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(REVIEW ARTICLE)

A review on carbamazepine in the treatment of epilepsy

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Abstract

Epilepsy is a chronic, debilitating neurological disorder defined by recurrent, unprovoked seizures and substantially reduces the quality of life of patients with the disease. Carbamazepine (CBZ) is one of the most commonly prescribed antiepileptic drugs (AEDs) for the management of focal and generalized tonic-clonic seizures. It mainly provides therapeutic effects by stabilizing hyperexcitable neuronal membranes and preventing repetitive firing through voltage gated sodium channel blockade. Although carbamazepine shows undeniable effectiveness, its clinical significance is limited by the emergence of dose-dependent adverse effects, drug resistance, metabolic interactions, and genetic variations of individual patients.

During the course of this review, we examine, in detail, the historical background of carbamazepine, its chemical structure, pharmacokinetics, mechanism of action, therapeutic efficacy and clinical applications in epilepsy management. Also, it reviews the drug's safety profile, including its adverse events, drug-drug interactions and contraindications. It also highlights recent inventions in drug delivery systems when embedding CBZ such as lipid nanocarriers and other new formulations that might be used to enhance CBZ bioavailability to improve therapeutic results and reduce side effects. In addition, the role of pharmacogenomics in personalizing CBZ therapy is reviewed along with interindividual differences in drug metabolism and tailored treatment.

While a mainstay in the management of epilepsy, research continues to assess the best formulation of CBZ, better side effects as well as alternative strategies with a goal of optimized seizure control. Through a critical review of the current literature, this review presents new perspectives on the role of carbamazepine in the management of epilepsy, highlighting recent trends, emerging challenges, and future research and clinical perspectives.

Keywords: Epilepsy; Seizures; Peptic mal; Carbamazepine

1. Introduction

Epilepsy is a disorder of CNS characterized by paroxymal cerebral dyrrhythmaia or recurrent seizures and disturbance of consciousness with or without characteristics movement.

A seizere is defined as the clinical manifestation of excessive or hypersynchronous activity of neuron within the cerebral cortex.

It is a condition that not only presents with significant clinical challenges but also poses substantial psychosocial and economic burdens on individuals and societies. Seizures in epilepsy are caused by abnormal, excessive electrical discharges in the brain, leading to varied manifestations ranging from brief lapses in attention to severe convulsions. The disorder can affect individuals of all ages, genders, and ethnic backgrounds.

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The burden of epilepsy extends beyond seizures, affecting cognitive, emotional, and social domains of life. It is a leading cause of disability-adjusted life years (DALYs) among neurological disorders. Recent advances in the understanding of epilepsy have led to better management strategies, yet there remains a considerable unmet need in terms of diagnosis, treatment, and patient quality of life. Collaborative research efforts are essential to address these gaps and develop comprehensive care strategies.

