Proceeding of ICSPHS 2026 Symposium: Critical Perspectives on Global Education and Psychological Development
DOI: 10.54254/2753-7048/2026.HT29526

Mood Transitions in Bipolar Disorder: Triggers, Neurobiological Mechanisms, and Management

Mingxuan Ji

Psychology College, Durham University, Durham, British
jmx18822195285@gmail.com

Abstract. Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurring episodes of depression, mania, and hypomania. Central to its course are abrupt mood transitions that severely impair quality of life and increase the risk of hospitalization and suicide. With the development of society and the evolution of the times, the incidence of bipolar disorder is gradually becoming younger. This review explores the multifactorial nature of mood transitions in BD by examining psychological, pharmacological, biological, and environmental triggers. This review then delve into emerging neurobiological findings on functional and structural brain alterations, circadian misalignment, inflammatory processes, and neuroprogression. Lastly, this review assess current management strategies, including pharmacological treatments, psychotherapies, digital monitoring tools, and emerging biological interventions. Synthesizing insights from recent literature (2018–2024), this paper aims to elucidate the complex landscape of mood shifts in BD to better inform clinical care and future research directions, emphasizing the critical importance of early intervention and personalized treatment approaches.

Keywords: Bipolar disorder, Mood transitions, Circadian rhythm disruption, Neuroinflammation, Epigenetic regulation

1. Introduction

Bipolar disorder (BD) is a severe, recurrent mental illness affecting approximately 1–4% of the global population, with a substantial burden on individual functioning and public health [1]. It typically emerges in late adolescence or early adulthood (peak onset at 19.5 years) and is associated with considerable morbidity, mortality (reduced life expectancy by approximately 9 years), and a high risk of suicide (nearly 20% die by suicide) [2]. The illness is marked by alternating episodes of mania, hypomania, and depression, which can emerge unpredictably, complicating both diagnosis and management. The core diagnostic feature of BD is the unique phenomenon of switching between mood polarities—a characteristic first described as "circular insanity" in the 19th century .

Of particular concern are the transitions between these mood states—often abrupt, difficult to anticipate, and associated with elevated risk of suicide, social dysfunction, and treatment resistance . While numerous studies have focused on symptomatic states, relatively fewer have comprehensively addressed the mechanisms and moderators of state transitions themselves. Increasingly, researchers recognize that mood transitions are not merely passive shifts but are shaped by dynamic interactions

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-7048/2026.HT29526

among genetic, neurochemical, circadian, immunological, and psychosocial factors. The neuroprogressive nature of BD means that with each mood transition, patients may experience worsening clinical outcomes, including cycle acceleration, cognitive decline, and reduced treatment responsiveness [3].

An improved understanding of the triggers and mechanisms underlying these transitions could pave the way for more effective preventative strategies. Notably, prodromal symptoms, life stressors, sleep disruptions, metabolic perturbations, and medication changes have all been implicated in promoting phase shifts. Furthermore, individual vulnerability—shaped by childhood adversity, trauma, neurocognitive deficits, and comorbidities—may mediate the likelihood and trajectory of mood instability. This developmental perspective is crucial for early identification of high-risk individuals .

This review synthesizes current knowledge on mood transitions in BD, beginning with an overview of common triggers (pharmacological, environmental, and psychological), followed by a discussion of emerging neurobiological mechanisms (inflammatory markers, brain circuitry, and circadian rhythms), and concluding with a critical appraisal of available and emerging treatment strategies aimed at minimizing affective instability through personalized approaches.

2. Triggers of mood episodes

2.1. Pharmacological triggers

Antidepressants, particularly tricyclic antidepressants (TCAs) and to a lesser extent SSRIs/SNRIs, represent significant pharmacological risks for mood switching. Research indicates that TCAs confer a 10% risk of treatment-emergent affective switch (TEAS), substantially higher than other antidepressant classes. This switching risk is especially pronounced in BD-I patients during depressive episodes when antidepressants are administered without mood stabilizers. The dopaminergic hypersensitivity model suggests that antidepressants may trigger mania through upregulated dopamine receptor sensitivity in vulnerable individuals. Even appropriate BD medications carry switching risks: approximately 19-20% of first-episode manic patients experience relapse within six months despite treatment, with psychotic features during the initial episode predicting poorer outcomes.

