Clinical Pharmacology of Bipolar Disorder: An Updated Review of Pharmacotherapeutic Strategies

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Abstract: Bipolar disorder (BD) is a chronic, recurrent psychiatric illness characterized by episodes of mania, hypomania, and depression that substantially impair psychosocial functioning and quality of life. Pharmacotherapy remains the cornerstone of both acute symptom management and long-term relapse prevention. Over the past decade, advances in clinical trials and international treatment guidelines have refined the role of mood stabilizers, second-generation antipsychotics, and adjunctive therapies across different phases of illness. This review summarizes the current clinical pharmacology of bipolar disorder, emphasizing mechanisms of action, pharmacokinetic and pharmacodynamic properties, efficacy, safety, and monitoring requirements of established and emerging pharmacological treatments. Attention is given to lithium, anticonvulsant mood stabilizers, second-generation antipsychotics, the management of bipolar depression, treatment-resistant bipolar disorder, medication adherence, and individualized treatment selection. Recent evidence regarding suicide prevention, renal safety, reproductive considerations, and novel therapeutic strategies is integrated with current guideline recommendations to provide an evidence-based framework for optimizing long-term clinical outcomes.

Keywords: Bipolar disorder, Bipolar depression, Mania, Antimanic agents, Antipsychotics, Lithium, Anticonvulsants, Mood stabilizers.

INTRODUCTION

Bipolar disorder (BD) is a severe, chronic psychiatric disorder affecting approximately 1–3% of the global population. It is characterized by recurrent episodes of mania, hypomania, depression, and mixed affective states that alternate with periods of partial or complete remission [1]. Despite advances in diagnosis and treatment, bipolar disorder remains among the leading causes of disability worldwide owing to its early age of onset, frequent relapses, high suicide risk, cognitive impairment, and substantial socioeconomic burden [2]. The principal objectives of pharmacological treatment are to achieve rapid symptom control during acute episodes, prevent future mood episodes, minimize treatment-related adverse effects, preserve cognitive and psychosocial functioning, and improve long-term quality of life. Because bipolar disorder follows a lifelong relapsing-remitting course in most patients, maintenance pharmacotherapy is usually required indefinitely [3]. Modern treatment strategies have evolved considerably over the past two decades. Although lithium remains the prototype mood stabilizer and continues to demonstrate unmatched efficacy in relapse prevention and suicide reduction, increasing evidence supports the use of several second-generation antipsychotics and selected anticonvulsants across different illness phases. Contemporary treatment therefore emphasizes individualized pharmacotherapy based on predominant polarity, episode characteristics, previous treatment response, psychiatric and medical comorbidities, reproductive status, and patient preferences [4].

CLASSIFICATION OF BIPOLAR DISORDER

Bipolar disorder (BD) comprises a spectrum of chronic mood disorders characterized by recurrent episodes of mania, hypomania, depression, and periods of euthymia. Accurate classification is essential because clinical subtype influences prognosis, treatment selection, and long-term management strategies [5].

Bipolar I Disorder

Bipolar I disorder (BD-I) is defined by the occurrence of at least one manic episode lasting a minimum of one week, or of any duration if hospitalization is required. Manic episodes are characterized by persistently elevated, expansive, or irritable mood accompanied by increased energy or goal-directed activity and symptoms such as grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased risk-taking behavior, and psychomotor agitation. Psychotic features may occur during severe episodes and are observed exclusively in Bipolar I disorder. Although major depressive episodes frequently occur during illness, their presence is not required for diagnosis. BD-I is associated with substantial functional impairment, frequent hospitalization, high rates of psychiatric comorbidity, and an elevated lifetime risk of suicide. Consequently, long-term maintenance

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pharmacotherapy is recommended following recovery from the initial manic episode [6].

Bipolar II Disorder

Bipolar II disorder (BD-II) is characterized by recurrent episodes of major depression together with at least one hypomanic episode. Unlike mania, hypomania lasts at least four consecutive days and does not cause marked functional impairment, psychosis, or require hospitalization. Although hypomanic episodes may be perceived positively by patients because of increased productivity and reduced need for sleep, depressive episodes usually predominate and account for most of the disease burden. Patients with BD-II often experience delayed diagnosis because depressive episodes frequently resemble unipolar major depressive disorder. Misdiagnosis may lead to inappropriate antidepressant monotherapy, potentially precipitating mood destabilization or hypomanic switching [7].

Cyclothymic Disorder

Cyclothymic disorder represents a chronic but milder form of bipolar spectrum illness. It is characterized by numerous periods of hypomanic symptoms and depressive symptoms that do not meet the full diagnostic criteria for hypomanic or major depressive episodes. Symptoms must persist for at least two years in adults (one year in children and adolescents), with symptom-free intervals lasting no longer than two months. Although symptom severity is generally lower than in Bipolar I or II disorder, the chronic and fluctuating nature of cyclothymia may significantly impair interpersonal relationships, occupational functioning, and quality of life. A proportion of affected individuals subsequently develop Bipolar I or Bipolar II disorder [8].

Mixed Features

Mixed features refer to the simultaneous presence of manic and depressive symptoms during the same mood episode. Patients may exhibit elevated mood together with feelings of hopelessness, psychomotor agitation accompanied by suicidal ideation, insomnia despite profound fatigue, or racing thoughts occurring alongside depressed affect. Episodes with mixed features are associated with greater illness severity, increased functional impairment, poorer treatment response, higher relapse rates, and a substantially increased risk of suicide. Recognition of mixed presentations is clinically important because antidepressants may exacerbate symptoms, whereas mood stabilizers and several second-generation antipsychotics generally demonstrate superior efficacy [9].

