**Review Article**

# Management of Depressive Episodes in Bipolar Disorder: Clinical Risks, Evidence Gaps, and Strategic Use of Antidepressants

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## Abstract

Bipolar depression represents a major clinical challenge due to its high prevalence, significant functional burden, and complex diagnostic and therapeutic considerations. Accurate diagnosis requires a structured approach that distinguishes bipolar depression from unipolar depression, incorporating clinical features such as atypical symptoms, family history, and illness course, as well as emerging neurobiological markers. Clinical phenotyping, including bipolar subtype and predominant polarity, plays a crucial role in guiding individualized treatment strategies and improving long-term outcomes. The neurobiological basis of bipolar depression is multifactorial, involving alterations in monoaminergic, glutamatergic, and GABAergic systems, as well as neuroinflammation, impaired neuroplasticity, and circadian rhythm dysregulation. These mechanisms contribute to both

symptom development and variability in treatment response, supporting the need for integrative therapeutic approaches. Mood stabilizers and atypical antipsychotics remain the foundation of treatment, with agents such as lithium, lamotrigine, and quetiapine demonstrating efficacy in symptom control and relapse prevention. In contrast, the role of antidepressants remains controversial. Although they may offer modest benefits in selected patients, particularly as adjunctive therapy, their use is limited by the risk of manic switching, rapid cycling, and mood destabilization. Current evidence from clinical trials and meta-analyses is inconsistent and often limited by methodological heterogeneity. Non-pharmacological interventions, including psychotherapy, chronotherapeutic, and lifestyle modifications, play an essential complementary role. Future directions emphasize personalized medicine, with a focus on clinical phenotyping, biomarker development, and novel therapeutic targets to optimize treatment outcomes in bipolar depression.

## Key words

Bipolar depression, mood stabilizers, antidepressants, manic switch, atypical antipsychotics, personalized treatment.

## Introduction

Bipolar disorder is defined by the presence of recurrent manic, hypomanic, and depressive episodes, interspersed with periods of euthymia, reflecting its inherently episodic nature. Patients experience fluctuations in both the frequency and intensity of these mood episodes, which contributes to the clinical heterogeneity of the disorder [1]. Within this framework, the concept of predominant polarity has emerged as a clinically relevant tool to characterize the longitudinal course of the illness. Predominant polarity refers to whether a patient experiences a greater number of depressive or manic episodes over time, thereby offering a useful approach for guiding individualized therapeutic strategies [2].

In this context, depressive episodes represent a central component of bipolar disorder and are often more prevalent than manic manifestations. Epidemiological data indicate a substantial proportion of patients exhibit depressive predominant polarity, highlighting the clinical importance of this phase of the illness [3]. Beyond their frequency, depressive episodes are associated with a considerable clinical burden, as they tend to be more resistant to treatment and are linked to poorer functional outcomes when compared to manic episodes. Consequently, bipolar depression constitutes a major determinant of long-term prognosis and disease-related disability [4, 5].

The impact of depressive episodes extends significantly into multiple domains of patient well-being. These episodes are strongly associated with marked functional impairment and a pronounced reduction in quality of life. Furthermore, they are closely linked to an increased risk of suicidal behavior, particularly among individuals with depressive predominant polarity, who frequently present with a history of suicide attempts and a higher overall burden of mood episodes [3, 4]. This clinical profile is further compounded by the presence of emotion dysregulation, a core feature of bipolar disorder that is especially prominent in patients with depressive predominance, thereby exacerbating both psychological instability and day-to-day functional limitations [6].

Despite the clinical significance of bipolar depression, misdiagnosis remains a critical challenge in routine practice. Bipolar disorder is frequently mistaken for unipolar depression, particularly during the early stages of the illness when depressive episodes predominate. This diagnostic inaccuracy often results in the inappropriate use of antidepressant monotherapy, which may precipitate adverse outcomes such as treatment-emergent mania or rapid cycling [7].

Therefore, early and accurate diagnostic assessment is essential, although it can be difficult due to the overlapping clinical features between bipolar and unipolar depressive disorders [8].

Given these complexities, the management of depressive episodes in bipolar disorder requires a carefully structured therapeutic approach aimed at achieving symptom control while minimizing the risk of mood destabilization. Mood stabilizers and atypical antipsychotics constitute the cornerstone of treatment, with agents such as lithium and cariprazine playing a key role in current clinical practice [1, 9]. In particular, cariprazine has demonstrated efficacy in the treatment of bipolar depression, representing a promising option for patients who exhibit resistance to conventional therapies [4, 5].

