

Bipolar Disorder in the Era of Precision Psychiatry: Biomarkers, Digital Innovations, and Global Challenges

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ABSTRACT

Bipolar disorder (BD) is a severe, recurrent psychiatric illness characterized by episodes of mania, hypomania, and depression, with profound consequences for individuals, families, and societies. Affecting an estimated 1–2% of the global population, BD ranks among the top contributors to years lived with disability and premature mortality. High suicide risk, cognitive impairment, and substantial functional disability compound its impact, while comorbid conditions such as anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and substance use disorders amplify diagnostic challenges and worsen prognosis. Diagnostic delay—often 6–10 years from illness onset—remains a major barrier, reflecting overlapping transdiagnostic symptoms and the absence of reliable biomarkers in routine clinical use. Over the past decade, advances in neuroscience and translational psychiatry have begun to reshape the landscape of BD research and care. A growing body of evidence implicates dysregulated circadian rhythms, immune-inflammatory pathways, mitochondrial dysfunction, and polygenic liability as key drivers of illness course. These insights are now converging with precision psychiatry initiatives that aim to integrate genomic, neuroimaging, and peripheral biomarker data into individualized treatment strategies. In parallel, the rapid growth of digital psychiatry and artificial intelligence-enabled tools provides unprecedented opportunities for real-time mood monitoring, early relapse detection, and personalized intervention delivery. Importantly, these technologies may bridge long-standing gaps in access to care, although concerns around privacy, equity, and algorithmic bias must be addressed. Therapeutic innovation has also accelerated, with evidence supporting the adjunctive use of anti-inflammatory and neuroprotective agents, alongside chronotherapeutic approaches that target circadian instability. These interventions complement, rather than replace, existing pharmacological and psychotherapeutic frameworks, reflecting a shift toward multimodal and mechanism-informed treatment paradigms. At a systems level, global mental health perspectives highlight persistent disparities in diagnosis and treatment, particularly in low- and middle-income countries where the treatment gap exceeds 70%. Policy reforms, equitable digital infrastructure, and culturally tailored care models will be essential to ensure that advances in precision psychiatry and therapeutics are accessible worldwide. This review synthesizes emerging insights across biological, clinical, technological, and policy domains, highlighting both achievements and unmet needs in BD research and care. By emphasizing biomarkers, digital psychiatry, novel therapeutics, and global health imperatives, it outlines a roadmap for translating discovery into improved outcomes, ultimately moving toward individualized, equitable, and sustainable care for those living with bipolar disorder.

Keywords- Bipolar Disorder; Comorbidity; Biomarkers; Digital Psychiatry; Precision Medicine; Chronotherapy; Global Mental Health; Therapeutic Innovation.

I. INTRODUCTION

1.1 Global burden & epidemiology of bipolar disorder

Bipolar disorder (BD) is a common, typically chronic psychiatric disorder, which often starts occurring at the stage of late adolescence and early adulthood. Meta-analyses conducted in communities showed the pooled lifetime prevalence of BD-I was 1.06 percent and BD-II 1.57 percent, but heterogeneity among studies was large with the diagnostic criteria varying as well as methodology[1]. Notwithstanding the rather stable trend in global age-standardized DALY rates of mental conditions over the period of 1990-2010, they, including bipolar disorder, are retained among the top contributors to years of disability in the world in the period of 1990-2010, which highlights a significant and persistent burden on the population health[2]. Bipolar disorder is characterized by a strong decrease in life expectancy and the increase in the overall mortality rate. Recent meta-analyses, incorporating the results of a large number of studies (hundreds of thousands of individuals), show a about twofold increase in all-cause mortality; suicide (10-11-fold), and some but not all natural causes, cardiovascular and respiratory disease being notable, show the largest relative risks[3].

There are socioeconomic consequences that are bankrupt in the context of borderline personality disorder (BD). Epidemiological research has demonstrated that patients having BD have lower rate of education, increased risk of employment instability, and high indirect cost, which can mainly be explained by low productivity, burden on the caregivers, and long-term disability payments[4]. These findings have confirmed with repeated empirical observations where mean diagnostic delay is 5-10 years with majority of patients having had recurrent symptomatic episodes without sufficient clinical response. This may encounter rather damaging consequences in terms of patient prognosis, not to mention that it leads to further expenses on the national health-care systems[5]. Epidemiology of bipolar disorder in the global perspective is a very complicated issue that is determined by the non-homogenous access to the health services, cultural definition of mental disorders, and comorbid substance abuse conditions, all of which have impact on the prevalence rates and clinical outcomes[6][7].

1.2 Clinical complexity and diagnostic challenges

Bipolar disorder (BD) has heterogeneous symptom patterns that often extend beyond the classical manic-depressive border and thus include mixed episodes, rapid cycling and subthreshold mood instability which negatively affect early diagnosis and longitudinal follow-up[8]. Clinical concordance between unipolar

depression, borderline personality disorder, and some anxiety disorders strongly aggravates diagnosing, particularly at the initial phases of the disease, when depressive symptoms could be typed as first manifestations of this disease[9]. Diagnostic delays in conditions associated with bipolar disorder (BD) can extend to over 6-8 years after the onset of the first symptoms and this is associated with poorer functional outcomes, increased risk of complications related to substance-use disorders, and an increased incidence of suicide-related deaths among patients[10]. Subsyndromal neurobiological and neurocognitive deficits, such as impairments in executive functioning, poor attentional control and aberrant emotional processing may outlive the episodic remission and may complicate the clinical manifestation of bipolar disorder (BD) and affirm that BD is not just a mere episodic disorder; but is a lifespan neuropsychiatric disorder of the brain[11]. Based on the extant literature, culture and sociodemographic factors modify the experience and reporting of an illness, thus creating regional variation in symptoms and symptom presentations, as well as treatment seeking behaviours. This variability makes diagnostic decision-making in global mental health potentially challenging because of potentially important clinical and public-health implications of misclassification[12].

