

# Mood Stabilizers in Bipolar Disorder: A Depth Comprehensive Review Article

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## ABSTRACT

Mood stabilizers are the preferred treatment modality for bipolar disorder. Given the global prevalence and the alarming risk of suicide among individuals suffering from bipolar disorder, it is pertinent to discuss the use and adverse effects associated with the commonly used mood stabilizers. Aim of the study: To establish a better understanding of the administration of mood stabilizers in the treatment of bipolar disorder. Materials and methods: This review is a comprehensive search of PUBMED from the year 2010 to 2026. Conclusion: Mood stabilizers are the foundation of pharmacological therapy in the treatment of bipolar disorders. Use of mood stabilizers helps patients of bipolar disorder to achieve normalcy in life by helping them manage the manic and depressive episodes. The advancement and more profound understanding of these drugs and possible combinations can help to provide a better quality of life to the patients and reduce the associated risk of suicide.

**Keywords:** *Bipolar disorder; Mood stabilizers; Lithium; Anticonvulsants; Diagnosis; Treatment*

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## INTRODUCTION

Mood stabilizers are psychiatric medications used in the treatment of bipolar disorder. These drugs help in preventing relapses into both manic and depressive episodes in bipolar disorder, and aid in maintaining long-term mood stability.<sup>[1]</sup> This group of drugs particularly involves lithium and anticonvulsants like lamotrigine and valproate.<sup>[2]</sup> These drugs are also utilized in bipolar type of schizoaffective disorders and as adjuncts for treatment-resistant major depressive disorder.<sup>[3]</sup> To establish a better understanding of the administration of mood stabilizers in bipolar disorder, a deeper comprehension of bipolar disorder is required.

### Bipolar Disorder

Bipolar disorder is a mental health condition that is characterized by 'periodic, intense emotional states affecting a person's mood, energy, and ability to function.' These periods- known as mood episodes can last from days to weeks. Mood episodes with predominantly intensely happy or irritable are referred to as manic/hypomanic episodes, and those with extremely intense sad mood or with the inability to experience joy or pleasure are referred to as depressive episodes.<sup>[4]</sup> bipolar disorder affects 1 in 200 people worldwide, with no significant gender predilection, but women get diagnosed

more often. It is primarily observed in the working-age group and in youth.<sup>[5]</sup> The average age of onset is in the mid-20s.<sup>[4]</sup>

### Etiopathogenesis

The etiology of bipolar disorder is not well-understood, but structural and functional MRI scan studies suggest differences in the areas of the brain involving risk-reward and regulating emotions due to gray matter reduction in the left rostral anterior cingulate cortex (ACC) and right fronto-insular cortex. In long-standing cases, there was evidence of increased gray matter in a cluster that included basal ganglia, subgenual ACC, and amygdala.<sup>[6]</sup> Strakowski et al suggest that early development disruptions with the neuronal network that modulate emotional behavior result in reduced connectivity among the ventral prefrontal networks and limbic brain regions- especially the amygdala. This developmental failure to institute healthy ventral prefrontal-limbic modulation leads to the onset of mania and eventually, with escalating changes within these networks with affective episodes, leads to bipolar illness.<sup>[7]</sup> Another theory suggests that bipolar disorder is caused by dysfunction of the HPA-axis.<sup>[8]</sup> Bipolar disorder has a genetic component: about 80-90 percent of individuals experiencing bipolar disorder have a relative with bipolar disorder or depression. Mood

*\*Author for Correspondence: Muhannad Abdulaziz Almoajil*

## Mood Stabilizers in Bipolar Disorder: A Depth Comprehensive Review Article

episodes may also be triggered by environmental factors such as stress, sleep disruption, drugs, and alcohol in vulnerable individuals.<sup>[4]</sup>

### Classification and diagnosis

Bipolar disorder can be classified as: bipolar I, bipolar II, and cyclothymic disorder.<sup>[4]</sup> If any of the symptoms are due to drug use or medical problems- they are not diagnosed with bipolar disorder.<sup>[9]</sup> Approximately 2% of the population suffers from bipolar I and II, while as much as 6% of the population is estimated to be affected by bipolar spectrum disorder.<sup>[10][11]</sup> Sleep disturbances are common in individuals experiencing bipolar disorder.<sup>[12]</sup>

Depressive episodes or symptoms comprise about 75% of the symptomatic time.<sup>[10]</sup>

### Bipolar Disorder I

Individuals with bipolar I can experience three types of mood episodes: manic episodes, hypomanic episodes, and major depressive episodes. Most individuals also experience periods of neutral mood. Individuals with bipolar disorder I frequently suffer from other mental disorders such as anxiety disorder, substance abuse disorder, and/or attention-deficit hyperactivity disorder (ADHD).<sup>[4]</sup> These individuals also have a higher risk of suicide, with nearly 15-20% people dying by suicide.<sup>[10]</sup>