Rapid Cycling

Rapid cycling is a clinical course specifier rather than a distinct diagnostic subtype and is defined as the occurrence of four or more mood episodes within a 12-month period. Episodes may consist of mania, hypomania, depression, or mixed states and are separated by either partial or complete remission or by a switch to an episode of opposite polarity. Rapid cycling affects approximately 10–20% of patients with bipolar disorder and is associated with earlier disease onset, increased depressive morbidity, greater psychiatric comorbidity, reduced treatment response, and poorer long-term prognosis. Potential contributing factors include antidepressant exposure, thyroid dysfunction, substance misuse, and non-adherence medication. Management often requires combination pharmacotherapy and careful reassessment of medications that may contribute to mood instability [10].

PATHOPHYSIOLOGY OF BIPOLAR DISORDER

The pathophysiology of bipolar disorder is complex and incompletely understood. Current evidence supports a multifactorial model involving genetic susceptibility, abnormalities in neurotransmitter systems, intracellular signaling pathways, circadian rhythm regulation, neuroinflammatory processes, mitochondrial dysfunction, and impaired neuroplasticity. Rather than resulting from dysfunction of a single neurotransmitter, bipolar disorder appears to arise from disturbances in interconnected neural networks that regulate mood, cognition, reward processing, and emotional regulation.

Neurotransmitter Dysregulation

Dopamine

Alterations in dopaminergic neurotransmission are considered central to the pathophysiology of bipolar disorder. The dopamine hypothesis proposes that manic episodes are associated with increased dopamine synthesis, release, and receptor activation within mesolimbic pathways, producing heightened reward sensitivity, increased goal-directed behavior, reduced need for sleep, and psychomotor activation. [11] Conversely, depressive episodes are thought to involve relative dopaminergic deficiency, contributing to anhedonia, psychomotor retardation, reduced motivation, and impaired cognitive function. The clinical efficacy of dopamine D_2 receptor antagonists and partial agonists in acute mania further supports the role of dopaminergic dysregulation [12].

Glutamate

Glutamate is the principal excitatory neurotransmitter in the central nervous system.

Neuroimaging and magnetic resonance spectroscopy studies have demonstrated abnormal glutamatergic activity in several cortical and limbic regions in patients with bipolar disorder. Excessive glutamate signaling may contribute to neuronal hyperexcitability during manic episodes, whereas chronic glutamatergic dysregulation may promote excitotoxicity, impaired synaptic plasticity, and neuroprogression. Several mood stabilizers, including lithium and lamotrigine, indirectly modulate glutamatergic neurotransmission, while growing evidence suggests that glutamate-modulating agents such as ketamine may offer rapid antidepressant effects in treatment-resistant bipolar depression [13].

Gamma-Aminobutyric Acid (GABA)

GABA serves as the principal inhibitory neurotransmitter within the brain and plays a crucial role in maintaining the balance between neuronal excitation and inhibition. Reduced GABAergic activity has been reported in patients with bipolar disorder and may contribute to cortical hyperexcitability, emotional dysregulation, and vulnerability to manic episodes. Enhancement of GABAergic neurotransmission is believed to contribute to the therapeutic effects of valproate and several adjunctive pharmacological agents [14].

Serotonin

Serotonergic dysfunction has long been implicated in affective disorders. Reduced serotonin neurotransmission is thought to contribute primarily to depressive symptoms, impulsivity, and suicidal behaviour observed in bipolar disorder. However, serotonin also modulates dopamine and glutamate signaling, illustrating the complex interactions among neurotransmitter systems. Although antidepressants targeting serotonin may improve depressive symptoms, their use in bipolar disorder remains controversial because of the potential risk of inducing mania or accelerating mood cycling [15].

Noradrenaline

Noradrenergic pathways influence attention, arousal, stress responses, and emotional regulation. Increased noradrenergic activity has been associated with manic episodes, whereas diminished activity may contribute to fatigue, impaired concentration, and psychomotor slowing during bipolar depression. Interactions between noradrenaline, dopamine, and serotonin further underscore the neurochemical complexity of bipolar disorder [16].

Intracellular Signaling Pathways

Increasing evidence indicates that bipolar disorder involves abnormalities in intracellular signaling cascades that regulate neuronal survival, synaptic plasticity, and gene expression [17].

Glycogen Synthase Kinase-3 (GSK-3)

GSK-3 is a serine/threonine protein kinase involved in neurodevelopment, apoptosis, circadian regulation, and inflammatory signaling. Excessive GSK-3 activity has been associated with impaired neuroplasticity and mood dysregulation. Lithium directly inhibits GSK-3, promoting neuronal resilience, synaptic plasticity, and neuroprotective effects that are believed to contribute substantially to its long-term mood-stabilizing properties [18].

Protein Kinase C (PKC)

Protein kinase C regulates neurotransmitter release, receptor sensitivity, and neuronal excitability. Increased PKC activity has been implicated in manic episodes through enhancement of excitatory neurotransmission. Experimental studies suggest that both lithium and valproate indirectly inhibit PKC signaling, providing a potential mechanism for their antimanic efficacy [19].