A comorbid combination of anxiety related disorders, attention-deficit/ hyperactivity disorder (ADHD) and substance use disorders further confounds the clinical picture and further muddies diagnosis overshadowing[13]. The presenting phenomena in children with essential tremor (ET), dystonic tremor (DT) and psychogenic tremor (PT) often merge on the spectrum of similar clinical manifestations. As a result, the difference between these diagnoses is rather difficult and usually requires the provision of several assessments and reinforcing data provided by the caregivers[13]. Varying temporal patterns of symptoms is another problem. In casual clinical settings, manic or hypomanic episodes are often not reported because of minimal insight, euphoric minimization of problems or because of a cultural appropriation of the elevated energy level.

On the other hand, the depressive phases have more chances to receive immediate medical care since they are more likely to interfere with the normal functioning and cause social discomfort[14]. Current biological markers to support objective diagnosis are still in their developmental phase, with available neuroimaging, electrophysiological and biochemical information having inadequate specificity and insensitivity to fit into clinical practice[15]. Comorbid psychiatric disorders-especially that of anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and

substance use disorders-combine with the bipolar disorder to cover-up mood episodes and increases the possibility of wrong diagnosis[16].

Comorbid psychiatric disorders, namely, generalized anxiety disorder, attention deficit hyperactivity disorder (ADHD) and substance use disorders are important determinants of clinical direction bipolar disorder, as they often complicate timely diagnosis and make prescribing treatment difficult due to the similarity of symptoms and mutual exacerbation[17].

1.3 Rationale for the review

Bipolar disorder is a lifelong recurrent mood disorder that causes substantial disability throughout the world, and therefore the prompt diagnosis and the adequate management of this disorder are a critical public health issue[18]. Nevertheless, despite the steady advances in psychiatric research, the etiological background of bipolar disorder remains unclear, which only highlights the necessity to provide the comprehensive, state-of-the-art synthesis of both neurobiological and clinical data on the condition[19]. Diagnostic lag: lengthy delays of several years (and greater) following the start of symptoms are common and are reliably associated with worse functional status, as well as higher levels of suicidal risk[20]. The aspect of psychiatric comorbidity whereby presence of multiple disorders occurs simultaneously in the same individual is well-documented as a characteristic aspect of bipolar disorder. Among them one may list out anxiety disorders, attention-deficit/hyperactivity disorder (ADHD) and substance use disorders. These comorbidities often render the diagnosis process, as well as further treatment strategy, even more complicated[21]. The existing reviews of topics of post-traumatic stress disorder (PTSD) are disjointed; each with its own plethora of studies regarding epidemiology, genetics, neuroimaging, pharmacotherapy, and psychosocial interventions, and the lines of inquiry overlap. This level of fragmentation is reason to conclude that integrative, together with comprehensive, reviews that have the capacity to synthesize and critically evaluate the evidence within these areas are necessary[22]. The recent developments of precision psychiatry, digital biomarkers, as well as artificial intelligence-based diagnostics also require the critical academic analysis that would inform the evidence-based clinical decision-making[23].

An evidence-based, carefully updated summary of the new developments in oncology is an essential requirement to inform clinical practice and outline priorities of future investigations[24]. The world burden of psychiatric disorders, including bipolar disorder and schizophrenia, increases progressively who puts big challenges for the healthcare systems and socioeconomical structures[25]. Although severe mental disorders have been subjected to empirical study over several decades, its pathophysiological substrates are still incomplete, thus limiting the development of strictly customized therapeutic treatments[26]. Pursuit of precision psychiatry necessitates a systematic combination of multi-omics data sets composed of genomics, proteomics, and metabolomics[27]. The inequality in access by geography, socioeconomic, and cultural differences to psychiatric care adds to the lack of equality in patient outcomes and requires strident policy-focused analyses. Unfavourable psychiatric service delivery, access and outcomes of treatment across disciplines continues to be unequal, and differing outcomes commonly are attributed to spatial, socioeconomic and cultural circumstances. Spatial mismatch of psychiatric services, particularly density measures, are associated highly with those at a disadvantage financially, a trend that carries across the regions that have a widely variable population. Geographic differences can also be considerable, they would manifest in terms of service access as measured through the financial burden or opportunity cost of travel, indicating that not everyone has access to affordable, good affordable, and equitable care. These geographical inequalities are put in juxtaposition by cultural inequalities. Patients with minority ethnicities indicate a greater barrier to the uptake of services, especially where there are language or communication problems. On the other hand, socially, economically disadvantaged persons, regardless of ethnicity are more likely to encounter increased barriers to care. Due to the complexity of such disparities, multi-sector reviews, including spatial redistribution of services, financial mechanisms to limit out-of-pocket expenses and models of culturally responsive care provision are necessitated in order to achieve progress towards universal access[28].

Table 1: All-Inclusive Overview of Global Epidemiology of Bipolar Disorder

Epidemiological Parameter	Detailed Findings	REFERENCES
Global lifetime prevalence	Bipolar disorder (BD) affects ~2.4% of the population (BD-I: 0.6%, BD-II: 0.4%, subthreshold BD: 1.4%), with variations by region and diagnostic criteria.	[29]
Point prevalence	The global point prevalence is ~1.02%, with no significant gender difference, but slightly higher rates in high-income countries.	[30]
DALYs (2019)	BD accounted for 8.52 million DALYs worldwide, ranking among the top 20 causes of disability in individuals aged 15–49 years.	[31]

Temporal trends (1990–2017)	Incident cases increased from 3.06 million to 4.53 million (+47.7%), while DALYs rose by 54.4% ; age-standardized rates remained stable.	[32]
Diagnostic delay	Mean delay from first mood episode to formal diagnosis: 6.46 years ; longer delays linked to poorer functional outcomes.	[33]
Suicide risk	Lifetime suicide attempt prevalence in BD: 20–60% ; suicide death risk ~ 20–30 times higher than the general population.	[34]
Comorbidity – anxiety disorders	Anxiety disorders co-occur in 40.5% of BD patients; panic disorder 18.1%, GAD 13.3%, OCD 9.7%, social anxiety disorder 13.5%.	[35]
Comorbidity – Substance use	Substance use disorder prevalence: 42.0% in BD patients; alcohol use disorder most common, followed by cannabis and cocaine use.	[36]
Economic burden	Annual direct and indirect costs exceed \$45 billion USD in the U.S., driven by hospitalization, lost productivity, and comorbidity care.	[37]

