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# CARBAMAZEPINE IN BIPOLAR DISORDER: AN OVERVIEW

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## ABSTRACT

The aim of this review is to provide an overview on the bipolar disorder and potential use of carbamazepine (CBZ) in such bipolar disorder. Bipolar disorder is characterized by affective episodes such as manic, hypomanic or major depressive. This paper covers the information about the bipolar disorder, its consequences and pathophysiology in brief. Also, it focuses on the potential use of anticonvulsant drug, carbamazepine in such disorder and its superiority over other drugs such as chlorpromazine and lithium. Bipolar disorder is a complex disorder and carbamazepine is effective in combination therapy with other drugs as compared to monotherapy. More emphasis should be given on the treatment adherence by the patient while treating bipolar disorder.

**KEYWORDS:** Bipolar disorder, manic, anticonvulsant, Gamma-amino butyric acid, Carbamazepine.

## INTRODUCTION

Bipolar disorder is brain disorder associated with sudden changes in human behavior. The incidences of bipolar disorder across the world vary from 0.3 to 1.2 percent. Worldwide data showed that 46 million people in the world suffered from bipolar disorder in 2017, with 52 and 48 percent being female and male, respectively.[1] The prevalence of bipolar disorder was found to be higher in United States (U.S.) adults aged group in between 18 to 29 as per data from National Co - morbidity Survey Replication (NCS-R).[2] According to World Health Organization (WHO), at least 6.5 per cent of the Indian population suffers from some form of the serious mental disorder, with no discernible rural-urban differences.[3] In 1991, it has reported that the total costs to society for bipolar disorder in the USA were estimated at $45billion, approx. 70% of that for schizophrenia. In the UK, the total annual cost to society has been estimated at £2 billion, and it is significant that only 10% of this was attributed to health service resource use, while 86% was due to indirect costs.[4] Its symptoms do not meet the diagnostic requirements for a hypomanic and depressive episode.[5] Bipolar disorders are treated to minimize the frequency of manic and depressive episodes, and to reduce the severity of symptoms to enable a relatively normal and productive life.[6] Lithium carbonate is the most commonly prescribed long-term drug to treat long-term episodes of depression and mania or hypomania.[7] Other treatments include anticonvulsants, antipsychotics. Due to side effects of antipsychotic drugs anticonvulsants drugs are preferred in bipolar disorders.[8]

Amongst the various anticonvulsants Carbamazepine is widely used as a second line treatment in bipolar disorder.[7] Carbamazepine is used in Bipolar Disorders since 1970.[9] It was first evaluated as a potential treatment in manic depressive psychosis.[10] Traditionally, carbamazepine is used alone or in combination with other medications to control certain types of seizures in people with epilepsy. It works by reducing abnormal electrical activity in the brain. Nowadays, carbamazepine is used to treat episodes of mania or mixed episodes in patients with bipolar I disorder.[11]

The aim of this review is to focus on the bipolar disorder and potential use of Carbamazepine in the treatment of bipolar disorder.

### Bipolar disorder

Bipolar Affective [Mood] Disorders are a class of psychiatric disorders that are most distressing either from the point of view of patients [as in depressive phase] or from that of the care givers [as in manic counterpart]. These disorders have potential remission inbuilt in their defining criteria [American Psychiatric Association, 2000; World Health Association, 2002]. They also are recognized as the Psycho-behavioral disorders that are the most well studied ones from the point of view of efficacy of Pharmacotherapy. Lithium Carbonate was the first drug that demonstrated its therapeutic and prophylactic potential against recurring Bipolar Affective [Mood] Disorder. Over the years, many new molecules have been examined regarding their thymoleptic properties and a huge literature has gathered. In the other vein, data regarding individual-based and family-based psycho-social interventions have also accumulated.

There is a compelling need to review all such data to see where we stand as far as global scientific database is concerned. Simultaneously, we also need to see from the point of view of our country i.e. whether and how our unique circumstances suggest any differences to be considered in management of Bipolar Affective [Mood] Disorders in India. It should be emphasized that observations and opinions made in this review are only general guidelines and the exact and the best treatment strategies in an individual case have to be based on a number of considerations unique to that case. Further, the data reviewed-principally pertain to the pharmacological management and refers to the adult population unless specified otherwise. The abbreviation 'BPAD' has been repeatedly used in this paper to represent the term 'Bipolar Affective Disorders'.