2. Classification

2.1. Epilepsy

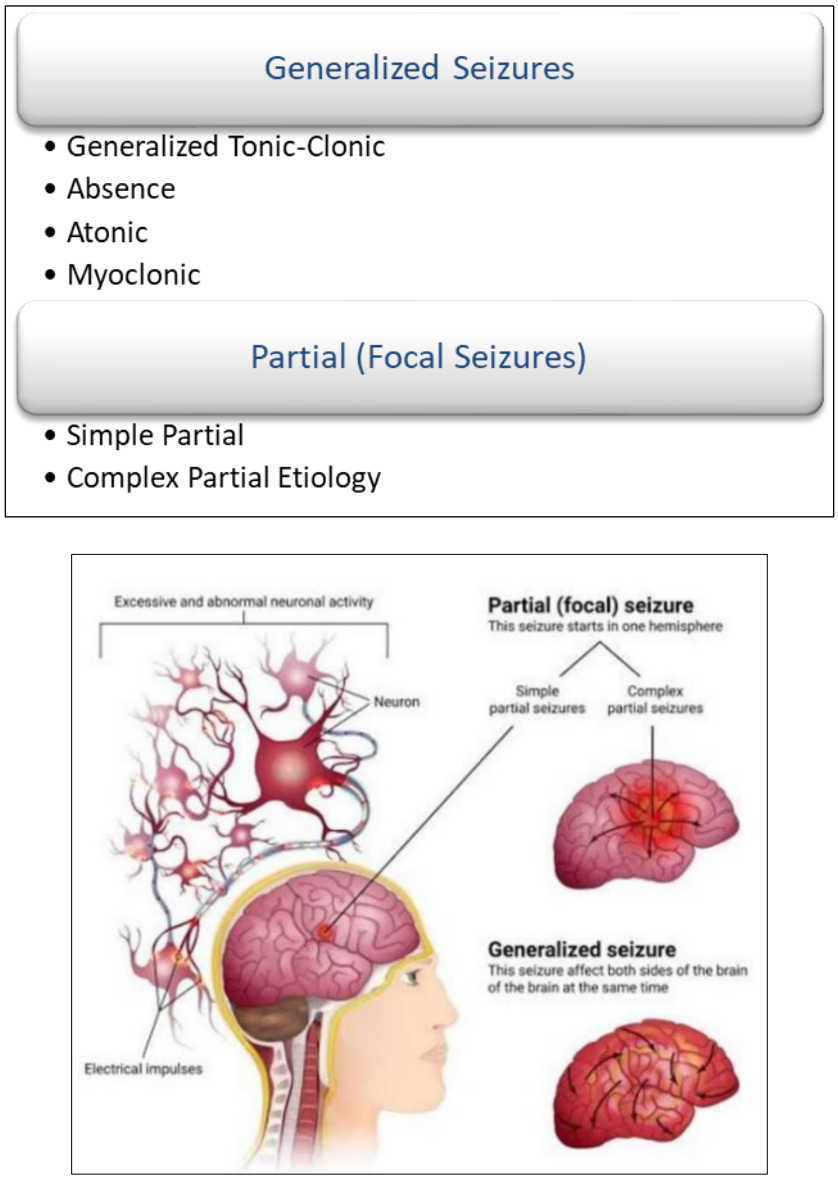

Figure 1 Classification of Epilepsy

2.2. Generalized Seizures

Generalized seizures involve both hemispheres of the brain simultaneously and often result in a loss of consciousness.

2.2.1. Generalized Tonic-Clonic Seizure (Grand Mal)

- **Description**: This is the most recognizable type of seizure. It begins with muscle stiffening (tonic phase) followed by rhythmic jerking movements (clonic phase).

- **Symptoms**: Loss of consciousness, muscle stiffness, jerking movements, possible incontinence, and tongue biting.

2.2.2. Absence Seizure (Peptic Mal)

- **Description**: Common in children, this type involves brief episodes of staring or loss of awareness.
- **Symptoms**: Sudden staring spells, lip-smacking, or blinking, lasting only a few seconds.

2.2.3. Atonic Seizure

- **Description**: Also called "drop attacks," these seizures cause a sudden loss of muscle tone, leading to falls or drooping.
- **Symptoms**: Sudden collapse or head nodding without warning.

2.2.4. Myoclonic Seizure

- **Description**: Involves sudden, brief jerking or twitching of muscles, usually affecting both sides of the body.
- **Symptoms**: Quick muscle jerks, often occurring shortly after waking up.

2.3. Partial (Focal) Seizures

Partial seizures originate in a specific area of the brain and may or may not involve loss of consciousness.

2.3.1. Simple Partial Seizure

- **Description**: Does not impair consciousness but may cause abnormal sensations or movements.
- **Symptoms**: Tingling, muscle twitching, or sensory changes (e.g., seeing flashes of light).

2.3.2. Complex Partial Seizure

- **Description**: Impairs consciousness and may include repetitive behaviors or confusion.

3. Pathophysiology

Flow chart of pathophysiology of Epilepsy is as follows:

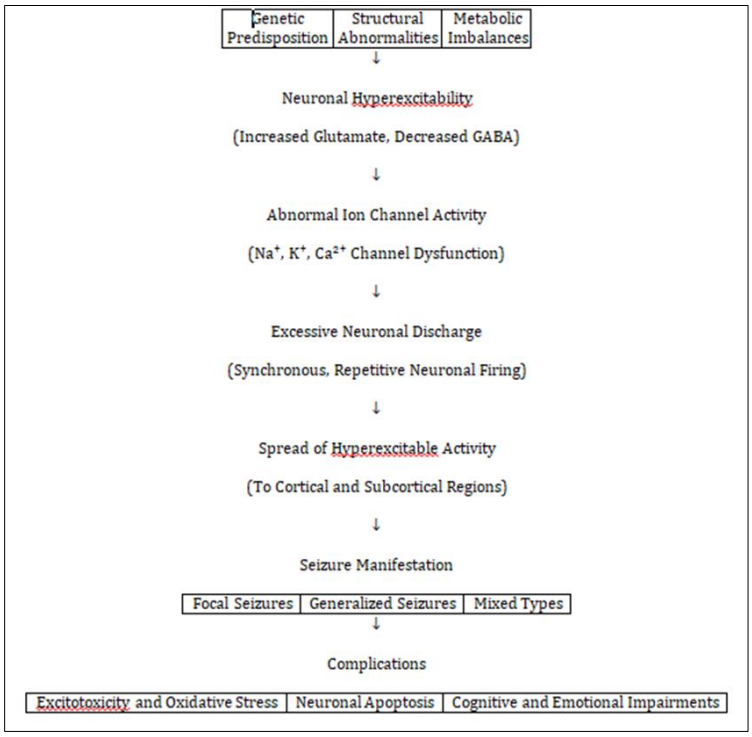

Figure 2 Pathophysiology

3.1. Diagnosis

The diagnosis of epilepsy requires a meticulous approach to differentiate it from other conditions such as syncope, migraines, or psychogenic non-epileptic seizures. The diagnostic process involves:

- **Clinical History:** A detailed history of seizure events, including triggers, duration, and postictal state, is essential. Witness accounts can provide critical insights.
- **Electroencephalogram (EEG):** This is a cornerstone diagnostic tool that records electrical activity in the brain, identifying epileptiform patterns. Prolonged EEG monitoring or video EEG may be necessary in complex cases.
- **Neuroimaging:** MRI is preferred for detecting structural abnormalities, while CT scans are used in emergencies. Advanced techniques like functional MRI and PET scans provide additional information.
- **Laboratory Tests:** These include blood tests to identify metabolic or infectious causes. Biomarkers of epileptogenesis are an area of active investigation.
- **Genetic Testing:** Particularly useful for syndromic epilepsies, enabling personalized management.

Accurate and early diagnosis is critical to managing epilepsy effectively and preventing unnecessary interventions. Innovations in diagnostic technologies, such as machine learning algorithms and wearable devices, are expected to enhance diagnostic precision.

3.2. Treatment

The primary goal of epilepsy treatment is seizure control with minimal side effects. Therapeutic options include:

- **Surgical Interventions:** For drug-resistant epilepsy, options include resective surgery, laser ablation, or neuromodulation techniques like vagus nerve stimulation (VNS) and responsive neurostimulation (RNS).
- **Dietary Therapies:** The ketogenic diet and its variations have proven effective, particularly in children with refractory epilepsy. These diets alter metabolic pathways to reduce excitability in neurons.
- **Emerging Therapies:** These include targeted gene therapies, monoclonal antibodies, and anti-inflammatory treatments. Advances in pharmacogenomics are paving the way for precision medicine approaches in epilepsy management.
- **Behavioral and Lifestyle Modifications:** Stress management, adequate sleep, and avoiding known seizure triggers are integral to holistic care.
- **Antiepileptic Drugs (AEDs):** These are the first-line treatments. Newer AEDs, such as brivaracetam and eslicarbazepine, offer improved efficacy and tolerability. AED selection depends on seizure type, age, comorbidities, and patient preferences. Combination therapies may be used in refractory cases.

Table 1 Classification of Anti-Epileptic Drug

S.No	Drug Class	Agent
1	Barbiturate	Phenobarbiturate
2	Deoxybarbiturate	Primidone
3	Hydantoin	Phenytoin, Fosphenytoin
4	Iminostilbene	Carbamazepine, Oxcarbazepine
5	Succinimide	Ethosuximide
6	Aliphatic carboxylic acid	Valproic acid, Divalproex
7	Benzodiazepines	Diazepam, Clonazepam, Lorazepam, Clobazam
8	Phenyltriazine	Lamotrigine
9	Cyclic GABA analogue	Gabapentin, Pregabalin
10	Newer drug	Zonisamide, Lacosamide