II. PATHOPHYSIOLOGY OF BIPOLAR DISORDER

2.1 Neurochemical Mechanisms

Bipolar disorder (BD) is now universally accepted as a neuroprogressive disorder whose pathophysiology is dominated by neurochemical imbalance[38]. Disturbances in the monoaminergic system e.g. deficiencies in processing serotonin or dopamine and norepinephrine have been confirmed to play the role in the development of mood episodes and maintenance[39]. Irregularity of dopamine neurotransmission is often suggested as the leading mechanism by which switches between manic and depressive episodes in the bipolar disorder (BD) occur. The supporting data behind this hypothesis takes the form of a conglomeration of results such as increased release of striatal dopamine in mania, depressed dopaminergic reinforcing to stimulus signals in depression and the like blunted striatal dopaminergic activity over the course of the bipolar mood phase. Collectively, these data imply that abnormalities in front striatal dopaminergic circuitry are decisive in maintaining an affective symptomatology in both polarized and mixed states of BD[40]. The evidence is consistent showing that changes in the glutamatergic system, namely an increased level of concentration of glutamate in certain parts of the brain, is typical of the population of a disease such as bipolar disorder (BD)[41]. Since, mood instability has been attributed to the depletion of Gamma-aminobutyric acid (GABA), attention to impaired inhibitory neurotransmission in the neurobiology of bipolar disorder (BD) is the most important feature in the neurobiology of bipolar disorder (BD)[42]. Neurochemical abnormalities in bipolar disorder (BD) also cover more than the traditional neurotransmitter pathways involving the metabolic processes of the cell as interventional data regarding disorders of mitochondrial bioenergetics and an increase in the magnitude of oxidative stress markers support this statement[43]. Bipolar disorder (BD) is a condition that is related to upon initiation of mood episodes caused by stress; this disorder is accompanied by dysregulation and excess of long-term activation of the hypothalamic-pituitary-adrenal (HPA). These neurochemical disruptions entail corticotrophin-releasing

hormone, adrenocorticotrophic hormone, and cortisol that facilitates the control of the hypothalamic-pituitary-adrenal axis. Each of these findings are primarily supported by imaging studies, including cross-sectional research findings, although it is less known how much these mediators move mood episodes[44]. Disturbances in neuroinflammatory signalling (which can be seen e.g. via the increase in pro-inflammatory cytokine levels), influence the synthesis and re-take of neurotransmitters thus contributing to the symptoms of bipolar disorder[45]. Disturbances of intracellular calcium signalling, especially in the nervous system (in neurons and glial cells), have been identified as contributing to the synaptic and neurochemical pathology of bipolar disorder (BD)[46]. Neurochemical changes in the circadian system, particularly melatonin synthesis and signalling pathways may be responsible for rhythmic disruptions in BD[47]. Dysfunction of both 5-HT1 and 5-HT2 receptors is indicative of aberrant serotonergic neurotransmission that has been suggested to contribute to lack of emotional regulation in the bipolar disorder (BD)[48]. The empirical fact that there is increased dopamine D2/ D3 receptor striatum binding in manic episode suggests existence of dopaminergic hypersensitivity[49]. Disruption in the action of norepinephrine transporter has been indicated to worsen hyperarousal and increase stress responsivity in bipolar disorder [50]. Full Text Interested in MRS proton spectroscopy (MRS) studies of brain tissue indicate an increase in myo-inositol concentration in bipolar disorder (BD) that may indicate dysfunction in the compartment of glial cells and malfunctions of the phosphoinositide cycle[51]. The persistent aberrant functioning of the glutamate-glutamine cycle characterises chronic bipolar disorder (BD), and, as a result, disrupts synaptic plasticity[52]. The prefrontal cortex degenerates GABAergic interneurons that is associated with poor mood regulation in the Bipolar Disorder (BD)[53]. The observed relations of an increased immune activation and glutamatergic dysregulation in patients with bipolar disorder may be mediated by alterations of kynurenine pathway, one of the major pathways of tryptophan metabolism. It has been observed several times in patients with bipolar disorder that there are higher concentrations of kynurenine metabolic products in their plasma, namely 3-hydroxykynurenine, kynurenine, and quinolinic acid

which may lead to the fact that these products contributed to the pathology of the disorder. All three derivatives are neuroactive (quinolinic acid acts as an endogenous antagonist of N-methyl-D-aspartate receptors and 3-hydroxykynurenine as a precursor or competitive metabolite of the neuroprotective kynurenic acid). Such results suggest that the products of the kynurenine pathway could have a direct or indirect effect of altering the glutamatergic neurotransmission in bipolar disorder and play a part in the phenotyping of this pathway[54]. In bipolar disorder (BD), increased levels of biomarkers of oxidative stress marker- in particular, malondialdehyde and 8-OHdG- have been found to be indicators of neuronal membrane and DNA damage[55]. According to neurobiological research, mitochondrial complex I dysfunction compounded by the reduction in the availability of ATP exacerbates bipolar disorder (BD) due to its energy deficiency in the neurons[56]. The increase in cortical 5-HT, norepinephrine, and dopamine levels compared to healthy controls indicate a disturbance of the neurochemistry equilibrium in the case of bipolar disorder (BD). Moreover, the reduced level of BDNF suggests the poor synaptic resilience in the BD pathophysiology[57].