**Table 1: Symptoms of Bipolar Disorder I.**<sup>[4]</sup>

Types of Mood Episode	Characteristics
Maniac Episode	<ul style="list-style-type: none"> <li>• It is a period of at least one week where the person is extremely high-spirited or irritable most of the day for most days, possesses more energy than usual, and experiences at least three of the following changes in behavior:                             <ol style="list-style-type: none"> <li>1. Reduced need for sleep</li> <li>2. Increased or faster speech</li> <li>3. Increased activity (e.g., restlessness, working on several projects at once)</li> <li>4. Increased risky or impulsive behavior (e.g., reckless driving, spending sprees, sexual promiscuity)</li> <li>5. Uncontrollable racing thoughts or quickly changing ideas or topics when speaking</li> <li>6. Distractibility</li> </ol> </li> <li>• The symptoms must be severe enough to cause dysfunction with regards to work, family, or social activities and responsibilities</li> <li>• Some people might even experience psychotic symptoms such as disorganized thinking, false beliefs, and/or hallucinations</li> </ul>
Hypomanic Episode	<ul style="list-style-type: none"> <li>• It is characterized by less severe manic symptoms that are required to last only four days in a row rather than a week.</li> <li>• These hypomanic episodes do not lead to major problems in daily functioning that might be commonly caused by manic symptoms</li> </ul>
Major Depressive Episode	<ul style="list-style-type: none"> <li>• It is a period of at least two weeks in which a person experiences intense sadness or despair or a loss of interest in activities the person once enjoyed and at least four of the following symptoms:                             <ol style="list-style-type: none"> <li>1. Feelings of worthlessness or guilt.</li> <li>2. Fatigue.</li> <li>3. Restlessness (e.g., pacing) or slowed speech or movement.</li> <li>4. Difficulty concentrating.</li> <li>5. Increased or decreased sleep.</li> <li>6. Increased or decreased appetite.</li> <li>7. Frequent thoughts of death or suicide.</li> </ol> </li> </ul>

### Bipolar Disorder II

These individuals are diagnosed by experiencing at least one depressive episode and at least one hypomanic episode. It is common for these individuals to return to their usual functioning between the episodes. Depressive episodes are the main reason individuals with bipolar disorder II seek treatment, since hypomanic episodes often feel pleasurable and can even increase performance at school or work. Other disorders, such as anxiety disorder or substance use disorder, the latter of which can cause exacerbation of depressive or hypomanic symptoms.<sup>[4]</sup>

### Cyclothymic Disorder

Cyclothymic disorder is a milder form of bipolar disorder that involves many 'mood swings' with hypomania and depressive symptoms that occur frequently. Compared to bipolar I and II, people with cyclothymia experience emotional ups and downs but with less severe symptoms.<sup>[4]</sup>

The symptoms of cyclothymia include<sup>[4]</sup>

- Many periods of hypomanic and depressive symptoms for at least two years, but the symptoms do not match the criteria for hypomanic or depressive episodes
- During the two-year period, the symptoms (mood swings) would last for at least half the time and have never stopped for more than two months

## Mood Stabilizers in Bipolar Disorder: A Depth Comprehensive Review Article

### Treatment

The major modality of treatment of bipolar disorder involves the use of medication and psychotherapy. In cases where treatment is not effective, electroconvulsive therapy (ECT) can be used.<sup>[4]</sup> It is especially effective in acute mania and depressive episodes, especially those with psychosis or catatonia.<sup>[13]</sup> Diagnosis and optimal care in patients are often delayed by an average of approximately 9 years following the onset of the initial depressive episode. It is also noted that more than 50% patients with bipolar disorder do not adhere to treatment.<sup>[7]</sup>

The medication for bipolar disorder involves the use of mood stabilizers and antipsychotics.

### Mood Stabilizers

Mood stabilizers are the primary pharmacotherapeutic agents used in the treatment of bipolar disorder. According to Rybakowski et al, the mood stabilizers should fit the following three criteria: demonstrate therapeutic efficacy on manic and/or depressive symptoms during acute episodes, prevent the recurrence of manic and/or depressive episodes, and ensure that the drug neither induces nor exacerbates manic or depressive episodes or mixed states. The drug should be administered for a minimum of 1 year and should not worsen manic or depressive episodes.<sup>[14]</sup> These agents can be classified as: minerals (lithium), anticonvulsants, antipsychotics, and others-omega-3 fatty acids and levothyroxine.