Inositol Signaling

The inositol depletion hypothesis proposes that lithium inhibits inositol monophosphatase, thereby reducing intracellular inositol availability and attenuating phosphatidylinositol-mediated second messenger signaling. This modulation may stabilize neuronal activity and reduce excessive neurotransmission associated with manic states. Although this mechanism does not fully explain lithium's therapeutic effects, it remains one of the most extensively studied molecular pathways [20].

Circadian Rhythm Dysregulation

Disturbances of circadian rhythm represent a hallmark of bipolar disorder. Altered sleep-wake cycles, reduced need for sleep during mania, hypersomnia during depressive episodes, and irregular daily activity patterns often precede mood episodes. Genetic studies have identified abnormalities in circadian clock genes, including CLOCK, BMAL1, PER, and CRY, suggesting that disrupted biological timing contributes to disease susceptibility. Circadian disruption influences neurotransmitter release, hormonal regulation, immune function, and synaptic plasticity, potentially increasing vulnerability to mood episodes. The therapeutic benefits of structured sleep routines, interpersonal and social rhythm therapy, and several mood stabilizers further support the importance of circadian regulation in bipolar disorder [21].

Neuroinflammation and Oxidative Stress

Accumulating evidence indicates that bipolar disorder is associated with chronic low-grade

neuroinflammation. Elevated circulating concentrations of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been observed during both manic and depressive episodes, although inflammatory activity may persist during euthymia in some patients. These inflammatory mediators may alter neurotransmitter metabolism, impair neuroplasticity, and disrupt blood-brain barrier integrity [22]. Oxidative stress also appears to contribute to disease progression. Increased production of reactive oxygen species together with reduced antioxidant capacity may result in lipid peroxidation, protein oxidation, DNA damage, and impaired neuronal function. Repeated mood episodes have been associated with cumulative oxidative injury, supporting the concept of neuroprogression in bipolar disorder. Mitochondrial dysfunction has emerged as another important component of disease pathophysiology. Abnormalities in mitochondrial energy metabolism, calcium homeostasis, and ATP production may impair neuronal resilience and synaptic function, thereby contributing to both mood instability and cognitive impairment. Experimental evidence suggests that several established mood stabilizers, particularly lithium, exert neuroprotective effects by improving mitochondrial function and reducing oxidative stress [23]. Collectively, these findings support the concept that bipolar disorder is a systemic disorder involving complex interactions among neurotransmitter dysregulation, intracellular signaling abnormalities, circadian disruption, inflammatory pathways, oxidative stress, and impaired neuroplasticity. Understanding these mechanisms provides the biological rationale for current pharmacological treatments and may facilitate the development of more targeted therapeutic strategies in the future [24].

MOOD STABILIZERS

Mood stabilizers constitute the cornerstone of pharmacological treatment for bipolar disorder. These agents are effective in controlling acute manic episodes, preventing recurrent mood episodes, and maintaining long-term mood stability. An ideal mood stabilizer should demonstrate efficacy against both manic and depressive episodes without precipitating mood switching, while exhibiting an acceptable safety profile for long-term use [25]. Although no currently available medication fulfills all these criteria, lithium, selected anticonvulsants, and several second-generation antipsychotics possess clinically significant mood-stabilizing properties and are recommended by contemporary international treatment guidelines. The choice of mood stabilizer should be individualized according to the predominant polarity of illness, previous treatment response, comorbid medical and psychiatric conditions, adverse-effect profile, reproductive considerations, potential drug interactions, and patient preference [26].

Lithium (Lithium Salts)

Since its introduction into psychiatric practice in the mid-twentieth century, lithium has remained the prototype mood stabilizer and continues to represent the gold standard for maintenance treatment of bipolar disorder. It is the only pharmacological agent consistently shown to reduce the risk of both manic and depressive relapses while significantly lowering suicide attempts, completed suicide, and all-cause mortality. Consequently, lithium remains the preferred first-line maintenance therapy for many patients with Bipolar I disorder [27].

Clinical Indications

Lithium is indicated as: Acute mania, either as monotherapy or combined with an antipsychotic for moderate-to-severe episodes. Maintenance treatment of Bipolar I and Bipolar II disorders. Prevention of recurrent manic and depressive episodes. Reduction of suicidal behavior and suicide mortality. Augmentation therapy in selected patients with treatment-resistant bipolar depression and refractory major depressive disorder. Its efficacy is greatest in patients with classical episodic Bipolar I disorder characterized by distinct manic episodes, relatively complete inter-episode recovery, and a positive family history of lithium responsiveness. Conversely, lithium appears less effective in rapid-cycling illness, mixed affective states, and bipolar disorder associated with prominent substance misuse [28].

Pharmacodynamics

Lithium exerts complex neurobiological effects through multiple intracellular signaling pathways rather than acting on a single neurotransmitter system. Although its precise mechanism of action remains incompletely understood, several complementary mechanisms have been identified. Lithium inhibits inositol monophosphatase, thereby reducing phosphatidylinositol second-messenger signaling and attenuating excessive neuronal excitability. It also inhibits glycogen synthase kinase-3 (GSK-3), an enzyme involved in apoptosis, neuroplasticity, circadian regulation, and inflammatory signaling. Inhibition of GSK-3 promotes neuronal survival, enhances synaptic plasticity, and may underline lithium's neuroprotective effects [29]. Additional pharmacodynamic actions include modulation of dopaminergic, glutamatergic, serotonergic, and GABAergic neurotransmission, increased expression of neurotrophic factors such as brain-derived

neurotrophic factor (BDNF), reduced oxidative stress, stabilization of mitochondrial function, and attenuation of neuroinflammatory pathways. Collectively, these effects are believed to contribute to lithium's unique ability to prevent both manic and depressive recurrences [30].

