Review Article

Carbamazepine and Bipolar Disorder: Pharmacodynamics, Pharmacokinetics, Pharmacogenomics, and Adverse Drug Reactions – A Comprehensive Review

Lochana P., Megha Banerjee, Nidhi Bansal, Jitender Aanjana Patel, Ruby Varghese*

Department of Chemistry and Biochemistry, School of Sciences, Jain Deemed to be University, Bangalore, Karnataka-560035 India

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Abstract

Bipolar disorder is a psychiatric illness characterized by episodes of mania or hypomania that oscillate with depression. In India around 1 in 150 people encounter this disorder but the majority of them remain untreated or misdiagnosed. The review focuses on the FDA-approved Carbamazepine (CBZ), a mood stabilizer for bipolar illness. Additionally, it is authorized for the management of generalized tonic-clonic seizures, complex partial temporal lobe epilepsy, and trigeminal neuralgia. It is largely metabolized in the liver by the variants of cytochrome enzymes such as CYP3A4, CYP3A5, CYP2C19, and CYP2C8. It manages to control maniac activities by modulating voltage-gated sodium channels, reducing dopamine and glutamate turnover while increasing serotonin and Gaba Aminobutyric Acid (GABA) levels through a variety of actions of synthesis and degradation. Though being used extensively for bipolar diseases, it has shown adverse effects which cause anemia, hepatitis, rashes, neural tube abnormalities, weight gain, hearing loss, and some cognitive effects. CBZ, either alone or in combination with other drugs, is effective in the maintenance treatment of bipolar disorder in naturalistic clinical settings. With the aid of Therapeutic Drug Monitoring (TDM), additional pharmacogenetic research may be required to more clearly define the effects of drug-metabolizing polymorphisms in everyday situations.

Keywords: Carbamazepine, Gaba Aminobutyric Acid, serotonin, voltage-gated sodium channels, cytochrome

Introduction

Bipolar disorder is a chronic recurring illness marked by swings in mood and energy. Regardless of nationality, ethnic background, or socioeconomic status, it affects more than 1% of the world's population1. It is marked by recurring episodes of mania and depression in bipolar disorder (Carvalho et al., 2020) and of hypomania and depression in bipolar disorder (Harrison et al., 2018). Patients with bipolar disorder usually have additional medical conditions in addition to their serious mental disorders (Zareifopoulos et al., 2018). There is evidence of a neurotransmission imbalance, polygenic inheritance, and illness progression in these individuals. Patients frequently take many medications at once, with varying degrees of therapeutic efficacy, especially in the case of depression. Numerous people commit suicide (Dome et al., 2019). In comparison to the general population, the suicide rate is 5–17 times greater, with a lifetime risk of 10%–20% (Miller and Black, 2020).

Anticonvulsant medications are frequently prescribed for these psychiatric purposes. Although various additional anticonvulsant medications have been tested with conflicting or inconclusive results, carbamazepine, valproate, and lamotrigine are known mood stabilizers for bipolar disorder (Simonetti et al., 2020). Carbamazepine (CBZ) is a crucial second-line treatment for bipolar disorder when treatment with a conventional antipsychotic alone fails. CBZ otherwise is typically used in the treatment of seizure disorders and neuropathic pain (Sparacino et al., 2022). CBZ is structurally similar to tricyclic antidepressant imipramine. In 2002, the FDA gave CBZ the drug approved for the treatment of acute mania (Sparacino et al., 2022). Hence this review in detail discusses carbamazepine for the treatment of bipolar disorder, its underlying mechanism, and adverse effects.

Chemistry of CBZ

Systemic chemical name: 5H-Dibenz[b,f]azepine-5-carboxamide

Address for Corresponding Author:
Dr. Ruby Varghese
Department of Chemistry & Biochemistry, School of Sciences, Jain Deemed to be University, Bangalore, Karnataka-560035
Email: rubybiochemistry@gmail.com

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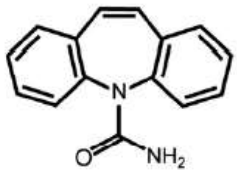

Figure 1: Structure of CBZ

Empirical formula: $C_{15}H_{12}N_2O$

Pharmacodynamics: Mechanism of action of CBZ in the treatment of bipolar disorder

