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Emerging Pharmacotherapies for Mania and Bipolar Disorder: A Neuropharmacological Perspective

SHIVAM KUMAR JHOOMUCK*

GITAM School of Pharmacy, GITAM (Deemed to be University)

ajhshiv00@gmail.com

Gandhi Nagar, Rushikonda, Visakhapatnam - 530045, Andhra Pradesh, India

ABSTRACT

Bipolar disorder (BD) is a recurrent and chronic mental condition characterised by episodic mood switching between mania, hypomania, and depression. Despite the available treatment with mood stabilisers and atypical antipsychotics, most patients are poorly responsive, experience delayed therapeutic effects, and suffer from severe side effects. Recent advances in the field of neuropharmacology have identified new therapeutic targets and drugs that aim to improve efficacy and tolerability in the treatment of bipolar disorder, particularly in manic episodes. This review focuses on new pharmacological interventions in bipolar disorder from a neuropharmacological perspective, such as dopamine and serotonin modulators, glutamatergic system modulators, and anti-inflammatory agents, such as minocycline and N-acetylcysteine. Further, the involvement of endocannabinoid modulators, gut-brain axis-targeting and the growing contribution of pharmacogenomics towards personalising the treatment approach to bipolar disorder is discussed. These developments represent a transition towards mechanism-based, individualised treatment approaches in bipolar disorder. Such studies are needed to define the long-term safety, efficacy, and optimal use of these novel agents, which have the potential to significantly enhance clinical outcomes in this complex disorder.

KEYWORDS: Neuropharmacology, Bipolar Disorder**,** Mania**,** Mood Stabilisers**,** Pharmacogenomics

INTRODUCTION

Bipolar disorder (BD) is a severe, chronic psychiatric illness that is defined by the presence of recurrent episodes of mania, hypomania, and depression, and it occurs in approximately 1-2% of the global population[1]. Manic episodes are marked by increased mood, increased energy, reduced need for sleep, and impulsive behaviour, which are typically followed by significant social and occupational impairment [2]. The illness is associated with high morbidity rates, high suicide risk, and significant reduction in quality of life[3]. Pharmacological treatment remains the cornerstone of the management of bipolar disorder. Conventional mood stabilisers such as lithium, valproate, and carbamazepine, and atypical antipsychotics are widely used in clinical practice[4]. However, the effectiveness of these treatments is often compromised by slow onset of action, incomplete response, and side effects like metabolic changes, sedation, and cognitive impairment[5]. In addition, a significant number of patients are refractory to these treatments, and thus new therapeutic strategies need to be developed[6]. Recent progress in the area of neuropharmacology has greatly improved the understanding of the complex neurobiological mechanisms of bipolar disorder. Apart from the traditional focus on monoamines, recent evidence indicates that the pathophysiology of the illness is dominated by glutamatergic neurotransmitter dysfunctions, neuroinflammation, oxidative stress, and the gut-brain axis[7,8]. These developments have hastened the creation of new pharmacological therapies for these processes, such as glutamate modulators, anti-inflammatory agents, cannabidiol (CBD), and neuroprotective drugs[9,10]. Furthermore, pharmacogenomics and personalised medicine strategies are gaining more prominence, with the focus on maximising treatment according to genetic variation and patient response patterns[11].

CURRENT STANDARD PHARMACOTHERAPIES

Until recent years, the foundation of bipolar disorder treatment was a combination of mood stabilisers, antipsychotics, and in certain instances, antidepressants. Lithium, the most widely utilised mood stabiliser, is the standard drug in treating bipolar disorder, especially in the prophylaxis of manic assault and suicide attempts. The effectiveness of lithium is well established, and it has been demonstrated to decrease the frequency and intensity of manic and depressive attacks. Yet, its narrow therapeutic index, necessitating regular blood monitoring, and its potential to include side effects such as renal impairment, thyroid dysfunction, and weight gain, are still major drawbacks[12].