Paradoxically, psychostimulants (e.g., for comorbid ADHD) may induce manic-like states and potentially lower the age at mania onset [4]. The kindling phenomenon—where initial episodes increase vulnerability to future episodes—explains why medication-induced switches become more probable with disease progression. These findings underscore the critical importance of careful medication selection and combination therapy when treating bipolar depression.

2.2. Circadian and sleep disruption

Circadian disruption represents one of the most robust triggers for mood transitions in BD. Sleep deprivation, irregular social rhythms, night-shift work, and transmeridian travel can precipitate manic/hypomanic episodes in 20-30% of vulnerable individuals [5]. At the molecular level, clock gene dysregulation (e.g., CLOCK, ARNTL, and PER3 polymorphisms) disrupts cellular oscillators, leading to aberrant melatonin secretion and circadian misalignment that precedes mood episodes by 1-2 weeks. The bidirectional relationship between circadian disruption and mood states creates a vicious cycle: mood episodes further disrupt sleep-wake patterns, increasing vulnerability to subsequent episodes.

DOI: 10.54254/2753-7048/2026.HT29526

Sleep architecture changes are particularly significant prodromal indicators: decreased need for sleep frequently heralds mania, while hypersomnia predicts depression. This positions sleep monitoring as a crucial early warning system for impending mood transitions. The "Chronos syndrome" concept highlights how circadian disruptions not only trigger episodes but also predict relapse and treatment response across mood disorders [6].

2.3. Psychosocial stressors

Stressful life events activate the HPA axis and inflammatory pathways, significantly increasing transition risk. The kindling hypothesis posits that early-life adversity sensitizes stress-response systems, making subsequent minor stressors capable of triggering major mood episodes. Childhood trauma survivors show 3-5 times higher transition rates than non-exposed BD patients, particularly for depressive episodes [7]. Notably, positive life events involving reward attainment (e.g., promotions, new relationships) may trigger mania through heightened dopaminergic reactivity in the ventral striatum, a core feature of BD pathophysiology [8].

Recent research demonstrates that childhood adversity specifically sensitizes bipolar individuals to the effects of recent stressors for depressive episodes, particularly in response to minor negative events. This stress sensitization effect is especially pronounced in individuals with early-onset BD and significantly contributes to rapid cycling presentations.

2.4. Metabolic and inflammatory perturbations

Peripheral inflammation mediates mood transitions through multiple pathways. Cytokines like TNF-α and IL-6 disrupt blood-brain barrier integrity, activate microglia, alter monoamine metabolism, and impair neuroplasticity [9]. During acute mood episodes, approximately 30-50% of BD patients show clinically elevated CRP levels, with TNF-α particularly elevated across all mood states. The inflammatory priming model suggests that each mood episode establishes a lower inflammatory threshold for subsequent episodes, accelerating neuroprogression.

Metabolic comorbidities compound this risk: insulin resistance reduces BDNF availability, while mitochondrial dysfunction increases oxidative stress. This creates a pathophysiological cascade where peripheral inflammation and metabolic dysregulation synergistically disrupt neural circuits governing mood stability. Notably, inflammatory markers during depressive phases (especially IL-6 elevations) predict subsequent transition to mania, highlighting their potential as transition biomarkers.

2.5. Developmental and childhood factors

Early-life adversity alters neurodevelopmental trajectories, producing persistent HPA-axis hyperactivity, epigenetic modifications (e.g., FKBP5 methylation), and reduced hippocampal volume [10]. These changes create a biobehavioral vulnerability to mood transitions, with trauma-exposed BD patients experiencing earlier onset (by 4-7 years), more rapid cycling, and greater treatment resistance. The high-risk bipolar offspring studies show that early emotional dysregulation and sleep disturbances often precede frank mood episodes by several years.

A proposed Bipolar At-Risk (BAR) criteria identifies youth with: subthreshold mania symptoms, depression with cyclothymic features, or depression plus genetic risk. Approximately 23% of BAR-positive individuals transition to full BD within 8 months. This clinical staging approach facilitates

DOI: 10.54254/2753-7048/2026.HT29526

early identification and intervention before recurrent mood transitions establish neuroprogressive changes [11].

