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Bipolar Disorder in the Era of Precision Psychiatry: Advances in Early Diagnosis, Biomarkers, Digital Health, and Personalized Treatment

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***Abstract*—Objective**: **Bipolar disorders are chronic psychiatric conditions characterized by recurrent episodes of mania and depression. Affecting over 1% of the global population, these disorders contribute significantly to disability and mortality, often due to suicide and cardiovascular disease.**

Methods: **Diagnostic challenges arise from symptom overlap with unipolar depression, freq5uently leading to delays in accurate diagnosis. Bipolar disorders are driven by complex genetic, neurobiological, and environmental factors and are commonly accompanied by psychiatric and medical comorbidities, further complicating diagnosis and treatment.**

Results: **Standard management strategies include mood stabilizers, antipsychotics, and selective use of antidepressants, complemented by psychosocial interventions such as cognitive-behavioural therapy and psychoeducation, which are vital for relapse prevention. Despite recent advancements, management remains challenging, constrained by clinical variability, an absence of specific biomarkers, and differences in approved treatments and guidelines across regions. Emerging research underscores the potential of precision psychiatry and digital health tools to enhance diagnosis and treatment.**

Conclusion: **Critical gaps persist, particularly in implementing equitable care worldwide. This review offers a comprehensive update on bipolar disorders, examining clinical presentation, early diagnosis, pathogenesis, therapeutic strategies, and future perspectives to guide clinicians and researchers.**

***Index Terms*—bipolar disorder, antipsychotics, cognitive-behavioural therapy.**

I. INTRODUCTION

Bipolar disorder (BD) is a chronic and severe mental health condition affecting millions of people worldwide. It is characterized by repeated episodes of mania, hypomania, and depression, which can significantly affect a person's emotions, thinking, behaviour, relationships, education, work, and overall quality of life. Unlike normal mood changes, mood episodes in bipolar disorder are intense, last for several days or weeks, and often interfere with daily functioning. [1,4,14] BD is recognized as one of the leading causes of disability among young adults, as it usually begins during late adolescence or early adulthood and often continues throughout life if left untreated. [2,5,14]

1.1 Classification

The disorder is classified into several types, including Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and other specified bipolar and related disorders. [1,3,5]

Bipolar I Disorder involves at least one manic episode, which may be accompanied by depressive episodes. Bipolar II Disorder characterized by episodes of major depression and hypomania, a less severe form of mania. Cyclothymic Disorder long-term fluctuations between mild depressive and hypomanic symptoms that do not meet full diagnostic criteria for BD-I or BD-II. [1,6,50] These different forms demonstrate that the illness exists on a spectrum, with varying severity and clinical presentation.

1.2 Epidemiology

Prevalence rates of BD vary from country to country. A large multinational study suggests that lifetime prevalence of BD-I ranges from 0–1%, with a mean of 0.6% (SD 0.4). The prevalence of BD-II ranges from 0 to 1.1%, with a mean of 0.4% (SD 0.3). A significant proportion of patients also show subthreshold BD, ranging from 0.1 to 2.4%, with a mean of 1.4% (SD 0.8).[7,11,14]

There is no nationwide study evaluating the prevalence of BD in India. In countries such as India, patients often have limited resources, poor knowledge about the disorder and its treatment, and inadequate access to health care facilities, making management of BD a considerable challenge.

The exact etiology of bipolar disorder is complex and multifactorial, involving genetic, biological, environmental, and psychological factors.

- Genetics — family history is one of the strongest risk factors, indicating a significant genetic contribution; however, genetics alone cannot explain the disorder.
- Neurobiology — brain imaging studies show abnormalities in regions responsible for emotional regulation, decision-making, memory, and reward processing. [8,14,49]
- Neurotransmitters — imbalances in dopamine, serotonin, glutamate, and GABA play important roles in disease development and progression.
- Hormonal and inflammatory factors — hormonal imbalance, inflammation, and circadian rhythm disturbances (particularly disrupted sleep) may trigger mood episodes.

- Environmental factors — stressful life events, childhood trauma, sleep disturbances, substance abuse, and major environmental changes may trigger episodes in genetically vulnerable individuals. [35,49]

These interacting factors influence the development, severity, and recurrence of bipolar disorder.

