippocampal sclerosis, lesional epilepsy caused by identifiable brain lesions, and cryptogenic epilepsy, where the cause is unknown.

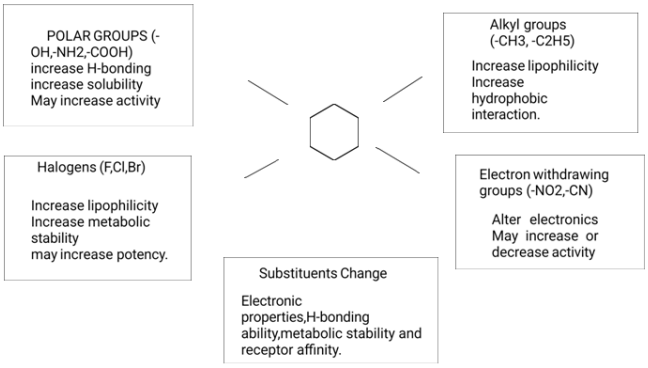
MTLE is one of the most common forms of epilepsy and is widely studied using animal models to understand its mechanisms and develop better treatments. Cryptogenic temporal lobe epilepsy remains difficult to diagnose and requires further research.[9]

In this review, we have introduced the SAR and beneficial effect of the following drugs are gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, by review the article and review article.[10]

GABAPENTIN

Gabapentin has been associated with a number of side-effects in clinical use but is generally well tolerated (Ramsey, 1995). Its pharmacokinetic profile and use in combination with other medications have been described (McLean, 1995). Gabapentin was originally developed as a drug for treating spasticity and reducing polysynaptic spinal reflexes .

SAR OF GABAPENTIN ON CYCLOHEXANE



Gabapentin

↓

Binds to a2d subunit of voltage-gated calcium channels

↓

Decreases calcium influx into presynaptic neurons

↓

Reduces release of glutamate, norepinephrine, and substance P

↓

Decreases neuronal excitability

↓

Controls seizures and neuropathic pain

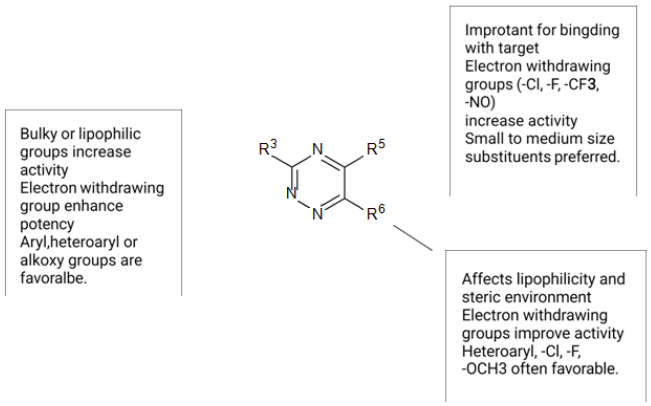
BENEFICIAL USES

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA) and is widely used for the treatment of partial seizures. Clinical studies have demonstrated its effectiveness in reducing seizure frequency in patients with epilepsy. Besides its anticonvulsant activity, gabapentin is highly effective in the management of neuropathic pain conditions such as postherpetic neuralgia and diabetic neuropathy. It has also shown benefits in restless leg syndrome and certain anxiety disorders. Due to its favourable safety profile and minimal drug interactions, gabapentin remains a valuable therapeutic option.[11]

Lamotrigine is a phenyltriazine derivative used as an anticonvulsant and mood stabilizer. It works by blocking

sodium channels, and decreasing the release of glutamate. It is used for epilepsy and bipolar disorder and causes less sedation than older antiepileptic medicines