The objective of this article is to provide a comprehensive and clinically oriented analysis of the management of depressive episodes in bipolar disorder, with particular emphasis on the risks, limitations, and considerations associated with the use of antidepressants.

## Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of the management of depressive episodes in bipolar disorder, with particular emphasis on the risks, limitations, and clinical considerations associated with the use of antidepressants. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the clinical heterogeneity of bipolar disorder, the variability in diagnostic presentations, and the complexity of treatment responses across different patient subgroups, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate neurobiological, pharmacological, and clinical perspectives into a coherent and clinically applicable framework. Special attention was given to the risk of treatment-emergent affective switch, mood destabilization, rapid cycling, and the comparative role of antidepressants within established treatment strategies based on mood stabilizers and atypical antipsychotics. The objective was to provide a structured synthesis capable of supporting individualized and evidence-based decision-making in the management of bipolar depression.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2026. The final search was performed in December 2026. This timeframe was selected to capture contemporary advances in the pharmacological management of bipolar depression, including updated guideline recommendations, emerging evidence on atypical antipsychotics and novel agents, and evolving perspectives on the safety and efficacy of antidepressants. Foundational studies were incorporated when necessary to contextualize pathophysiological mechanisms and the historical evolution of treatment paradigms. The search strategy combined MeSH and free-text terms using Boolean operators related to bipolar disorder, bipolar depression, antidepressants, mood stabilizers, atypical antipsychotics, affective switch, rapid cycling, treatment resistance, and suicide risk. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 208 records. After removal of duplicates, 149 articles remained for title and abstract screening. Of these, 97 underwent full-text evaluation, and 51 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports, editorials without clinical outcome data,

studies lacking specific focus on depressive episodes in bipolar disorder, redundant datasets, and investigations not directly addressing treatment strategies, antidepressant-related risks, or clinical outcomes.

Eligible studies included randomized controlled trials, large observational cohorts, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines from psychiatric and neuropsychopharmacology societies. Priority was assigned to multicenter studies, research with well-defined diagnostic criteria distinguishing bipolar from unipolar depression, and investigations evaluating clinically relevant outcomes such as symptom response, remission rates, treatment-emergent mania, rapid cycling, functional outcomes, and suicide risk. Extracted variables included study design, patient population characteristics (bipolar I vs bipolar II), type of intervention, use of antidepressants (monotherapy vs adjunctive), comparator treatments, duration of follow-up, and reported efficacy and safety outcomes. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, diagnostic accuracy, follow-up duration, and consistency of outcome reporting. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

## Diagnostic Framework and Clinical Phenotyping

The diagnostic evaluation of bipolar depression requires a structured and clinically nuanced approach that accurately situates depressive episodes within the broader bipolar spectrum. The 2020 RANZCP guidelines provide updated recommendations that emphasize the importance of precise diagnostic characterization, particularly in distinguishing bipolar depression from other mood disorders and in recognizing its heterogeneity [10]. Within this framework, bipolar depression is frequently associated with atypical clinical features, including hypersomnia, hyperphagia, and leaden paralysis, which can aid in differentiating it from unipolar depression and support a more accurate diagnostic formulation [11].

This differentiation is further reinforced by specific clinical and biological markers. Early age of onset, a positive family history of bipolar disorder, and the presence of atypical depressive symptoms represent key distinguishing features between bipolar and unipolar depression [12]. In addition, neuroimaging studies have demonstrated distinct patterns of brain activity in regions such as the insula and anterior cingulate cortex, suggesting potential neurobiological substrates that may contribute to diagnostic differentiation and, in the future, serve as biomarkers for clinical use [12, 13].

A comprehensive diagnostic assessment must also consider the full bipolar spectrum, which encompasses bipolar I disorder, bipolar II disorder, and subthreshold forms. Bipolar I disorder is defined by the presence of full manic episodes, whereas bipolar II disorder is characterized by hypomanic episodes in combination with more frequent and often more persistent depressive episodes. Subthreshold forms, although not meeting the full diagnostic criteria for bipolar I or II, remain clinically significant and require careful evaluation, as they may influence both prognosis and therapeutic decision-making [11].