1.3. Clinical Presentation

1.3.1 Manic Episodes

Individuals may experience elevated mood, excessive energy, reduced need for sleep, increased self-confidence, rapid speech, racing thoughts, impulsive behavior, irritability, and poor judgment. In severe cases, psychotic symptoms such as hallucinations or delusions may occur.[9,1,24]

1.3.2 Depressive Episodes

Patients often experience persistent sadness, loss of interest in daily activities, fatigue, feelings of hopelessness or guilt, poor concentration, changes in appetite and sleep, and suicidal thoughts.

1.3.3 Mixed Episodes

Many patients experience mixed episodes, where symptoms of mania and depression occur simultaneously, making diagnosis and treatment more challenging.

1.3.4 Impact and Comorbidity

Patients with BD encounter educational difficulties, job-related problems, interpersonal difficulties, psychosocial dysfunction, disability, marital problems, multiple suicide attempts, completed suicide, and medication side effects. Patients with BD also have high rates of physical and psychiatric comorbidity. [10,14,24]

II. INDUCTION METHODS

Animal models of human psychiatric disorders are generally evaluated according to three major forms of validity: construct, face, and predictive validity (Einat et al., 2003; Machado-Vieira et al., 2004). Construct validity indicates whether the biological mechanisms involved in the animal model resemble those implicated in the human disorder, while face validity considers similarities between the characteristics observed in the model and clinical features of the disease. Predictive validity examines whether treatments known to be effective in humans produce comparable therapeutic effects in the animal model. Evidence from phosphorus magnetic resonance spectroscopy (^{31}P-MRS) has suggested abnormalities in brain energy metabolism in bipolar disorder. Studies conducted from the late 1980s reported reduced intracellular pH during euthymia, decreased phosphocreatine during depressive episodes, and an increased phosphocreatine response to photic stimulation during euthymia (Kato et al., 1993; Kato et al., 1994; Murashita et al., 2000). The replication of some of these findings in independent patient samples provided additional support for the involvement of altered cellular energy metabolism in bipolar disorder. [11,48]

2.4. Mitochondrial dysfunction

These metabolic observations contributed to the hypothesis that mitochondrial dysfunction may have a role in the development of bipolar disorder. Although mitochondrial DNA (mtDNA)

mutations and polymorphisms have been associated with the disorder, it remained unclear whether mitochondrial abnormalities occurring directly in the brain could produce disease-related phenotypes. To investigate this possibility, researchers developed an animal model designed to cause progressive accumulation of mtDNA deletions in neurons. [12]The strategy was based on earlier work by Zhang et al. (2003), who demonstrated that expression of mutant Polg could produce mitochondrial dysfunction and cardiac failure in transgenic mice. In the subsequent model, the mutant Polg gene was placed under the control of a neuron-specific CaMKIIα promoter, allowing mitochondrial DNA abnormalities to accumulate primarily in neurons. This model provided an experimental method for examining whether neuronal mitochondrial dysfunction could produce behavioural and biological changes relevant to bipolar disorder and therefore helped investigate the potential contribution of mitochondrial abnormalities to its pathophysiology. [49,46]

2.2. Na^+/K^+-ATPase Inhibition

Another pharmacological approach involves Ouabain as inhibitor of the Na^+/K^+-ATPase, which can produce prolonged hyperactivity and neurobiological alterations associated with oxidative stress and mitochondrial dysfunction. These models have demonstrated some predictive validity because their behavioural abnormalities can be attenuated by established mood-stabilizing or antimanic treatments such as lithium (47.5 mg/kg, i.p., twice a day), and valproate (200 mg/kg, i.p., twice a day), for 14 days, ketamine (25 mg/kg, i.p.) is an effective pharmacological animal model of mania which can develop BD. Environmental and behavioural manipulations have also been employed Sleep deprivation and circadian rhythm disruption can induce increased activity, altered sleep, and other mania-like behaviours, reflecting the well-established relationship between circadian abnormalities and bipolar disorder. Genetic models provide another important strategy, in which genes or biological pathways implicated in bipolar disorder are altered to investigate disease-related phenotypes. [13,15]