2.1.1 Monoaminergic dysregulation (dopamine, serotonin, norepinephrine)

Dearth in the regulation of dopaminergic signalling is a critical neurochemical symptom of bipolar. Consistent with the findings of empirical studies include the probabilities that manic episodes are linked to the enhanced dopamine D₂ / D₃ responsivity level and the enhanced presynaptic dopamine synthesis, whereas the depressive stage is accompanied by the impoverished dopaminergic tone[58]. Research reports have shown that lack of serotonin levels, especially the reduced binding of the 5-HT 1A receptor in the prefrontal and hippocampus to be the cause of poor emotional control and easy-mood sensitivity among bipolar patients[59]. It has also been discovered that the two components of the manic phases are the increased norepinephrine turnover and locus coeruleus elevation through clinical studies. Depressive episodes, on the other hand, are associated with reduction of the noradrenergic neurotransmission. Altogether, the results attest to a different catecholamine imbalance across the stages of bipolar disorder[60]. Altered neuroimaging and postmortem studies have characterized the different aberrations of monoamine transporters i.e., DAT, SERT, and NET in bipolar disorder. Such changes encroach upon the neurotransmitter synaptic clearance thus enabling longer signalling along definite circuits specifically designed to make this move[61]. The foundational disconnection in the dopamine-serotonin network with strong evidence of disconnection between the ventral tegmental area, dorsal raphe nucleus and prefrontal-limbic circuits according to functional MRI studies has been shown to be associated with instability of moods[62]. Pharmacological evidence is suggestive of a role for monoamines: dopamine agonists can induce mania, and serotonin-norepinephrine reuptake inhibitor

(SNRI) can lead to destabilization of mood in susceptible people[63]. Over the last 10 years, the dopamine hypothesis of bipolar disorder has evolved to a biphasic model based on a belief that hyperdopaminergic causes mania and hypodopaminergic mediates depressive episodes[64].

2.1.2 Circadian rhythm & sleep biology

Circadian and sleep-wake disturbances are prevalent among patients with bipolar disorder and correlate to poorer performance, more relapses, and suicidal behaviour[65]. Consistent with these findings during euthymia, bipolar patients exhibit trait-like evening Ness (late chronotype), enhanced sleep fragmentation and a higher amount of individual variability in the time of sleep[66]. Variants in clock-genes (e.g., CLOCK, PER, BMAL1) and circadian-related signalling are likely to contribute to vulnerability to the development of bipolar and help determine mood regulation[65]. Those circadian misalignment and sleep loss dysregulate emotion circuitry (increased amygdala, reduced medial-PFC control), which caused them to develop affective instability[65]. Sleep-wake rhythm disturbance is a continuous characteristic of manic-depression, which appears both during mood disorders and in the manic-depression free state, indicating that it is a trait feature[67]. Actigraphy indicates that the rest-activity rhythms are more variable and lack stability in bipolar patients where even between-episodes there is irregularity in the patterns[68]. Euthymic bipolar individuals may exhibit advanced dim light melatonin onset (DLMO) and greater phase-angle differences compared to controls[69]. Even before the onset of the disease, unaffected children whose parents have bipolar showed flattened melatonin secretion curves and phase-angle distortion[70]. Even before the onset of the disease, unaffected children whose parents have bipolar showed flattened melatonin secretion curves and phase-angle distortions[71]. The interpersonal and social rhythm therapy (IPSRT) involves stabilization of the daily routine, and in RCTs, has been demonstrated to lengthen time to relapse[68]. Chronotherapeutic measure after the midday bright light or blue-light blocking can be a fast-acting intervention to treating mood symptoms in BD and reset the body clock[68]. Sleep disturbance is a common precursor of mood episodes in BD, therefore, sleep dysregulation may serve as an alerting phenomenon[67].

2.1.3 Inflammation, oxidative stress, genetics

2.1.3.1 Inflammation in Bipolar Disorder

Inflammation is a prime convergence point in the pathophysiology of bipolar disease, connecting mitochondrial, endoplasmic reticular, and calcium homeostasis, purinergic, kynurenic, and hormonal/neurotransmitter signalling pathotypes[72].

Peripheral inflammatory markers have also been linked to illness progression in bipolar disorder and therefore it appears that inflammatory processes are involved in the neuroprogressive components of the disorder[73].

2.1.3.2 Oxidative Stress in Bipolar Disorder

Oxidative stress markers, including raised concentrations of malondialdehyde have been found to be higher in bipolar patients that indicates the oxidation of lipids[74]. Oxidative stress products such as superoxide dismutase and malondialdehyde have elevated rates with a correlation with manic symptoms and cognitive impairment in bipolar disorder[74]. These have been supported by the oxidative stress biomarkers, 8-hydroxy-2-deoxyguanosine, which is elevated in patients with bipolar disorder, indicating neuroprogression through oxidation of DNA[75].

2.1.3.2 Genetics in Bipolar Disorder

The CLOCK gene harbouring polymorphisms is linked to circadian rhythm impairments in the patients of bipolar disorder and it thus indicates that there is a genetic impairment in solving the problem of sleep-wake disruptions[76]. A variant within the PER3 gene is associated with sleep phase preference and possibly with bipolar predisposition, suggesting that circadian genes play the role of moderators in mood[76]. GSK-3 beta gene variants have been implicated in the onset age, treatment outcome in bipolar disorder thus showing the predisposed nature of the disease[76]. The gene associated with neuroplasticity, BDNF gene, contains polymorphisms that impact the development of bipolar disorder and its progression, indicative of a genetic component to bipolar disorder pathophysiology. Epigenetic variations, particularly alterations to DNA methylation, are noted in bipolar disorder and may impact its gene expression, so DNA methylation alterations play a role in the development of bipolar disorder[76].

III. CLINICAL FEATURES & SUBTYPES

3.1 Bipolar I

Bipolar I Disorder is a diagnosis in which patient experienced at least one episode characterized by mania, commonly accompanied by depressive episodes causing impairment in functioning[77].

3.2 Bipolar II

The symptoms of BD-II are intermittent depressive occurrences as well as at least one hypomanic outcure without a complete manic attack[68]. Lifetime prevalence of BD-II is 0.8%, and the average age of onset is 20 years[68].