An additional layer of complexity arises from the presence of mixed features, in which symptoms of mania and depression coexist within the same episode. These presentations complicate the clinical picture and are associated with distinct therapeutic implications, including an increased risk of mood destabilization when certain treatments are used. Current guidelines, including those from CANMAT and ISBD, underscore the importance of identifying mixed features in order to tailor treatment strategies appropriately and avoid adverse outcomes [14].

In this context, clinical phenotyping plays a central role in guiding therapeutic decisions. The concept of predominant polarity, whether depressive or manic, provides valuable insight into the longitudinal course of the disorder and has important implications for treatment selection and prognosis [2, 3]. Moreover, the identification of specific bipolar subtypes based on clinical presentation allows for a more individualized approach to management, as certain patient profiles may demonstrate preferential responses to particular treatments, such as lithium or atypical antipsychotics. Together, these considerations highlight the importance of a comprehensive and integrative diagnostic framework in optimizing the management of bipolar depression [11].

## Neurobiological Basis of Bipolar Depression

The pathophysiology of bipolar depression involves complex and interrelated neurobiological mechanisms that contribute to mood dysregulation and clinical heterogeneity. Among these, alterations in monoaminergic neurotransmission play a central role. Serotonin, dopamine, and norepinephrine are key neurotransmitters implicated in mood regulation, and disturbances in these systems have been consistently associated with the development of depressive symptoms in bipolar disorder. Neuroimaging studies using positron emission tomography have demonstrated abnormalities in serotonin receptor binding in individuals with bipolar depression; however, these alterations do not appear to reliably predict clinical response to selective serotonin reuptake inhibitors, highlighting the limitations of monoaminergic models in explaining treatment outcomes [15].

Beyond monoamines, increasing evidence supports a significant role for glutamatergic and gamma-aminobutyric acid dysfunction in the pathophysiology of bipolar depression. Proton magnetic resonance spectroscopy studies have identified altered levels of glutamate and related metabolites in the brains of affected individuals, suggesting an imbalance in excitatory and inhibitory neurotransmission [16, 17]. This dysregulation has important therapeutic implications, as demonstrated by the rapid antidepressant effects observed with ketamine, a glutamate receptor modulator. Despite its promising short-term efficacy, concerns remain regarding its long-term safety and sustained effectiveness, limiting its current role in routine clinical practice [18, 19].

In parallel, neuroinflammatory processes and oxidative stress have emerged as key contributors to the underlying pathophysiology of bipolar disorder. These mechanisms are thought to exacerbate neuronal dysfunction and promote the persistence of mood symptoms, thereby representing potential targets for emerging therapeutic strategies. Closely related to these processes are alterations in neuroplasticity, which further compromise the brain’s capacity to adapt to stress and maintain emotional stability. Brain-derived neurotrophic factor and other markers of synaptic plasticity are frequently dysregulated in bipolar disorder, and reductions in N-acetylaspartate levels have been observed, indicating impaired neuronal integrity and resilience [16, 20].

Additionally, disruptions in circadian rhythms and dysregulation of the hypothalamic-pituitary-adrenal axis play a crucial role in the pathogenesis of bipolar depression. These disturbances affect both mood stability and

treatment responsiveness, contributing to the recurrent and cyclical nature of the disorder [21]. In this context, chronotherapeutic interventions, including total sleep deprivation and light therapy, have demonstrated efficacy in modulating glutamatergic neurotransmission and alleviating depressive symptoms, further supporting the relevance of circadian mechanisms in bipolar depression. Collectively, these findings underscore the multifactorial nature of bipolar depression and the need for integrative treatment approaches that address its diverse neurobiological underpinnings [17].

## Evidence-Based First-Line Treatments (Non-Antidepressant Strategies)

Lithium remains a cornerstone in the treatment of bipolar disorder due to its well-established mood-stabilizing and anti-suicidal properties. It is particularly effective in patients with bipolar I and II disorders who present with typical clinical features, reinforcing its central role in long-term disease management [1, 22]. However, despite its recognized efficacy in mood stabilization, the evidence supporting its effectiveness specifically in the treatment of acute bipolar depression is limited and, in some cases, conflicting, which has influenced its positioning within treatment guidelines [23]. Nevertheless, major international guidelines, including those from CANMAT and ISBD, continue to recommend lithium as a first-line option for maintenance therapy, emphasizing its importance in preventing relapse and reducing suicide risk [14, 22].