4. Site of Action

4.1. Effect on Sodium Channel

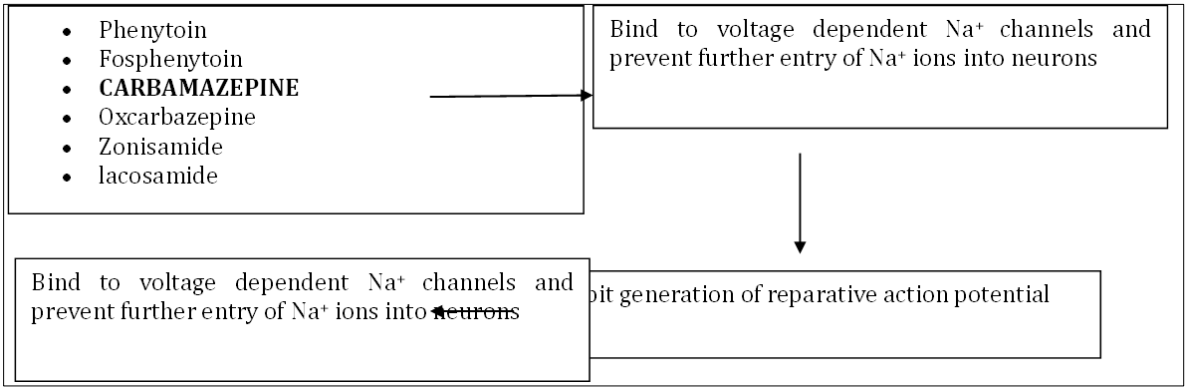

Figure 3 Effect on sodium Channel

4.2. Effect on GABA, Glutamic acid decarboxylase

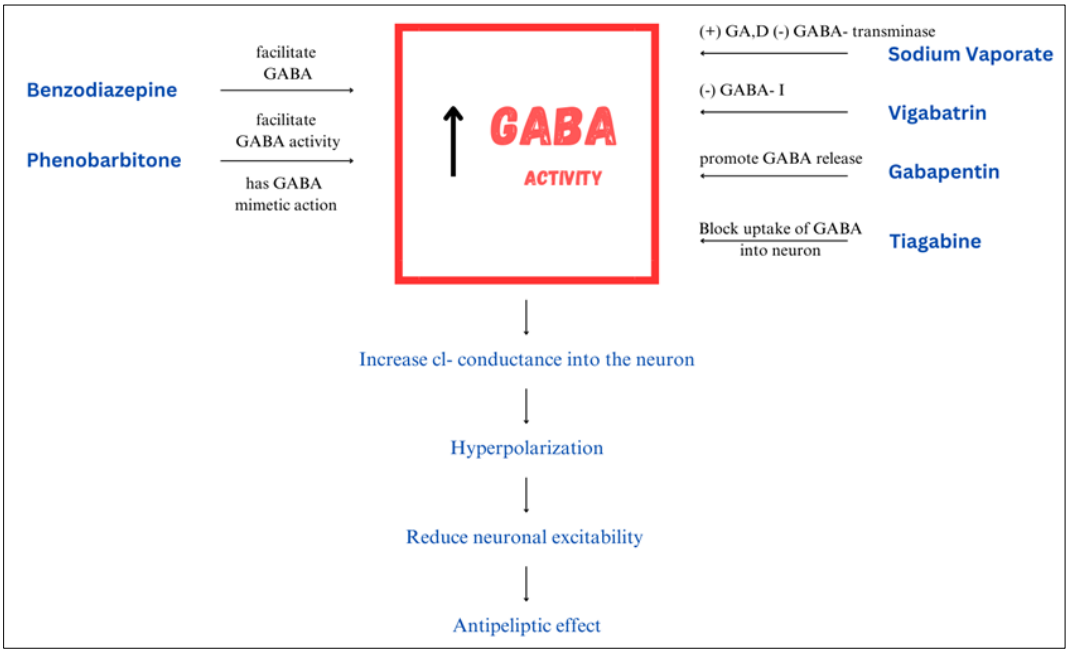

Figure 4 Effect on GABA

5. Carbamazepine

Carbamazepine is an anticonvulsant and mood-stabilizing drug widely used for the treatment of epilepsy and other neurological disorders. It was first approved in the 1960s and is classified as a dibenzazepine derivative. Its primary function is to control seizures, although it is also effective for certain types of chronic pain and mood disorders. Carbamazepine is available in various formulations, including tablets, chewable tablets, extended-release forms, and oral suspensions.