3.3 Cyclothymia

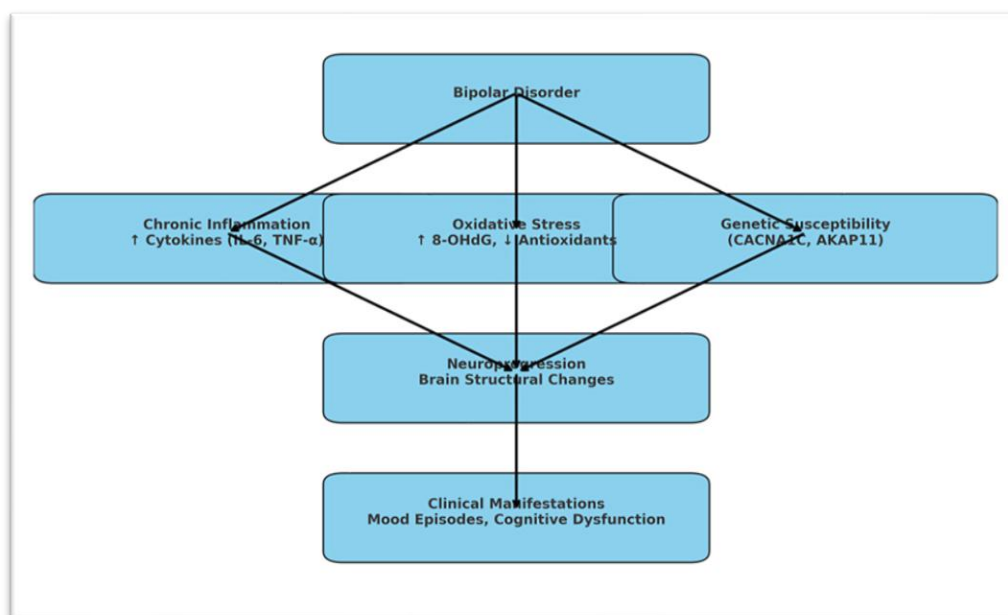
Cyclothymic disorder is characterized by the persistence of instability of the mood, which nevertheless fails to meet the full-blown hypomanic or major depressive episode[78]. The available epidemiological evidence indicates that cyclothymia can be a highly common but as of yet an underappreciated bipolar spectrum disorder-particularly among young people[79].

3.4 Mixed states

Mixed states- in which manic and depressive symptoms develop simultaneously- have been associated with more severe disease, resistance to treatment and diminished recovery[80]. Around 40 percent of bipolar patients have mixed episodes, which are more related to an increased risk of suicide and a greater clinical burden[81].

Table 2: Inflammation, Oxidative Stress & Genetics In Bipolar Disorder

Mechanism	Connected Scientific Insight	REFERENCES
Inflammation (IL-6)	Elevated interleukin-6 (IL-6) is consistently observed in Bipolar I patients across mood states, and higher levels correlate with poorer neurocognitive performance.	[82]
Inflammatory Trait	Systematic reviews show persistent activation of peripheral cytokines, suggesting that low-grade inflammation is a trait marker of bipolar disorder rather than state-dependent.	[83]
Oxidative Stress – 8-OHdG	Meta-analysis demonstrates significantly elevated levels of oxidative DNA damage marker 8-hydroxy-2'-deoxyguanosine (8-OHdG) in bipolar patients, especially in urine samples.	[84]
Mitochondrial Oxidative Dysfunction	Bipolar patients exhibit reduced antioxidant defenses (e.g., glutathione) and higher lipid peroxidation, indicating systemic mitochondrial dysfunction.	[85]
Trait Oxidative Damage	Newly diagnosed bipolar patients and their unaffected siblings show increased oxidative DNA/RNA damage, supporting its role as an inherited vulnerability factor.	[86]
Genetics – Rare Variants (AKAP11)	Exome sequencing reveals rare protein-truncating variants in the AKAP11 gene that significantly increase BD risk, overlapping with schizophrenia pathways.	[87]
Genetics – Polygenic Risk	Genome-wide association studies (GWAS) confirm a polygenic architecture for BD, identifying >30 loci and estimating heritability at 60–80%.	[88]
Genetics – Calcium Channel Genes	CACNA1C and other calcium channel genes repeatedly emerge as susceptibility loci, linking BD to neuronal excitability and circadian regulation.	[89]



Flowchart 1: Pathophysiological Pathways in Bipolar Disorder

IV. COMORBIDITY AND DIAGNOSTIC COMPLEXITY IN BIPOLAR DISORDER

Bipolar disorder (BD) is progressively being identified as a condition not merely characterized by frequent persist mood swings but a condition with high frequencies of psychiatric and medical comorbid states, therefore, making diagnosis and therapeutic management challenging. Psychiatric comorbidities between anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and substance use disorders (SUD) underscore the problem of diagnosis that can blur disease trajectories, impede prompt diagnosis, and negatively influence therapy. It is widely recognized that these comorbidities are not incident but based on consistent epidemiological and clinical studies within the past decade that shared neurobiological substrates, overlapping genetic vulnerability, and shared risk exposures to the environment are all conscious of driving an illness course over time.

4.1.1: Anxiety Disorders as a Comorbidity in Bipolar Disorder

One of the most frequent comorbidities of bipolar disorder (BD) is anxiety disorder, and their co-occurrence has a strong impact regarding the severity and chronicity of the disease and successful treatment outcomes of bipolar disorder. One seminal systematic review and meta-analysis study has shown that a significant proportion (estimated at 45 percent) of patients with BD carries a lifetime comorbid anxiety disorder, and that specific diagnoses, such as generalized anxiety disorder (GAD), panic disorder, or social anxiety disorder are associated with a significant proportion of added burden[90].

The co-occurring of anxiety disorders and bipolar disorder (BD) is related to early age of onset, high risk of rapid cycling and an elevated risk of suicide. These correlations are of clinical importance; they imply that comorbid anxiety changes the phenomenology of BD, often leading to further depressive episodes and making attempts at stabilization of mood more difficult.

