Bipolar disorders: an update on critical aspects

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Summary

Bipolar disorders are chronic psychiatric conditions characterized by recurrent episodes of mania and depression. Affecting over 1% of the global population, these disorders contribute significantly to disability and mortality, often due to suicide and cardiovascular disease. Diagnostic challenges arise from symptom overlap with unipolar depression, frequently leading to delays. Bipolar disorders are driven by complex genetic, neurobiological, and environmental factors and are commonly accompanied by psychiatric and medical comorbidities, further complicating diagnosis and treatment. Standard management strategies include mood stabilizers, antipsychotics, and selective use of antidepressants, complemented by psychosocial interventions like cognitive-behavioral therapy and psychoeducation, which are vital for relapse prevention. Despite recent advancements, the management of bipolar disorders remains challenging, constrained by clinical variability, an absence of specific biomarkers, and differences in approved treatments and treatment guidelines across regions. Emerging research underscores the potential of precision psychiatry and digital health tools to enhance diagnosis and treatment. Nonetheless, critical gaps persist, particularly in implementing equitable care worldwide. This review offers a comprehensive update on bipolar disorders, examining clinical presentation, early diagnosis, pathogenesis, therapeutic strategies, and future perspectives to guide clinicians and researchers in addressing these ongoing challenges in research and clinical practice.

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Introduction

Bipolar disorders are chronic mental illnesses encompassing bipolar I and bipolar II disorders, characterized by the presence of acute mood episodes (manic, hypomanic, depressive, or mixed), with inter-critical periods of absent or sub-syndromic symptomatology.

The lifetime prevalence is estimated between 0.4% and 1.1%.[1] According to the latest Global Burden of Disease report (2019),[2] the prevalence of bipolar disorders remains relatively stable worldwide, similar to schizophrenia, highlighting their strong genetic basis.[3] However, disparities exist, with prevalence increasing from low-income to high-income countries and varying across regions. Specifically, prevalence is lower in South, East, and Southeast Asia, as well as in Oceania, and higher in North and Latin America, Western Europe, North Africa, the Middle East, and Asia Pacific.[2] These disparities may be influenced by various factors beyond economic status, such as risk factors, cultural differences, illness stigma, diverse access to mental health services and the quality of reported data. The prevalence of bipolar disorders has risen by 59.3% since 1990,[4] likely due to greater diagnostic awareness and an expanding, aging global population, with an expected continued increase.[5] Although the first episode of bipolar disorders can occur at any age, most cases (45%) have an early-onset, with an average age of 17 years, with two other mean peaks at 26 years (mid-onset), and at 42 years (late-onset).[6] The early-onset group faces the highest disease burden and incident risk.[4] As the number of prevalent cases increases, the economic

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burden of bipolar disorders will inevitably rise. Our understanding of the economic burden of bipolar disorders is largely based on data from the United States, where the annual cost of bipolar I disorder was estimated to reach $202 billion in 2015, with 72% attributed to indirect costs, such as unemployment and productivity loss.[7] In Europe, estimates are limited and based on small samples, highlighting a critical gap in fully assessing the economic impact of bipolar disorders across the region. In the U.K., the cost of bipolar disorders was estimated at £6.43 billion in 2019, primarily driven by lost productivity and informal care,[8] while in France, the direct healthcare cost per patient was €6910 annually.[9] Regarding sex, previous studies suggested that bipolar I disorder is equally prevalent in males and females, while bipolar II and other bipolar spectrum disorders are more prevalent in females. However, new evidence indicates a higher preponderance of female patients across all forms of bipolar disorders, supporting the hypothesis of an increasing diagnosis of bipolar disorders in females.[10] Additionally, the clinical course and management of bipolar disorders in females require special consideration due to the impact of hormonal changes across different life stages, such as pregnancy, postpartum, and menopause, which can influence treatment decisions and outcomes.[11] In contrast, there is a notable data gap regarding the prevalence and clinical correlats of bipolar disorders in relation to gender identity and sexual orientation. Higher rates of mental health conditions like depression and suicidal behavior are consistently reported in the LGBTQIA + community,[12] while only one study suggests a potentially higher prevalence of bipolar disorders among LGBTQIA + individuals.[13]

Research papers often conclude with calls for further studies, emphasizing the need for ongoing investigation. These quite obvious assessments reflect the recognition that, despite significant advancements, many critical aspects remain open questions. While there has been notable global progress in various areas of clinical and research psychiatry in recent years, bipolar disorders remain one of the conditions where the more we discover, and we have discovered a lot, the more we realize there is still to uncover. In this narrative review we aim to provide a comprehensive and focused update on the most critical aspects of bipolar disorders, with a particular focus on clinical presentation, early detection and diagnosis, causes and pathogenesis, management, and future perspectives (Panel 1). This approach is intended to guide readers through the latest developments and unresolved challenges in bipolar disorders research and clinical practice.

