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Defining Treatment-Resistant Bipolar Depression: Recommendations From the ISBD Task Force

Eduard Vieta[1,2,3,4] | Roger S. McIntyre[5] | Trisha Suppes[6] | Tamsyn E. Van Rheenen[7,8] | Balwinder Singh[9] | Kamilla Woznica Miskowiak[10] | Allan H. Young[11] | Lakshmi N. Yatham[12] | Kyooseob Ha[12] | Michael Berk[13] | Holly A. Swartz[14] | Chantal Henry[15,16] | Maja Pantovic Stefanovic[17,18] | Gerard Anmella Diaz[1,2,3,4] | Aysegul Ozerdem[9] | Wiesław J. Cubała[19] | Diego Hidalgo-Mazzei[1,2,3,4] | Mauricio Tohen[20] | Isabella Pacchiarotti[1,2,3,4] | Paula Villela Nunes[21,22] | Carlos Lopez-Jaramillo[23] | Ana Gonzalez-Pinto[24] | Paolo Brambilla[25,26] | Robert Post[27] | Jair C. Soares[28] | Michael Bauer[29] | Ana C. Andreazza[30] | Xavier Justes Fradera[31] | Montserrat Cosials-Lopez[31] | Giovanna Fico[1,2,3,4]

Correspondence: Eduard Vieta (evieta@clinic.cat)

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ABSTRACT

Objective: Despite the availability of approved treatments, a substantial proportion of patients with bipolar disorder experience treatment-resistant bipolar depression (TRBD), characterized by persistent depressive symptoms unresponsive to standard therapies. However, a universally accepted definition of TRBD is lacking. This consensus document, developed by the International Society for Bipolar Disorders (ISBD) Task Force on TRBD, aims to provide a standardized definition of TRBD to facilitate clinical trials, research, and treatment strategies.

Methods: The Task Force employed a literature review, clinical trials analysis, and expert consensus meetings to define TRBD.

Results: TRBD was defined as the failure to achieve a significant and sustained clinical response after at least two approved and adequately dosed pharmacological treatments, administered for a sufficient duration with treatment adherence. For bipolar I (BD-I) depression, approved treatments included quetiapine (300–600 mg/day for ≥ 8 weeks), lurasidone (20–120 mg/day for ≥ 6 weeks), the combination of olanzapine (6–12 mg/day) and fluoxetine (25–75 mg/day for ≥ 8 weeks), cariprazine (1.5–3 mg/day for ≥ 6 weeks), and lumateperone (42 mg/day for ≥ 6 weeks). For bipolar II (BD-II) depression, approved treatments included quetiapine (300–600 mg/day for ≥ 8 weeks) and lumateperone (42 mg/day for ≥ 6 weeks).

Conclusion: This consensus definition aims to provide clarity for clinical trials, improve consistency in research, and guide treatment approaches and inform regulatory pathways. It represents a foundational step in addressing the unmet needs in TRBD and promoting the development of innovative therapeutic strategies. Future efforts will focus on adapting the definition to better align with real-world clinical challenges and optimize patient care.

Fradera Xavier Justes and Montserrat Cosials-Lopez are experts by experience.

For affiliations refer to page 419.

1 | Introduction

Depression is the major challenge in the management of bipolar disorder (BD) [1]. Unlike unipolar depression, bipolar depression alternates with periods of mania or hypomania, which adds complexity to its management [2]. BD affects approximately 1%–2% of the global population, with bipolar depression accounting for the major proportion of the disease burden [3]. Depressive episodes not only diminish quality of life and functioning but also significantly increase all-cause mortality risk, including suicide [4].

The significant and disproportionate burden of depressive symptoms in BD can be attributed to several factors, including the challenge of achieving a prompt therapeutic response during acute depressive episodes [5]. Misdiagnosis of bipolar depression is also common, often due to overlapping symptoms with other disorders, diverse phenotypic presentation [6] and the delayed recognition of manic or hypomanic episodes [7]. These factors lead to prolonged untreated [8] or improperly treated illness [9] and increase the risk of treatment-emergent affective switching, particularly in the absence of a mood stabilizer, thereby worsening disease progression and impairing treatment response [10].

Five medications have been approved for the treatment of bipolar depression. In the United States, the Food and Drug Administration (FDA) approved quetiapine, lurasidone, and the combination of olanzapine and fluoxetine; more recently, it approved cariprazine and lumateperone. Similarly, the European Medicines Agency (EMA) has approved quetiapine for this indication. The Japanese medication regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA) also approved olanzapine monotherapy [11]. While all approved medications are available for treating BD type I (BD-I) depression, only quetiapine and lumateperone are specifically approved for BD type II (BD-II) depression. However, in clinical practice and guidelines, there is widespread use of off-label treatments for bipolar depression, including antidepressants [12, 13], mood stabilizers such as lithium and lamotrigine, and other atypical antipsychotics [14–16].