In addition, comorbid anxiety is predicting worse treatment results. It has been reported that patients with bipolar disorder (BD) and anxiety disorders who also co-occur in terms of remission rates after lithium and other mood stabilizer treatments enjoy lower remission rates than those with no anxiety comorbidity[90]. Both conditions are neurobiologically dysregulated, thus displaying amygdala-prefrontal cortex circuitry dysregulation and alterations in serotonergic and noradrenergic signalling, and as a consequence, the rates of comorbidities have been observed to be high. In the clinical picture, this overlap calls for a judicious diagnostic approach in that such signs of anxiety can be mistaken to undergo prodrome symptoms of mania or depression, and thus the psychology of comorbidity.

4.1.2: ADHD and Bipolar Disorder: A Challenging Diagnostic Overlap

Another major comorbidity that makes the diagnostic process of bipolar disorder (BD) a difficult one is ADHD. Symptom overlap—specifically distractibility, impulsivity, and hyperactivity—can obscure diagnostic boundaries, particularly in adolescents and young adults. A more recent systematic review and meta-analysis of 71 studies and over 646,000 participants across 18 countries found a concerted prevalence of ADHD in adults diagnosed with BD to be 17.1 in 95 per cent CI 13.1 to 21.6 per cent. On the other hand, it was also found that the BD frequency in the adult population with ADHD could

be estimated at 7.95% (95% CI: 5.31-11.06%) percentage[91].

The strong two-way comorbidity of Attention-Deficit/Hyperactivity Disorder (ADHD) and bipolar disorder (BD) is evidence of a genetic commonality. Association studies Genome wide Polymorphisms in CACNA1C and ANK3 have been found as being risk factors in both conditions. The overlap is further explained by neurocognitive dysfunction, especially, executive control and mechanisms of attention. ADHD in BD is clinically linked to the increased risk of substance abuse as well as more severe mood instability in the premature onset of bipolar illness.

The problem of treatment is particularly acute: first-order treatments of ADHD which are used to achieve success, i.e. stimulants, may cause a manic/hypomanic episode in patients of BD, whereas the mood stabilizers do not reveal the attentional deficits typical of ADHD. Such a circumstance poses a treatment crisis where

professionals must decide to stabilize the mood of the individual versus improving attention. Combination Mood stabilizers with careful dosage of stimulants or non-stimulants (atomoxetine, guanfacine) are under consideration and must be cautiously observed to avoid destabilizing mood.

4.1.3: Substance Use Disorders in Bipolar Disorder

The comorbidities of the disorder under review are one of the most frequently diagnosed substance use disorders, which significantly worsen the clinical prognosis. Numerous population-based studies and clinical research indicate that in general one-third of individuals with the traditions of bipolar disorder meet lifetime criteria of a substance use disorder, the alcohol use disorder being the most common subtype. An estimate of the prevalence of any and alcohol use disorder, respectively, based on a systematic review and meta-analysis identified a pooled prevalence of 33% and 24% in bipolar disorder patients[92].

Comorbidity	Key Findings	Study Type	REFERENCES
Anxiety Disorders	Meta-analysis found 45% lifetime prevalence of anxiety disorders in BD, especially GAD, panic disorder, and social anxiety, significantly increasing risk of suicide and rapid cycling.	Systematic Review & Meta-analysis	[93]
Anxiety Disorders	Comorbid anxiety in BD predicted lower remission rates with lithium and mood stabilizers, showing strong neurobiological overlap in amygdala-prefrontal circuits.	Longitudinal Study	[94]
ADHD	Large meta-analysis (71 studies, n=646,000) reported 17.1% prevalence of ADHD in adults with BD , and 7.9% prevalence of BD in ADHD adults.	Systematic Review & Meta-analysis	[95]
ADHD	Shared genetic risk via CACNA1C and ANK3 polymorphisms highlights overlapping pathophysiology of BD and ADHD.	Genetic Association Study	[96]
Substance Use Disorders (SUDs)	Meta-analysis estimated 33% pooled prevalence of any SUD and 24% alcohol use disorder in BD patients.	Systematic Review & Meta-analysis	[97]
Substance Use Disorders (SUDs)	Lifetime prevalence of SUDs in BD estimated 30–40% , associated with earlier onset, more hospitalizations, and higher suicide risk.	Epidemiological Review	[98]
Diagnostic Complexity	Comorbidities contribute to 6–10-year diagnostic delay in BD, with worsened functional impairment and reduced quality of life.	Global Burden Study / Review	[99]

V. EMERGING DIRECTIONS AND FUTURE PERSPECTIVES IN BIPOLAR DISORDER

1. Biomarkers & Precision Psychiatry

The current psychiatry shift is type of paradigm shift whereby the traditional one-size-fits-all approach to providing care is being replaced by personalised approaches of diagnosis and treatment based on biological stratification. This shift has conceptualised the emergence of staging models to trace the natural history of the disease through prodromal stage into chronic stages, in both cases increasing the ability to intervene at an earlier stage or to precisely adjust therapeutic interventions, a

methodological strategy known as precision staging, as it would be in the case of bipolar disorder (BD)[100]. Parallel studies in the field of omics such as genomics, proteomics and metabolomics as well as neuroimaging studies have attempted to find objective biomarkers that will allow predicting the onset of disease, forecasting episodic exacerbations and tracking the response to treatment. As noted by several systematic reviews in recent years, metabolomic biomarkers, serum protein assays and imaging biomarkers have strong potential to diagnose with a high level of early diagnosis and allows the design of specific treatment management of bipolar disorder[101]. Other studies focus on the use of high-resolution neuroimaging technologies, e.g., detection of personal deviations in brain circuits, which have the

potential to refine not only diagnostic accuracy but also prognostic assessments[102]. Taken together, all of these findings highlight a path to the genuinely personalised psychiatry.

Additionally, a multi-domain methodology that puts together clinical, biological and electronic information is being increasingly appreciated. Fernandes et al. established the use of precision psychiatry tools which are aimed at assisting in objective diagnosis of differentiation which include differentiating between bipolar disorder and schizophrenia and improve the confidence of the diagnosis[103]. Smeland et al. contributed to the field by proposing multi modal developmental profile mapping, thus, improving subtyping of bipolar disorder and forecasting of disease progression[104].