***Panel 1*: Key Messages**

Prevalence and impact

Bipolar disorders affect over 1% of the global population.
Major contributors to disability and mortality, primarily but not only through cardiovascular disease and suicide.

Clinical characteristics

Characterized by recurrent episodes of mania and depression influenced by genetic, neurobiological, and environmental factors.
Initial diagnosis often delayed as depressive episodes can mimic unipolar depression.
Cognitive impairment and poor functioning can complicate the outcome.

Treatment approaches

Treatment involves mood stabilizers, antipsychotics, and cautious use of antidepressants for bipolar depression.
Psychosocial interventions like cognitive-behavioral therapy and psychoeducation are crucial for symptom management and prevention.

Challenges in management

Clinical heterogeneity, absence of specific biomarkers, and variability in international treatment guidelines pose challenges.
High prevalence of comorbid psychiatric and medical conditions complicates treatment efficacy.

Barriers to care

Diagnostic delays, treatment variability, and economic disparities limit access to effective care.
Stigma associated with mental illness and medication adherence issues further hinder management.

Collaborative care approach

Multidisciplinary collaboration among healthcare providers, researchers, and patients is essential.
Education and support for patients and caregivers improve treatment adherence and outcomes.
Prevention of mortality and suicide is paramount.

Diagnosis

Bipolar disorders pose significant diagnostic challenges due to their complex and often overlapping symptomatology with other psychiatric conditions. The utilization of standardized diagnostic criteria, such as those outlined in the diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR) (Panel 2) or the international classification of diseases 11th revision (ICD-11), enhances diagnostic precision, although the diverse combinations of symptoms result in significant clinical heterogeneity. Accurate diagnosis requires at least one episode of mania or hypomania, and the exclusion of other conditions, such as major depressive disorder and schizoaffective disorder. Mania involves a week-long period of elevated or irritable mood, increased energy, grandiosity, decreased need for sleep, racing thoughts, distractibility, and risk-taking. Hypomania, a milder form, lasts at least four days without significantly affecting daily functioning or

Panel 2: DSM-5-TR diagnosis of bipolar and related disorders

Bipolar I disorder
- Characterized by at least one manic episode.
- Major depressive episodes are common but not required for diagnosis.

Bipolar II disorder
- Requires at least one hypomanic episode and one major depressive episode.

Cyclothymic disorder
- Involves numerous hypomanic and depressive periods that do not meet the criteria for hypomania or major depression individually, persisting for at least 2 years.

Substance or Medication-Induced Bipolar and Related Disorder
- Diagnosed when bipolar-like symptoms are attributed to substance use or withdrawal.

Bipolar and related disorder due to another medical condition
- Diagnosis is given when bipolar symptoms are a direct consequence of another medical condition.

Other specified bipolar and related disorder
- Encompasses bipolar-like conditions that do not fully meet criteria for any of the disorders in the bipolar and related disorders diagnostic class
- Examples include:
  - o Short-duration hypomanic episodes (2–3 days) and major depressive episodes.
  - o Hypomanic episodes with insufficient symptoms for a diagnosis and major depressive episodes.
  - o Hypomanic episode without a prior major depressive episode.
  - o Short-duration cyclothymia (less than 24 months).
  - o Manic episode superimposed on schizophrenia spectrum and other psychotic disorder

Unspecified bipolar and related disorder
- Includes characteristic symptoms of bipolar and related disorders that do not meet full diagnostic criteria for any specific category mentioned above.

requiring hospitalization. Both DSM-5-TR and ICD-11 subdivide bipolar disorders into bipolar I (mania) and bipolar II (hypomania). However, many individuals with bipolar disorders first present with depressive episodes, often indistinguishable from major depressive disorder. Indicators of bipolar depression include mixed features, atypical symptoms, psychotic symptoms, treatment-resistance, catatonia, and family history. The absence or failure to recognize these characteristics can lead to delays in making an accurate diagnosis and subsequently implementing appropriate management strategies.[14] Longitudinal assessment is crucial, as the episodic nature of bipolar disorders often requires observation over time to capture the characteristic mood

Panel 3: Differences between Mixed Features Specifier in DSM-5-TR and Mixed Episodes in ICD-11

Mixed features specifier in DSM-5-TR
- **Definition**: Presence of symptoms from the opposite mood state (i.e., depressive symptoms during a manic episode and vice versa) that do not meet full criteria for a major depressive or manic episode.
- **Context**: Occurs within the context of a major depressive, manic, or hypomanic episode.
- **Usage**: Used to describe mood episodes where symptoms of the opposite polarity are present but do not dominate the clinical picture.