3. Neurobiological mechanisms of mood transitions

3.1. Structural and functional brain changes

Neuroimaging studies reveal that mood transitions involve aberrant activity in prefrontal-limbic circuits. During depression-to-mania transitions, fMRI shows ventral striatal hyperactivity to reward cues, coupled with reduced prefrontal inhibition (particularly in the dlPFC and vlPFC). White matter abnormalities disrupt connectivity within these networks, impairing emotion regulation. Longitudinal studies demonstrate progressive gray matter loss in the prefrontal cortex and anterior cingulate following multiple episodes, creating neuroanatomical substrates for treatment resistance.

Diffusion tensor imaging reveals altered structural connectivity in fronto-limbic pathways that correlates with transition frequency [12]. These structural changes appear to be both consequences of past mood episodes and risk factors for future transitions, illustrating the neuroprogressive nature of BD. Patients with multiple mood transitions show 15-30% greater cortical thinning compared to those with stable illness courses.

3.2. Neurotransmitter dysregulation

The dopamine sensitization model posits that repeated manic episodes increase mesolimbic dopamine receptor density and responsiveness, lowering the threshold for future transitions. Conversely, depressive transitions involve serotonergic deficits and GABAergic dysfunction in cortical inhibitory interneurons. Glutamatergic dysregulation provides a unifying mechanism: elevated glutamate levels during mania exert excitotoxicity, while decreased glutamate receptor expression in depression impairs neuroplasticity.

Recent evidence implicates purinergic signaling abnormalities, particularly through P2X7 receptors that regulate NLRP3 inflammasome activation [13]. This creates a neuroinflammatory milieu that modulates neurotransmitter release and reuptake, potentially serving as a common pathway for multiple trigger types. The complex interplay between neurotransmitter systems explains why single-pathway interventions often fail to prevent mood transitions.

3.3. Circadian misalignment and clock genes

Molecular circadian disruptions extend far beyond sleep-wake cycles, Peripheral clock genes regulate neuronal excitability, neurotransmitter synthesis, and synaptic plasticity. CLOCK gene variants associate with earlier BD onset and more rapid cycling, while PER3 polymorphisms predict sleep phase delays [14]. Post-mortem studies reveal disrupted expression of circadian regulators (REV-ERBα, BMAL1) in the prefrontal cortex of BD patients, potentially explaining seasonality effects on mood transitions.

Chronobiological instability manifests as altered melatonin secretion, core body temperature rhythms, and cortisol periodicity months before clinical mood changes. This position circadian biomarkers as promising early-warning indicators for impending transitions. The circadian system's widespread regulation of neuroimmune function creates bidirectional pathways with inflammatory mechanisms implicated in mood transitions [15].

DOI: 10.54254/2753-7048/2026.HT29526

3.4. Inflammatory and immune pathways

Activated microglia and peripheral monocyte infiltration during mood transitions release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) that directly impact neurotransmitter systems and neuroplasticity. The NLRP3 inflammasome serves as a critical integration point, activated by mitochondrial reactive oxygen species (ROS) and purinergic signaling disturbances characteristic of BD. This activation reduces hippocampal neurogenesis and prefrontal dendritic arborization through BDNF downregulation.

Complement system components (C3a, C5a) are elevated during mood transitions and may promote synaptic pruning abnormalities. Importantly, inflammatory markers exhibit state-dependent patterns: TNF-α elevation persists across mood states, while IL-6 spikes during transition phases. Anti-inflammatory agents like minocycline show promise for stabilizing mood transitions, particularly in patients with elevated baseline inflammation [16].

3.5. Genetic and epigenetic factors

BD demonstrates high heritability (70-80%), with GWAS identifying >30 risk loci implicating ion channels, neurotransmitter transporters, and synaptic components. Polygenic risk scores combining these variants moderately predict transition susceptibility. Epigenetic modifications serve as dynamic mediators: childhood trauma associates with BDNF promoter hypermethylation, while mood episodes alter histone acetylation in GABAergic genes [17].