Bipolar disorder also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.[12] It was found that patients with bipolar disorder had lower GABA levels, which results in excitotoxicity and can cause apoptosis (cell loss).[10] According to some experts the Bipolar disorder is caused by severe emotional distress, sexual or physical abuse, traumatic events, losing someone very close to you, like a parent or career, some stressful life events like a relationship breakdown, money worries and poverty, experiencing a traumatic loss etc. In some instances, symptoms occur during stressful period or self - esteem problems, brain chemistry or genetic inheritance, biological differences, neurotransmitters and hormones.[11,13]

There are four basic types of bipolar disorder such as Bipolar I Disorder which is defined by manic episodes or symptoms that last for at least 7 days. Usually, depressive episodes that last for at least 2 weeks. Episodes of depression with mixed features (having depression and manic symptoms at the same time) are also possible. Bipolar II Disorder is a pattern of depressive episodes and hypomanic episodes, but not the full-blown manic episodes described above. Cyclothymic Disorder (also called Cyclothymia) defined as numerous periods of hypomanic symptoms as well as depressive symptoms lasting for at least 2 years (1 year in children and adolescents). Other Specified and Unspecified Bipolar and Related Disorders are defined by bipolar disorder symptoms that do not match the three categories listed above.[12]

The pathophysiology of bipolar disorder discourses to the changes of normal physiological and biochemical functions associated with the disorder.[14] There is a relapse in patients suffering from bipolar disorder which is a common problem. Long-term maintenance treatment is required to prevent or attenuate the risk of relapse due to its chronic nature of illness.[9] The main goals of treatment in bipolar disorder are the acute management of manic and depressive episodes and the prevention of future episodes. Mood stabilizers are currently the basis of most treatment regimens. Amongst the various drugs, lithium is the classic mood stabilizer used in treating acute and chronic bipolar disorder.[4] However, it exhibits inadequate prophylactic response in the patient. Nowadays, it is not ideal for many patients due to its narrow therapeutic index undesirable side effects and its zero effect in patients with atypical disease and rapid cycling.[15]

So, Carbamazepine (CBZ), the first anticonvulsant used in bipolar disorder, was recognized as a useful medication in the 1970s. Substance abuse is a common problem in bipolar disorder (present in approx. 50% of patients) and it can com-plicate treatment. Comorbid psychiatric and neurological disorders are also prevalent and include panic disorder, social phobia, obsessive–compulsive disorder and post-traumatic stress disorder.[4]

**Convulsion**

Epilepsy or Convulsion is a chronic non - communicable disease of the brain that affects people of all ages. Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. Approximately 80% of people with epilepsy live in low- and middle-income countries. It is estimated that up to 70% of people living with epilepsy could live seizure- free if properly diagnosed and treated. The risk of premature death in people with epilepsy is up to three times higher than for the general population.[16] In 2015, 1.2% of the US population had active epilepsy (95% Critical Illness (CI) = 1.1-1.4). Near about 3.4 million people are suffering from epilepsy nationwide of whom 3 million are adults and 470,000 are children.[17] Of the 70 million Persons With Epilepsy (PWE) worldwide, nearly 12 million PWE are expected to reside in India; which contributes to nearly one-sixth of the global burden.[18]

A convulsion is a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body.[19] The word "fit" is sometimes used to mean a convulsion or epileptic seizure.[20] Convulsion is sometimes used as a synonym for seizure and epileptic seizures typically include convulsions. However, not all epileptic seizures lead to convulsions, and not all convulsions are caused by epileptic seizures. Convulsions are also consistent with an electric shock and improper enriched air scuba diving.[21] Convulsive states have been observed in the systems where the conc. of GABA in brain is below certain level, the effect of GABA is blocked and in epileptic or convulsive patients it is observed that there is an accumulation of sodium ions within cerebral neurons.[22] There are major two types of epilepsy such as focal seizures and generalized seizures. Focal (or partial) Seizures occur when seizure activity is limited to a part of one brain hemisphere. There are two types of focal seizures such as Focal seizures with retained awareness and Focal seizures with loss awareness.