Mixed episodes in ICD-11
- **Definition**: Recognized as a distinct episode where criteria for both manic and depressive episodes are met simultaneously.
- **Context**: Explicitly categorized as a separate episode within the ICD-11 classification system.
- **Usage**: Describes episodes where symptoms of mania and depression co-occur to a significant degree, meeting diagnostic criteria for both.

fluctuations between depressive and manic or hypomanic states.[15] Diagnosis can be delayed by up to seven years,[14] leading continued impaired functionality, psychosocial and interpersonal diffilculties, greater treatment resistance, and increased suicide risk. Suicidal behaviour is significantly increased in bipolar disorders. About 30–50% of adults with bipolar disorders have attempted suicide in their lifetime, and 5–20% have completed it.[16]

Mixed states, involving simultaneous or rapid-sequence manic and depressive symptoms, have been variably classified (Panel 3). The ICD-11 retains mixed episodes as distinct entities, while DSM-5-TR allows for mixed features to be specified within manic and depressive episodes. The DSM-5-TR reflects a more flexible approach, allowing to clinicians to capture opposite-polarity symptoms across episodes, which reflects better the complexity of mood presentation in bipolar disorders. Patients with frequent mixed episodes often have a more severe and chronic illness course, rapid mood swings, increased aggression, irritability, treatment resistance, comorbid disorders, and cognitive impairment.[17]

Current classification systems offer valuable guidance but may not fully capture the spectrum of bipolar disorders's presentations with the current included specifiers. This is not just a classification exercise, but a search for more homogeneous phenotypes, both clinically and biologically, on which to focus research and clinical efforts.[18] Predominant polarity, indicating whether depressive or manic/hypomanic episodes prevail, helps delineate clinical

subtypes with distinct prognoses.[19] Cognitive impairment exists in a continuum of severity. Both neurocognitive impairments,[20] such as those affecting attention, memory, and executive function, and affective cognitive impairments,[21] involving emotion regulation and decision-making, have a significant impact on the clinical and functional outcomes and quality of life of people with bipolar disorders.[22] Unique challenges exist in diagnosing bipolar disorders in females. Bipolar disorders in females are often characterized by a higher incidence of depressive episodes and suicide attempts. Early recognition and appropriate treatment are essential to mitigate these risks and enhance the quality of life for affected females.[10]

Bipolar disorders are associated with a high prevalence of psychiatric and medical comorbidity. Approximately 65% of individuals with bipolar disorders have at least one psychiatric comorbidity, including anxiety, substance use, personality disorders, attention deficit hyperactivity disorder (ADHD), and obsessive compulsive disorder (OCD).[23] These comorbidities exacerbate symptoms, precipitate rapid cycling, and impede treatment. Bipolar disorders also have higher rates of medical conditions like cardiovascular disease, metabolic syndrome, and diabetes, contributing to premature mortality.[24] Although medications may increase cardiovascular risk, bipolar disorders themself pose a moderate-risk condition independent of medication effects.[25]

Causes, pathogenesis and biomarkers

Bipolar disorders arise from a significant genetic predisposition interacting with various environmental factors, leading to epigenetic, endocrine, and inflammatory alterations. These changes produce neuronal modifications that contribute to the disorders' development and progression.

Family and twin studies estimate the heritability of bipolar disorders at 90%.[26] The largest genome-wide association study (GWAS) to date has identified 64 independent loci across the genome associated with bipolar disorders,[3] offering insights into the biological processes involved in bipolar disorders, including ion channel regulation (e.g., CACNA1C, ANK3), synaptic transmission and neurotransmitter signaling (e.g., GRIN2A, ODZ4), neuroplasticity (e.g., NCAN, SYNE1), and cellular signaling and neurodevelopmental pathways (e.g., TRANK1). Some loci overlap with risk factors for schizophrenia, depression, childhood-onset psychiatric disorders, and problematic alcohol use, indicating a shared genetic architecture.[3] However, the genetic architecture of bipolar disorders is polygenic, with each single nucleotide polymorphism (SNP) contributing a small effect or showing low penetrance. SNP-based heritability is estimated at only 25%, emphasizing the importance of other factors. Gene-environment interactions are crucial. Recognized risk factors include perinatal influences (e.g., maternal infections, smoking during pregnancy), early-life adversities (e.g., childhood trauma, cannabis use in adolescence), and certain medical conditions (e.g., multiple sclerosis, endocrine disorders).[27] Environmental triggers like seasonal changes, particularly shifts in light exposure, have been linked to the disorders' course.[28] Recent discussions highlight the possible role of climate change in psychiatric disorders,[29] including bipolar disorders.

Epigenetic mechanisms, such as DNA methylation, histone modifications, and noncoding RNA activity, mediate gene–environment interactions. These processes regulate gene expression without altering the DNA sequence, affecting brain development and function.[30] Longitudinal neuroimaging studies have shown that bipolar disorders are associated with progressive brain changes, including cortical thinning and reduced gray matter volume,[31] particularly in the prefrontal, temporal, and parietal cortex, amygdala, and hippocampus.[32] Damage to the limbic network, a key system for emotion regulation, has been suggested as a major factor in the disorders.[33] This damage affects neurotransmitter systems, particularly dopamine and serotonin, which are crucial for mood regulation. These neuronal changes are also due to mitochondrial dysfunction, the loss of dendritic spines, and altered membrane permeability. The "mitochondrial hypothesis" suggests that dysfunction in mitochondria may contribute to bipolar disorders, as mitochondria are vital for neuronal activity, plasticity, and resilience.[34] Additionally, immune-inflammatory changes, especially T cell activation and pro-inflammatory cytokine production, contribute to the structural and functional brain alterations observed in bipolar disorders.[35] Chronic stress and dysregulation of the hypothalamic-pituitary-adrenal axis exacerbate inflammation and oxidative stress, increasing vulnerability to stress and raising the risk of relapse. These processes also compromise neuronal function by creating energy imbalances and promoting neurotoxicity.[36]