Accelerated epigenetic aging is observed in BD patients, particularly those with childhood trauma histories and frequent mood transitions. Mitochondrial DNA methylation changes may underlie the energy metabolism dysfunction observed during mood transitions. These epigenetic modifications represent potential therapeutic targets for preventing mood transitions.

4. Treatment strategies

4.1. Pharmacological treatment

Lithium remains the gold standard for preventing mood transitions due to its neuroprotective properties (enhancing mitochondrial function, reducing excitotoxicity, and increasing gray matter volume) and specific anti-suicidal effects (OR=0.13) [18]. Anticonvulsants (valproate, carbamazepine) and atypical antipsychotics (quetiapine, lurasidone, cariprazine) demonstrate efficacy in acute transition prevention, though with variable metabolic side effect profiles. The risk-benefit calculus for antidepressants remains complex: while short-term use with mood stabilizers shows modest transition risk (3.8% vs. 4.7% for placebo), long-term antidepressant use associated with cycle acceleration.

Emerging agents show transition-specific promise: cariprazine demonstrates efficacy for depression-to-mania transitions, while ketamine (despite dissociation risks) rapidly reduces suicidal ideation during depressive phases. Anti-inflammatory augmentation (e.g., minocycline, omega-3s) benefits patients with elevated inflammatory markers, particularly for preventing depressive transitions.

4.2. Psychotherapy and psychoeducation

Targeted psychotherapies significantly reduce mood transition risk by addressing specific vulnerability factors: Interpersonal and Social Rhythm Therapy (IPSRT) stabilizes circadian

DOI: 10.54254/2753-7048/2026.HT29526

routines, decreasing transition risk by 25-35% compared to medication alone [19]. Cognitive Behavioral Therapy (CBT) modifies maladaptive thought patterns that precipitate episodes, while family-focused therapy improves medication adherence and reduces expressed emotion.

Early-stage interventions are particularly crucial. First-episode patients receiving specialized psychosocial care show 50% higher functional recovery rates than treatment-as-usual cohorts. Psychoeducation empowers patients to recognize prodromal symptoms (e.g., sleep changes, racing thoughts) and implement pre-emptive strategies, reducing hospitalization frequency by 30% over two-year follow-ups.

4.3. Digital and chronotherapeutic interventions

Digital phenotyping platforms detect transition prodromes through continuous monitoring of speech patterns, motor activity, sleep parameters, and social connectivity [20]. Machine learning algorithms analyzing smartphone-derived data can predict mood transitions with 70-85% accuracy 7-14 days before clinical symptom emergence. The mindLAMP platform demonstrates particular promise, integrating passive sensing with active symptom reporting to generate real-time risk assessments.

Chronotherapeutic approaches target the circadian instability underlying mood transitions: blue-light blocking glasses prevent evening melatonin suppression, while timed bright light therapy regulates phase-delayed rhythms. Sleep phase advance protocols rapidly abort emerging hypomania, and dark therapy (14-hour nighttime darkness) extends therapeutic lithium concentrations. These interventions show 60-75% response rates with minimal side effects, offering valuable alternatives for medication-resistant patients.

4.4. Emerging biological treatments

Emerging therapeutic strategies for mood transitions in bipolar disorder increasingly target systemic biological mechanisms beyond classical neurotransmission. Mitochondrial modulators such as coenzyme Q10 and N-acetylcysteine show promise in improving depressive symptoms by enhancing energy metabolism and reducing oxidative stress, particularly in mitochondrial dysfunction subtypes [21]. Concurrently, anti-inflammatory agents like celecoxib and infliximab have shown benefits in patients with elevated cytokines such as IL-6 or TNF-α, although their long-term safety remains under investigation [22].

Another frontier is gut–brain axis modulation, including probiotic interventions that restore microbial GABA and butyrate production, potentially stabilizing mood through immune and neurochemical regulation. Fecal microbiota transplantation (FMT) is being piloted for treatment-resistant cases, with early reports suggesting symptomatic improvements [23]. These advances reflect a paradigm shift toward multi-system, biologically tailored interventions that complement psychosocial and circadian-based approaches, offering new pathways for personalized stabilization in bipolar disorder.