SAR OF LAMOTRIGINE ON 1,2,4-TRIAZINE RING



MECHANISM OF ACTION

Lamotrigine

↓

Blocks voltage-gated sodium channels

↓

Stabilizes neuronal membranes

↓

Reduces glutamate and aspartate release

↓

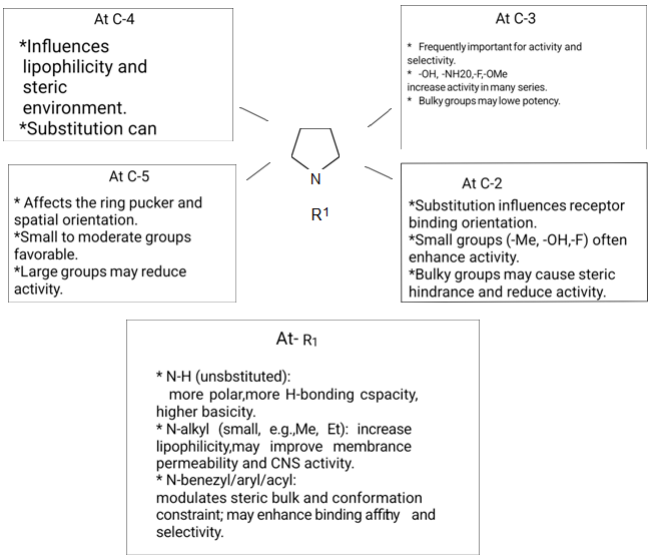
Suppresses seizure propagation

Lamotrigine is a broad-spectrum antiepileptic drug effective against both focal and generalized seizures. It acts primarily by inhibiting voltage-gated sodium channels and reducing glutamate release. One of its major advantages is its efficacy in the maintenance treatment of bipolar disorder, particularly in preventing depressive episodes. Lamotrigine is associated with fewer cognitive adverse effects compared with many traditional antiepileptic drugs, thereby improving patient quality of life and treatment adherence.[12]

LEVETIRACETAM

Levetiracetam is an antiepileptic drug (AED) which belongs to the second generation of AEDs. Levetiracetam is a pyrrolidone carboxylic acid analog, and is structurally similar to Piracetam, yet it has strong anticonvulsant properties. Levetiracetam has wide spectrum of effectiveness, safe use, lack of interactions with other drugs, and easy administration.

SAR OF LEVETIRACETAM ON PYRROLIDINE



Levetiracetam

↓

Binds to synaptic vesicle protein 2A (SV2A)

↓

Modulates neurotransmitter release

↓

Reduces abnormal neuronal synchronization

↓

Decreases neuronal hyperexcitability

↓

Prevents seizures

BENEFICIAL USES

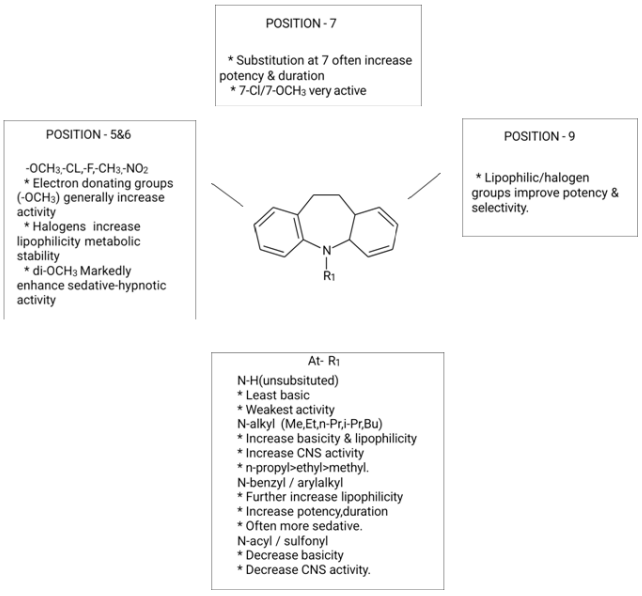
Levetiracetam has become one of the most commonly prescribed antiepileptic drugs due to its broad-spectrum efficacy and favorable tolerability profile. It is effective in focal seizures, generalized tonic-clonic seizures,

and myoclonic seizures. The drug exhibits minimal hepatic metabolism and very few drug-drug interactions, making it suitable for patients receiving multiple medications. Its rapid onset of action and ease of dose adjustment contribute to its widespread clinical use. Levetiracetam has become one of the most commonly prescribed antiepileptic drugs due to its broad-spectrum efficacy and favorable tolerability profile. It is effective in focal seizures, generalized tonic-clonic seizures, and myoclonic seizures. The drug exhibits minimal hepatic metabolism and very few drug-drug interactions, making it suitable for patients receiving multiple medications. Its rapid onset of action and ease of dose adjustment contribute to its widespread clinical use. [13]