Pharmacokinetics

Lithium is rapidly and almost completely absorbed following oral administration, with peak plasma concentrations occurring approximately 1–3 hours after immediate-release formulations and 4–8 hours after sustained-release preparations. Because lithium is not protein bound and undergoes no hepatic metabolism, it is eliminated almost exclusively by renal excretion. Approximately 80% of filtered lithium is reabsorbed in the proximal renal tubule alongside sodium. Consequently, conditions associated with sodium depletion including dehydration, excessive sweating, vomiting, diarrhea, or diuretic therapy may substantially increase lithium reabsorption and precipitate toxicity. The elimination half-life averages 18–36 hours in younger adults but may exceed 48 hours in elderly individuals or those with impaired renal function [31]. Steady-state concentrations are generally achieved within five to seven days after treatment initiation or dosage adjustment.

Therapeutic Drug Monitoring

Because lithium possesses a narrow therapeutic index, routine serum concentration monitoring is mandatory. For maintenance treatment, target serum concentrations generally range from 0.6 to 0.8 mmol/L, although concentrations up to 1.0 mmol/L may be appropriate in patients with recurrent manic episodes. Acute mania typically requires higher concentrations between 0.8 and 1.2 mmol/L, provided these are well tolerated. Serum lithium concentrations should be measured approximately 12 hours after the previous dose. Levels should be obtained five to seven days after treatment initiation or dosage adjustment and subsequently every three to six months during stable maintenance therapy [32].

Baseline evaluation should include: serum creatinine and estimated glomerular filtration rate (eGFR); Thyroid function tests (TSH and free T4); Serum calcium and electrolytes; Complete blood count; Body weight and body mass index; Pregnancy testing in women of child-bearing potential; Electrocardiography in older adults or patients with cardiovascular disease. Long-term follow-up should include regular assessment of renal function, thyroid function, calcium concentrations, body weight, and serum lithium concentrations.

Adverse Effects

Adverse effects are common during lithium therapy but are frequently dose-dependent and may improve following dosage adjustment. Common early adverse effects include: fine postural tremor; polyuria and polydipsia secondary to nephrogenic diabetes insipidus; nausea and diarrhea; metallic taste; mild cognitive slowing; fatigue; weight gain; peripheral oedema. Long-term treatment may result in hypothyroidism, hyperparathyroidism with hypercalcemia, chronic kidney disease, nephrogenic diabetes insipidus, and, less commonly, cardiac conduction abnormalities. Dermatological reactions, including acne, psoriasis exacerbation, and folliculitis, are also well recognized. Recent long-term cohort studies suggest that although lithium is associated with gradual reductions in renal function, progression to end-stage kidney disease is relatively uncommon when serum concentrations remain within the therapeutic range and renal function is monitored regularly. These findings support the continued use of lithium when clinically indicated, provided appropriate surveillance is maintained [33].

Drug Interactions

Several commonly prescribed medications significantly influence lithium clearance. Drugs that increase serum lithium concentrations include : non-steroidal anti-inflammatory drugs (NSAIDs); Angiotensin-converting enzyme (ACE) inhibitors ; Angiotensin II receptor blockers (ARBs) ;Thiazide diuretics ;Potassium-sparing diuretics to a lesser extent conversely, caffeine, theophylline, acetazolamide, and osmotic diuretics may reduce lithium concentrations. Patients should be advised to maintain adequate hydration, avoid abrupt dietary sodium restriction, and promptly report illnesses associated with vomiting, diarrhea, or excessive fluid loss [34].

Lithium Toxicity

Lithium toxicity constitutes a medical emergency and may occur despite previously stable treatment, particularly following dehydration, renal impairment, or interacting medications. Early manifestations include: worsening tremor; nausea and vomiting; diarrhea; dysarthria; ataxia; muscle weakness; severe toxicity may progress to: confusion; delirium; seizures; coma; cardiac arrhythmias; acute kidney injury. Serum concentrations above 1.5 mmol/L increase the likelihood of toxicity, while concentrations exceeding 2.5 mmol/L are associated with severe neurological complications and frequently require hemodialysis [35].

ANTICONVULSANT MOOD STABILIZERS

Several antiepileptic medications possess clinically important mood-stabilizing properties and are widely

used in bipolar disorder. Compared with lithium, these agents differ substantially in efficacy across illness phases, mechanisms of action, adverse-effect profiles, and monitoring requirements. Selection should therefore be guided by individual clinical characteristics and treatment goals [36].

Valproate (Divalproex Sodium, Sodium Valproate, Valpromide)

Valproate is among the most extensively studied alternatives to lithium and is recommended as a first-line treatment for acute mania in many international guidelines. It demonstrates efficacy in mixed affective states, rapid-cycling bipolar disorder, and patients who respond inadequately to lithium.

Mechanism of Action

Valproate enhances GABAergic neurotransmission by increasing cerebral GABA concentrations while also inhibiting voltage-gated sodium channels and modulating calcium channel activity. Additional effects on histone deacetylase (HDAC) inhibition, intracellular signaling pathways, and neuroinflammation may contribute to its mood-stabilizing properties [37].

Clinical Uses

Valproate is effective for: acute manic episodes; mixed episodes; rapid-cycling bipolar disorder ;maintenance therapy in selected patients . However, evidence supporting its efficacy in bipolar depression remains considerably weaker than for manic relapse prevention [38].