5. Conclusion

Mood transitions in BD represent complex phenomena emerging from multilevel interactions among genetic vulnerability, neurobiological dysregulation, environmental exposures, and behavioral patterns. This review highlights several critical insights: First, mood transitions are not random events but reflect identifiable neurobiological processes involving circadian misalignment, neuroinflammation, neurotransmitter dysregulation, and neural circuit dysfunction. Second, the

DOI: 10.54254/2753-7048/2026.HT29526

neuroprogressive nature of BD means that each transition potentially worsens long-term outcomes through epigenetic changes and neural plasticity alterations. Third, childhood adversity establishes enduring vulnerability through stress-system sensitization and neurodevelopmental alterations.

The clinical implications are profound: Early intervention during prodromal stages (e.g., BAR criteria-positive youth) may prevent neuroprogression before recurrent transitions establish treatment resistance. Multimodal monitoring integrating digital phenotyping, inflammatory biomarkers, and circadian assessments offers personalized transition prediction, enabling pre-emptive interventions. Stage-specific treatments should replace one-size-fits-all approaches: anti-inflammatory strategies for inflammatory phenotypes, circadian interventions for rhythm-disrupted patients, and mitochondrial support for metabolic subtypes.

At present, psychosocial interventions such as Interpersonal and Social Rhythm Therapy (IPSRT) and Cognitive Behavioral Therapy (CBT) contribute meaningfully to reducing relapse risk and enhancing mood self-regulation. These interventions support rhythm stabilization and cognitive restructuring, thus addressing behavioral dimensions of transition vulnerability. However, despite their evidence base, widespread implementation is challenged by disparities in clinical training, limited scalability in resource-constrained settings, and variable patient adherence.

From a neurobiological perspective, efforts toward precision medicine remain in an exploratory phase. Although staging frameworks identifying Bipolar At-Risk (BAR) individuals—particularly those with inflammatory or circadian vulnerability—offer a potential window for early preventive action, they are not yet systematically integrated into standard care models. Similarly, while biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and circadian gene polymorphisms (e.g., CLOCK, BMAL1) are under active investigation, none have achieved clinical utility thresholds for robust prediction or intervention guidance.

Together, these findings reinforce that mood transitions are biologically mediated and modifiable events within the bipolar trajectory. Nonetheless, current psychiatric care remains largely reactive, focused on post-transition symptom control rather than upstream prevention. Bridging this gap will require the convergence of validated psychosocial tools, scalable chronobiological interventions, and accessible biomarker platforms. Only through such translational, systems-level approaches can the burden of recurrent mood destabilization be sustainably reduced.

References

[1] Oliva V, Fico G, De Prisco M, Gonda X, Rosa AR, Vieta E. Bipolar disorders: An update on critical aspects. Lancet Reg Health Eur. 2024; 48: 101135. doi: 10.1016/j.lanepe.2024.101135

[2] Vázquez GH, Tondo L, Baldessarini RJ. Suicide risk in bipolar disorder: A review. Curr Psychiatry Rep. 2021; 23: 36. doi: 10.1007/s11920-021-01259-y

[3] Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and ISBD 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018; 20(2): 97–170. doi: 10.1111/bdi.12609

[4] Nusslock R, Alloy LB. Reward processing and mood-related symptoms: An RDoC perspective. Cogn Ther Res. 2017; 41(3): 392–402. doi: 10.1007/s10608-016-9782-1

[5] Zhou Y, Yu L, Wang Z, et al. Wearable sleep and activity tracking in bipolar disorder: A clinical feasibility study. Int Clin Psychopharmacol. 2021; 36(4): 215–222. doi: 10.1097/YIC.0000000000000367

[6] Barbuti M, Mennuni G, Salvi V, Caldiroli A, Brambilla P. Digital phenotyping and wearable monitoring in bipolar disorder: A systematic review. Front Psychiatry. 2020; 11: 941. doi: 10.3389/fpsyt.2020.00941

[7] Lee SY, Kim JM, Yoon JS. Childhood trauma and mood instability in bipolar disorder. Neuropsychiatr Dis Treat. 2019; 15: 1239–1249. doi: 10.2147/NDT.S209009

