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CURRENT STATE OF RESEARCH ON BIPOLAR AFFECTIVE DISORDER: A NARRATIVE REVIEW

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ABSTRACT Bipolar disorder, ranking as the 17th leading cause of global disability, affects millions worldwide with varying prevalence rates across countries. The onset during childhood or adolescence impacts developmental milestones. Alarmingly, individuals with bipolar disorder face higher suicide rates compared to the general population, emphasizing the need for effective management strategies. Understanding the genetic and neural pathways is crucial for improved diagnosis and treatment. Genomewide association studies offer insights into the genetic basis, yet much heritability remains unaccounted for. The "kindling" hypothesis explores stress sensitization's impact on recurring affective episodes. Neuroprogression complicates the disorder's chronic nature, leading to cognitive impairments. Effective collaborative care models, careful diagnostic assessment, and early initiation of maintenance treatment are crucial. Lithium remains effective in preventing depressive and manic relapses, but side effects must be monitored. Various treatments, including quetiapine and ECT, contribute to maintaining stability. Careful decisions regarding medication continuation are vital for women of childbearing age.

INTRODUCTION

Bipolar disorder presents a significant global health challenge, ranking as the 17th leading cause of disability worldwide. This mental health condition affects millions of individuals, with varying prevalence rates across countries. The onset typically occurs during childhood or adolescence, impacting developmental and occupational milestones. Suicide rates are alarmingly higher in individuals with bipolar disorder compared to the general population, highlighting the urgent need for effective management strategies (1).

Understanding the genetic and neural pathways of bipolar disorder is crucial for improved diagnosis and treatment. Genomewide association studies have provided valuable insights into the genetic basis of this condition, though much of the heritability remains unaccounted for. The "kindling" hypothesis sheds light on stress sensitization and its impact on recurring affective episodes. Neuroprogression, involving changes in brain structure and function, further complicates the disorder's chronic nature and associated cognitive impairments (2).

METHODS

A systematic search was conducted by the author across reputable databases, including PubMed, PsycINFO, and Google Scholar. The search utilized relevant keywords and terms such as "bipolar disorder," "bipolar affective disorder," "manic depression," "treatment," and "diagnosis." Only peer-reviewed articles published within the last 10 years and written in English were included in the study.

After rigorous screening based on title, abstract, and full-text reviews, a total of 15 studies were selected for data extraction. The authors meticulously extracted information from these selected studies, including study design, sample size, demographic characteristics, diagnostic criteria employed, and various treatment modalities explored.

The extracted data were then synthesized and organized into thematic categories, allowing the authors to gain insights into the multifaceted aspects of BAD. Through this meticulous analysis, the authors provide readers with a deeper understanding of this complex mental health condition.

Additionally, this narrative review highlights areas of consensus and contention within the literature, offering valuable perspectives for future research and clinical practice.
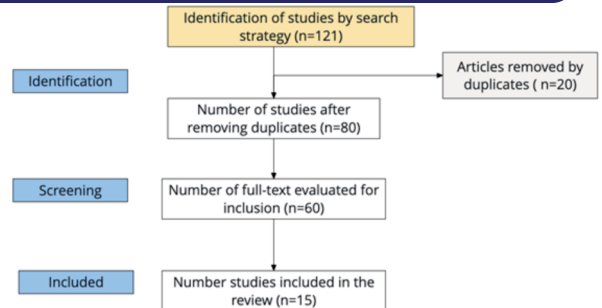

Figure 1. PRISMA.

Epidemiology Trends and Perspectives

Bipolar disorders represent a significant global health concern, ranking as the 17th leading cause of disability worldwide among all diseases. According to the World Mental Health Survey Initiative, the lifetime and 12-month prevalence estimates for bipolar disorders are 2.4% and 1.5%, respectively. However, these rates vary across countries, possibly due to methodological differences and cultural factors. In China, for instance, a systematic review and meta-analysis revealed a lower lifetime prevalence rate of 0.11% for bipolar disorder. Interestingly, the prevalence of bipolar I disorder is comparable between males and females, while bipolar II disorder tends to occur more frequently among females. Notably, bipolar disorder is prevalent in primary care practices, as studies have indicated a significant number of primary care patients with positive screening tests for bipolar disorder, often being underrecognized and undertreated (3).

Various nonpsychiatric medical and sociological conditions have been identified as potential risk factors for bipolar disorder based on observational studies. For instance, recent reviews have suggested tentative associations between irritable bowel syndrome, childhood adversity, and bipolar disorder. The onset of bipolar disorder typically occurs during childhood and adolescence, impacting the achievement of developmental, educational, and occupational milestones. Cognitive and psychosocial dysfunction during acute episodes or remission further exacerbates the challenges faced by individuals with bipolar disorder. Tragically, individuals with bipolar disorder face a heightened risk of suicide, with approximately 6 to 7% of them committing suicide. The suicide rates in this population are estimated to be 20 to 30 times higher than those in the general population. To better understand and address this risk, several

sociodemographic and clinical factors have been identified that may aid in stratifying the risk for suicide among patients with bipolar disorder (4,5).