CBZ does not appear to have a single mechanism of action. CBZ therapy for bipolar disease works on multiple levels, including ion channels, receptors, and signaling pathways. However, it is yet unknown which particular mechanism is engaged in a given context and how much each mechanism contributes to the therapeutic action of CBZ. The various mechanism by which CBZ acts are:

(A). **Voltage-Gated Sodium Channels**

Voltage-Gated Ion Channels (VGICs) are transmembrane proteins that play a crucial role in cell signaling. VGICs are characterized as voltage-gated sodium, potassium, calcium, or chloride channels based on the ions they conduct. The membrane potential of a cell controls the activity of VGICs and opens channels for ions to pass across cellular membranes along an electrochemical gradient (de Lera Ruiz and Kraus, 2015).

The voltage-dependent sodium channels are the primary target of CBZ. CBZ and carbamazepine-epoxide lower the frequency of prolonged repeated action potential firing. High-frequency firing is inhibited by CBZ, whereas low-frequency firing is unaffected (Wu et al., 2022). Carbamazepine blocks and maintains the inactivated state of voltage-gated sodium channels, reducing the number of channels that can be opened later. Until the drug dissociates, the afflicted cells become less excitable (Pal et al., 2021). The inactivated conformation of sodium channels has a higher affinity for CBZ than the resting conformation (Goodchild et al., 2023).

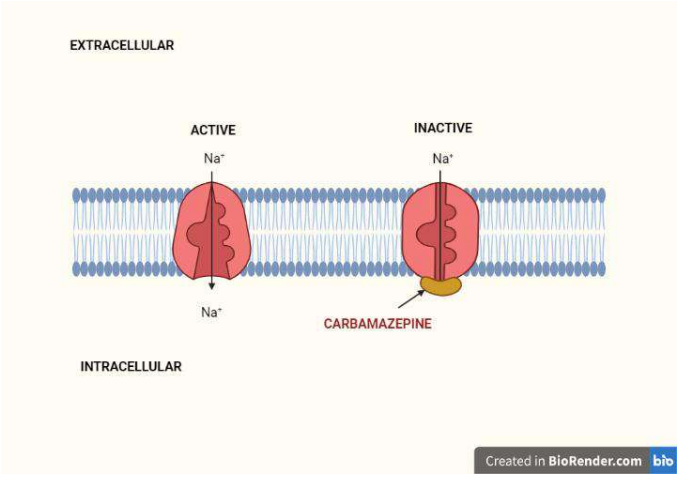

Figure 2: Diagrammatic representation of CBZ blocking sodium ion channel.

(B). **GABA Neurotransmission**

Gamma Amino Butyric Acid (GABA) is an amino acid that serves as the central nervous system's major inhibitory neurotransmitter. It works by blocking nerve transmission to lower neuronal excitability (Lee et al., 2019). It regulates dopamine and glutamate neurotransmission in the brain (Ochoa-de la Paz et al., 2021). The GABA levels are seen to be decreased in bipolar disorder individuals, resulting in excitotoxicity and the potential for apoptosis (Scotti-Muzzi et al., 2021).

CBZ stimulates GABA receptors made up of α1, β2, and γ2 subunits, making it a GABA receptor agonist (Chen et al., 2020). GABAB receptor levels are upregulated after long-term CBZ treatment, While short-term treatment does not affect GABAB levels (Chen et al., 2021).

(C.) **Serotonergic System**

Serotonin is a naturally occurring chemical that acts as a neurotransmitter, allowing signals to travel between neurons and throughout the body (Deneris et al., 2018). Serotonin is involved in mood regulation and is known as a feel-good chemical (Lv et al., 2017). In bipolar disorder, cerebral serotonergic activity is diminished, which leads to depression. When bipolar patients are euthymic, reduced serotonin activity could be a characteristic diagnostic for bipolar disorder (Maddaloni et al., 2018).

CBZ exerts dose-dependent anticonvulsant effects by causing substantial increases in extracellular serotonin levels. CBZ causes serotonin release through a method that does not involve the serotonin transporter. CBZ is likewise a potent inhibitor of serotonin reuptake. This inhibitory property is linked with CBZ's ability to block biogenic amine transporters. As a result, CBZ is a serotonin-releasing agent as well as a serotonin reuptake inhibitor (Rodrigues et al., 2023; Prakash et al., 2021; Rissardo and Caprara, 2020).