Given the complexity of bipolar disorders, identifying reliable biomarkers is a key research priority. Biomarkers can aid early diagnosis, predict treatment response, and monitor disease progression, moving towards a precicion psychiatry paradigm.[37] Although many biomarkers have been investigated, none have yet achieved clinical utility. Genetic variants associated with bipolar disorders cannot reliably predict individual risk, disease course, or treatment response and only a few peripheral biomarkers have shown a good level of evidence for bipolar disorders. Convincing evidence has been found for elevated cortisol awakening response levels in euthymic patients with bipolar disorders compared to controls, and highly suggestive evidence for elevated C-reactive protein (CRP) levels in both euthymic and manic patients,

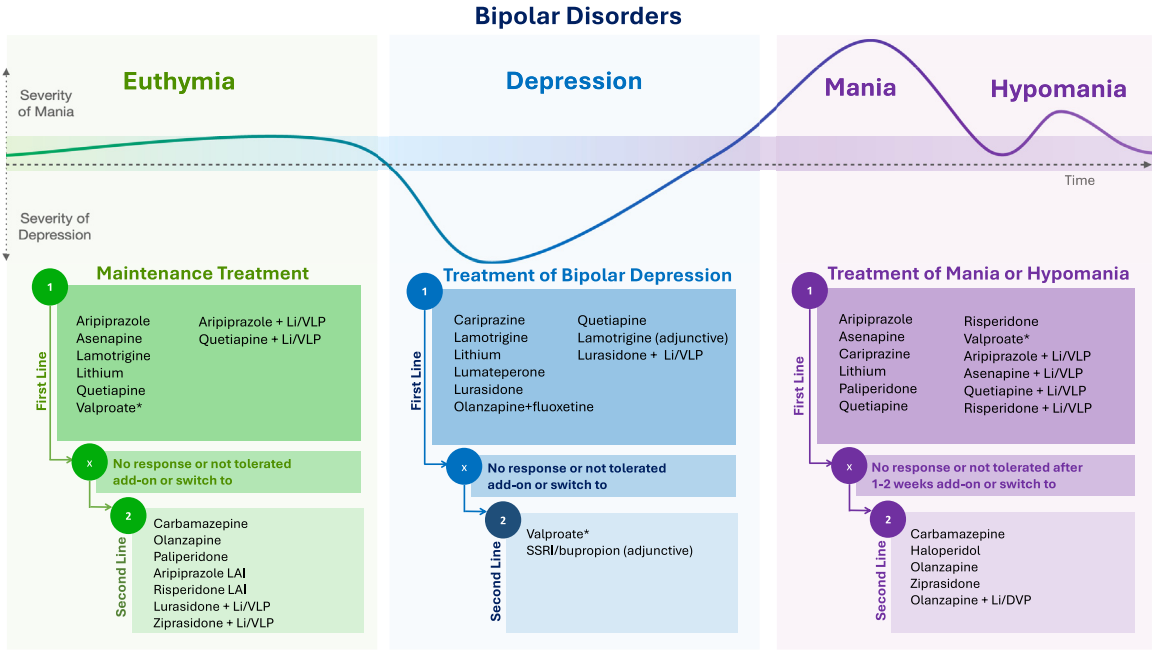

Fig. 1: **Lifechart showing progression of bipolar disorders and recommended pharmacological treatments**. LAI, Long acting injectable. Li, Lithium; SSRI, Selective serotonin reuptake inhibitor; VLP, Valproate. *Valproate should be avoided in patients of childbearing age due to its teratogenic risk and other significant side effects.

elevated insulin-like growth factor 1 (IGF-1) levels in manic patients, and elevated levels of antibodies against the NMDA receptor in patients with bipolar disorders.[38] However, these markers are not specific to bipolar disorders, as they also appear in other psychiatric or inflammatory conditions. Moving beyond the paradigm of searching for a single biomarker, times are changing.

Artificial intelligence (AI) and machine learning models are showing promise in predicting, diagnosing, and assessing the course of bipolar disorders. Although these models are not yet fully validated for clinical use, studies suggest that robust predictive models could be developed by integrating biomarkers, which might enable more personalized treatments in the future. However, for these advancements to progress, there is a need for standardized methods and best practices to ensure reliable and generalizable results in future research.

Management of bipolar disorders

The primary therapeutic aims in bipolar disorders encompass the treatment of acute hypomania, mania, and depression, alongside sub-syndromal inter-episodic symptoms, and the prevention of mood relapses (Fig. 1).

