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Bridging Biology and Therapy: Advances in Management of Bipolar Disorder

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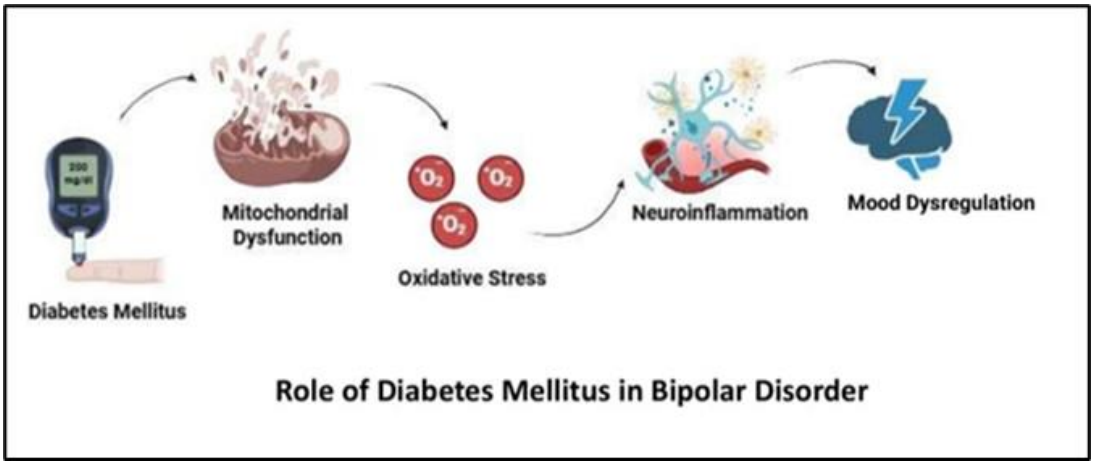
Abstract

Bipolar disorder is a complex psychiatric illness that is characterized by alternating episodes of mania and depression that significantly affect the quality of life. It is a chronic condition that has multifactorial pathophysiological mechanisms that remain incompletely understood, and therapeutic outcomes often fail to achieve long-term remission. This review visits the changing landscape of the development of bipolar disorder, in particular, the contributions of metabolic dysfunction and diabetes, which are increasingly acknowledged as important contributors to disease onset, progression, and treatment resistance. The review also explores current advancements, both pharmacological and non-pharmacological advancements for the management of the disease. By integrating the insights from several biological domains, the need for a broader and personalized treatment paradigm that goes beyond neurotransmitter theories is highlighted for improving patient outcomes.

Keywords: Bipolar disorder; Diabetes Mellitus; Oxidative stress; Neuroinflamation; Treatment

Graphical abstract

Current advancements in the treatment of Bipolar Disorder



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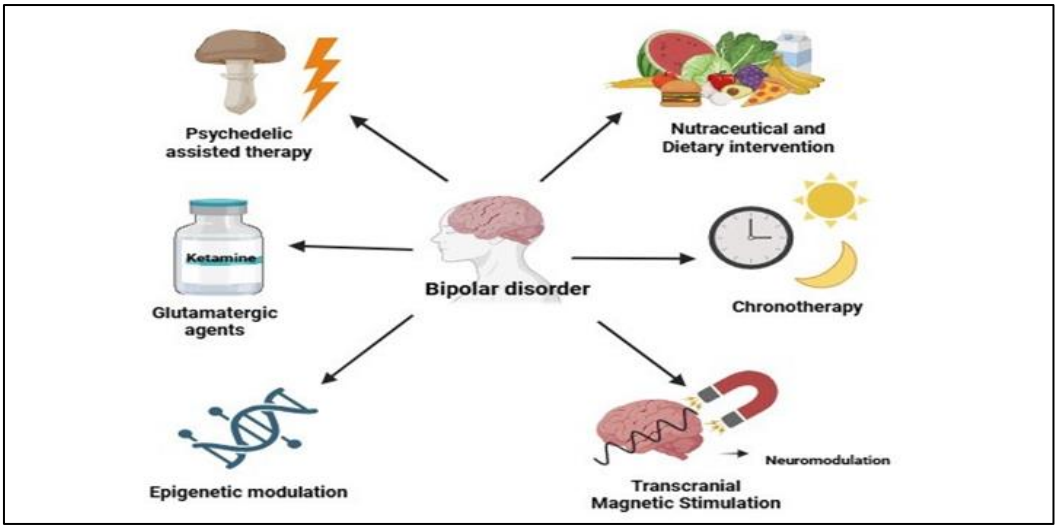