Pharmacokinetics

Valproate is well absorbed following oral administration, undergoes extensive hepatic metabolism primarily through glucuronidation and mitochondrial β-oxidation, and exhibits high plasma protein binding. Because of its hepatic metabolism, clinically significant drug interactions are more frequent than with lithium [39].

Adverse Effects

Common adverse effects include: weight gain; sedation; tremors; gastrointestinal disturbances; alopecia; thrombocytopenia; elevated hepatic transaminases; hyperammonaemia. Long-term therapy may contribute to metabolic syndrome and polycystic ovarian syndrome in susceptible women [40].

Monitoring

Baseline investigations should include: liver function tests; complete blood count with platelet count ;body weight; pregnancy testing when appropriate. Periodic monitoring of liver enzymes, hematological parameters, and serum valproate concentrations is recommended during treatment [41].

Pregnancy and Reproductive Safety

Valproate is strongly contraindicated during pregnancy unless no safer therapeutic alternative exists. In utero exposure substantially increases the risk of major congenital malformations, neural tube defects, reduced cognitive development, and neurodevelopmental disorders, including autism spectrum disorder. Consequently, valproate should generally be avoided in women of childbearing potential unless strict pregnancy prevention measures are implemented [42].

Lamotrigine

Lamotrigine is an anticonvulsant with established efficacy as a maintenance treatment for bipolar disorder, particularly in preventing depressive relapse. Unlike lithium and valproate, its therapeutic benefit is largely confined to bipolar depression, with minimal efficacy in the treatment of acute mania [43].

Mechanism of Action

Lamotrigine inhibits voltage-gated sodium channels, thereby reducing presynaptic glutamate release and decreasing excitatory neurotransmission. These effects are thought to stabilize neuronal activity and reduce vulnerability to depressive recurrence [44].

Clinical Indications

Lamotrigine is indicated for: maintenance treatment of Bipolar I disorder ; maintenance treatment of Bipolar II disorder; prevention of recurrent bipolar depressive episodes. It has little or no efficacy in acute manic episodes and should not be used as monotherapy for the treatment of mania [45].

Pharmacokinetics

Lamotrigine is well absorbed after oral administration and undergoes hepatic metabolism predominantly through glucuronidation. It has relatively few pharmacokinetic drug interactions; however, concomitant medications can significantly alter its metabolism. Valproate markedly inhibits lamotrigine metabolism and approximately doubles serum concentrations, whereas enzyme-inducing agents such as carbamazepine, phenytoin, and phenobarbital accelerate its clearance [46].

Adverse Effects

Lamotrigine is generally well tolerated and is associated with minimal weight gain, sedation, cognitive impairment, or metabolic adverse effects. Common adverse effects include headache, dizziness,

diplopia, blurred vision, nausea, and insomnia. The principal safety concern is the risk of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Although these reactions are rare, the risk is greatest during the first two months of therapy, particularly following rapid dose escalation or concomitant use of valproate [47].

Dosing and Monitoring

To minimize the risk of severe skin reactions, lamotrigine must be introduced using a slow dose-titration schedule. Dose adjustments are required when administered with medications that either inhibit or induce hepatic glucuronidation. Routine laboratory monitoring is generally unnecessary, although patients should be instructed to discontinue treatment immediately and seek medical attention if a rash or other symptoms suggestive of hypersensitivity develop [48].

Carbamazepine

Carbamazepine is an anticonvulsant with established efficacy in the treatment of acute mania and maintenance therapy for bipolar disorder. It is generally considered a second-line mood stabilizer because of its extensive drug interaction profile and less favourable tolerability compared with lithium and valproate [49].

Mechanism of Action

Carbamazepine inhibits voltage-gated sodium channels, reducing repetitive neuronal firing and stabilizing neuronal membranes. These effects decrease excessive neuronal excitability associated with manic episodes [50].

Clinical Indications

Carbamazepine is indicated for: acute manic episodes; maintenance treatment of bipolar disorder particularly in patients who respond inadequately to lithium; selected patients with mixed features or rapid-cycling illness. Its efficacy in bipolar depression is limited [51].

Pharmacokinetics

Carbamazepine is well absorbed following oral administration and undergoes extensive hepatic metabolism, primarily via cytochrome P450 (CYP3A4). It induces its own metabolism (autoinduction), resulting in a gradual reduction in serum concentrations during the first several weeks of treatment. As a potent inducer of multiple cytochrome P450 enzymes, carbamazepine significantly reduces serum concentrations of numerous medications, including oral contraceptives, anticoagulants, antipsychotics, antidepressants, corticosteroids, and several antiepileptic drugs. Careful review of concomitant medications is therefore essential before treatment initiation [52].

Adverse Effects

Common adverse effects include dizziness, diplopia, blurred vision, sedation, nausea, vomiting, hyponatraemia, and mild leukopenia. Serious adverse reactions include: agranulocytosis; aplastic anaemia; severe hepatic injury; Stevens-Johnson syndrome; toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) [53].

Monitoring

Baseline evaluation should include complete blood count; liver function tests ;serum sodium concentration ; pregnancy testing where appropriate ; comprehensive review of potential drug interactions; periodic monitoring of hematological parameters, liver function, serum sodium, and clinical assessment for adverse effects should be performed throughout treatment [54].

Pharmacogenetic Considerations

Genetic screening for the HLA-B*15:02 allele is recommended before initiating carbamazepine in individuals of Asian ancestry because carriers have a markedly increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. Screening for HLA-A*31:01 may also be considered in selected populations, as this allele has been associated with an increased risk of carbamazepine-induced hypersensitivity reactions [55].