Pharmacological intervention serves as the cornerstone for achieving these objectives, complemented by psychosocial interventions, neurostimulation, and lifestyle modifications (Panel 4). Mood stabilizers and atypical antipsychotic drugs are recommended for both acute and long-term management of bipolar disorders. Antidepressants, used in augmentation or combination with mood stabilizers or antipsychotics, can be used in the treatment of bipolar depression, despite controversies.[39] However, given the complex and multifaceted nature of bipolar disorders, management should extend beyond addressing mood episodes. Additional

Panel 4: **Evidence based non-pharmacological interventions for bipolar disorders**

Brain stimulation interventions
- Cranial electrotherapy stimulation
- Electroconvulsive therapy
- Theta-burst stimulation
- Transcranial direct current stimulation
- Transcranial magnetic stimulation

Circadian rhythm-based interventions
- Bright light therapy
- Interpersonal and social rhythm therapy
- Total sleep deprivation

Psychosocial interventions
- Carer focused intervention
- Cognitive behavioral therapy
- Family/conjoint therapy
- Functional remediation
- Mindfulness-based cognitive therapy
- Psychoeducation
- Supportive therapy

Panel 5: **Barriers complicating the management of bipolar disorders**

Diagnostic challenges
- Delayed diagnosis due to initial presentation often resembling unipolar depression.
- Misdiagnosis or underdiagnosis, particularly in younger patients.
- Lack of biomarkers to confirm clinical impression.

Clinical heterogeneity
- Variability in symptom presentation and disease course.
- Lack of specific biomarkers for accurate diagnosis and treatment guidance.

Treatment variability
- Differences in approved medications and guidelines internationally.
- Personalized treatment plans needed due to variability in treatment response and side effects.

Comorbidities
- High prevalence of psychiatric and medical comorbidities complicating treatment efficacy.
- Co-occurrence of substance use disorders further complicating management.

Adherence and stigma
- Challenges in medication adherence due to side effects and mood fluctuations.
- Social stigma associated with mental illness affecting treatment-seeking behaviors.

Access to care
- Disparities in access to specialized mental health services.
- Economic barriers limiting access to medications and psychosocial interventions.

Patient and caregiver education
- Limited awareness about the nature of bipolar disorders and available treatments.
- Importance of ongoing education to enhance treatment adherence and management skills.

therapeutic goals include enhancing cognitive function, addressing circadian disturbances, managing psychiatric and medical comorbidities, improving functionality and quality of life, and reducing suicidality.

The management of bipolar disorders remains a challenge, but this is not due to a lack of effort. Substantial financial investments and extensive research are aimed at improving treatment efficacy and safety,[40–43] alongside the continuous development and updating of guidelines.[44–49] Several barriers complicate the effective management of bipolar disorders (Panel 5). Despite decades of effort to translate research findings into new treatments, the benefits to patients remain somewhat limited. On average, patients with bipolar disorders are euthymic only about 50% of the time. The remaining time is spent more than half in depression or with depressive symptoms, and the rest equally in mood elevation and with rapid cycling/mixed symptoms.[50] As a result, the prevalence of polypharmacy has increased during the past decade in people with bipolar disorders,[51] even though the combination of drugs is recommended only in selected cases. The limited progress in this area can be attributed to various factors, including the biological and physiological complexity of brain disorders, the heterogeneity underlying clinical diagnostic entities, and the lack of biomarkers for diagnoses, patient stratification, response prediction, and surrogate endpoints. Additionally, suboptimal endpoints that rely on subjective assessments by clinicians of the patients' symptoms and complaints, high placebo responses in some indications, the exclusion of individuals with the most commonly encountered forms of bipolar disorders in clinical practice (such as those with multiple psychiatric or medical comorbidities and suicidality), as well as the inclusion of patients with low ethnic and economic diversity from pharmacological studies that are predominantly conducted in high-income countries, hinder the extrapolation of study results to real-world clinical practice.[52] The reluctance of the pharmaceutical industry over the past decades to embrace truly innovative thinking and approaches in study design and conceptualizations of mental disorders, with studies largely developed for the purpose of regulatory approval and with less emphasis on patient-reported outcomes (e.g., quality of life, wellbeing, and function), further complicates the development process.[53] Moreover, bipolar disorders are usually a second indication for most new drugs, which are generally tested first in schizophrenia, depression, or epilepsy, hampering or delaying their test in this indication. This translates into a very major barrier for the adequate and consistent treatment of bipolar disorders worldwide. Not all new medications approved for the treatment of bipolar disorders receive the same approval from all regulatory agencies. For example, there are discrepancies between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Panel 6). This is evident with medications like lurasidone, cariprazine, and lumateperone, which were approved by the FDA for bipolar depression in 2013, 2019, and 2021 respectively, but not by the EMA, because the owners of those products failed to comply with the EMA guidance on preferred clinical trial design. As a knock-on effect, dfferences in the geographical regions where guidelines are formulated, coupled with different years of drafting, may result in different treatment recommendations. Additionally, in low-income countries, modern and expensive medications are not always accessible to everyone. As a final result, clinicians may face challenges in identifying the most reliable guideline and integrating it into their