Valproate and lamotrigine, both anticonvulsants, are also commonly used as mood stabilisers in bipolar disorder. Valproate is especially useful in the acute treatment of mania, and it is usually reserved for lithium-resistant or lithium-contraindicated patients. Valproate is not without side effects, however, such as hepatotoxicity and teratogenicity, which restrict its long-term use; its use is especially restricted in females of childbearing age[13]. Lamotrigine, in particular, is more effective in the prevention of depressive episodes and possesses a better side effect profile, and therefore it is the drug of choice in maintenance therapy[14]. Atypical antipsychotics olanzapine, quetiapine, and aripiprazole are generally utilised as adjuncts to mood stabilisers in the management of acute mania and depression. These medications operate on multiple systems of neurotransmitters like serotonin, dopamine, and glutamate to stabilize mood and control psychotic symptoms. Olanzapine and quetiapine have proven to be efficacious in both manic and depressive states, while aripiprazole is generally utilised in maintenance therapy for the prevention of relapses. Although effective, atypical antipsychotics have side effects, such as metabolic dysfunctions like weight gain, diabetes, and dyslipidemia, which constrain their long-term use in certain patients[15].

Antidepressant use in bipolar disorder remains controversial due to the risk of inducing mania or rapid cycling, particularly in patients with type I BD. They are, however, used in bipolar depression, but only as an adjunct to mood stabilisers, the most commonly used being selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Vigilant monitoring for the development of manic symptoms is necessary when antidepressants are used in patients with BD[16].

EMERGING PHARMACOLOGICAL TARGETS AND THERAPIES

1. Dopamine and serotonin modulators

The dopaminergic and serotonergic systems are central to the pathophysiology of bipolar disorder, particularly in mania. Dopamine neurotransmission deregulation is associated with mood lability and affective symptoms[17,18]. The classical antipsychotic drugs primarily act on dopamine D2 receptors but are limited because of the risk of extrapyramidal side effects and metabolic disorders[19]. The progress in pharmacotherapy has introduced atypical antipsychotics with multi-receptor activity with increased tolerability and efficacy.

Cariprazine, a new atypical antipsychotic medication, is a partial agonist at dopamine D3 and D2 receptors with greater affinity for D3 receptors. It is also a partial agonist at serotonin 5-HT1A receptors, but also an antagonist at 5-HT2B receptors[20]. This distinctive receptor interaction profile is the foundation of its efficacy to induce antimanic, antidepressant, and procognitive effects. Clinical trials have demonstrated that cariprazine is effective in the treatment of acute manic and mixed states of type I BD, and it has a superior safety profile compared to traditional pharmacological agents[21].

Lumateperone is another new agent with a multimodal action. It is an antagonist of serotonin 5-HT2A receptor, a dopamine D2 receptor modulator, and a serotonin reuptake inhibitor[22]. The balanced activity of lumateperone at these receptors is responsible for its antimanic and mood-stabilising action, with a very low risk of motor side effects typical of other antipsychotics[23]. Its clinical utility in treating depressive and mixed features of bipolar disorder has been established in clinical trials, and further trials have evaluated its use in acute mania[24].

These new medications are a considerable step forward in the pharmacologic treatment of BD, with greater receptor selectivity, greater tolerability, and greater mood-stabilising activity.

2. Glutamate system modulation

The glutamatergic system has been identified as a major target in neurobiological research of bipolar disorder, particularly that of mood instability and neurotoxicity in manic and depressive states. The brain's major excitatory neurotransmitter, glutamate, is involved in processes like synaptic plasticity, neurogenesis, and mood stabilization[25]. Glutamate signalling and receptor function, particularly the N-methyl-D-aspartate (NMDA) receptor, have been implicated in the pathophysiological processes of BD[26].

Ketamine, a noncompetitive antagonist at the NMDA receptor, has gained widespread attention due to its rapid action on antidepressant effects in treatment-resistant depression and bipolar disorder[27]. Subanesthetic doses of ketamine have yielded immediate effects in stabilizing mood, most notably in the reduction of suicidal ideation and improvement in depressive symptoms within hours of intake[28]. The mechanism is thought to involve blocking NMDA receptors on GABAergic interneurons, resulting in increased glutamate release and downstream AMPA receptor activation, culminating in synaptic plasticity and neurogenesis[29].