In contrast, lamotrigine has a more specific therapeutic profile within bipolar disorder, particularly in the prevention of depressive relapses. While its efficacy in acute depressive episodes appears to be limited, it is widely utilized in maintenance treatment due to its favorable tolerability and low propensity to induce manic switching. This safety profile makes lamotrigine an attractive option for long-term management, especially in patients with a predominant depressive course [24, 25].

Valproate also plays a role in the pharmacological management of bipolar disorder, particularly in specific clinical subtypes such as mixed presentations and rapid-cycling forms. Its effectiveness in these populations supports its use as a targeted therapeutic option; however, its clinical applicability is limited in individuals of childbearing potential due to significant teratogenic risks, which necessitates careful patient selection and consideration of alternative treatments [1, 24].

Atypical antipsychotics have emerged as key agents in the treatment of bipolar depression, with several compounds demonstrating efficacy in reducing depressive symptoms. Agents such as quetiapine, lurasidone, and cariprazine are supported by robust clinical evidence, although their use is often influenced by differences in side effect profiles [25, 26]. Quetiapine is frequently recommended due to its favorable balance between efficacy and tolerability, although it is associated with adverse effects such as sedation and weight gain [1]. The combination of olanzapine and fluoxetine has also demonstrated significant efficacy in bipolar depression; however, its use is limited by metabolic side effects, including weight gain and metabolic dysregulation [26].

When comparing efficacy and tolerability, atypical antipsychotics generally show superior outcomes to placebo in the reduction of depressive symptoms, with quetiapine and the olanzapine-fluoxetine combination among the most effective options [26]. However, adverse effects vary considerably between agents, with olanzapine being more strongly associated with metabolic complications, while quetiapine is more commonly linked to sedation. Tolerability therefore becomes a critical factor in treatment selection, particularly given the chronic nature of bipolar disorder. In this context, newer agents such as lumateperone have shown promise due to a potentially lower risk of weight gain, further expanding therapeutic options [25].

International guidelines from CANMAT, ISBD, NICE, and APA consistently emphasize the use of mood stabilizers and atypical antipsychotics as first-line treatments for bipolar depression. These recommendations underscore the importance of individualized treatment strategies that consider efficacy, safety profiles, and patient-specific factors, thereby optimizing clinical outcomes while minimizing the risk of adverse effects and mood destabilization [14].

## Antidepressants in Bipolar Depression; Pharmacological Rationale and Use Patterns

The pharmacological rationale for the use of antidepressants in bipolar depression is primarily based on their effects on monoaminergic neurotransmission. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors increase the availability of serotonin and norepinephrine in the central nervous system, which can contribute to the improvement of depressive symptoms. However, this same mechanism may also predispose patients with bipolar disorder to mood destabilization, particularly through the induction of manic or hypomanic episodes [27]. In contrast, older classes of antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors, exert broader effects across multiple neurotransmitter systems. Although potentially effective, they are generally considered third-line options due to their less favorable side effect profiles and a higher risk of triggering mood instability [28].

Over time, the role of antidepressants in bipolar depression has undergone significant evolution. Historically, these agents were used more liberally in clinical practice; however, growing concerns regarding their safety, particularly the risk of treatment-emergent mania and rapid cycling, have led to a more cautious and restrictive approach. As a result, the contemporary therapeutic paradigm emphasizes the use of antidepressants primarily as adjunctive therapy rather than as standalone treatments. This shift reflects an effort to balance potential benefits in alleviating depressive symptoms with the need to minimize the risk of affective destabilization [7, 29].

Within this framework, the distinction between adjunctive therapy and monotherapy is of critical importance. The combination of antidepressants with mood stabilizers or atypical antipsychotics is a commonly employed strategy aimed at enhancing therapeutic efficacy while reducing the likelihood of manic switching. Evidence suggests that such combination approaches may improve response rates and lead to greater reductions in depressive symptomatology compared to antidepressant use alone [30, 31]. In contrast, antidepressant monotherapy is generally discouraged in bipolar disorder due to the significantly increased risk of inducing mania, hypomania, or rapid cycling. Nevertheless, there are select clinical scenarios in which cautious use of antidepressant monotherapy may be considered, particularly in patients with bipolar II disorder or in those with a clear predominance of depressive episodes [29, 32].