Panel 6: **Approved Treatments for Bipolar Disorder by FDA and EMA (some compounds are EMA approved by country specific mutual recognitions)**

FDA approved	EMA approved
Bipolar depression	
Cariprazine	
Lumateperone	
Lurasidone	
Olanzapine/fluoxetine combination	
Quetiapine	Quetiapine
Mania[a]	
Aripiprazole	Aripiprazole
Asenapine	Asenapine
Carbamazepine ER	
Cariprazine	
Iloperidone	
Lithium	Lithium
Olanzapine	Olanzapine
Olanzapine/samidorphan combination	
Quetiapine	Quetiapine
Risperidone	Risperidone
Valproate	Valproate
Ziprasidone	Ziprasidone
Maintenance	
Aripiprazole	Aripiprazole
Asenapine	
Lamotrigine	Lamotrigine
Lithium	Lithium
Olanzapine	Olanzapine
Olanzapine/samidorphan combination	
Quetiapine	Quetiapine
Risperidone	
Ziprasidone	

[a]Some very old compounds do not hold a specific indication in mania because they had a broader indication in psychoses.

routine clinical practice. Finally, stigma, misinformation, and cultural differences with respect to attitudes towards bipolar disorders and their treatment contribute to worsening the picture.

Acute depression

The treatment of bipolar depression continues to be a significant critical aspect in the management of bipolar disorders. Only five antipsychotic drugs or combinations have been approved by the FDA for acute bipolar depression: olanzapine/fluoxetine combination, quetiapine, lurasidone, cariprazine, and lumateperone, and not all agents are available in all countries and regions. Although lithium and lamotrigine are often recommended as first-line treatments for bipolar depression,[45] especially in combination, the acute effects of lithium on depressive symptoms are less well established.[40] There is ongoing controversy regarding the safe and appropriate use of antidepressants in bipolar disorders. The concern stems from evidence that antidepressants may induce manic and hypomanic episodes and trigger more frequent affective switches compared to other classes of medications.[40] However, when individual antidepressants are considered together with other medications in network meta-analyses, no increased risk of switch to mania has emerged for the molecules studied so far in randomized controlled trials (RCTs).[40] Specifically, the combination of olanzapine/fluoxetine, effective even against psychotic depression,[43] has shown no increase in mania switches or other safety issues.[40] Several guidelines recommend using antidepressants only as adjunctive agents to mood-stabilizer or second-generation antipsychotics in individuals with episodic bipolar depression who do not exhibit rapid cycling, mixed features, a history of antidepressant-induced destabilization, or combinations of these presentations.[54] However, over one-third of patients do not respond to treatment interventions, which is commonly known as treatment-resistant bipolar depression. Treatment-resistant bipolar depression is an entity still in search of a definition.[55] The most authoritative definition is that of the most recent guidelines of the International College of Neuropsychopharmacology on treatment resistance in bipolar disorders,[56] adapted from the International Society for Bipolar Disorders' definition of treatment response and recovery. Resistance is defined as no significant reduction in Montgomery-Asberg Depression Rating Scale or Hamilton Depression Rating Scale scores or a significant increase in Young Mania Rating Scale or Mania Rating Scale scores, after 10–12 weeks of treatment. Ketamine or esketamine may be potential treatment strategies in these cases, without causing switches to mania.[57] However, the most effective treatment for severe and resistant bipolar depression is electroconvulsive therapy (ECT), with meta-analytic response and remission rates of 77% and 52%, respectively.[58] Despite this, its use remains controversial, probably due to its potential potential cognitive side-effects. Several medications have been studied to mitigate the cognitive effects of ECT, but only a few and non-robust results have been produced so far.[59] The evidence for other brain neuromodulation techniques, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), is less robust than for ECT, but tDCS and rTMS are more acceptable to patients and have a lower risk of cognitive impairment.[60]

Acute mania

Acute mania is a medical emergency requiring urgent treatment due to high-risk behaviors that can negatively impact relationships, employment, and finances. Pharmacological treatments are the standard for adults experiencing an acute manic episode. The effectiveness

of pharmacological treatment for mania is more well-established compared to pharmacological treatment for bipolar depression. However, treatment acceptance and adherence are often compromised by diminished insight during manic episodes. Consequently, inpatient care is often recommended for safety reasons, and involuntary admission may be necessary if appropriate treatment cannot be otherwise provided (e.g., patients with aggressive behaviours or psychosis). The same principles apply to assessing and managing hypomania, with similar treatment options, although hypomanic episodes, by definition, do not require hospitalization. Before initiating pharmacological treatment, every secondary cause of the (hypo)manic episode (e.g., drugs of abuse, medications such as antidepressants, other medical or neurological conditions) must be addressed. Treatment involves discontinuing agents that may exacerbate or prolong symptoms and initiating appropriate pharmacotherapy. Multiple agents have established antimanic efficacy, notably antipsychotics (e.g., aripiprazole, asenapine, cariprazine, paliperidone, quetiapine, and risperidone, but not brexpiprazole or lurasidone) and mood stabilizers (e.g., lithium and divalproex, but not lamotrigine). Combination therapy with both classes of drugs is often necessary and should be considered based on factors such as the rapidity of response needed, previous treatment response, severity of mania, tolerability concerns, and willingness of the patient.[44–49]