### Lithium

Lithium is the classic mood stabilizer, which was the first drug to be approved by the FDA.<sup>[15]</sup>

Lithium has a very low therapeutic index- 2.8 and requires regular dose monitoring. The serum levels for maintenance dosage in bipolar disorder should range from 0.40 mmol/L to 0.80 mmol/L. The toxicity associated with lithium commonly affects the CNS and renal system.<sup>[16]</sup> It has been shown to erode kidneys and thyroid function over time.<sup>[2]</sup> The clinical features of lithium toxicity include nausea, vomiting, diarrhea, and ataxia.<sup>[13]</sup> Lethargy and weight gain (up to 2kg) are the most common side effects, with the less common ones being blurred vision, a slight tremble in the hands, and malaise.<sup>[17]</sup> These symptoms can be mitigated by reducing the dose.<sup>[18]</sup>

The hypothesized mechanisms of action include ion dysregulation, effects on neurotransmitter signaling, the interaction with the adenylyl cyclase system, inositol phosphate and protein kinase C signaling, and possible effect on arachidonic acid metabolism.<sup>[13]</sup> Lithium is preferred for long-term stabilization of mood.<sup>[19]</sup> Lithium is associated with enlargement of ACC gray matter volumes, which overlapped with the regions that were reduced in bipolar disorder.<sup>[6]</sup> It is a unique psychiatric medication that has proven anti-suicidal properties.<sup>[1]</sup> Lithium has the strongest evidence for long-term relapse prevention.<sup>[19]</sup>

### Anticonvulsants

This is a group of pharmaceutical agents that is primarily indicated for the treatment of epilepsy and seizure disorders. Despite their primarily antiseizure activity, these drugs have shown efficacy as mood-stabilizing agents in the treatment of mood disorders.<sup>[20]</sup>

**Table 2:** Anticonvulsants used in bipolar disorder.

Anticonvulsants	Indications	Mechanism of Action	Adverse Effects
Valproate	<ul style="list-style-type: none"> <li>Acute mania</li> <li>Maintenance of bipolar disorder <sup>[21]</sup></li> </ul>	<ul style="list-style-type: none"> <li>Inhibits GABA transaminase and ↑ GABAergic activity → ↓neuronal excitability</li> <li>Inactivation of sodium and calcium channels <sup>[22]</sup></li> </ul>	<ul style="list-style-type: none"> <li>Sleepiness</li> <li>Nausea</li> <li>Dry mouth</li> <li>Liver dysfunction</li> <li>Pancreatitis</li> <li>Polycystic ovary syndrome</li> <li>weight gain <sup>[23]</sup></li> <li>Potentially teratogenic <sup>[24]</sup></li> </ul>
Carbamazepine	<ul style="list-style-type: none"> <li>Second-line bipolar disorder <sup>[25]</sup></li> </ul>	<ul style="list-style-type: none"> <li>Inhibits sodium channels <sup>[22]</sup></li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms</li> <li>Stevens-Johnson syndrome</li> <li>Toxic epidermal necrolysis</li> <li>Weight gain</li> <li>Potentially teratogenic <sup>[24]</sup></li> </ul>
Lamotrigine	<ul style="list-style-type: none"> <li>Maintenance therapy for bipolar disorder <sup>[26]</sup></li> </ul>	<ul style="list-style-type: none"> <li>inhibiting voltage-gated sodium channels</li> <li>reducing neuronal hyperexcitability</li> </ul>	<ul style="list-style-type: none"> <li>Stevens-Johnson syndrome <sup>[26]</sup></li> <li>Potentially teratogenic <sup>[28]</sup></li> </ul>

		<ul style="list-style-type: none"> <li>• suppressing the release of excitatory neurotransmitters like glutamate [27]</li> </ul>	
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**Antipsychotics**

Atypical antipsychotics are utilized for acute manic episodes or in case mood stabilizers are not effective or not tolerated by the patient. Long-term injectables are available to aid in adherence issues with patients.<sup>[11]</sup> Most commonly used antipsychotic agents are quetiapine, aripiprazole, asenapine, lurasidone, and cariprazine, but they are associated with weight gain.<sup>[10]</sup> A study by Kishi et al found that asenapine outperformed other drugs such as aripiprazole, carbamazepine, lamotrigine, lithium, paliperidone, RISLAI, and valproate.<sup>[29]</sup>

**Combination therapy**

As noted by Geoffroy et al, monotherapy is often inadequately effective for acute and/or maintenance therapy. This necessitates the need for combination therapy. Combination therapy involving antipsychotics with lithium or valproate has demonstrated effectiveness in dealing with the control of manic episodes along with the prevention of relapse.<sup>[30]</sup> Kishi et al noted that the combination of aripiprazole and valproate outperformed lamotrigine and paliperidone.<sup>[29]</sup> However, in contrast to monotherapy, there are higher rates of discontinuation due to the frequency of side effects in combination therapy.<sup>[30]</sup>

**CONCLUSION**

Mood stabilizers are the foundation of pharmacological therapy in the treatment of bipolar disorders. Use of mood stabilizers helps patients with bipolar disorder to achieve normalcy in life by helping them manage the manic and depressive episodes. The advancement and more profound understanding of these drugs and possible combinations can help to provide a better quality of life to the patients and reduce the associated risk of suicide.

**Conflict of Interest**

The authors declare they don't have any conflict of interest.

**Author contributions**

The original author and the supervisor of the cross-pending author write the work's initial drafts. Each author contributed to the article, gathered information, revised it, made tables, and was authorized to submit it to a journal for publication.

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Not Applicable

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Mood Stabilizers in Bipolar Disorder: A Depth Comprehensive Review Article

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