1. Introduction

Bipolar disorder is a chronic, recurrent psychiatric condition characterized by episodes of mania and hypomania accompanied by depression, significantly impacting daily functioning (1). According to the DSM-5-TR, Bipolar I disorder is identified by at least one manic episode. In comparison, Bipolar II disorder involves at least one hypomanic and one major depressive episode without any history of full mania (2). Globally, Bipolar I Disorder affects approximately 1.06% of the adult population. Meanwhile, Type II Bipolar Disorder has an incidence of 1.57% worldwide, with a moderately higher occurrence in the United States (3,4,5). From being misunderstood as paranormal behaviour or "madness," bipolar disorder has evolved from a heavily stigmatized condition to being formally recognized as a mood disorder within psychiatric frameworks (6).

The symptoms of bipolar disorder often coincide with comorbidities such as schizophrenia and depression, resulting in misdiagnosis. This often delays the therapeutic outcomes and worsens mania, risk of suicide, and substance abuse (7,8,9). A latest report by Global Burden of Disease (GBD) concludes that there was a hike in the population affected by bipolar disorder, with the number increasing from 2 million in 1990 to around 4 million in 2019. Although there is a significant increase globally in the years lived with disability (YLDs), while age-standardized incidence remains constant, this demonstrates disability endurance regardless of therapeutic advancements(10,11).

While there is no cure for bipolar disorder, several therapies have proven to manage acute episodes and sustain long-term remission, which include mood stabilizers such as lithium, some atypical anti psychotics, and anti-epileptics (12). The conventional treatments produce extensive side effects while also overlooking the interconnected role of genetic susceptibility, HPA axis dysfunction, neurotransmitter dysregulation, and inflammatory pathways and impairment in neural circuitry that aggravate the disorder (13,14,15). While these factors have been studied extensively for years, they're often explored individually, failing to capture the interactions among multiple physiological systems. The role of systemic factors, such as metabolism of glucose and impairment in glucose metabolism, was highlighted as a predisposing factor in the progression of mood disorders by recent research. (16). Dysfunction in metabolism may contribute to the generation of reactive oxygen species which elevates the oxidative stress in neuronal cells. Oxidative stress is highly associated with inflammation of neurons and dysfunction of mitochondria, which further potentiates neuronal damage (17,18,19). The cascade of events contributes to mood instability and may describe the relationship between metabolic disorders like Diabetes mellitus with bipolar disorder. Hormonal imbalance is another key systemic contributor with elevated cortisol levels, impaired negative feedback, and glucocorticoid resistance serving as a biological marker for bipolar disorder (15,20,21).

This review aims to focus on key findings across three key areas-metabolic dysregulation (related to Diabetes mellitus), hormonal imbalance, and oxidative stress, with an emphasis on recent advances in treatment approaches of bipolar disorder.

2. Pathophysiology

2.1. Role of Metabolic Dysregulation

Type 2 Diabetes Mellitus is characterized by chronic hyperglycemia and insulin resistance, which leads to impaired glucose uptake and systemic metabolic disturbance, that not only disrupts peripheral metabolism but also brain homeostasis (22). These changes in biochemistry impairs the PI3K/Akt pathway and lower the glucose transporter activity (GLUT 3 and GLUT 4) in the neurons and impair the neuronal energy metabolism thus contributing to alteration in insulin signalling and impaired mitochondrial function (23,24).