The clinical context therefore plays a decisive role in determining the appropriateness of antidepressant use. Patients with bipolar II disorder, who experience hypomanic rather than full manic episodes, may derive greater benefit from antidepressant therapy, especially when depressive symptoms are persistent and disabling [33]. Similarly, in individuals with a depressive predominant polarity, antidepressants may be incorporated into the treatment regimen, although always with careful monitoring and typically in combination with mood stabilizing agents to mitigate potential risksñThese considerations underscore the need for a highly individualized approach, in which therapeutic decisions are guided by clinical phenotype, longitudinal course of illness, and risk-benefit assessment [34].

## Risks and Adverse Outcomes Associated with Antidepressant Therapy

The use of antidepressants in bipolar disorder is associated with several clinically significant risks, among which the induction of mania or hypomania represents one of the most important concerns. This phenomenon, commonly referred to as a manic switch, occurs when a depressive episode transitions into a manic or hypomanic state following antidepressant exposure. The risk of such switching appears to vary according to the class of antidepressant, being more pronounced with tricyclic antidepressants compared to selective serotonin reuptake inhibitors, which are generally considered to have a lower risk profile [7, 35]. However, emerging evidence suggests that this risk may not be uniform across all clinical contexts. A nationwide study reported that, after adjustment for propensity scores, the association between antidepressant use and the onset of mania was not statistically significant, indicating that the magnitude of this risk may be overestimated in certain populations [36].

In addition to mood switching, antidepressant therapy has been implicated in the induction of rapid cycling, defined as the occurrence of four or more mood episodes within a one-year period. This pattern represents a particularly challenging clinical subtype of bipolar disorder, as it is associated with increased treatment complexity and poorer long-term outcomes. The prevalence of rapid cycling varies across patient populations, but it is more frequently observed in individuals with a prior history of antidepressant-induced mood destabilization, suggesting a potential vulnerability in certain subgroups [7, 38].

Another critical concern is the potential for antidepressants to precipitate or exacerbate mixed states, in which depressive and manic symptoms coexist simultaneously. These presentations are associated with increased morbidity and represent a significant therapeutic challenge, as they often respond poorly to conventional treatment approaches. More broadly, antidepressant use may contribute to overall mood destabilization, leading to an increased frequency and severity of mood episodes over time, thereby negatively impacting the longitudinal course of the disorder [7, 35].

Importantly, the risk of these adverse outcomes is not uniform and varies according to the specific antidepressant class. Tricyclic antidepressants are consistently associated with a higher likelihood of inducing manic episodes, whereas selective serotonin reuptake inhibitors exhibit a comparatively lower risk, although they are not entirely devoid of this potential complication [36]. Despite these concerns, antidepressants continue to be used in clinical practice, frequently in combination with mood stabilizers or atypical antipsychotics, with the aim of mitigating the risk of mood destabilization while preserving their antidepressant effects [29, 32].

The likelihood of adverse outcomes is further influenced by specific patient-related factors. A history of previous mood switching, a diagnosis of bipolar I disorder, and the absence of concurrent mood-stabilizing treatment are among the most significant predictors of antidepressant-induced complications [7, 35]. In this context, the use of mood stabilizers such as lithium has been shown to reduce the risk of recurrence and promote mood stability, reinforcing the importance of adjunctive therapeutic strategies in the safe management of bipolar depression. Collectively, these considerations highlight the need for careful patient selection, close monitoring, and individualized risk assessment when considering antidepressant therapy in bipolar disorder [38].

## Critical Appraisal of Clinical Evidence

The efficacy of antidepressants in bipolar depression remains a subject of ongoing debate, largely due to inconsistent findings across randomized controlled trials. Some studies have reported modest improvements in depressive symptoms with antidepressant use, whereas

others have failed to demonstrate a significant benefit over placebo, highlighting the variability in treatment response and the uncertainty surrounding their clinical utility. This inconsistency has contributed to a cautious approach in their use and has limited their role as primary therapeutic agents in bipolar depression [7, 39].

Meta-analytic evidence further reflects this ambiguity. While some analyses suggest that adjunctive antidepressant therapy may lead to slight improvements in response rates and reductions in depressive symptom severity, these effects are often statistically significant without translating into meaningful clinical benefits [30]. Importantly, concerns regarding the risk of mood switching appear to be less pronounced in the context of adjunctive use, as current evidence indicates that combining antidepressants with mood stabilizers does not significantly increase the risk of manic or hypomanic episodes [39].