Maintenance

Patients with bipolar disorders require lifelong treatment aimed at preventing mood relapses, minimizing subthreshold symptoms and cognitive decline, improving functioning, and enhancing quality of life. Adequate long-term treatment has been shown to reduce the neuroprogression associated with bipolar disorders.[61] Lithium is considered the gold standard mood-stabilizing agent, possessing anti-suicidal effects, and potentially reducing the incidence of dementia in individuals with bipolar disorders.[62] However, many medications have demonstrated efficacy in the maintenance phase of bipolar disorders. In clinical practice, if a medication has been effective in treating an acute episode, it is typically recommended to continue it throughout the maintenance phase. The standard approach involves a mood stabilizer, such as lithium, divalproex, or lamotrigine, or atypical antipsychotics such as quetiapine, aripiprazole, asenapine, or lurasidone. Long-term use of antidepressants in the maintenance phase is generally not recommended, even though discontinuing an antidepressant in patients who have shown a good response and stability can lead to destabilization. Recent data indicate that responders to adjunctive antidepressants during a depressive episode may have fewer depressive recurrences than those stopping the antidepressants in the short term.[63] Some medications are typically more effective in preventing depressive episodes, such as lamotrigine, while others, like lithium and atypical antipsychotics, are more effective in preventing manic episodes. However, quetiapine seems to demonstrate similar efficacy for both mood episodes, as its polarity index—a measure of a drug's effectiveness in preventing depression versus mania—is close to 1.[64] If adequate symptom control is not achieved, switching to other medications or drug combinations are possible. Patients who do not respond adequately to maintenance treatment may experience an increased frequency of mood episodes. The cycling patterns can vary, ranging from rapid cycling (four or more episodes per year) to ultra-rapid or even ultradian cycling, where mood shifts occur within weeks, days, or even within the same day. Factors such as genetic predisposition, stress, psychiatric comorbidities, hypothyroidism, and treatment non-adherence can exacerbate these patterns. Additionally, the use of antidepressants without mood stabilizers can further contribute to mood destabilization. In these cases, combinations of mood-stabilizing drugs are often recommended, as monotherapy is typically inadequate for managing the frequent and severe mood fluctuations associated with more complex cycling patterns.[45] However, efficacy profiles should not be the sole consideration in choosing the appropriate maintenance therapy. All medications have specific profiles of short-term and long-term side effects that must be carefully considered. Lithium is associated with short-term tremors, polyuria, and moderate weight gain, while long-term use may lead to hypothyroidism and renal toxicity, along with a narrow therapeutic index that may pose significant overdose risk. Divalproex is linked to menstrual irregularities, polycystic ovarian syndrome, and teratogenicity in women, and recent concerns have also emerged regarding teratogenic effects in men.[65] Antipsychotic agents are associated with various side effects, including weight gain, metabolic disturbances, elevated prolactin levels, sedation, somnolence, akathisia, QT interval prolongation, and tardive dyskinesia. Therefore, a critical aspect in maintenance treatment is patient adherence. In fact, half of the patients do not adhere to their prescribed treatment regimen.[66] It is essential to reach a shared decision with the patient and their caregivers regarding the optimal treatment, and to promote active patient involvement in adhering to therapy. In this context, psychosocial treatments such as cognitive behavioral therapy, individual and group psychoeducation are essential to improve treatment compliance, reduce affective symptoms, and enhance quality of life.[67] These therapies also help patients cope with the illness, adhere not only to treatment but also to long-term lifestyle recommendations, and manage stress through more adaptive coping strategies. Additionally, interpersonal and social rhythm therapy, which specifically targets bipolar disorders, plays a crucial role in stabilizing daily routines and improving

social relationships, further contributing to overall treatment success.[68]

Outlook

The challenges of understanding and managing bipolar disorders are compounded by various demographic and environmental factors, such as an aging population, sex and gender differences in treatment response, migration, poverty, urbanization, and climate change. These factors require healthcare systems to adapt in ways they may not be fully prepared for.

Diagnosing bipolar disorders accurately remains difficult. In the context of biomarkers research, EDIT-B® is a European Union co-funded project aimed at developing a blood test to differentiate between bipolar and unipolar depression. This test, based on specific RNA sites with post-transcriptional modifications in nucleotides and a machine learning model that integrates data from seven candidate genes, could improve treatment access and outcomes. Promising preliminary results from a validation cohort of 255 patients are encouraging,[69] with clinical trials underway in Denmark, France, Italy, and Spain. If validated, this test could significantly enhance diagnostic precision.