SELECTION OF MOOD STABILIZERS

Selection of an appropriate mood stabilizer should be individualized according to the patient's clinical characteristics and treatment objectives. Factors influencing medication choice include the predominant polarity of illness, frequency of mood episodes, previous response to treatment, psychiatric and medical comorbidities, potential adverse effects, drug-drug interactions, renal and hepatic function, reproductive plans, and patient preference. Lithium remains the preferred first-line maintenance treatment for patients with classical Bipolar I disorder because of its superior efficacy in preventing relapses and reducing suicide risk. Valproate may be preferred in patients with acute mania, mixed presentations, or rapid-cycling illness, whereas lamotrigine is particularly useful in individuals with predominant bipolar depression. Carbamazepine is generally reserved for patients who fail to respond adequately to first-line

therapies or in whom alternative agents are contraindicated. In clinical practice, combination therapy is frequently required, particularly in patients with severe, recurrent, or treatment-resistant bipolar disorder. Shared decision-making, careful monitoring for adverse effects, and regular reassessment of treatment response remain essential components of successful long-term pharmacological management [56].

EVALUATION OF INADEQUATE TREATMENT RESPONSE

Before concluding that a patient has treatment-resistant bipolar disorder, several potentially reversible causes of inadequate response should be systematically evaluated. These include poor medication adherence or premature discontinuation of treatment; administration of an inadequate therapeutic dose or failure to achieve therapeutic serum drug concentrations when appropriate; pharmacokinetic or pharmacodynamic drug-drug interactions that reduce treatment efficacy. The presence of medical or psychiatric comorbidities that may complicate symptom control. Only after these factors have been carefully excluded should treatment resistance be considered and alternative therapeutic strategies explored [57].

THE CORE ROLE OF ANTIPSYCHOTICS IN BIPOLAR DISORDER

Antipsychotic medications are a cornerstone of pharmacological treatment for bipolar disorder, with therapeutic roles extending well beyond the management of psychotic symptoms. Unlike their primary use in schizophrenia, where they are mainly prescribed to control psychosis, antipsychotics in bipolar disorder are employed across different phases of the illness to manage acute mood episodes and reduce the risk of relapse. Their clinical applications can be categorized into three principal domains: treatment of acute mania, management of bipolar depression, and long-term maintenance therapy [58]. During acute manic episodes, antipsychotics provide rapid control of agitation, aggression, psychomotor overactivity, racing thoughts, and accompanying psychotic symptoms such as delusions and hallucinations [59]. Their fast onset of action makes them indispensable in emergency and inpatient settings, either as monotherapy or in combination with mood stabilizers. In acute bipolar depression, several second-generation (atypical) antipsychotics have demonstrated significant antidepressant efficacy, representing a major advancement in bipolar pharmacotherapy. Unlike first-generation agents, which have limited utility in depressive episodes, certain second-generation antipsychotics are approved specifically for bipolar depression and may be used alone or in combination with antidepressants or mood stabilizers. For maintenance treatment, antipsychotics contribute to long-term mood stabilization by reducing the frequency of recurrent manic and depressive episodes. Although lithium remains the reference standard for relapse prevention, several second-generation antipsychotics have established efficacy as maintenance agents, either as monotherapy or adjunctive therapy, particularly in patients with incomplete response or intolerance to traditional mood stabilizers [60].

First-Generation Versus Second-Generation Antipsychotics

Antipsychotics are broadly classified into first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), with important differences in efficacy, tolerability, and adverse-effect profiles. FGAs, including haloperidol and chlorpromazine, are highly effective in rapidly controlling acute mania but are associated with a substantial risk of extrapyramidal symptoms (EPS), including parkinsonism, dystonia, akathisia, and the potentially irreversible movement disorder tardive dyskinesia [61]. Consequently, their use is generally restricted to short-term treatment of severe manic episodes. In contrast, SGAs such as olanzapine, quetiapine, risperidone, aripiprazole, lurasidone, asenapine, and cariprazine possess broader therapeutic efficacy, encompassing acute mania, bipolar depression, and maintenance therapy. These agents exhibit a lower propensity for EPS but are associated with other clinically significant adverse effects, including weight gain, metabolic syndrome, dyslipidemia, glucose intolerance, and sedation. The extent of these metabolic effects varies considerably among individual agents and should be considered when selecting long-term therapy [62].

Evidence for Individual Antipsychotic Agents

Acute Mania

Among currently available antipsychotics, olanzapine remains one of the most effective agents for the treatment of acute mania, although its clinical utility is often limited by substantial weight gain, sedation, and metabolic disturbances. Risperidone is similarly effective, particularly at higher doses, but carries an increased risk of dose-dependent extrapyramidal symptoms and hyperprolactinemia, which may lead to amenorrhea, galactorrhea, or sexual dysfunction.

Haloperidol, a first-generation antipsychotic, has long been considered the reference treatment for rapidly controlling severe manic agitation because of its

potent antimanic effects and rapid onset of action. However, its high incidence of extrapyramidal adverse effects and tardive dyskinesia generally limits its use to short-term treatment or combination therapy. Quetiapine is also effective in acute mania but typically requires higher doses (600–800 mg/day), frequently resulting in significant sedation [63]. Aripiprazole offers comparable antimanic efficacy with a relatively favorable metabolic profile, although akathisia is a common adverse effect. Asenapine, administered as a sublingual formulation, has demonstrated efficacy in acute mania and is distinguished by its route of administration and the relatively frequent occurrence of oral hypoesthesia or taste disturbances. Cariprazine, a dopamine D3-preferring partial agonist, is effective in treating manic episodes while presenting a relatively low risk of metabolic complications [64].