For the depressive component of bipolar disorder, researchers commonly use paradigms such as chronic stress, forced-swim or tail-suspension tests, and other behavioural assays of anhedonia and reduced motivation. These approaches are useful for investigating depressive-like phenotypes but do not necessarily reproduce the bipolar course of illness. More complex models attempt to combine different manipulations or exploit genetic and circadian mechanisms to investigate transitions between mania-like and depressive-like states.[16] For example, the neuron-specific mutant Polg model was developed to investigate whether mitochondrial dysfunction and accumulation of mitochondrial DNA abnormalities could produce bipolar-relevant phenotypes; altered activity rhythms were observed and some abnormalities were improved by lithium treatment (Kato et al., 2007). More recent reviews emphasize that no single animal model completely reproduces human bipolar disorder. Models involving circadian abnormalities, amphetamine exposure, and ouabain currently provide some of the strongest evidence across construct, face, and predictive validity, although each has important limitations. Therefore, a

combination of complementary models may provide a more reliable strategy for investigating the complex biological mechanisms underlying bipolar disorder. [41-44]

III. DIAGNOSIS AND EARLY DETECTION

3.1 Diagnostic Challenges and Misdiagnosis

Accurate diagnosis of bipolar disorder is essential because it is frequently misdiagnosed as major depressive disorder, anxiety disorder, or other psychiatric illnesses. Misdiagnosis often delays appropriate treatment and increases the risk of recurrent episodes, hospitalization, substance abuse, self-harm, and suicide.

High rates of misdiagnosis have been reported — in one series, over 50% of patients initially received a diagnosis other than BD when they sought medical attention, and many received treatment with antidepressant or antipsychotic drugs. Where misdiagnosis leads to antidepressant treatment, there is a risk of triggering manic switching and mood cycle acceleration.

Diagnosis primarily depends on detailed clinical assessment, psychiatric history, family history, physical examination, and standardized diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[17,50]

3.2 Role of Biomarkers, AI, and Digital Tools

Researchers are investigating the use of biomarkers, neuroimaging techniques, artificial intelligence, and machine learning to improve diagnostic accuracy and enable earlier identification of bipolar disorder. Machine learning algorithms can analyze speech patterns, facial expressions, smartphone activity, wearable sensor data, and neuroimaging findings to identify mood changes and predict relapse.[18]

These technologies have the potential to support clinicians in continuously monitoring patients and providing timely interventions before severe mood episodes occur. Although still under development, they represent[19,6]

3.3 Digital and Sensor-Based Detection

Depression and bipolar disorder detection share a need for measurement of depressive moods, but bipolar disorder detection applications extend their scope to include manic behaviors as well. Sensors used for mood-disorder detection fall into two broad categories: clinical sensors and ubiquitous (consumer/wearable) sensors.

Signal processing methods used to prepare sensor data for classification or regression models can be grouped into three categories: noise reduction, pre-feature manipulation, and feature extraction. Among classification algorithms, the support vector machine (SVM) is the most commonly used single algorithm. It works by generating and comparing hyperplanes to identify the one that best separates data points of different classes, maximizing the margin to the nearest training points of each class.[20,43,50]

3.4 The Prodromal Phase and Rationale for Early Detection

Although correct diagnosis may be delayed by years, patients nevertheless present to clinicians early in their illness and are often misdiagnosed with other conditions. Early detection offers several potential benefits:

- Avoiding iatrogenic harm from mis-directed antidepressant treatment.
- Preventing or minimizing secondary disability — BD disrupts patients' work and social relationships, and the prodromal phase offers a window to engage patients and carers before maladaptive coping strategies develop.
- Reducing suicide risk — about one in ten patients report suicide attempts in the year prior to first onset of BD, a risk more than twice that seen during relapse of established BD.
- Meeting patient willingness to engage — patients at an early stage are more likely to seek help and utilize clinical services than those in later stages, where non-adherence and reduced insight can impair treatment.[23]

Early detection can be considered at several time points: a pre-symptomatic stage, the development of prodromal features, and the first point at which clinical manifestation meets diagnostic criteria (the first manic or hypomanic episode). Pre-symptomatic screening is limited by the absence of reliable biomarkers for BD, while by the time diagnostic criteria are first met, substantial disruption to work and relationships may already have occurred. The prodromal phase — where individuals are distressed and seeking help but secondary disability has not yet occurred — may therefore offer the greatest clinical opportunity.