Although there are approved and guideline-recommended medications for bipolar depression, a significant unmet need remains in effectively addressing its treatment. Achieving improvement often necessitates the use of multiple drug classes in combination; yet this approach does not always guarantee clinically meaningful improvement in depressive symptoms.

Indeed, approximately 25% of patients experience treatment-resistant bipolar depression (TRBD), defined by severe, persistent depressive symptoms unresponsive to standard treatments [17]. TRBD is characterized by significant heterogeneity, influenced by factors such as genetic predisposition, bipolar subtype distinctions [18, 19], rapid cycling course, cognitive impairments, and increased suicide risk [20]. Comorbid psychiatric and physical conditions, including anxiety, substance use disorders, metabolic syndrome, and cardiovascular disease [21], further compound this complexity, resulting in diverse depressive phenotypes and challenges in achieving uniform therapeutic responses. Some authors have argued that clinical formulation is a pragmatic way to individualize treatment in such circumstances [22].

Similar to treatment-resistant Major Depressive Disorder (MDD), no universal and validated definition of TRBD exists [23]. This absence complicates prevalence estimates and hinders the development of precise treatment strategies.

A consensus definition of TRBD is essential for several reasons. It would provide a basis for reliable diagnosis, enable interpretable research results, and ensure uniformity in clinical trials and regulatory submissions. Such standardization could also improve estimates for research and development (R&D), facilitate clinical decision-making, and inform reimbursement policies. Furthermore, defining TRBD with clinical and predictive validity could support the development of innovative therapeutic interventions tailored to individual patient profiles.

Recognizing these challenges, the International Society for Bipolar Disorders (ISBD) Task Force on TRBD was established. The Task Force aims to refine the definition of TRBD, identify mechanisms underlying treatment resistance, develop evidence-based guidelines for clinicians, researchers, regulators, and the industry, and promote research into novel therapeutic approaches. This report focuses on establishing a clear definition of TRBD and providing initial evidence-based management recommendations. While the Task Force's mandate includes broader aims (e.g., identifying biological mechanisms and promoting novel therapies), the present manuscript addresses the definition and clinical consensus recommendations as a foundational first step. This consensus document represents a foundational step in achieving these objectives and aims to provide a clear and actionable definition of TRBD for clinical trials while recognizing the ongoing need to address the intricate realities of TRBD in everyday clinical settings.

2 | Materials and Methods

Following the ISBD procedures, a Task Force was built based on expertise on the topic and keeping in mind cultural diversity and gender balance. Experts by experience was also invited to participate. The Task Force comprised 25 international experts in bipolar disorder (23 clinical researchers and 2 experts by experience), representing different countries across 5 continents (North America, South America, Europe, Asia, and Australia). Members included academicians with expertise in bipolar disorder clinical trials, pharmacology, psychotherapy, and guideline development. We conducted a comprehensive search on PubMed that included review articles, clinical investigations, and meta-analytic studies published in any language up to August 19th, 2024. The search utilized a combination of keywords including "treatment-resistant bipolar depression," "bipolar disorder," "treatment resistance," "bipolar depression," "refractory bipolar depression," "inadequate response," "treatment failure," "non-response," "clinical trials," "pharmacotherapy," "bipolar treatment guidelines," and "novel therapies." Additionally, ClinicalTrials.gov was searched to obtain the most recent information on ongoing and completed clinical trials related to TRBD. Approximately

60 relevant publications (including meta-analyses, clinical trials, and guidelines) were identified. The Task Force reviewed evidence from clinical trials, prior definitions, FDA- and EMA-approved agents, and recent guidelines [14, 15, 24] which were summarized and discussed during the meetings. The review was followed by expert meetings where the findings were discussed, and consensus was achieved on definitions and recommendations.

3 | Current Definitions of Treatment-Resistant Bipolar Depression

Over the years, definitions of TRBD have been proposed, each one with its strengths and limitations [25]. Determining the epidemiology of TRBD is challenging due to inconsistencies and differences in definitions. However, it is estimated that recovery rates from acute depressive episodes of BD are lower than 60%, with recurrence rates exceeding 50% [26]. Sachs [27] defined TRBD as a depressive episode without remission despite two adequate trials of standard antidepressant agents for at least 6 weeks each, with or without augmentation strategies. This approach, while clear, is too narrow as it focuses solely on antidepressants, ignoring the broader treatment landscape required for bipolar depression. Yatham et al. [28] specified treatment refractoriness in bipolar depression as a non-response to a 6-week trial with lithium at serum levels of ≥ 0.8 mmol/L, a definition limited by the exclusion of other mood stabilizers or combination treatments.