(D). **Glutamergic System**

Glutamate is an excitatory neurotransmitter. Bipolar disease causes an elevation in brain glutamate levels further leading to excitotoxicity (Shen and Tomar, 2021). CBZ inhibits glutamate release or ionotropic glutamate receptors. Carbamazepine exerts anti-glutamatergic effects by:

a). Reduced glutamate release. CBZ hinders glutamate release elicited by potassium in the brain.

b). Limited calcium influx. Glutamate's postsynaptic

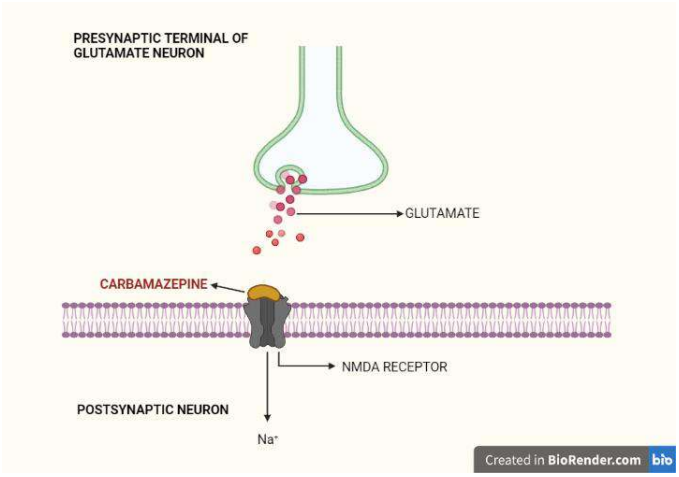

Figure 3: Diagrammatic representation of CBZ blocking calcium ion influx, and allowing only sodium ions to pass

effectiveness is reduced. Calcium influx through glutamate receptors of the NMDA subtype is slightly blocked by CBZ (Ghasemi et al., 2014; Okada et al., 2019; Aiyer et al., 2018).

Pharmacokinetics: Metabolism of CBZ in BD patients

A thorough understanding of pharmacokinetic interactions is necessary for the best use of CBZ in pharmacotherapy. Carbamazepine is effectively absorbed when ingested orally (Missio et al., 2019; Grunze et al., 2021). Metabolism of CBZ happens in the liver and a brief increase in the hepatic enzymes is observed at 5-15% incidence. It is predominantly metabolized by CYP 3A4 (Grunze et al., 2021). Carbamazepine-10,11 epoxide is carbamazepine's active metabolite. CBZ has an initial half-life of 26–65 hours that decreases to 12–17 hours with repeated dosages. The active metabolite has a half-life of about 34 hours (Ayano, 2016).

CBZ evokes cytochromes (CYP P450 2D6, 3A4), glucuronizing enzymes, and P-glycoprotein in the body leading to interactions with other drugs' metabolism (Zaccara and Franco, 2023). It is important to note that CBZ is a CYP450 3A4 inducer in addition to being its substrate (Fuhr et al., 2021). The extent of CBZ autoinduction is slightly dose sensitive but is typically resolved after 3-5 weeks of medication (Gaies et al., 2021). Only 1% of CBZ is removed through biliary excretion, thus the kidneys are responsible for the majority of excretion (Ngo et al., 2022; Methaneethorn et al., 2020).

Pharmacogenomics: CBZ and BD

Pharmacogenomics can detect polymorphisms in the genes that control the pharmacokinetics and pharmacodynamics of drugs, resulting in variations in their safety and efficacy in the body (Dadwai et al., 2021). It investigates how a person's unique genetic variation affects their response to medication to customize therapy and achieve optimal efficacy (Cuéllar-Barboza et al., 2020).

Due to the clinical and biological variability of the disease, pharmacodynamic and pharmacokinetic changes brought on by polytherapy, the presence of comorbidities, and poor treatment compliance, the response to CBZ for the treatment of BD is highly diverse (Corponi et al., 2018).