Bipolar Depression

The development of second-generation antipsychotics with proven antidepressant efficacy has significantly expanded treatment options for bipolar depression [65]. Quetiapine is among the most extensively studied agents and has consistently demonstrated efficacy at doses around 300 mg/day, although sedation remains its principal adverse effect [66]. Lurasidone is another effective option with a comparatively favorable metabolic profile and minimal weight gain; however, adequate absorption requires administration with a meal containing at least 350 kcal. The fixed-dose combination of olanzapine and fluoxetine has demonstrated robust efficacy in bipolar depression but is associated with one of the highest risks of weight gain and metabolic complications among available therapies [67]. Cariprazine has also received approval for bipolar depression and is generally well tolerated, although its activating properties may necessitate morning administration to minimize sleep disturbance [68].

Maintenance Therapy

Several antipsychotics have demonstrated efficacy in preventing relapses during the maintenance phase of bipolar disorder. Aripiprazole and risperidone are particularly effective in reducing the recurrence of manic episodes, whereas quetiapine has shown efficacy in preventing both manic and depressive relapses, making it one of the most versatile maintenance agents. Olanzapine is likewise effective in relapse prevention but is frequently reserved for selected patients because of its unfavorable metabolic profile. Despite the expanding role of antipsychotics, lithium remains the benchmark maintenance treatment because of its robust evidence for relapse prevention and reduction in suicide risk. Nevertheless, second-generation antipsychotics are widely used as monotherapy or in combination with lithium or other mood stabilizers, particularly in patients with recurrent episodes, mixed features, or persistent psychotic symptoms [69].

TREATMENT-RESISTANT BIPOLAR DISORDER AND EMERGING THERAPEUTIC STRATEGIES

Definition and Clinicals Significance

Treatment-resistant bipolar disorder (TRBD) represents a substantial clinical challenge that affects approximately 30–50% of patients with bipolar disorder [70]. Despite the availability of multiple pharmacological agents with established efficacy, a considerable proportion of patients experience inadequate response, partial improvement, or intolerable adverse effects that preclude continued treatment. The definition of TRBD has evolved considerably over recent years, moving beyond simplistic criteria based solely on the number of failed medication trials to encompass a more nuanced understanding of treatment resistance across different illness phases and clinical dimensions [71].

Defining Treatment Resistance in Bipolar Disorder

Treatment resistance in bipolar disorder is conceptually distinct from that in unipolar depression because of the biphasic nature of the illness and the requirement that treatment address both poles of mood disturbance. A widely accepted definition requires failure of at least two adequate trials of evidence-based treatments administered at appropriate doses for sufficient durations, with documented adherence [72]. However, this definition requires refinement according to the specific phase of illness being treated. Resistance during acute manic episodes differs fundamentally from resistance in bipolar depression, and both differ from resistance to maintenance prophylaxis [73].

Phase-Specific Definitions

For acute mania, treatment resistance is generally defined as failure to achieve clinically meaningful improvement following two adequate trials of antimanic agents, which may include lithium, valproate, or second-generation antipsychotics used at appropriate doses for at least two weeks [74]. For bipolar depression, resistance requires failure of at least two adequate treatments with established antidepressant efficacy in bipolar disorder, including quetiapine, lurasidone, cariprazine, lamotrigine, or the olanzapine-fluoxetine combination, each administered for an adequate duration of six to eight weeks [75]. For maintenance treatment, resistance is defined as the recurrence of mood episodes despite ongoing

prophylactic therapy with therapeutic drug concentrations or appropriate doses of mood stabilizers or antipsychotics.

The Concept of Predominant Polarity and Treatment Resistance

An important consideration in defining treatment resistance is the recognition that patients may demonstrate differential responsiveness across illness phases. Some patients respond well to antimanic treatments but experience frequent depressive episodes (depressive-predominant polarity), whereas others achieve good depressive control but continue to experience manic recurrences (manic-predominant polarity) [76]. Treatment resistance should therefore be characterized according to the specific polarity that remains problematic, as this distinction has direct implications for subsequent therapeutic selection.

Pseudo-Resistance and its Evaluation

Before confirming true treatment resistance, clinicians must systematically exclude several potentially reversible factors that may masquerade as resistance.

These include medication adherence issues; non-adherence represents one of the most common causes of apparent treatment failure in bipolar disorder. Studies consistently demonstrate that 40–60% of patients with bipolar disorder exhibit partial or complete non-adherence to prescribed medication regimens [77]. Contributing factors include adverse effects, perceived stigma, lack of insight during manic episodes, cognitive impairment, substance use disorders, and the desire to maintain hypomanic states perceived as productive or pleasurable. Objective monitoring strategies, including serum drug concentration measurements, pill counts, pharmacy refill records, and electronic medication monitoring devices, may help identify adherence problems that would otherwise be misattributed to treatment resistance.