Generalized seizures occur when there is widespread seizure activity in the left and right hemispheres of the brain. The different types of generalized seizures are - a)absence seizures (formerly known as petit mal) b) tonic-clonic or convulsive seizures (formerly known as grand mal) c) atonic seizures (also known as drop attacks) d) clonic seizures e) tonic seizures f) myoclonic seizures. Apart from this there are two types of seizure such as infantile spasms and psychogenic Non-epileptic Seizures (PNES).[23]

Anticonvulsants (also commonly known as antiepileptic drugs or as antiseizure drugs) are a diverse group of pharmacological agents used in the treatment of epileptic seizures.[24] Conventional antiepileptic drugs like Carbamazepine may block sodium channels or enhance γ-aminobutyric acid (GABA) function. Several antiepileptic drugs have multiple or uncertain mechanisms of action.[25] Anticonvulsant drugs inhibit the neuronal discharge or its spread. It reduces cell membrane permeability to ions, particularly sodium ions which are responsible for generation of action potential. It also enhances the activity of GABA which increases the membrane permeability of chloride ions. It also inhibits the excitatory neurotransmitters e. g. Glutamate.[26,27] Generally, carbamazepine decreases neuronal excitability or enhances inhibition by altering sodium, potassium or calcium conductance or by affecting the δ-aminobutyric acid (GABA), glutamate or other neurotransmitters that may be concerned in seizure activity.[26]

**Carbamazepine**

Carbamazepine, 5H-dibenz [b, f] azepine-5-carboxamide is an anticonvulsant and specific analgesic for trigeminal neuralgia.[27] Carbamazepine was discovered in 1953 by Swiss chemist Walter Schindler in Basel, Switzerland.[28,29,30,31] Dalby reported its psychotropic effects, most notably mood stabilization, in patients with temporal lobe epilepsy (TLE) (I) in 1971.[32] It was first marketed as a drug to treat epilepsy in Switzerland in 1962 under the brand name "Tegretol" for its use to treat trigeminal neuralgia. It has been used as an anticonvulsant and antiepileptic.[33] It is included in World Health Organization's List of Essential Medicines, which lists the most effective and safe medicines needed in a health system. It is approved medication in 1968 in the United States, with more than 2 million prescriptions written yearly.[34]

Carbamazepine is structurally similar to the tricyclic antidepressant imipramine.[35] Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol, acetone, chloroform, dimethylformamide and in propylene glycol. Its molecular weight is 236.27.[36] Its partition coefficient ($K_{o/w}$) and dissociation constant (pKa) values are 2.45 and 13.9 respectively.[37] Its plasma half-life is about 30 h in a single dose. Its oral bioavailability is 80% and peak plasma level is achieved within 2-8 h after a single dose. 70-80% drug bound to the plasma proteins.[10] CSF levels are dependent on the level of unbound drug in plasma. Metabolism occurs primarily in the liver via the cytochrome P-450 oxidase system, producing carbamazepine- l0, l1-epoxide which is as active and may reach levels up to half that of carbamazepine. This is almost entirely converted to carbamazepine-trans-l0, l1 - dihydrodiol by epoxide hydrolase before excretion in the urine.[38] The epoxide is 50% protein-bound in plasma. It induces hepatic enzymes, thus enhancing its own metabolism.[39] Therefore, 30 -hour half-life of a single oral dose drops to 20 hours at three weeks at 12 hours after several months. The half-life is reduced in patients who simultaneously take other inducers of hepatic enzymes such as phenobarbital, phenytoin, or alcohol. Carbamazepine also enhances the metabolism of phenytoin and warfarin for the same reason. The most common side effect is an allergic skin rash which occurs in 5% to 15% of treated patients. This may be accompanied by sore throat, mucosal ulceration and low grade fever. Antihistamines can be effective in eliminating allergic symptoms, though the rash may require discontinuation of carbamazepine. Carbamazepine-induced agranulocytosis has received much attention because of its mortality rate of up to 50%. However, less than thirty cases have been reported. This idiosyncratic reaction has a prevalence of one in 20,000 to 40,000 and is unrelated to a harmless 25% decrease in white cell count which is fairly common. About 10% of patients receiving the drug develop a mild dose-related leukopenia which resolves within the first four months. Of these, approximately 2% continue with a persistent leukopenia which necessitates discontinuation of therapy. Neurotoxic side effects of carbamazepine may include drowsiness, vertigo, ataxia, diplopia, and blurred vision. Patients acutely intoxicated on the drug can exhibit sedation, respiratory depression, hyper irritability, and even seizures. Other side effects include nausea and vomiting, and hepatotoxicity ranging from mild elevation of serum transaminases to acute hepatitis. In addition, chronic administration can also cause a condition resembling the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), with water retention, hyponatremia, and possible water intoxication.[32]