The existence of polymorphisms in the genes encoding the enzymes involved in CBZ metabolism helps partially explain individual and ethnic heterogeneity in how patients respond to CBZ medication. A few of the gene polymorphisms are:

EPHX1: CBZ 10,11-epoxide is converted to CBZ 10,11-diol by the microsomal epoxide hydrolase encoded by the epoxide hydrolase 1 (EPHX1) gene (Balestrini and Sisodiya, 2018). The 9 exons and 8 introns of the polymorphic EPHX1 gene are found on chromosome 1q42. EPHX1 activity and plasma concentrations of CBZ are impacted by two frequently polymorphic regions in the gene.

(a) Tyrosine to histidine conversion on exon 3 decreases the enzyme activity.

(b) Histidine to arginine conversion on exon 4 increases the enzyme activity (Venkatraman et al., 2023).

CYP3A4: The activity of CBZ metabolizing enzymes is regulated in part by CYP3A4. Inter-individual variability in CBZ metabolism is greatly influenced by the CYP3A4*22 polymorphism, which is prominently associated with reduced cytochrome activity (Laska et al., 2017).

CYP3A5: Due to the high polymorphism of CYP3A5, the most prevalent non-functional variant, the CYP3A5*3 allele, affects plasma CBZ concentrations (Shnayder et al., 2020). To maintain steady-state CBZ concentrations, functional CYP3A5 polymorphisms are crucial, and as a result, they are directly related to drug toxicity. Patients with the CYP3A5 mutant allele typically experienced CBZ toxicity and had slower clearance rates and longer half-lives than those with the wild type (Iannaccone et al., 2021).

CYP2C19: The bioactivation of CBZ is mediated by CYP2C19 in the body (Fricke-Galindo et al., 2018). Following CBZ treatment, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) propensity are linked to CYP2C19*2 and CYP2C19*3 polymorphisms of CYP2C19 respectively (Husain and Yatham, 2023).

CYP2C8: Despite not being the primary enzyme, CYP2C8 can aid in the conversion of CBZ into its active metabolite, CBZ 10,11-epoxide. The CYP2C8*5 variant is a rare polymorphism of CYP2C8, but it has the potential to result in a variant of the enzyme that is completely inactive as it could decide a shortened form of the cytochrome (Bobo,

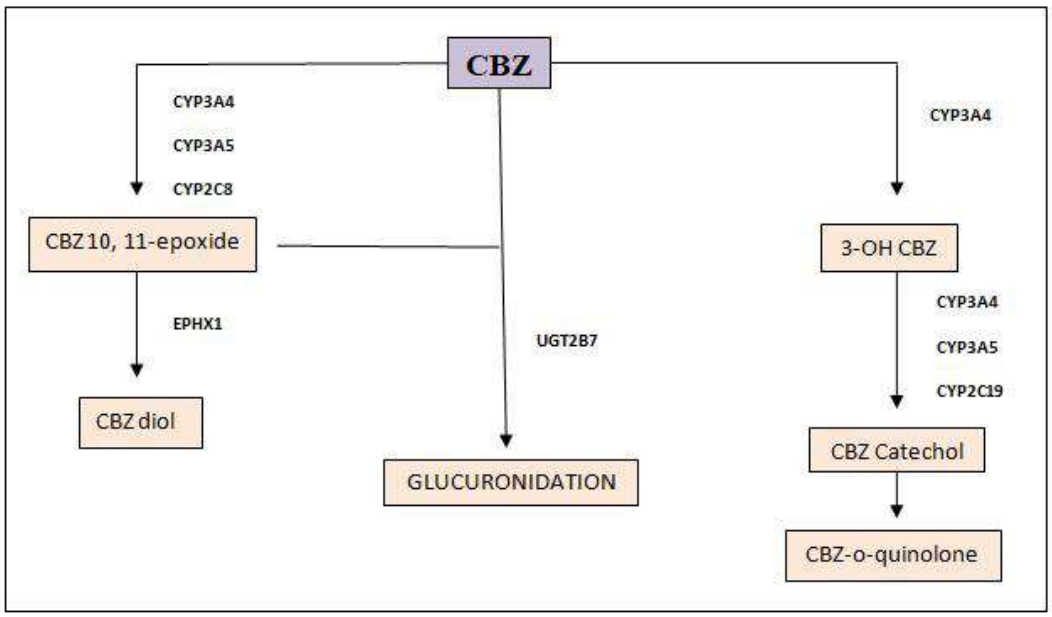

Figure 4: Metabolism of CBZ in liver

2017). The most prevalent non-synonymous mutation, CYP2C8*3, is commonly linked to lower enzyme activity and elevated CBZ blood concentrations (Schwarz et al., 2021).