Other biomarker discovery initiatives, particularly those utilizing high-throughput omics techniques, have also emerged. These methods provide detailed data on RNA, proteins, and metabolites, enabling researchers to identify molecular signatures and pathways involved in bipolar disorders. Combining these techniques with computational analyses offers insights into complex diseases, aiding biomarker identification and revealing new therapeutic targets for better clinical management.[70]

AI is expanding beyond genetics and epigenetics into new areas of psychopathological assessment. AI can now quantify traditionally subjective features, such as speech tone, prosody, volume, and fluency, to improve diagnostic accuracy. Models analyzing acoustic features from free speech or text reading tasks have shown promise in both diagnostics and predicting clinical outcomes or treatment progress.[71]

There is growing recognition of the need to address symptoms beyond the affective realm in bipolar disorders. Many patients experience cognitive, functional, and emotion regulation difficulties that traditional treatments fail to adequately target. Emerging approaches, such as cognitive and functional remediation, aim to improve cognition and overall functioning. However, variability in study protocols complicates comparisons, highlighting the need for well-powered research to guide future interventions. Innovations like virtual reality are being explored for their potential to enhance cognitive remediation through immersive, life-like experiences.[72]

Future treatment strategies may also include new pharmacological interventions with anti-inflammatory, antioxidant, and neuroprotective effects. Various interventions, including omega-3 fatty acids, riluzole, verapamil, N-acetylcysteine, nonsteroidal anti-inflammatory drugs, coenzyme Q10, minocycline, and allopurinol have been investigated in meta-analyses,[40,41] though their optimization in treating bipolar disorders is ongoing. New drug trials are evaluating molecules like a Kv7 potassium channel activator (BHV-7000) for acute mania and an ATP-gated P2X7 ion channel antagonist (JNJ-55308942) for bipolar depression. Moreover, psychedelic drugs like psilocybin combined with psychotherapy sessions,[73] alongside new molecules such as GH001, are also being studied. Additionally, the muscarinic-cholinergic system may become a target for future treatments.[74]

Managing bipolar disorders in the future will not only focus on diagnosis and treatment but also on continuous monitoring. Digital devices like actigraphs and smartphones can track physical, behavioral, psychopathological, and circadian rhythm data, offering a more comprehensive view of the disorders' progression. These digital biomarkers can help monitor bipolar disorders between mood episodes, providing valuable insights into intermediate periods.[75] However, challenges like cost, technical limitations, and patient adherence need to be addressed for these tools to reach their full potential. Finally, novel neuromodulation techniques, such as deep TMS[76] and deep brain stimulation (DBS),[77] may prove effective in treating symptoms of bipolar disorders in the near future, offering additional hope for patients who do not respond to current treatment options.

Search strategy and selection criteria

We conducted a comprehensive search on PubMed for review articles, clinical investigations, and meta-analytic studies published in any language up to June 3rd, 2024. The search utilized a combination of keywords including "bipolar disorder" alongside terms such as "prevalence", "onset", "economic", "diagnosis", "dimensional", "pathogenesis", "biomarkers", "neurobiology", "guidelines", "management", "treatment", "novel treatments", and "perspective". Priority was accorded to studies employing meta-analytic techniques to enhance the likelihood of identifying articles pertinent to this review. This approach aimed to streamline the retrieval of relevant literature while minimizing superfluous citations.

Conclusions

Bipolar disorders are recognized as severe mental illnesses that are receiving increasing attention, but not yet enough to make them a priority for funding agencies and industry. While progress has been made in understanding their mechanisms and improving patient outcomes, adressing the critical issues raised in our review

will further advance our understanding of these disorders (Panel 5). With the implementation of precision psychiatry and artificial intelligence paradigms, the current state-of-the art as described in this article may hopefully become obsolete in the near future. Meanwhile, improving healthcare access, early intervention, and evidence-based practice all over the world is necessary for improved patient outcomes in these conditions.

Contributors

VO and EV conceptualised and planned the review. VO managed and coordinated the research activity planning and execution. VO, GF, and MDP screened the literature and prepared the first draft of the review, with important contributions from EV, XG, and ARR. All authors critically reviewed and commented on the manuscript, and approved the final version. EV had supervisory and leadership responsibility for the research activity planning and execution. All authors had full access to all the matherials of the study and had final responsibility for the decision to submit for publication.

Declaration of interests

GF served as a paid consultant for Lundbeck. EV has received grants and served as a paid consultant, advisor, or CME speaker for AB-Biotics, Abbott, AbbVie, Adamed, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Cambridge University Press, Casen-Recordati, Celon, Compass, Dainippon Sumitomo, Elsevier, Ethypharm, Ferrer, Galenica, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Neuraxpharm, Newron, Novartis, Oxford University Press, Orion, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, out of the submitted work.

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