When compared with non-antidepressant treatments, mood stabilizers and atypical antipsychotics demonstrate more consistent efficacy in the management of bipolar depression. Agents such as lamotrigine have shown effectiveness both as adjunctive therapy during acute depressive episodes and in the prevention of relapse, supporting their role in long-term management strategies [40]. Similarly, atypical antipsychotics, including quetiapine and lurasidone, have demonstrated superiority over placebo in reducing depressive symptoms, reinforcing their position as first-line treatments in many clinical guidelines [25]. In this context, combination therapies have also been explored, with evidence suggesting that the addition of antidepressants to mood stabilizers or antipsychotics may enhance treatment outcomes in selected cases. For instance, the combination of fluoxetine and olanzapine has been associated with improved response rates compared to monotherapy, indicating a potential role for carefully selected adjunctive strategies [41].

Despite these findings, the interpretation of the available evidence is complicated by significant methodological heterogeneity across studies. Variability in study design, including differences in patient populations, diagnostic criteria, types of antidepressants used, and outcome measures, limits the comparability of results and contributes to conflicting conclusions. In addition, many studies are subject to potential biases, such as publication bias and selective outcome reporting, which further affect the reliability and generalizability of the evidence. The lack of robust long-term safety data and the considerable interindividual variability in treatment response represent additional limitations that must be considered when evaluating the role of antidepressants in bipolar depression [7, 30].

These limitations highlight important gaps in the current evidence base and underscore the need for more individualized treatment approaches. The heterogeneity in clinical response suggests that patient-specific factors, including clinical phenotype, illness course, and prior treatment history, should be carefully considered when making therapeutic decisions. There is a clear need for well-designed, long-term studies to better define the efficacy and safety profile of antidepressants in bipolar depression. Future research should focus on identifying reliable predictors of treatment response and clarifying the long-term implications of antidepressant use, with the aim of informing more precise and evidence-based clinical guidelines [7, 30].

## Clinical Decision-Making and Personalized Treatment Algorithms

The management of bipolar depression requires a structured approach based on patient stratification and individualized risk profiling, given the marked heterogeneity of the disorder. One of the most clinically relevant tools in this context is the concept of predominant polarity, which identifies whether a patient experiences a greater number of depressive or manic episodes over time. This distinction is associated with

specific clinical profiles and has important implications for prognosis and treatment planning, allowing clinicians to tailor therapeutic strategies according to the longitudinal course of the illness [2]. In parallel, the recognition of bipolar subtypes, such as bipolar I and bipolar II disorder, further refines clinical decision-making, as each subtype presents distinct patterns of symptomatology and treatment response. The presence of comorbid conditions, as well as clinical features such as rapid cycling and mixed states, adds an additional layer of complexity, reinforcing the need for personalized and context-specific management strategies [1, 42].

Within this individualized framework, the use of antidepressants remains a contentious issue due to their potential to induce adverse outcomes, including manic switching and rapid cycling. For this reason, their use should be approached with caution and is generally recommended only in combination with mood stabilizers or atypical antipsychotics, with the aim of reducing the risk of mood destabilization [7]. Mood stabilizers, particularly lithium and valproic acid, continue to represent the cornerstone of both acute and long-term management of bipolar disorder. During acute phases, these agents are often combined with atypical antipsychotics to enhance therapeutic efficacy, whereas monotherapy is typically preferred during maintenance phases when clinically feasible, to minimize adverse effects while preserving stability [1].

An essential component of safe and effective management is the implementation of regular and systematic monitoring strategies. Early detection of emerging manic or hypomanic symptoms is particularly important in patients receiving antidepressants, as timely intervention can prevent progression to full mood episodes and reduce the risk of clinical deterioration [7]. In addition, treatment duration and discontinuation strategies must be carefully considered, with a focus on relapse prevention and the management of residual or subthreshold symptoms. Current recommendations suggest initiating treatment with monotherapy when appropriate and subsequently adjusting therapeutic regimens based on clinical response, tolerability, and the emergence of side effects [43].

Ultimately, therapeutic decision-making in bipolar depression requires a comprehensive and individualized risk-benefit analysis. Treatment plans should be tailored to the specific characteristics of each patient, including clinical history, risk factors, prior treatment response, and personal preferences, and should involve a collaborative approach between clinicians, patients, and their families to optimize outcomes [42]. In this context, the selection of pharmacological agents must carefully balance efficacy with safety considerations. For example, while lithium is highly effective in reducing the risk of recurrence, its use must be weighed against its potential side effect profile, underscoring the importance of individualized and evidence-based treatment strategies [44].