Carbamazepine is a mood stabilizer which is approved for use in bipolar disorder with manic and mixed episodes.[40] Carbamazepine is a GABA receptor agonist so it potentiates GABA receptors made up of α1, β2, and γ2 subunits and this mechanism may contribute to its efficacy in neuropathic pain and bipolar disorder. It exerts effects by decreasing dopamine turn over, enhancement of brain γ-aminobutyric acid (GABA) levels via multiple actions of synthesis, degradation and modulation of other neurotransmitters, voltage sensitive Na+ channels, extra hypothalamic neuropeptides, secondary messenger systems, and neuro protection.[41] In the review article, pharmacological management of bipolar disorder; Rajasuriya M et al (2014) synthesized

current evidence for management of bipolar disorder and concluded that for prophylaxis lithium, valproate and carbamazepine are effective while lamotrigine is primarily effective in preventing depressive episodes.[42] From the available data of carbamazepine, Brambilla et al. 2001 reviewed the available literature on the efficacy of carbamazepine, valproate, and other newer anticonvulsants for the treatment of bipolar disorder and concluded that Carbamazepine and valproate have been shown to be effective in the acute treatment of bipolar disorder, and are the first-choice treatments for lithium-refractory patients.[43]

Chen CH et al. reported a follow - up study of Carbamazepine treated bipolar patients and concluded that the carbamazepine is efficacious and tolerable in the maintenance therapy of bipolar disorder in naturalistic clinical practice, either as monotherapy or in combination with other medication.[9]

In the review of Anticonvulsants used in Psychiatric conditions Khouzam HR summarized US FDA approved drugs such as Carbamazepine, Divalproex and Lamotrigine in the treatment of various psychiatric disorders and concluded that carbamazepine and divalproex, are FDA approved for treating acute manic or mixed episodes associated with bipolar I disorder in adults and may be beneficial for bipolar disorder maintenance treatment.[44]

Okuma et al. (1979) performed the first double-blind trial of carbamazepine in comparison with the antipsychotic chlorpromazine in mania and found that 70% and 60% of patients improved respectively and the efficacy of carbamazepine was demonstrated in treating the acute manic and depressive symptoms of bipolar disorder, as well as in prophylaxis.[45]

Weisler RH (2005) studied two randomized, double blind, placebo controlled trials and open label extension studies and demonstrated that extended release capsules are safe and efficacious for the patients with Bipolar –I Disorder.[46]

Gould et al 2004 studied the mechanism of action of CBZ as an antagonist at Adenosine Receptors, which are generally G-protein-coupled receptors that modulate neurotransmitter release and numerous behavioral and cognitive functions. Also, it is reported that CBZ inhibits the enzyme adenylyl cyclase, which attenuates cyclic AMP-mediated signaling and may lead to inhibition of downstream activities with ion channels and transcription factors.[47]

Denicoff et al. 1994, Di Costanzo and Schifano, 1991, Kishimoto 1992 have noted the improved efficacy of lithium and carbamazepine as combination therapy than monotherapy.[48]

## CONCLUSION

Carbamazepine is most effective and tolerable drug particularly used in the maintenance therapy of bipolar disorder in naturalistic clinical practice. In naturalistic clinical practice, many times CBZ is used either as monotherapy or in combination with other medications. Most of the patients give a good response to CBZ in bipolar disorders and tend to continue to do well over the long term. CBZ treatment improved illness condition of patient with bipolar disorder.

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