Genetic Insights and Neural Pathways

Bipolar disorder is recognized as a highly heritable condition, with estimates ranging from 70% to 90%. Genomewide association studies have provided valuable insights into the genetic basis of bipolar disorders, identifying numerous genes with small effect sizes that contribute to the disorder. However, these common genetic variants collectively account for only around 25% of the overall heritability (6).

The "kindling" hypothesis proposes that stress sensitization gradually leads to recurring affective episodes, with subsequent episodes potentially occurring without identifiable stressors. Lifestyle risks, exposure to psychoactive substances, and poor treatment compliance may strengthen the mechanisms underlying this phenomenon. Additionally, poorly characterized epigenetic mechanisms may also play a role. Neuroprogression, characterized by progressive changes in brain structure and function, has been observed in individuals experiencing recurrent episodes of affective disorders. Factors such as epigenetic dysregulation, mitochondrial dysfunction, inflammation, oxidative stress, and aberrations in the hypothalamic-pituitary-adrenal axis contribute to neuroprogression. This process may lead to cognitive and functional impairments, increased prevalence of coexisting medical conditions, and potentially reduced response to mood-stabilizing medications as the illness progresses (7).

Treatment Considerations in Bipolar Disorder

Collaborative care models in primary care have demonstrated positive impacts on mental and physical health outcomes for individuals with bipolar disorder. The diagnostic assessment for affective disorders requires careful ruling out of medical and psychiatric conditions that may mimic symptoms. Early phases of frontotemporal dementia, neurosyphilis, and certain antineural antibody syndromes are among the differential diagnoses. The selection of initial treatment depends on patient preferences, comorbidities, and treatment history. Ensuring patient safety during acute episodes is crucial, particularly when suicide risk is present. Defining treatment-resistant bipolar disorder remains debatable, and expert panels have proposed operational definitions (8,9).

For acute mania, pharmacologic treatment with antipsychotic agents or mood stabilizers is the mainstay. Nonpharmacologic strategies can be employed for severe or treatment-resistant cases. There is limited evidence regarding medication choice for hypomania. Safety and acceptability profiles of antimanic treatments vary. In cases of non-response, a different medication may be considered. Combining antipsychotic agents and mood stabilizers may be more efficacious for severe mania. Bifrontal electroconvulsive therapy (ECT) has shown effectiveness for refractory mania (10).

Table 1. Treatment.

Drug	For Mania or Mixed Features	For Depression	Maintenance Therapy	Adverse Effects
Mood stabilizers				
Lithium	Yes†	No	Yes	Hypothyroidism, increased calcium levels, reduced renal function
Carbamazepine, extended release	Yes	No	No	
Divalproex Delayed release	Yes	No	No	CYP450 inhibition, teratogenic effects, liver toxicity, tremors, thrombocytopenia
Divalproex Extended release	Yes	No	No	CYP450 inhibition, teratogenic effects, liver toxicity, tremors, thrombocytopenia
Lamotrigine	No	No	Yes	Rash, Stevens–Johnson syndrome
Antipsychotic agents				
Aripiprazole	Yes†	No	Yes‡	Akathisia (restlessness and inability to sit still)
Lurasidone	No	Yes§	No	Akathisia and sedation
Olanzapine	Yes	No	Yes	Drowsiness, high risk of metabolic abnormalities
Olanzapine–fluoxetine	No	Yes¶	No	High risk of metabolic abnormalities
Quetiapine Immediate release	Yes†§	Yes¶	Yes¶	Drowsiness, weight gain, metabolic abnormalities
Quetiapine Extended release	Yes	Yes¶	No	Drowsiness, weight gain, metabolic abnormalities
Risperidone	Yes	No	Yes	Extrapyramidal side effects, weight gain, metabolic abnormalities, hyperprolactinemia
Ziprasidone	Yes	No	No	Prolonged QTc interval on ECG, akathisia, hypotension

Sustaining Treatment

Managing the chronic and recurrent nature of bipolar disorder necessitates a robust maintenance treatment approach. This involves a combination of pharmacologic, psychological, and lifestyle interventions, aimed at averting the reoccurrence of affective episodes and distressing symptoms. Early initiation of maintenance treatment, soon after the onset of the illness, is considered ideal. Lithium continues to be one of the most effective drugs in preventing depressive and manic relapses in bipolar disorder. Multiple studies have shown its superiority in reducing relapse risk compared to a placebo. Nevertheless, long-term use may lead to side effects such as renal failure, hypothyroidism, tremors, and disturbances in calcium levels (11-13).

Other maintenance treatments include quetiapine alone or in combination with lithium or divalproex. Industry-sponsored trials often utilize enriched designs, limiting the generalizability of their results. In contrast, evidence supporting the prophylactic effects of lithium comes from randomized, controlled trials without enrichment design. While pharmacotherapy is essential, it is crucial to monitor patients closely for potential side effects. Additionally, psychosocial treatments and maintenance ECT can be considered as adjunctive therapies, contributing to preventing relapses and improving long-term outcomes during the maintenance phase. For women of childbearing age, careful decisions regarding medication continuation should be made before planned pregnancies, considering the risks and benefits for both the mother and the baby (14,15).

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