Oxcarbazepine is a second generation AED that is mainly used for the treatment of partial and generalized tonic-colonic seizures. This drug is the keto analog of Carbamazepine and has been synthesized to have similar anticonvulsant effects like those of carbamazepine with better tolerance and less interaction with other drugs.

From a chemical point of view, Oxcarbazepine is a dibenzoazepine carboxamide compound. Once taken into the body, this compound gets activated by conversion into 10-monohydroxy derivative (MHD).

SAR OF OXCARBAZEPIN ON DIBENZAZEPINE RING



Oxcarbazepine

↓

Blocks voltage-gated sodium channels

↓

Stabilizes hyperexcited neurons

↓

Inhibits repetitive neuronal firing

↓

Prevents spread of abnormal electrical activity

↓

Controls seizures

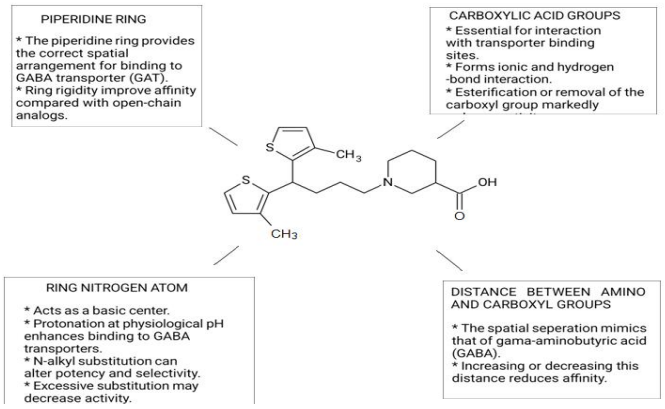
BENEFICIAL USES

Oxcarbazepine is a second-generation antiepileptic drug developed as an alternative to carbamazepine. It effectively controls focal seizures and is generally associated with fewer adverse effects and drug interactions than carbamazepine. The drug offers improved tolerability, better patient compliance, and reduced risk of serious haematological complications. These advantages make oxcarbazepine a preferred option for long-term epilepsy management.[14]

Tiagabine is an AED of the second generation which is mainly employed as an add-on treatment for partial (focal) seizures. It is a selective GABA reuptake inhibitor which raises the level of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS.

The structure of tiagabine is derived from the structure of nipecotic acid, a known GABA uptake inhibitor. Tiagabine decreases neuronal excitability by augmenting GABA-mediated inhibition.

SAR OF TIAGABINE ON NIPECOTIC ACID



Tiagabine

↓

Inhibits GABA transporter (GAT-1)