2. Digital Psychiatry & AI-Based Diagnostic Tools

There is significant potential in the timely and objective evaluation of the bipolar disorder through the emergence of digital phenotyping, i.e., the method of collecting and analysing behavioural and environmental data in a systematised fashion with the help of smartphones and wearable devices. In this paper, Saccaro et al. provide a systematic review of portable digital technologies, such as sensor-, mobile phone use-based measures, audiovisual, data that can be utilised to detect mood states and distinguish different subtypes of bipolar disorder, which highlights the first but promising evidence[105]. Elaborating on this idea, Orsolini et al. point out that digital phenotyping inclusion in clinical practise can help clinicians detect early relapse, measure therapeutic responses, and predict mood changes through the combination of digital, biological, and endophenotypic data[106]. In more recent work, classification and clustering of bipolar disorder versus unipolar depression and healthy controls with digital phenotypes has demonstrated promising albeit variably accurate and hence real-world feasibility[107]. A study named Digital Phenotyping Capacity to ensure that digital phenotyping is selective in distinguishing bi-polar and unipolar depression- which holds the utmost importance in providing therapeutic accuracy- was underpinned by Zhong et al. in 2025, and this volume qualifies the technology as a crystal-clear diagnostic tool[108]. Zhang et al. further showed that digital phenotyping and integration into a P4 medicine paradigm-Predictive, Preventive, Personalised, and Participatory-les to improve effective early disease detection to develop personalised intervention strategies[109]. Regarding a more general mental-health infrastructure view, Torous et al. note that integrating smartphone applications, virtual reality, and generative artificial intelligence, though explicit to bipolar disorder, represents a digital pathway that digital psychiatry must keep with, especially in terms of implementation, clinician-institution interaction, and equity[110]. In the context of a bipolar-specific digital innovation, de Azevedo Cardoso et al. outline the potential of applications as well as

wearable computers to detect and control early on, being careful with navigating the real-world barriers on the road to their use[111].

3. Novel Therapeutic Targets (Anti-Inflammatory, Chronotherapy, Neuroprotective Agents)

In addition to standard mood stabilisers, modern therapy approaches also pay increased attention to the underlying pathophysiology, such as inflammatory pathways, dysregulation of the circadian rhythm, and neurodegenerative pathways.

Anti-Inflammatory Agents

Neuroinflammation has been fronted as a critical pathophysiological characteristic of depression bipolar disorder. Rosenblat et al. demonstrated in a meta-analytical evaluation that daily use of anti-inflammatory therapy in the form of non-steroidal anti-inflammatory drugs (NSAIDs), N-acetylcysteine (NAC), and minocycline produced moderate antidepressant effects in bipolar disorder (standardised mean difference -0.40) with a rare occurrence of considerable adverse events (para. 23)[112]. A meta-analysis study in 2024 further supported the therapeutic effectiveness and acceptability of different anti-inflammatory agents, including statins and minocycline, in the management of mood disorders; discrimination in study samples, nonetheless, remains a challenging challenge[113]. The efficacy and tolerability of various anti-inflammatory and inhibitory groups, such as statins or minocycline, in the setting of mood disorders was supported by meta-analysis in 2024, although the range of study samples is recognised as a methodological issue[114].

Chronotherapy (Circadian-Based Treatments)

Recently, the attention has been drawn to the chronotherapeutic approaches, including bright light therapy, sleep deprivation, and social rhythm stabilisation because of their rapid mood-altering results. A meta-analysis of the perspective that is presented by Gottlieb et al. shows evidence that supports the effectiveness and tolerability of these treatments in bipolar disorder (BD), and in the final evaluation by Dagostino, of triple chronotherapy; the use of sleep deprivation, exposure to light and phase advancements revealed that it was safe and potentially effective, but there have so far been few randomised controlled studies to verify it[115]. Moreover, the randomised controlled trials with high-intensity light therapy at the luminous of 5,000 L Укpaї trips have studied a considerable temporary reduction of depression symptoms in bipolar disorder[116]. In addition, there existed controlled trials using high-intensity light therapy of 5000lux that found substantial short-term depression alleviation in the case of bipolar disorder[117]. Sleep deprivation, together with light treatment did not fail to perform well[118].

Neuroprotective and Mitochondrial Agents

The small number of large randomised controlled trials (RCTs) notwithstanding, the neutral groundwork findings incorporate the influential prospective, randomised adjunctive trial by Savitz et al.

who combined minocycline and aspirin statistically significantly influencing the study of bipolar depression reported significant effect sizes (odds ratio=2.93), thus implicating the inflammatory and neuroprotective contributions[119]. The interventions imply the shift toward only symptomatic treatment to the treatment of underlying neural pathology.

All of these new types of therapeutic interventions, especially when, as with biomarker-guided patient selection, combined to add value, are potentially viable enable more specific, mechanism-focused treatment regimens.

4. Policy and Global Mental Health Implications

Biomarkers, digital diagnostics and new therapies have limited transamination potentials because they are critical to coherent policy and sound integration into health systems.

Coelho et al. (2025) propose a digital health model that involves social media and AI-based virtual agents to advance issues of health literacy and advance behaviour intervention practises. They warn, though, that

every type of digital modality should be stringently evaluated on the basis of safety, access, and effectiveness, especially when reaching underserved groups[120]. Titov et al. among others emphasise the critical role of preparatory steps that incorporate in their process the unrelenting conceptualization of the nature of digital mental-health services, codified development of governance platforms, and the intentional design of scalable ecosystems to make deployment not only responsible but also sustainable[121]. Moreover, despite the advantage of precision biomarker and antipsychotic management models, Fornaro et al. point out regulatory, cost, and ethical issues, highlighting that evidence-based guidelines have to consider the complexity inherent in the real world of bipolar disorder management[122]. At the health-system level, Sackey et al. (2024) had proven that the use of digital tools supports unremitting surveillance of long-term mental illnesses, and as such, presented them as applicable in relapse prevention in the context of bipolar disorders when these tools are properly supported[123].