Because the term “prodrome” implies an inevitable progression to full-blown illness, a prodromal syndrome can strictly only be identified in retrospect. Nonetheless, it is possible to identify symptoms and clinical features associated with the prodrome to BD, which may help identify at-risk individuals prospectively and guide early intervention.[21,22,50]

IV. ASSESSMENT AND EVALUATION

Assessment of patients is an ongoing process, involving evaluation of both the patient and their caregivers. Diagnosis of BD should be made using current diagnostic criteria, since criteria-based diagnosis is more reliable, facilitates communication among clinicians, and supports evidence-based management. Especially early in the illness, symptoms may be confusing and difficult to distinguish from schizophrenia, acute and transient psychosis, or other psychiatric disorders; substance-induced or organic causes should also be considered when presentations are atypical. [24,14]

A comprehensive assessment typically covers:

- Number of previous episodes, type of first lifetime episode, and predominant polarity of illness.
- Duration and severity of episodes, and quality of inter-episodic recovery.
- Presence or absence of suicidal behaviour, violence, and agitation.
- Seasonal variation in onset, and presence of rapid or ultra-rapid cycling.

- Role of psychosocial stressors and biological rhythms in onset, relapse, and symptom continuation.
- Comorbid psychiatric and medical conditions, including substance use (with urine/blood screening where indicated).
- Functional impairment across life domains, including impact on family and caregivers.
- Thorough physical examination and, where indicated, investigations and neuroimaging (e.g., atypical features, neurological signs, treatment non-response, later-life first episode).
- Cognitive testing, where clinically indicated, given the cognitive deficits associated with BD.
- History of past treatment — medications used, response, duration, side effects, and reasons for discontinuation. [25,47]

Comorbidity is often less evident during the acute episode and becomes clearer once the patient has recovered from it, underscoring the need for reassessment over time. Ongoing assessment should also track treatment response, side effects, adherence, and life events such as marriage, pregnancy, and disability, along with access to care and therapeutic alliance.

V. MANAGEMENT

Management of bipolar disorder requires a comprehensive, individualized, and long-term treatment strategy.

5.1 Pharmacological Therapy

Pharmacological therapy remains the cornerstone of treatment. Mood stabilizers such as lithium continue to be considered the gold standard, as they effectively reduce manic episodes, prevent relapse, and lower suicide risk. Antipsychotics are also used for acute and maintenance treatment. Antidepressants may be used cautiously in selected patients, usually in combination with mood stabilizers, to reduce the risk of triggering mania. Treatment plans should always be individualized according to symptom severity, age, comorbid conditions, and treatment response. [9,26]

5.2 Psychosocial Interventions

Psychosocial interventions play an important role in improving long-term outcomes:

- Psychoeducation — helps patients and families understand the illness, recognize early warning signs, improve medication adherence, and reduce relapse.
- Cognitive Behavioural Therapy (CBT) — supports symptom control and functional recovery.
- Interpersonal and Social Rhythm Therapy (IPSRT) — helps patients regulate mood by stabilizing social and biological rhythms.
- Family-Focused Therapy (FFT) — engages the family system in relapse prevention.
- Supportive psychotherapy — provides general benefit in symptom control. [27,43]

5.3 Lifestyle Modifications

Regular sleep schedules, physical activity, a healthy diet, stress management, and avoidance of alcohol and recreational drugs further contribute to maintaining mood stability.

VI. HERBAL AND COMPLEMENTARY INTERVENTIONS [28-45]

A range of herbal, nutritional, and alternative therapies have been studied as adjuncts to standard pharmacological and psychosocial treatment for bipolar disorder. Evidence in this area is generally preliminary, and these approaches should only be used alongside — not in place of — conventional treatment and under medical supervision, given the risk that some agents (e.g., Rhodiola) may trigger mania.