To thoroughly understand the role of these polymorphisms as potential indicators of responsiveness to CBZ therapy, extensive research is necessary (Fricke-Galindo et al., 2018).

Adverse drug reactions

Understanding CBZ-induced adverse drug reactions is crucial for achieving safer treatment outcomes. Adverse drug reactions can have a detrimental effect on a patient's life and ramp up medical expenses (Ayano, 2016). The most frequent adverse effects of CBZ administration include dizziness, ataxia, forgetfulness, drowsiness, nausea, vomiting, constipation, and diarrhea. These can be avoided or considerably diminished by gradually raising the regular dosage (Sadock et al., 2009).

A) **BLOOD**: In 0.005% of patients, CBZ may result in aplastic anemia, agranulocytosis, and life-threatening thrombocytopenia. Transient and small drops in blood cell indices during the initial stages of treatment are possible but do not necessitate stopping CBZ. If the WBC falls below 3000 mm, the absolute neutrophil count falls below 1500 mm, or the platelet count falls below 100,000 cells per mm, carbamazepine should be stopped (Dean, 2012; Shah et al., 2017).

B) **LIVER**: Rare reports of severe hepatitis have been linked to carbamazepine, and elevated enzyme levels have been linked to cholestatic jaundice. If the patient contracts hepatitis, the drug needs to be stopped right away (Grunze et al., 2021; Sadock et al., 2009).

C) **SKIN**: Urticaria and rash are rather typical adverse drug reactions with CBZ. Exfoliative dermatitis and toxic epidermal necrolysis (Stevens-Johnson syndrome) are two potentially serious, though extremely rare, dermatological side effects that frequently call for prompt drug withdrawal (de Kleine et al., 2022; Witt et al., 2013).

D) **Teratogenic effects**: CBZ use during pregnancy is particularly linked to teratogenic effects, including neural tube abnormalities such as spina bifida. Pregnant women should all receive preconception information and folate-vitamin B complex supplements (Fricke-Galindo et al., 2018; Im et al., 2019).

C) WEIGHT GAIN: The use of CBZ over an extended period is linked to slight weight gain (Ahmed et al., 2021).

D) AUDITORY AND VESTIBULAR: A reduction in conduction in the auditory and vestibular pathways is likely a contributing factor in CBZ-induced ADRs. But no proof taking CBZ can cause permanent hearing loss.

Cognitive side effect: Numerous cognitive and psychomotor traits, primarily in the areas of attention and language, have been associated with CBZ, including lower information processing speed and attention, memory impairment, and subpar arithmetic skills. The tolerability, compliance, and long-term retention of medication, as well as everyday functioning and quality of life, can all be negatively impacted by cognitive side effects. The cognitive condition of patients using CBZ medication should be evaluated on several occasions. A baseline examination should be finished before starting or changing a treatment, and regular assessments should follow (Barr et al., 2019).

Conclusion

A growing focus on personalized medicine is intended to confirm the significance of a patient's genetic background

in the course of their treatment. Pharmacogenomics, which studies the relationship between certain human genome polymorphisms and the variety of neuropsychiatric medication responses, has advanced significantly in recent years. Despite the widespread use of anticonvulsants with mood stabilizer activity, such as CBZ, in the treatment of bipolar disorder and other therapeutic areas, it is still challenging to predict each patient's unique response to treatment in terms of genetic susceptibility. The advancement of pharmacogenetic studies has made it possible to investigate a significant number of potential genes that may influence the Pharmacokinetics variability of CBZ. However, there have been inconsistent findings. The majority of investigations have concentrated on the SNPs of the CYP and UGT genes.

In conclusion, there are potential biomarkers for CBZ therapy, but they are not sufficiently robust to allow for the personalization of treatment in BD patients, and no guidelines have yet been published. With the aid of Therapeutic Drug Monitoring, additional pharmacogenetic research may be required to more clearly define the effects of drug-metabolizing polymorphisms in everyday situations.

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