↓

Blocks GABA reuptake into neurons and glial cells

↓

Increases extracellular GABA concentration

↓

Enhances inhibitory neurotransmission

↓

Reduces seizure activity

BENEFICIAL USES

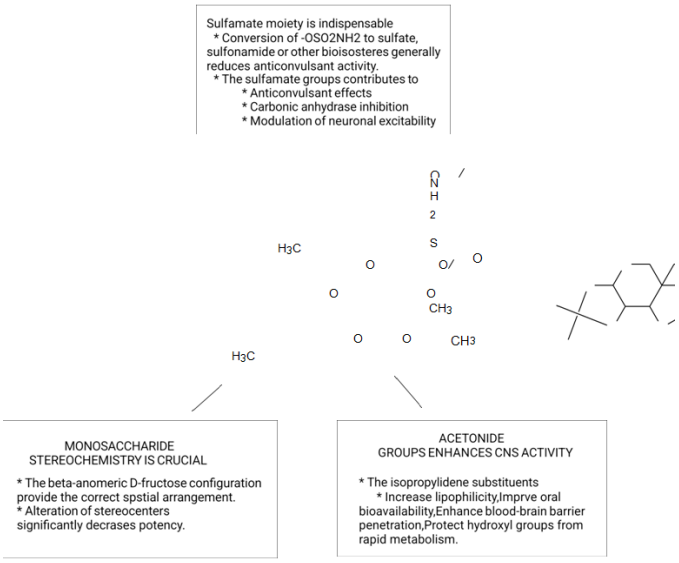
Tiagabine is a selective inhibitor of GABA reuptake and enhances inhibitory neurotransmission in the central nervous system. It is primarily used as adjunctive therapy for partial seizures. By increasing extracellular GABA concentrations, tiagabine improves seizure control and decreases seizure frequency. The drug has demonstrated effectiveness in patients with refractory epilepsy who do not adequately respond to conventional therapies.[15]

TOPIRAMATE

Topiramate is a versatile antiepileptic drug (AED) that is used to treat different types of epilepsy as well as to prevent migraines. Topiramate is an artificial product derived from the sulfamate-substituted monosaccharide of D-fructose. Due to its multifunctional nature, topiramate has a wide spectrum of effectiveness on various forms of epilepsy.

Topiramate is one of the most commonly prescribed drugs due to its high efficacy, versatility, and safety profile.

SAR OF TOPIRAMATE ON SULFAMATE-SUBSTITUTED MONOSACCHARIDE



MECHANISM OF ACTION

Topiramate

↓

Blocks voltage-gated sodium channels

↓

Enhances GABA activity

↓

Inhibits AMPA/kainate glutamate receptors

↓

Reduces excitatory neurotransmission

↓

Decreases neuronal excitability

↓ Prevents seizures

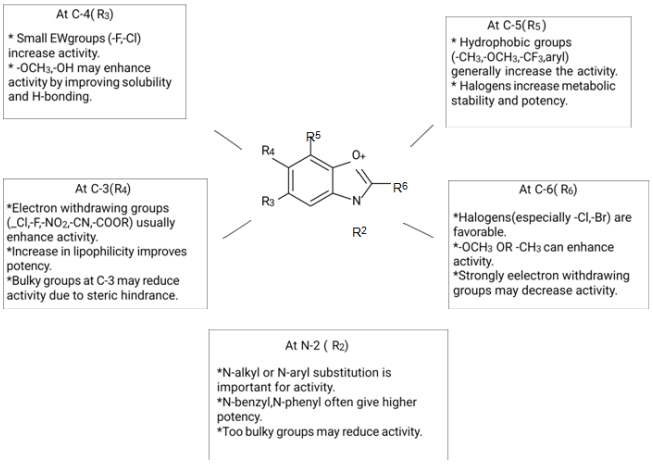
BENEFICIAL USES

Topiramate is a broad-spectrum anticonvulsant with multiple mechanisms of action, including sodium channel blockade and enhancement of GABA-mediated inhibition. It is effective in the treatment of focal and generalized seizures. In addition to epilepsy management, topiramate is widely used for migraine prophylaxis and has shown benefits in weight reduction among certain patient populations. These additional therapeutic effects make topiramate a versatile drug in neurological practice.[16]

ZONISAMIDE

Zonisamide is an anti-epileptic drug that is derived from a sulfonamide and is utilized for the management of focal and generalized convulsions. This drug works through the blockade of voltage-dependent sodium and T-type calcium channels. As a result of having wide therapeutic spectrum, long half-life, and easy dosing regimen, it is commonly used in epilepsy treatment.