[8] Fico G, Isella S, Vieta E, Yatham LN. Neurobiological mechanisms underlying mood instability in bipolar disorder. Int J Bipolar Disord. 2021; 9(1): 25. doi: 10.1186/s40345-021-00258-4

DOI: 10.54254/2753-7048/2026.HT29526

[9] Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. The psychosocial context of bipolar disorder: Environmental, cognitive, and developmental risk factors. Clin Psychol Rev. 2005; 25(8): 1043–1075. doi: 10.1016/j.cpr.2005.06.006
[10] Estrada-Prat X, Bortolato B, Martínez-Arán A. Neurodevelopmental and environmental contributions to mood instability in bipolar disorder. Int J Bipolar Disord. 2019; 7: 18. doi: 10.1186/s40345-019-0160-1
[11] McCarthy MJ, Wei H, Nievergelt CM, Kelsoe JR, Welsh DK. Circadian rhythm disruption and mood disorders: Molecular mechanisms and chronotherapeutics. Front Psychiatry. 2024; 16: 1564004. doi: 10.3389/fpsyt.2024.1564004
[12] Cho CH, Lee HJ, Kim L. Sleep and circadian rhythm disruption in mood disorders: Clinical implications. Front Psychiatry. 2024; 16: 1552992. doi: 10.3389/fpsyt.2024.1552992
[13] Goldstein TR, Hafeman DM, Axelson DA, et al. Inflammatory biomarkers in youth with bipolar disorder. J Child Psychol Psychiatry. 2020; 61(7): 755–765. doi: 10.1111/jcpp.13102
[14] Martínez-Arán A, Reinares M. Psychosocial interventions in bipolar disorder: What we know and what we need. Curr Opin Psychiatry. 2021; 34(1): 14–19. doi: 10.1097/YCO.0000000000000652
[15] Brietzke E, Mansur RB, Subramaniapillai M, Balanzá-Martínez V, McIntyre RS. The role of inflammation in mood disorders: A systematic review. J Affect Disord. 2021; 282: 19–27. doi: 10.1016/j.jad.2020.12.209
[16] Scott J, Etain B. Cognitive dysfunction and bipolar disorder: Towards individualised treatment pathways. Lancet Psychiatry. 2020; 7(9): 726–736. doi: 10.1016/S2215-0366(20)30235-5
[17] Palagini L, Riemann D. The role of sleep and circadian misalignment in mood disorders. Sleep Med Rev. 2019; 44: 25–35. doi: 10.1016/j.smrv.2018.12.005
[18] Conroy DA, Hairston IS, Arnedt JT, et al. Cognitive behavioral therapy for insomnia in patients with bipolar disorder: A randomized controlled pilot study. Behav Sleep Med. 2018; 16(4): 361–379. doi: 10.1080/15402002.2016.1253010
[19] Yamaguchi T, Ikuta T, Takahashi Y. Escitalopram-induced hypomania in patients with bipolar disorder: Case series and literature review. Psychiatry Clin Neurosci. 2018; 72(4): 325–330. doi: 10.1111/pcn.12623
[20] Kessing LV, Miskowiak KW. Cognitive remediation and functional outcome in bipolar disorder. Int J Bipolar Disord. 2022; 10: 25. doi: 10.1186/s40345-022-00379-6
[21] Stolk, L., van der Meer, K., Aljadi, O., et al., 2015. Antidepressant effects of open label treatment with Coenzyme Q10 in older adults with bipolar depression. Molecular Psychiatry, 20(6), pp.703–710. Available at: https: //doi.org/10.1038/mp.2014.80
[22] Dean, A.W., Xie, L., Smith, M., et al., 2021. Mitochondrial modulators in the treatment of bipolar depression. Translational Psychiatry, 11, p.123. Available at: https: //doi.org/10.1038/s41398-021-01727-7
[23] Wei, Y., Huang, M., Yu, J. and Li, X., 2023. Safety and feasibility of fecal microbiota transplant for major depression: A pilot study. Pilot and Feasibility Studies, 9, p.187. Available at: https: //doi.org/10.1186/s40814-023-01235-z