## Adjunctive Therapies and Future Perspectives

The management of bipolar depression extends beyond pharmacological strategies and incorporates a range of adjunctive psychotherapeutic interventions that play a critical role in improving clinical outcomes. Cognitive-behavioral therapy and interpersonal and social rhythm therapy are among the most widely studied approaches. Cognitive-behavioral therapy has demonstrated efficacy in stabilizing depressive symptoms and reducing their severity through mechanisms such as cognitive restructuring [45]. In parallel, interpersonal and social rhythm therapy is specifically designed to regulate social and biological rhythms, making it particularly effective both in the acute treatment of depressive episodes and in the prevention of future mood instability. The timing and context of psychotherapeutic interventions are also relevant, as family therapy and systematic care models have shown greater effectiveness in preventing recurrences when implemented after

acute episodes, whereas cognitive-behavioral therapy and group psychoeducation appear to be more beneficial during recovery phases [46, 47].

In addition to psychotherapy, biological therapies represent an important component of the therapeutic armamentarium. Electroconvulsive therapy remains a well-established and effective option for the treatment of bipolar depression, particularly in severe or treatment-resistant cases and in elderly populations. It has demonstrated robust clinical responses and, in some contexts, has shown superior outcomes compared to newer interventions such as ketamine. Transcranial magnetic stimulation also represents a potential therapeutic alternative; however, current evidence regarding its efficacy in bipolar depression remains limited, warranting further investigation [48].

Lifestyle interventions and the regulation of circadian rhythms are equally important in the comprehensive management of bipolar disorder. Chronotherapeutic approaches, including light therapy and sleep deprivation, have demonstrated effectiveness in alleviating depressive symptoms. Light therapy, in particular, can be utilized either as a standalone intervention or in combination with pharmacological treatments to enhance therapeutic response. More broadly, lifestyle modifications that promote regular sleep patterns and healthy behavioral routines are essential for maintaining mood stability and reducing the risk of recurrence, reinforcing the importance of non-pharmacological strategies in long-term disease management [46].

Emerging therapies are expanding the range of available treatment options, particularly for patients with treatment-resistant depression. Ketamine, a glutamate receptor modulator, has shown rapid antidepressant effects in bipolar depression and is often used as an adjunct to mood stabilizers. However, its long-term efficacy and safety remain uncertain, limiting its current role in sustained management. Other glutamatergic agents, such as memantine and riluzole, have also been investigated, although the evidence supporting their clinical effectiveness remains limited [49, 50].

In this evolving landscape, precision psychiatry has emerged as a promising approach aimed at tailoring treatment strategies to individual patient characteristics. The concept of predominant polarity provides a clinically useful framework for guiding personalized treatment decisions and improving outcomes. Additionally, the development of biomarkers and tools such as the Polarity Index may further enhance the ability to individualize treatment; however, these approaches require further validation before widespread clinical implementation [2].

Despite these advances, significant gaps remain in the current evidence base. There is a clear need for further research focused on specific clinical subgroups to better understand the heterogeneity of bipolar disorder and refine treatment strategies. This includes efforts to standardize the definition of predominant polarity and to validate neurobiological markers that may inform clinical decision-making [2]. Investigating the potential synergistic effects of combining multiple therapeutic modalities and evaluating long-term outcomes will be essential for advancing the management of bipolar depression and improving patient prognosis [51].

## Conclusions

The management of bipolar depression requires a highly individualized diagnostic and therapeutic approach, given the marked clinical, biological, and longitudinal heterogeneity of the disorder. Accurate identification of the clinical phenotype, including bipolar subtype, predominant polarity, and the presence of mixed features, is essential to guide treatment decisions and improve prognosis.

Mood stabilizers and atypical antipsychotics remain the cornerstone of first-line treatment for bipolar depression due to their more consistent efficacy and safety profiles compared to

antidepressants. Although antidepressants may provide benefit in selected cases, their use remains controversial because of the risk of manic switching, rapid cycling, and overall mood destabilization, and they should generally be used cautiously as adjunctive therapy.

Current evidence regarding the use of antidepressants in bipolar depression remains limited and methodologically heterogeneous, preventing definitive conclusions. Future progress in clinical management depends on the development of more personalized strategies that integrate clinical phenotyping, biomarkers, adjunctive therapies, and emerging treatments targeting the diverse neurobiological mechanisms underlying the disorder.

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