In addition, esketamine, the S-enantiomer of ketamine, has been studied for its antidepressant effects in patients with bipolar disorder. Although most of the available evidence is limited to unipolar depression, initial studies suggest potential benefits in treating bipolar depression when combined with mood stabilisers[30].

Other glutamate modulators that have been studied include memantine, a low-affinity NMDA antagonist, and NR2B-selective antagonists. Although clinical data are scarce, these medications are promising as adjunctive therapy for mood stabilisation and cognitive impairment in bipolar disorder[31].

3. Anti-inflammatory and antioxidant agents

Elevated pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), have been detected during mania and depression and also contribute to further neuroprogression and mood changes[32,33].

Minocycline, a second-generation tetracycline antibiotic with anti-inflammatory and neuroprotective activities, is one of the promising early-stage agents. It effectively exerts its effects by suppressing microglial activation, decreasing the production of pro-inflammatory cytokines, and suppressing oxidative stress[34]. Adjunctive minocycline has been tested in clinical trials to demonstrate that it can reduce depressive symptoms and cognitive impairment in bipolar depression but more large trials are required[35].

N-acetylcysteine (NAC), an anti-inflammatory, antioxidant agent and a glutathione precursor, has also been the focus of extensive research in mood disorders. NAC reduces oxidative damage and modulates glutamate neurotransmission, which might stabilize the mood and improve functional outcomes[36]. Numerous randomized controlled trials and meta-analyses have demonstrated that NAC, added to the standard therapies, actually reduces depressive symptomatology and also enhances the functioning of patients with BD[37,38].

In addition, omega-3 fatty acids rich in anti-inflammatory eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have demonstrated mild effectiveness in stabilising mood, particularly in bipolar depression. Their mechanisms of action include downregulation of pro-inflammatory cytokines and modulation of the neurotransmitter systems[39].

4. Endocannabinoid modulators

The endocannabinoid system (ECS), with endogenous cannabinoids (such as anandamide and 2-arachidonoylglycerol), cannabinoid receptors (CB1, CB2), and related enzymes, is now known for its involvement in regulating mood, stress response, and neuroprotection. Dysregulation within the whole system has been implicated throughout the pathophysiology of bipolar disorder, alongside altered endocannabinoid levels that are reported amid manic and depressive episodes[40].

Cannabidiol (CBD), a phytocannabinoid without psychoactive effects, exhibits pharmacological effects of complexity, including modulation of CB1 and CB2 receptors, serotonin receptors of 5-HT1A, and channels of transient receptor potential vanilloid type 1 (TRPV1) [41]. CBD exerts anxiolytic, antipsychotic, as well as neuroprotective, and anti-inflammatory effects, as suggested in preclinical studies[42]. These effects of CBD include anxiolytic, antipsychotic, and neuroprotective ones, along with anti-inflammatory properties[43]. Clinical trials, throughout earlier phases, have explored its possible role as an adjunctive treatment with respect to mood disorders, including BD; although larger well-controlled studies are still needed still[44].

Also, research on fatty acid amide hydrolase (FAAH) inhibitors, which do elevate endogenous anandamide levels via preventing its degradation, has also shown a little promise in modulating mood and stress responses within animal models of mania and depression[45].

5. Gut-brain axis and microbiota-targeted therapies

More recent studies have also identified the gut-brain axis as an important modulator of mood and behavior and have gone as far as to propose that dysbiosis of gut microbiota has a role to play in BD pathophysiology. Dysbiosis of gut microbiota has been linked to systemic inflammation, imbalance of neurotransmitters, and modification of stress response, all which have a role to play in mood disorders like BD[46].

Differences in the gut microbiota composition of bipolar disorder patients and healthy controls have also been reported in recent studies, including a significant decrease in beneficial bacterial species like Lactobacillus and Bifidobacterium and an increase in inflammatory bacteria[47].