SAR OF ZONISAMIDE ON 1,2-BENZISOXAZOLE CORE



Zonisamide

↓

Blocks voltage-gated sodium channels and T-type calcium channels

↓

Stabilizes neuronal membranes

↓

Reduces hypersynchronous neuronal firing

↓

Prevents spread of epileptic discharges

↓ Controls seizures

BENEFICIAL USES

Zonisamide is a sulfonamide-derived anticonvulsant effective in both focal and generalized epilepsy. It offers the advantage of once-daily dosing, which improves patient adherence.

Clinical studies have reported significant reductions in seizure frequency with long-term therapy. Furthermore, zonisamide may contribute to weight reduction and is generally well tolerated, making it a useful option for chronic epilepsy treatment. [17]

II. FUTURE PERSPECTIVES

This review summarizes the structure–activity relationship (SAR), mechanisms of action, and beneficial therapeutic effects of selected newer antiepileptic drugs. Understanding the relationship between chemical structure and pharmacological activity may facilitate the development of novel anticonvulsants with enhanced efficacy and reduced adverse effects. In future we can develop some novel antiepileptic drug newly.

Modern antiepileptics have made great contributions to the treatment of epilepsy due to their broad spectrum of activity, better tolerance, and fewer drug interactions. Structural modification is one of the key determinants of pharmacological activity and efficacy.

Knowledge about their synthesis, SAR, mode of action, and advantages gives important information regarding the development of new anticonvulsants in the future. Further investigations in medicinal chemistry and neuropharmacology will lead to the creation of new antiepileptics.

REFERENCES

[1] Davinsky O, Vezzani A, O'Brien TJ, Jatte N, Scheffer IE, de Curtis M, et al. Epilepsy, Nature Reviews Disease Primers, 2018;4:18024. doi:10.1038/nrdp.2018.24,

[2] Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet. 2006;367(9516):1087-1100.
[3] Stafstrom CE, Carmant L. Seizures and epilepsy. An overview for neuroscientists. Cold Spring Harbor Perspectives in Medicine. 2015;5(6):0022426.doi:10.1101/cshperspect.a022426. PM
[4] Fisher RS. Redefining epilepsy. Current Opinion in Neurology. 2015;28(2):130-135. doi:10.1097/WCO.0000000000000174.
[5] Moshé SL, Parucca E, Ryulin P, Tomson T. Epilepsy: New advances. Lancet. 2015;385(9971):884-898.
[6] Maguire MJ, Weston J, Singh J, Marson AG. Epilepsy: A Clinical Overview, American Journal of Medicine. 2021;134(7):840-847. doi:10.1016/j.amjmed.2021.01.038,
[7] Engel J Jr, Pedley TA Comprehensive Textbook↓ Williams & Wilkins; 2008. tors. Epilepsy: A ladelphia: Lippincott Engel J Jr, Pedley TA. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven Publishers; 1997. pp. 1-10.
[8] Devinsky O, Vezzani A, O'Brien TJ, et al. Epilepsy. Nature Reviews Disease Primers. 2018;4:18024. DOI: 10.1038/nrdp.2018.24. PubMed
[9] Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet. 2006;367(9516):1087-1100.
[10] Backonja M, Glanzman RL. *Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials.* Clinical Therapeutics. 2003;25(1):81-104. DOI: 10.1016/S0149-2918(03)90011-7.
[11] Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. *Palliative Medicine.* 2004;18(1):5–11.
[12] Haneen N, Kamperman AM, Prodan A, Nolen WA, Boks MP, Wesseloo R. The efficacy of lamotrigine in bipolar disorder: A systematic review and meta-analysis. Bipolar Disorders. 2024;26(5):431–441.
[13] Schachter SC. Lamotrigine: An Overview of Efficacy and Safety. Expert Opinion on Pharmacotherapy. 1999.
[14] Wellington K, Goa KL. Oxcarbazepine: an update of its efficacy in the management of epilepsy. CNS Drugs. 2001;15(2):137-163.
[15] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice.*Epilepsia.* 2004;45(Suppl 6):13–18.
[16] Beydoun A, Uthman BM, Sackellares JC. Gabapentin: Pharmacokinetics, efficacy, and safety. Clinical Neuropharmacology. 1995;18(6):469–481.