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Review Article

The Diagnostic Complexity of Bipolar II Disorder: Energy Dysregulation, Mitochondrial Dysfunction, and the Role of Therapeutic Probes

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Abstract

Bipolar II disorder (BD-II) represents a diagnostic and therapeutic challenge in contemporary psychiatry, characterized by alternating depressive and hypomanic episodes. Besides influencing mood, BD-II is frequently viewed as a condition marked by fluctuating energy levels, leading to periods of both low and high mental and physical vitality. Recent evidence implicates mitochondrial dysfunction as a core biological substrate underlying these energy alterations, influencing neurocognitive performance, circadian rhythm stability, and vulnerability to mood destabilization. This review synthesizes clinical, neurobiological, and therapeutic perspectives, highlighting how mitochondrial impairment can inform both the dimensional diagnosis of BD-II and individualized treatment strategies. In cases of diagnostic uncertainty, therapeutic probes using mood stabilizers may serve dual purposes, elucidate underlying energy dysregulation, and guide clinical management. Integrating mitochondrial function into the clinical and conceptual framework of BD-II may improve diagnostic precision, personalize treatment, and provide novel avenues for biomarker-driven interventions.

Keywords: bipolar II disorder; energy dysregulation; mitochondrial dysfunction; hypomania; depression; therapeutic probe; mood stabilizers; circadian rhythm

1.Introduction

Bipolar II disorder (BD-II) affects 0.8–1.1% of the global population [1], yet it remains underrecognized and frequently misdiagnosed, often as unipolar depression or anxiety disorders [2,3]. BD-II was once described as requiring at least one hypomanic episode and one major depressive episode, but no episodes of full mania [4]. These days, it is commonly understood as a disorder marked by problems with regulating energy, not just changes in mood.

Energy fluctuations in BD-II manifest across cognitive, affective, and physical domains, including fatigue, psychomotor slowing, hypersomnia, hyperactivity, and creative overdrive. These clinical observations parallel emerging evidence of mitochondrial dysfunction, which impairs cellular energy metabolism, disrupts neuronal signaling, and contributes to both depressive and hypomanic phenotypes [5–8]. Mitochondrial impairment also affects circadian rhythm regulation, oxidative stress homeostasis, and synaptic plasticity, all of which are central to BD-II pathophysiology [9–12].

This manuscript proposes an integrative model in which energy dysregulation and mitochondrial dysfunction underpin the clinical heterogeneity of BD-II. By combining clinical observations, molecular insights, and therapeutic strategies, this review highlights the potential of therapeutic probes and energy-focused interventions to improve diagnosis and individualized treatment.

2. Diagnostic Framework and Challenges

2.1 DSM-5-TR Criteria and Limitations

According to DSM-5-TR, BD-II diagnosis requires a major depressive episode (MDE) and a hypomanic episode, with no history of full mania [4]. Major depressive episodes involve persistent low mood, anhedonia, fatigue, psychomotor changes, and cognitive dysfunction. Hypomanic episodes involve elevated or irritable mood, increased energy, decreased need for sleep, and heightened goal-directed activity.

Clinical practice shows that many BD-II patients have subthreshold or atypical episodes that do not fully meet DSM criteria [6]. These include:

- Depressive equivalents: low energy, anergia, or cognitive slowing without pronounced sadness.

- Hypomanic equivalents: heightened creativity, restlessness, or elevated drive without overt euphoria.

These nuanced energy patterns are frequently mistaken for characteristics like personality traits, unipolar depression, or attention-deficit hyperactivity disorder (ADHD) [7].

2.2 The Energy Dysregulation Perspective

Recent models conceptualize BD-II along an energy continuum, where both mental and physical energy fluctuate independently of mood [8]. Low-energy states may include fatigue, hypersomnia, and psychomotor retardation, while high-energy states manifest as restlessness, and excessive goal-directed activity. Mixed states, combining mental overactivation with physical fatigue, further illustrate the spectrum nature of energy dysregulation [9]. Mitochondrial dysfunction provides a biological basis for these energy fluctuations, impairing ATP production, increasing oxidative stress, and disrupting neuronal excitability [5,10]. These cellular-level deficits manifest clinically as the energy extremes characteristic of BD-II.

3. Mitochondrial Dysfunction in BD-II

3.1 Evidence from Peripheral and Neuroimaging Studies

Peripheral biomarkers indicate mitochondrial impairments in BD-II patients. Studies demonstrate:

- Reduced mitochondrial respiratory chain activity in platelets and lymphocytes [11,12].
- Altered mitochondrial DNA (mtDNA) copy number and increased mtDNA deletions [13].
- Elevated markers of oxidative stress, including lipid peroxidation and protein carbonylation [14,15].

Neuroimaging studies further support mitochondrial involvement:

- Magnetic resonance spectroscopy (MRS) reveals decreased brain ATP and phosphocreatine levels in BD-II patients [16,17].
- Functional MRI studies demonstrate altered functional connectivity in fronto-limbic networks, potentially reflecting impaired mitochondrial energy supply [18].

3.2 Molecular Mechanisms

Mitochondria regulate cellular energy via oxidative phosphorylation. In BD-II:

Electron transport chain dysfunction reduces ATP availability, impairing neuronal signaling and synaptic plasticity [10].