Subtherapeutic dosing or drug concentrations: inadequate dosing represents another common cause of apparent treatment failure. For lithium, serum concentrations must be maintained within the therapeutic range of 0.6–1.0 mmol/L for maintenance treatment and 0.8–1.2 mmol/L for acute mania. Similarly, valproate serum concentrations of 50–125 µg/mL are generally recommended. Subtherapeutic concentrations may result from inadequate prescribing, rapid metabolism, or pharmacokinetic interactions. Systematic evaluation of drug concentrations, particularly for lithium and valproate, is essential before concluding that a patient has genuine treatment resistance [78].

Pharmacokinetic and pharmacodynamic Interactions: concomitant medications may reduce the efficacy of mood stabilizers and antipsychotics through induction of hepatic enzymes, competition for transport proteins, or pharmacodynamic antagonism. Carbamazepine, as a potent CYP3A4 inducer, reduces serum concentrations of numerous antipsychotics and antidepressants. Conversely, inhibitors of drug metabolism may increase concentration and mimics treatment failure through poor tolerability [79].

Comorbid psychiatric and medical conditions: untreated psychiatric comorbidities, including anxiety disorders, substance use disorders, attention-deficit/hyperactivity disorder, and borderline personality disorder, may complicate mood stabilization and produce symptoms that are misattributed to inadequate antimanic or antidepressant response. Similarly, medical conditions such as thyroid dysfunction, vitamin D deficiency, sleep apnea, chronic pain, and inflammatory disorders may contribute to persistent depressive symptoms or mood instability. Systematic assessment and treatment of these comorbidities is essential before designating a patient as treatment resistant [80].

Rapid Cycling and Mixed States

The presence of rapid cycling (≥4 mood episodes in 12 months) or mixed features (concurrent manic and depressive symptoms) represents a distinct and particularly challenging clinical scenario. These specifiers are consistently associated with poorer response to standard monotherapy, higher relapse rates, greater functional impairment, and a substantially elevated risk of suicide. Critically, these conditions are often induced or exacerbated by iatrogenic factors, most notably, antidepressant exposure, which can accelerate mood cycling and worsen mixed states [81]. Therefore, before labeling a patient as “treatment-resistant,” clinicians must:

-Audit the medication regimen for potentially destabilizing agents (antidepressants, stimulants, corticosteroids) and taper them if clinically feasible.

-Recognize that mixed states and rapid cycling often require combination therapy (*e.g.*, lithium plus valproate, or a mood stabilizer plus a second-generation antipsychotic) rather than high-dose monotherapy.

-Address underlying contributors such as thyroid dysfunction, substance misuse, or sleep disruption, which are common precipitants of rapid cycling.

Only after optimizing these factors and confirming true non-response rather than pseudo-resistance

should a patient be considered to have treatment-resistant bipolar disorder.

CONCLUSION

Bipolar disorder remains one of the most challenging psychiatric conditions to manage, requiring a sophisticated understanding of its complex pathophysiology, diverse clinical presentations, and the pharmacological properties of available treatments. This review examined the current clinical pharmacology of bipolar disorder, emphasizing the importance of individualized pharmacotherapy based on predominant polarity, episode characteristics, treatment history, comorbidities, and patient preferences. Lithium continues to occupy a unique position in the therapeutic armamentarium, demonstrating unparalleled efficacy in suicide prevention and long-term mood stabilization, particularly in classical Bipolar I disorder. Despite concerns regarding renal and thyroid toxicity, recent evidence supports its safety when serum concentrations are maintained within the therapeutic range and appropriate monitoring is conducted. The anticonvulsant mood stabilizers valproate, lamotrigine, and carbamazepine offer valuable alternatives with distinct efficacy profiles across different illness phases. Valproate remains a first-line option for acute mania and mixed episodes. Lamotrigine is uniquely effective for bipolar depression and depressive relapse prevention, and carbamazepine serves as an important option for patients who do not respond to lithium. However, the use of each agent is constrained by specific safety considerations: valproate by its teratogenicity and metabolic effects, lamotrigine by the risk of severe cutaneous reactions requiring slow dose titration, and carbamazepine by its potent enzyme-inducing properties and the need for HLA-B*1502 screening in at-risk populations. The selection of an appropriate mood stabilizer must be guided by a careful balance of efficacy and tolerability, with particular attention to reproductive status, medical comorbidities, and potential drug interactions. Combination therapy is frequently necessary in clinical practice, especially for patients with severe, rapid-cycling, or treatment-resistant illness. Before concluding that a patient has treatment-resistant bipolar disorder, clinicians should systematically evaluate potentially reversible causes of inadequate response, including poor adherence, subtherapeutic dosing, drug interactions, and untreated comorbidities. Looking forward, ongoing research into the neurobiological underpinnings of bipolar disorder including glutamatergic dysfunction, neuroinflammation, mitochondrial impairment, and circadian rhythm disruption holds promise for the development of novel therapeutic targets. Emerging agents such as ketamine and other glutamate-modulating compounds may offer new options for treatment-resistant bipolar depression, while advances in pharmacogenomics may eventually enable more precise prediction of treatment response and adverse effect risk.

The pharmacological management of bipolar disorder requires a lifelong, individualized, and carefully monitored approach. The foundation of successful treatment rests on the judicious selection and combination of mood-stabilizing agents, rigorous therapeutic drug monitoring when indicated, vigilant surveillance for adverse effects, and a strong therapeutic alliance that promotes medication adherence. By integrating the principles of clinical pharmacology with an understanding of each patient's unique clinical presentation and circumstances, clinicians can optimize outcomes and improve the long-term prognosis for individuals living with bipolar disorder.

CONFLICTS OF INTEREST STATEMENT

The author declared no conflicts of interest.

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