Mitochondrial dysfunction followed by inefficient oxidative phosphorylation results in the overproduction of reactive oxygen species (ROS), including superoxide and hydrogen peroxide, that surpasses the endogenous antioxidant systems like superoxide dismutase (SOD), glutathione, and catalase. This redox imbalance causes oxidative stress, lipid peroxidation, protein oxidation, and DNA fragmentation, contributing to neuronal injury and reduced synaptic plasticity and neurotransmitter regulation (25,26). Clinical studies have consistently reported elevated levels of oxidative biomarkers such as malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), often correlating with manic and depressive severity (27,28). Furthermore, oxidative stress acts as a central mediator that links metabolic dysregulation to neuroinflammation through pathways such as NF-κB activation and microglial overactivation that contribute to progressive neurodegeneration in bipolar disorder (26,29). Epidemiological evidence shows patients with diabetes have an increased risk of developing bipolar disorder, establishing a strong pathophysiological link between the metabolic dysfunction and mood dysregulation (30).

2.2. Hormonal Imbalance

Hormones play a vital role in regulating brain function and emotional stability. Disruptions in the body's hormonal systems- especially stress hormones, thyroid hormones, and sex hormones have been closely linked to mood and behavioral changes due to alterations in neurotransmitter signaling, synaptic plasticity, and neuroendocrine homeostasis.

2.3. HPA axis and Cortisol

Hypothalamic pituitary axis (HPA) controls the body's response to stress and is closely is consistently associated with mood disorders such as bipolar disorder. Overactivation of HPA leads to persistently high cortisol levels that can impair the hippocampal structure, reduce BDNF, and disrupt the serotonergic and dopaminergic transmission contributors in mood instability in bipolar disorder (15,20,31). Chronic cortisol elevation may also exacerbate oxidative stress and neuroinflammation, worsening mood dysregulation (32).

2.4. Thyroid hormones

Thyroid hormones, especially triiodothyronine (T3), are essential for brain metabolism and neurotransmitter regulation. They modulate CNS function through direct effect on serotonin, norepinephrine, and dopamine receptor sensitivity (33,34). Thyroid imbalance, both hypothyroidism and hyperthyroidism, is associated with mood disturbances (35). Studies show that reduced thyroid function is associated with depressive symptoms, while increased levels may potentiate manic features (36).

2.5. Sex hormones

Sex hormones play a modulatory role in the regulation of emotions and neurotransmission. Estrogen enhances serotonergic and dopaminergic signaling, providing a stabilizing effect on mood in addition to its neuroprotective activity (37,38). Fluctuations in estrogen, such as those observed during the menstrual cycle, postpartum, or menopause, are associated with increased vulnerability to mood episodes (39). Similarly, testosterone dysfunction in men may contribute to irritability, impulsivity, or aggression (40).

The disturbances in these hormones can collectively influence the synthesis, release, and receptor sensitivity of neurotransmitters such as dopamine, serotonin, and norepinephrine. Hormonal imbalance can cause an upstream trigger to precipitate neurotransmitter imbalance, which underlies mood instability in bipolar disorder.

2.6. Current approaches

The primary treatment approach involves mood stabilizers like lithium, antipsychotics, and sometimes antidepressants tailored to the patient's clinical phase and response (41,42). Combination therapy is often needed for efficient

management of the disorder. Psychotherapy, lifestyle modification, and psychoeducation are also crucial in achieving long-term stability. Maintenance care with regular follow-up is often crucial as it's chronic and prone to relapse even after symptom remission (43,44).

3. Advancements in the management of bipolar disorder

3.1. Pharmacological advancements

3.1.1. Psychedelic-assisted therapy

Psychedelics such as psilocybin, once used in non-medical or informal settings, are now gaining prominence within the scope of pharmacological advancements for mood disorders (45). Psilocybin, through its active metabolite psilocin, acts as a 5-HT $_2$A agonist that is known to increase the functional branching of brain networks, thereby enhancing communication and emotional modulation, effectively restoring dysregulated neural circuits implicated in neural disorders (46). A recent open-label clinical trial demonstrated that a single dose of synthetic psilocybin combined with psychotherapy led to rapid and sustained remission of depressive symptoms in individuals with bipolar II disorder without any serious adverse effects (47).

3.1.2. Ketamine and glutamatergic agents

Ketamine is a novel, innovative treatment for bipolar disorder. It primarily acts by blocking NMDA receptors, resulting in glutamate surge and AMPA activation, which engages in key neurotrophic pathways such as BDNF release, GSK-3 beta inhibition, and MTORC1 activation, which contribute to synaptic plasticity and enhanced neuronal connectivity compromised by depression (48). IV ketamine infusions have demonstrated significant short-term benefits by achieving antidepressant effects within almost 40 minutes; however, it is still being studied for long-term effects, safety profile, and dosing strategies (49).