Probiotics (live and active cultures of bacteria), prebiotics (digestive foods that promote growth of good bacteria), and psychobiotics (psychologically beneficial probiotics) are being explored for their mood-

stabilizing and anti-inflammatory effects in BD. Probiotics containing Lactobacillus and Bifidobacterium strains have been noted to have a beneficial effect on mood symptoms, inflammation, and oxidative stress in initial clinical trials[48].

For example, a double-blind, placebo-controlled trial demonstrated that adjunctive probiotic treatment reduced rehospitalization rates among patients with mania significantly[49]. Similarly, preclinical studies have implicated that modulation of gut microbiota affects neurotransmitter systems, i.e., GABA, serotonin, and dopamine, which have a central function in BD pathophysiology[50].

6. Pharmacogenomics and personalized medicine

Pharmacogenomics is an emerging discipline that investigates how gene variation affects what occurs when individuals receive medications. In BD, variation among people in what medicines do, drug tolerance, and the probability of side effects presents a formidable obstacle for doctors. Finding genetic markers linked to such variation holds a great deal of promise for designing individualised treatment regimens. One of the most investigated fields is lithium responders versus non-responders. Approximately 30–60% of BD patients are responders to long-term lithium therapy, but there are others with insufficient effects or side effects[51]. Genetic research has identified potential markers related to lithium response, e.g., GSK3β, BDNF, and SLC6A4 gene polymorphisms, which affect processes of neuroplasticity, neurotransmitter regulation, and stabilization of mood[52].

Aside from lithium, there have been pharmacogenomic studies of genetic influences on anticonvulsant (e.g., valproate, lamotrigine) and antipsychotic (e.g., olanzapine, aripiprazole) metabolism and tolerance. Variants of the cytochrome P450 enzyme (e.g., CYP2D6, CYP3A4) may influence drug metabolism, with consequences for plasma concentrations, efficacy, and toxicity risk[53].

The future of personalized treatment plans in BD lies in the implementation of pharmacogenomic testing within clinical psychiatric care. This will enable clinicians to predict drug response and tolerability, select best treatments, and minimize trial-and-error prescribing. A number of studies and clinical guidelines now recommend the utilization of pharmacogenomic data, particularly for drugs with a narrow therapeutic window like lithium and in those with histories of adverse reactions or treatment resistance[54].

CONCLUSION

Bipolar disorder remains a complex and multifaceted psychiatric illness, characterized by intense mood fluctuations that include both manic and depressive phases. Despite significant progress in the neurobiologic basis, current pharmacologic interventions are often short in efficacy, side effect profiles, and ability to rapidly stabilize mood in the acute phase. Recent advances in neuropharmacology, such as novel agents that influence neurotransmitter systems, inflammatory mechanisms, and oxidative stress, hold the promise to improve the therapeutic paradigm for bipolar disorder.

The exploration of modulation of the glutamate system, specifically by NMDA receptor antagonists such as ketamine and esketamine, has led to the development of rapid-acting antidepressant treatments that have potential applications in bipolar depression. In a similar way, anti-inflammatory and antioxidant drugs, such as minocycline and N-acetylcysteine, offer an adjunctive strategy to modulate the neuroinflammatory elements that define bipolar disorder. In addition, endocannabinoid modulators and novel mood stabilizers, such as vortioxetine and lurasidone, offer further treatment options, especially for individuals who suffer from treatment-resistant depression or unique patterns of symptomatology.

Recent developments in genetic and epigenetic techniques significantly extend the scope for personalized treatment approaches. Complete comprehension of the genetic vulnerability and epigenetic changes related to bipolar disorder might enable the establishment of more targeted treatments, making treatments more effective and safer. Personalized medicine, based on genetic and epigenetic markers, is set to play an important role in the treatment of bipolar disorder in the future. As pharmacogenomic research advances, the integration of polygenic risk scores and gene-environment interactions can potentially further enhance personalized psychiatry for BD treatment.

In summary, the development of these new pharmacotherapies illustrates the evolving knowledge of the intricate neurobiological mechanisms underlying bipolar disorder. Ongoing research is needed to further refine these treatments, expand their application, and provide their availability to patients most in need.

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