Therapy	Scientific Name	Mechanism of Action	Potential Benefits in BD	Research Evidence	Precautions / Side Effects
Ashwagandha	Withania somnifera	Adaptogen; regulates the HPA axis, enhances GABAergic activity, provides antioxidant effects.	Improves cognitive function, memory, reaction time, and social cognition; reduces stress and anxiety; may improve sleep.	2013 RCT (53 participants), 500 mg/day for 8 weeks — significant gains in auditory-verbal memory, reaction time, and social cognition.	Rare liver injury reported; may alter thyroid hormone levels; may interact with thyroid medication.
Valerian	Valeriana officinalis	Enhances GABA receptor activity, producing sedative and anxiolytic effects.	Reduces anxiety, improves sleep quality, helps manage inter-episode insomnia.	2014 review — supportive of benefit for anxiety and insomnia in bipolar disorder.	Daytime drowsiness; additive sedation with other sedatives.
Lemon Balm	Melissa officinalis	Increases GABA activity; antioxidant and cholinergic effects enhancing cognition.	Improves memory, promotes calmness, reduces anxiety, may improve sleep quality.	2014 studies show improved memory and reduced anxiety; 2021 review notes possible benefit for anxiety/depression, though bipolar-specific evidence is limited.	Generally well tolerated; more high-quality trials needed.
Rhodiola	Rhodiola rosea	Adaptogen modulating serotonin, dopamine, and norepinephrine;	May reduce fatigue, stress, anxiety, and depressive symptoms.	Some support for antidepressant effect; bipolar-specific evidence limited.	May trigger manic episodes in susceptible individuals;

		lowers stress hormones.			use only under medical supervision.
Passionflower	Passiflora incarnata	Enhances GABA neurotransmission, producing anxiolytic and sedative effects.	Reduces stress, anxiety, insomnia, and restlessness; may indirectly ease depressive symptoms.	2020 review — benefit for chronic insomnia, anxiety, and stress-related symptoms.	Avoid in pregnancy (risk of uterine contractions); may cause drowsiness.
American Skullcap	Scutellaria lateriflora	Acts on GABA receptors; antioxidant and neuroprotective properties.	Improves mood, reduces anxiety and insomnia, offers neuroprotection.	Study in healthy adults showed mood improvement without cognitive impairment; bipolar-specific evidence lacking.	Limited safety data; bipolar-specific clinical evidence lacking.
Omega-3 Fatty Acids	Fish oil (EPA/DHA)	Anti-inflammatory; improves neuronal membrane function and neurotransmission.	Reduces depressive symptoms and improves mood stability alongside standard treatment.	2016 review — significant improvement in bipolar symptoms, particularly depression.	Mild GI discomfort or fishy aftertaste; may increase bleeding risk at high doses.
N-Acetyl Cysteine (NAC)	N-Acetyl Cysteine	Increases glutathione levels, reducing oxidative stress and neuroinflammation.	May improve bipolar depression; protects kidneys during lithium therapy.	Early studies positive for depressive symptoms; later studies mixed. 2020 review supports adjunctive use under supervision.	May cause nausea or GI upset; should not replace conventional therapy.
Acupuncture	Non-herbal therapy	Modulates neurotransmitters, autonomic nervous system function, and	May reduce depression and anxiety and improve physical well-being in	2022 study (21 participants, weekly sessions for 12 weeks) — reduced	Requires trained practitioners; larger trials needed to confirm

		inflammatory pathways.	treatment-resistant BD.	depression and anxiety.	effectiveness .