3.1.3. Epigenetic modulators

Mood stabilizers such as lithium, valproate, quetiapine, and olanzapine have shown important epigenetic effects that contribute to the stabilization of mood in the long term. These medications act through DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which bring about chromatin remodelling and regulate the expression of genes. Lithium and valproate reduce methylation at the BDNF promoter, increasing the level of mRNA of BDNF and providing neurotrophic support (50). Valproate also inhibits HDAC, enhancing histone acetylation and upregulation of BDNF and GDNF. Overall, these epigenetic mechanisms improve neuroplasticity of the brain and regulate the neurotransmitters to bring about stabilization of mood (51).

3.2. Non-pharmacological and alternative

3.2.1. Nutraceuticals and lifestyle intervention

Nutraceutical interventions have gained attention as adjunct strategies in the management of bipolar disorder, by targeting inflammation, oxidative stress, and metabolic dysfunction (52). Omega-3 polyunsaturated fatty acids have beneficial effects in protecting neurons and reducing pro-inflammatory mediators and cytokines, making them responsible for antidepressant effects (53). N-acetylcysteine (NAC) exhibits antioxidant and anti-inflammatory action in addition to replenishing glutathione and modulating dopaminergic and serotonergic transmission, thereby desirable for bipolar depression (54). Dietary interventions like the ketogenic diet have demonstrated neuroprotective effects and are effective for improving mood and reducing depression (55). This diet is further validated as a significant portion of patients with bipolar disorder also suffer from type 2 diabetes mellitus, thus combating the comorbidities efficiently.

3.2.2. Chronotherapy

Triple chronotherapy (TCT), which is a combination of sleep deprivation, sleep phase advance, and sleep bright light therapy, has shown a rapid and sustained antidepressant effect by realigning circadian rhythm, hormonal timing, and mood dysregulation (56). TCT resets disrupted circadian rhythms by influencing sleep deprivation to induce mood elevation through increased neurotransmitter activity, while sleep phase advance and bright light therapy stabilize melatonin and support the establishment of a healthy circadian rhythm (57). Case reports also prove TCT to be successful in individuals with ECT-resistant bipolar disorder, where a single course led to durable remission (58).

3.2.3. Transcranial Magnetic Stimulation (TMS)

High-frequency repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex (rTMS) has shown good results in treatment-resistant bipolar depression, reducing symptoms in 50% of individuals without any notable serious side effects (59). It modulates the dopaminergic and serotonergic systems and increases expression of BDNF, contributing to enhanced neuroplasticity and antidepressant effects. It also improves the connectivity of the dysfunctional fronto-limbic system, a characteristic of bipolar depression (60).

4. Conclusion

Bipolar disorder remains an intricate and multifactorial mental illness that has dire implications on the healthcare system, with significant disease burden and affects the quality of living of individuals. Although Conventional research and treatment focus on neurotransmitters and monoamine dysregulation, there is a growing need to emphasize alternate and less explored pathways, particularly those involving metabolic dysfunction, such as diabetes and hormonal imbalance. While being critically relevant pathways for the pathophysiology of bipolar disorder, they also represent valuable targets for intervention. Although foundational, the current pharmacological regimen falls short in delivering long-term remission and combating a wide spectrum of symptoms, especially in treatment-resistant patients. This gap draws attention to the urgency of developing therapeutic options beyond traditional drug-based approaches. Emerging non-pharmacological interventions such as chronotherapy and lifestyle modifications show a promising performance as both adjuncts and standalones. However, the path to complete recovery is still a long way from being covered. Existing treatments must incorporate a more individualized and integrative framework that accounts for an array of biological pathways by bridging the fields of neuroscience, psychiatry, and endocrinology. Future research must focus on optimizing and validating the novel and innovative strategies in addition to refining pharmacological therapies. This outlook would increase the possibility of attaining inclusive long-term outcomes for individuals living with the challenging condition.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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