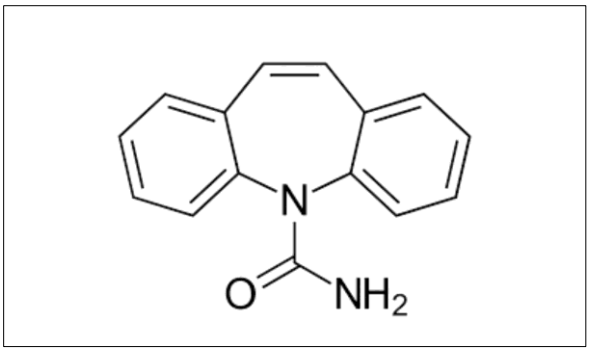

Figure 5 Structure of Carbamazepine

5.1.1. Mechanism of Action

Carbamazepine works primarily by inhibiting voltage-gated sodium channels in the neuronal membrane. By stabilizing the inactive state of sodium channels, it reduces the repetitive firing of neurons and prevents the propagation of abnormal electrical signals in the brain. This mechanism is particularly effective in controlling focal and generalized tonic-clonic seizures. Additionally, carbamazepine may influence neurotransmitter release, contributing to its efficacy in neuropathic pain and bipolar disorder.

5.1.2. Adverse Effects

Carbamazepine is generally well-tolerated but may cause a range of side effects, including:

- **Neurological Effects:** Drowsiness, dizziness, ataxia, blurred vision, and headaches.
- **Gastrointestinal Effects:** Nausea, vomiting, and constipation.
- **Haematological Effects:** Rare but serious effects like aplastic anaemia, agranulocytosis, and leukopenia.
- **Hypersensitivity Reactions:** Skin rashes, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), particularly in individuals with the HLA-B*1502 allele (more common in Asian populations).
- **Hepatic and Endocrine Effects:** Elevated liver enzymes and hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

5.1.3. Uses

Carbamazepine is a versatile drug used in the following conditions:

- **Epilepsy:** First-line treatment for focal seizures with or without secondary generalization and generalized tonic-clonic seizures.
- **Trigeminal Neuralgia:** Effective in relieving chronic pain associated with trigeminal nerve disorders.
- **Bipolar Disorder:** Approved as a mood stabilizer, particularly for the prevention of manic episodes.
- **Neuropathic Pain:** Used off-label for conditions like diabetic neuropathy and postherpetic neuralgia.
- **Other Uses:** Sometimes employed in alcohol withdrawal syndrome and restless legs syndrome.

5.1.4. Pharmacokinetics

Absorption

- Carbamazepine is absorbed slowly but almost completely after oral administration.
- Peak plasma concentrations occur within **4-8 hours** for immediate-release formulations and **12-24 hours** for extended-release formulations.
- Its bioavailability is approximately **75-85%**.

Distribution:

- Widely distributed in the body with a volume of distribution (Vd) of 0.8-1.8 L/kg.
- Approximately 70-80% is bound to plasma proteins, primarily albumin.

Metabolism

- Carbamazepine undergoes extensive metabolism in the liver via the cytochrome P450 (CYP3A4) enzyme to form its active metabolite, carbamazepine-10,11-epoxide.
- It induces its own metabolism (autoinduction), leading to a decrease in its half-life over time, from 25-65 hours on initial dosing to 12-17 hours with chronic use.

Excretion:

- Carbamazepine and its metabolites are primarily excreted through the kidneys (70%) and a smaller fraction through bile (30%).
- Less than 5% of the drug is excreted unchanged in the urine.

5.2. Pharmacodynamics

5.2.1. Therapeutic Effects

- Suppresses abnormal electrical discharges in epilepsy.
- Modulates pain pathways, reducing neuropathic pain in conditions like trigeminal neuralgia.
- Stabilizes mood by reducing neuronal hyperexcitability in bipolar disorder.

5.2.2. Receptor Targets:

- **Primary Target**: Voltage-gated sodium channels.
- **Secondary Effects**: May affect calcium and potassium channels, and modulate neurotransmitter release (e.g., glutamate, gamma-aminobutyric acid or GABA).

5.2.3. Dose-Response Relationship:

- Therapeutic plasma levels for seizure control are typically **4-12 µg/mL**, though individual response may vary.

5.2.4. Onset and Duration:

- Onset of action for seizure control is gradual due to the slow absorption and delayed achievement of steady-state plasma levels.
- Duration of therapeutic effects depends on the formulation, with extended-release forms providing prolonged action.

6. Conclusion

Epilepsy remains a multifaceted disorder with profound clinical and societal implications. While advances in research and technology have transformed its management, considerable gaps persist in understanding its mechanisms and addressing its broader impact on patients' lives. Collaborative efforts between researchers, clinicians, and policymakers are essential to overcome these challenges and improve the lives of individuals with epilepsy. Expanding global awareness and promoting education are key to addressing stigma and improving care delivery.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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