2.Reactive oxygen species (ROS) accumulation damages proteins, lipids, and DNA, contributing to neuroinflammation [15,19].

3.Calcium homeostasis disruption affects neurotransmitter release and neuronal excitability, leading to mood instability [20].

4.Impaired mitochondrial dynamics (fusion/fission imbalance) compromises energy distribution in neurons [21].

Together, these mitochondrial deficits offer a mechanistic explanation for both low- and high-energy states, as ATP deficits produce fatigue and hypoactivation, whereas compensatory hypermetabolism in certain neural circuits may underlie hypomanic or creative surges [5,22].

3.3 Circadian Rhythm and Mitochondrial Coupling

Mitochondrial function is tightly linked to circadian regulation. BD-II patients often display sleep disturbances and irregular activity patterns. Mitochondrial dysfunction can:

- Alter clock gene expression, disrupting metabolic and behavioral rhythms [23].
- Increase vulnerability to oxidative stress during circadian misalignment [24].
- Contribute to mood episodes triggered by sleep deprivation or irregular schedules [25].

This underscores the convergence of energy, mitochondrial, and circadian dysregulation in BD-II pathophysiology.

4. Clinical Assessment of Energy Dysregulation

4.1 Energy-Focused Evaluation

Effective BD-II assessment should evaluate both subjective and objective energy patterns:

- Self-reported fatigue, restlessness, or overactivity.
- Sleep-wake patterns, activity levels, and circadian rhythm consistency.
- Cognitive and psychomotor performance, including attention, processing speed, and motivation.

Incorporating mitochondrial biomarkers, such as peripheral ATP levels, oxidative stress markers, or MRS-based brain energy measurements, may eventually complement clinical assessment [11,16].

4.2 Differential Diagnosis

Energy-focused assessment aids in distinguishing BD-II from:

- Unipolar depression: persistent low energy without episodic activation.
- ADHD: chronic hyperactivity without mood cycling.
- Anxiety disorders: agitation with fatigue but without decreased sleep need.
- Substance-induced states: temporal correlation with drug use.

5. Therapeutic Probes in Diagnostic Uncertainty

When energy dysregulation is prominent but hypomanic episodes are subtle, therapeutic probes may clarify diagnosis [26].

- Lithium: stabilizes mood and energy through intracellular signaling, neuroprotection, and mitochondrial support [27,28].
- Lamotrigine: enhances neuronal energy efficiency and reduces glutamate excitotoxicity, particularly effective for depressive or low-energy states [29].
- Atypical antipsychotics (e.g., quetiapine, aripiprazole): modulate dopaminergic activity, balancing excess energy or deficit [30].

A monitored trial of these agents can indicate latent bipolarity if energy fluctuations normalize, whereas lack of response may suggest alternative etiologies.

6. Treatment Implications

6.1 Pharmacological strategies targeting mitochondrial and energy dysfunction

- Mood stabilizers: Lithium enhances mitochondrial respiration, increases Bcl-2 expression, and reduces oxidative stress [27,31].
- Lamotrigine: protects against glutamate-induced mitochondrial dysfunction and neuronal apoptosis [29].
- Adjunctive agents:
  - N-acetylcysteine (NAC): reduces oxidative stress and supports mitochondrial glutathione [32].
  - Coenzyme Q10 and creatine: improve mitochondrial ATP production [33].
  - Omega-3 fatty acids: modulate membrane fluidity and mitochondrial signaling [34].

6.2 *Psychotherapy and lifestyle interventions*

- Energy-focused psychoeducation: monitoring fluctuations, structuring activity/rest cycles.
- Interpersonal and social rhythm therapy (IPSRT): stabilizes circadian and energy rhythms [35].
- Sleep optimization: consistent sleep-wake schedules, light therapy, and melatonin to support mitochondrial circadian coupling [23,25].
- Exercise and nutrition: moderate aerobic exercise enhances mitochondrial biogenesis; balanced diet supports ATP production [36].

7. Future Directions

7.1 Biomarker Development

Integrating mitochondrial biomarkers, including ATP/ADP ratios, mtDNA copy number, and oxidative stress indices, could allow objective monitoring of energy dysregulation and predict treatment response [11,12,14].

7.2 Digital Phenotyping

Wearable devices and ecological momentary assessment (EMA) can track real-time energy fluctuations, circadian patterns, and activity levels, offering a dynamic, personalized approach to BD-II management [37].

7.3 Translational Research

Longitudinal studies linking mitochondrial function, energy dysregulation, and clinical outcomes will clarify whether BD-II represents a distinct mitochondrial endophenotype, informing precision psychiatry strategies [10,22].

7.4 Personalized Treatment

Characterizing individual energy phenotypes, such as low energy versus hyperactivated subtypes, may guide pharmacologic selection, lifestyle interventions, and timing of therapeutic probes for maximal benefit [8,9].

8. Conclusion

Bipolar II disorder can be understood primarily as a condition involving disrupted energy regulation, where mitochondrial dysfunction plays a central biological role. Recognizing energy fluctuations both deficits and surges enhance diagnostic sensitivity beyond traditional mood-focused criteria. Therapeutic probes with mood stabilizers can clarify diagnosis and guide individualized management. Integrating mitochondrial biomarkers and energy-centered assessments promises more precise, personalized, and biologically informed care, bridging clinical phenomenology with underlying cellular pathophysiology.

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