Nierenberg et al. [26], through the STEP-BD study, defined TRBD as individuals with BD with a current DSM-IV major depressive episode of at least 8 weeks, and non-response to treatment within the first 12 weeks, or documented failure to respond to at least two trials of antidepressants or an antidepressant and mood stabilizer. Gitlin [29] applied criteria used for treatment-resistant unipolar depression but added the failure to respond to mood stabilizers, which is a step toward specificity but still potentially insufficient for the complexities of bipolar depression. Gajwani [30] introduced a detailed staging system of response to treatment: Stage I involved a failed monotherapy trial of lithium, anticonvulsants, or atypical antipsychotics; Stage II added a failed trial of a combination of these medications; Stage III included failure after several adjunctive pharmacological compounds; Stage IV encompassed failure after neurostimulation treatments like electroconvulsive therapy (ECT) or vagus nerve stimulation (VNS). Although thorough, this staging system can be cumbersome in clinical practice. Pacchiarotti et al. [31] defined TRBD as a depressive episode within BD that fails to reach remission with adequately dosed lithium (0.8 mEq/L in plasma) or another ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or quetiapine monotherapy (≥ 600 mg/day). While this definition has the strength of specifying precise drug dosages, it is potentially restrictive by focusing on specific medication combinations and excluding newer approved treatments, limiting its applicability in contemporary clinical practice.

Lipsman et al. [32] specified nonresponse to adequate monotherapy trials with lithium or lamotrigine and their combination with at least one anticonvulsant or antipsychotic, adding an antidepressant if necessary and excluding neuromodulation failure. This criteria set is again limited to specific drugs, excluding other effective treatments, and may not apply to both BDI and BDII. The definition by Malhi et al. [33] required failure to reach remission despite two or three adequate trials of first-line medications like mood stabilizers. Hidalgo-Mazzei et al. [34] defined TRBD as the failure to achieve sustained symptomatic remission for 8 consecutive weeks following two different treatment trials at adequate therapeutic doses. These trials must include at least two recommended monotherapy treatments (quetiapine, lurasidone, lamotrigine, or olanzapine/fluoxetine combination) or one monotherapy treatment combined with another treatment (lamotrigine, valproate, or lithium). Additionally, they introduced the concept of multi-therapy-resistant bipolar depression (MTRBD), which includes the same initial criteria as TRBD but adds the failure of at least one trial with an antidepressant, a psychological treatment, and a course of ECT. This approach, although detailed, might not include all potential therapeutic options, nor reflect availability such as with ECT. Fountoulakis et al. [24] defined TRBD as no significant reduction in Hamilton Depression Rating Scale (HDRS) [35] or Montgomery–Åsberg Depression Rating Scale (MADRS) [36] scores, recommending a treatment duration of 10–12 weeks. This definition's reliance on specific scoring systems and rigid timeframes could be too restrictive and unfriendly to clinicians. These varied definitions, each with distinct criteria and challenges, highlight the need for a new and improved definition of TRBD that may include a broader range of treatments, setting standardized criteria, recognizing the unique complexities of BD, and simplifying the diagnostic process for clinical and research use.

4 | Biological and Environmental Factors Associated With Treatment-Resistant Bipolar Depression

The biological bases of TRBD are rather under-explored, especially in comparison to treatment-resistant MDD [37]. In treatment-resistant MDD, there is substantial evidence pointing to a significant genetic component, with heritability estimates from common genetic variation ranging from 17% to 25% compared to healthy controls and around 8% when compared to non-treatment-resistant MDD [38]. Although no specific genetic risk loci have been consistently replicated in genome-wide association studies (GWAS), pharmacogenetic studies have provided valuable insights. For instance, common genetic variation can explain up to 42% of the variance in antidepressant response [39]. In TRBD, genetic research has been less extensive. Specific pharmacogenetic variables, such as the ABCB1 gene, have been linked to the response and tolerability of serotonin-norepinephrine reuptake inhibitors (SNRIs) [40], while CYP3A4 variants predict the metabolism of quetiapine [41]. Individuals with BD with a long history of multiple drug failures or treatment resistance presented significantly higher rates of CYP2C19 poor metabolizer phenotype compared to those with MDD with a similarly defined history of treatment resistance. Having an S-allele of the serotonin transporter gene increased the difference between the groups significantly [42].