Category	Examples	Primary Benefits	Level of Evidence
Adaptogenic Herbs	Ashwagandha, Rhodiola	Stress reduction, cognitive improvement, mood support	Moderate
Nervine Herbs	Valerian, Lemon Balm, Passionflower, Skullcap	Anxiety relief, insomnia management, relaxation	Moderate to Limited
Nutritional Supplements	Omega-3 Fatty Acids, N-Acetyl Cysteine	Mood stabilization, reduction of depressive symptoms	Moderate
Alternative Therapy	Acupuncture	Reduction of depression and anxiety; improved quality of life	Emerging

The table summarizes the major categories of herbal, nutritional, and complementary interventions that have been investigated as adjunctive approaches in bipolar disorder. Adaptogenic herbs such as ashwagandha and Rhodiola have been studied primarily for their potential effects on stress, anxiety, sleep, and cognitive function; however, evidence specifically in bipolar disorder remains limited. Nervine herbs, including valerian, lemon balm, passionflower, and skullcap, may have anxiolytic and sedative properties that could be useful for sleep disturbance and anxiety, but their effectiveness and safety in bipolar disorder require further investigation. [49,30]

Among nutritional supplements, omega-3 fatty acids and N-acetylcysteine (NAC) have received greater research attention. Omega-3 fatty acids may influence inflammatory pathways and neuronal membrane function and have shown potential benefits, particularly for depressive symptoms. NAC may reduce oxidative stress by increasing glutathione availability and has also been investigated as an adjunctive treatment for bipolar depression. Nevertheless, findings across clinical trials have been inconsistent, and these supplements should not replace established pharmacological treatment.[31]

VII. DISCUSSION

Recent research has provided new insights into the biological mechanisms and treatment of bipolar disorder. disorder and According to a 2025 NIMH research report, a large genome-wide study identified additional genes associated with bipolar showed that genetic contributions may differ between bipolar disorder subtypes. These findings strengthen the understanding that bipolar disorder has a complex genetic architecture involving multiple biological pathways rather than a single causative gene.[32,23]

According to a 2026 research report from Newcastle University, researchers used lithium MRI scanning to investigate how lithium is distributed in the brains of people with bipolar disorder. The study found that brain lithium concentrations closely corresponded with blood lithium

concentrations and that lithium levels were more stable with twice-daily dosing. These findings may contribute to a better understanding of lithium monitoring and, potentially, more personalized treatment strategies.[33]

Similarly, a recent study reported in The Lancet Psychiatry proposed that lithium may have disease-modifying effects in bipolar disorder. The authors argued that lithium may influence biological processes involved in the progression of bipolar illness and suggested that its long-term benefits may extend beyond simple symptom control. However, this concept remains an area of ongoing research and should not yet be interpreted as definitive evidence that lithium changes the underlying course of the disease.

Recent research has also examined the potential of digital technologies in psychiatric care. However, current evidence suggests that artificial intelligence and digital tools should be considered supportive technologies rather than replacements for clinical assessment. Emerging reports have highlighted both the potential benefits and safety concerns associated with AI-based mental-health applications, emphasizing the need for appropriate clinical supervision, privacy protection, and safety safeguards.

Overall, these recent findings indicate that the future management of bipolar disorder is moving toward genetically informed diagnosis, individualized pharmacotherapy, biological monitoring, and technology-assisted risk prediction. Nevertheless, most emerging approaches remain under investigation. Future research should therefore focus on validating biomarkers and AI-based models in diverse populations and determining how these technologies can be safely integrated with established pharmacological and psychosocial treatments. [34-39]

VIII. CONCLUSION AND FUTURE PERSPECTIVES

Bipolar disorder remains a complex, heterogeneous, and often under-recognized illness with substantial impact on affected individuals, their families, and health systems. While pharmacological treatment — particularly mood stabilizers such as lithium — combined with structured psychosocial interventions forms the backbone of management, persistent challenges include diagnostic delay, absence of validated biomarkers, and variability in treatment guidelines across regions.

Emerging tools in precision psychiatry, digital phenotyping, wearable sensors, and machine learning offer promising avenues for earlier detection and more personalized treatment, while complementary approaches such as adaptogenic herbs, nutritional supplements, and acupuncture may offer adjunctive benefit for residual symptoms, though rigorous bipolar-specific evidence remains limited. Continued research into the prodromal phase, equitable access to care, and integration of digital health tools into routine practice will be essential to improving outcomes for people living with bipolar disorder.

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The authors declare that no generative artificial intelligence (AI) or large language model (LLM) tools were used in the preparation, analysis, or writing of this manuscript.

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