Table: Emerging Directions and Future Perspectives in Bipolar Disorder

Theme	Extended Review-Style Insight (Paraphrased)	DOI
Biomarkers & Precision Psychiatry	Precision psychiatry has shifted the focus in BD research from symptom-based approaches to biomarker-driven models, integrating genomics, proteomics, and neuroimaging. Recent work shows that peripheral inflammatory markers and multi-omics profiles can identify patient subgroups with distinct trajectories, supporting individualized treatment strategies.	[124]
	Polygenic risk scores, when combined with structural MRI and metabolomic signatures, significantly enhance the differentiation between BD and schizophrenia. Such integrative approaches illustrate how multi-modal biomarkers may soon guide diagnosis, treatment selection, and prognosis, transforming clinical psychiatry into a precision-driven discipline.	[125]
Digital Psychiatry & AI-Based Tools	Digital psychiatry represents a disruptive innovation for BD care. Smartphone-based digital phenotyping—tracking activity, speech, circadian rhythms, and social interaction—can predict mood fluctuations weeks before clinical relapse. Early trials demonstrate feasibility, scalability, and good predictive accuracy, though ethical and privacy issues must be addressed.	[126]
	Artificial intelligence models applied to wearable and mobile data show promise in distinguishing BD from MDD and healthy controls, with accuracies surpassing traditional clinical assessments. Importantly, clustering algorithms highlight the heterogeneity of BD, supporting a move toward individualized monitoring and real-time intervention.	[107]
	However, despite the promise of AI-driven psychiatry, concerns remain regarding data privacy, algorithmic bias, and unequal access across socioeconomic groups. Addressing these challenges is crucial for integrating AI as a standard clinical decision-support tool in psychiatry.	[108]
Novel Therapeutic Targets	A growing body of research implicates immune dysregulation and neuroinflammation in BD. Adjunctive anti-inflammatory agents such as N-acetylcysteine, aspirin, and minocycline have demonstrated significant though modest antidepressant effects in clinical trials, reinforcing the need to test immune-modulating strategies in larger cohorts.	[127]
	Chronotherapy interventions, including bright light exposure, dark therapy, and sleep-wake cycle stabilization, have emerged as rapid and well-tolerated adjunctive strategies for bipolar depression. Evidence indicates they can reduce depressive symptoms within days, offering an alternative to pharmacological treatments that are often slow to act.	[128]
	Beyond circadian and immune modulation, neuroprotective approaches focusing on mitochondrial dysfunction, oxidative stress, and synaptic plasticity are being actively tested. A combination of minocycline and aspirin, for instance, has shown promising	[119]



	efficacy, highlighting how targeting cellular resilience pathways may represent the next frontier of BD treatment.	
Policy & Global Mental Health Implications	Emerging innovations must be framed within policy and global health priorities. Digital psychiatry, though scalable, risks exacerbating disparities if not implemented with safeguards for equitable access, especially in low- and middle-income countries where BD is frequently underdiagnosed and undertreated.	[129]
	Precision psychiatry and novel therapeutics will only have meaningful global impact if regulatory, cultural, and ethical challenges are addressed. Experts argue that implementation science and health-policy integration are urgently needed to ensure that BD care innovations reach diverse populations rather than remain confined to academic centers.	[130]

VI. CONCLUSION: FUTURE PATHWAYS IN BIPOLAR DISORDER RESEARCH AND CARE

To conclude, the last 10 years have brought tremendous progress of understanding the complex picture of bipolar disorder, which was facilitated by a combination of research on biomarkers, precision psychiatry, digital innovations, a development of new treatment targets, and mental health policy efforts across the globe. Taken together, these escalating trends evidence a real-time paradigm shift in a universalist therapeutic paradigm into a customised, individualised model of care, which is supported by biological, behavioural and environmental predictors[131]. The first is the growing relevance of biomarkers on disease progressions and treatment responses. Although the candidate biomarkers involving inflammation, circadian rhythm genes and neurotrophic pathways have shown potential, their clinical applications are quite limited due to constrained sample size, inadequate replication and cross-population generalizability. Rapidly, therefore, an unmet goal is to ensure that all-large, multi-site biobanking efforts are undertaken which consolidate genomics, proteomics and neuroimaging into clinically applicable algorithms[132]. The other substantive progress is the expansion of digital psychiatry and AI-guided tools, which includes smartphone-based surveillance, ecological momentary assessment and passive senses technologies. These tools enable real-time, continual monitoring of affective nucleus and behavioural indices that can mitigate to a significant extent diagnostic latency. Nevertheless, replicable worries have to do with the privacy issues of data, biases in algorithms, and the digital divide, all of which can potentially increase healthcare disparities without addressing them[105]. New pharmacological and non-pharmacological treatment approaches are now undergoing research on the therapies side. Anti-inflammatory drugs, melatonin as a chronotherapy and neuroprotective are showing initial clinical effectiveness, hence, highlighting the bio-heterogeneity of bipolar disorder.

In spite of this progress there is still a large proportion of patients left to conventional mood

stabilisers and antipsychotics and a short list of newer drugs that have ever made it into routine clinical use in the last twenty years.

Future surveillance requires trial designs with precision-medicine-driven trial designs that selectively stratify patients based on the biological subtype and comorbidity profile[133].

Bipolar disorder remains a global mental health issue at a policy and systems level, presenting a sizeable and significant disability-adjusted life year (DALY) contribution, with disparities in treatment across more than 50percent in low- and middle-income nations and stigma hindering timely help-seeking. The current international models emphasise integration of digital platforms/services, task-shifting approaches, and cultural appropriate interventions in national mental-health plans. However, inequities in resource support, lack of sufficient trained professionals and fragmentation of service delivery remain as great impediments[129]. Conclusively, despite the fact that scientific advancement has shed new vistas of promise, the unsolved needs that pertain to replication, equity, and clinical transfer today are still very high and need to be addressed. An integrated system between the world of academics, industry, policymakers and patient advocated groups must be essential in order to bring these inventions into reality and show people with bipolar disorder their benefits[111].

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