The genetic response to lithium—a cornerstone mood stabilizer in BD—has also been explored. The ConLiGen cohort study of over 2000 individuals with BD found that genetic factors influencing lithium response might differ based on whether the individual is in a manic or depressive episode [43]. Furthermore, genetic ancestry has been shown to play a significant role in predicting lithium response. Models incorporating genetic ancestry outperform those relying solely on demographic or clinical characteristics, offering a more precise framework for understanding individual responses to lithium [44]. Emerging genetic evidence also supports the role of biological vulnerability in treatment resistance. For instance, the Pharmacogenomics of Bipolar Disorder (PGBD) study identified genomic variants associated with poor lithium response, particularly within loci involved in neuronal excitability, inflammation, and synaptic function [45]. However, these insights have yet to be applied specifically to TRBD populations.

In addition to genetic factors, neurobiological studies on cognitive function and brain structure have provided critical insights into TRBD. Cognitive impairments in areas such as memory, executive functioning, and attention are commonly observed in patients with TRBD. These deficits are often persistent and associated with poor treatment response. Neuroimaging studies suggest alterations in brain regions involved in mood regulation and cognition, including the prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala [46]. For example, reduced activity in the prefrontal cortex and abnormal connectivity between the prefrontal and limbic regions have been linked to poorer treatment outcomes in BD [47]. Additionally, structural abnormalities, such as reduced hippocampal volume, have been observed in individuals with treatment-resistant mood disorders, potentially contributing to the chronicity of depressive symptoms [48].

Environmental and psychosocial factors also play a crucial role in TRBD. Comorbidity is a major determinant of treatment response and possibly influences TRBD. Indeed, psychiatric comorbidities, including personality disorders, anxiety disorders, and substance use disorders, further complicate the clinical picture, often leading to non-response to standard treatments [23]. A history of trauma is a risk factor for treatment resistance in depression as well as BD [49]. Sociodemographic factors such as female gender, older age at illness onset, higher familial depression rates, unemployment, and exposure to lifetime stressors are additional predictors of treatment resistance [50]. The combination of biological and environmental factors underscores the heterogeneity of TRBD. This complexity suggests that a one-size-fits-all approach to treatment is inadequate; further research is needed to elucidate the interplay between these factors.

5 | Toward a New Definition of Treatment-Resistant Bipolar Depression

To define TRBD in a way that can guide the design of new clinical trials, it is essential to establish clear criteria that ensure consistency across studies. Given the challenges highlighted in recent research, a standardized definition will aid in comparing results and improving treatment strategies. TRBD should be defined as the failure to achieve a significant and sustained clinical response after a minimum of two consecutive pharmacological acute-phase treatments approved by international regulatory agencies with recognized authority over the approval of prescription medication (i.e., FDA, EMA) for bipolar depression. These agencies were selected for ther well-established processes for evaluating efficacy and safety. These treatments must be administered at therapeutic doses for an adequate duration according to current clinical guidelines, ensuring treatment adherence. The addition of newly approved medications at the recommended dosage for the recommended duration and adherence in the definition should also be considered in the future. In this context, a "significant and sustained clinical response" refers to a clinically meaningful improvement in depressive symptoms, operationalized as at least a 50% reduction from baseline on a validated depression rating scale—such as the Montgomery–Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAM-D)—maintained for a minimum of 2 to 4 weeks. This definition is consistent with standard response thresholds used in clinical trials [51].

For BD-I depression, currently approved pharmacological treatments should include quetiapine at 300–600 mg per day for at least 8 weeks, lurasidone at 20–120 mg per day for at least 6 weeks, olanzapine at 6–12 mg per day in combination with fluoxetine at 25–75 mg per day for at least 8 weeks, cariprazine at 1.5–3 mg per day for at least 6 weeks, and lumateperone at 42 mg per day for at least 6 weeks. Failure to respond to at least two of these treatments, administered as specified during the current depressive episode, will define TRBD for BD-I. The Task Force agreed to exclude olanzapine monotherapy, despite being approved for bipolar I depression in some countries (e.g., Japan), as one of the medications involved in the definition.

For BD-II depression, the range of approved treatments is narrower. Specifically: quetiapine at 300–600 mg per day for at least 8 weeks, lumateperone at 42 mg per day for at least 6 weeks. A diagnosis of TRBD in BD-II will require a failure to achieve a significant and sustained clinical response after at least two consecutive trials of these approved medications, administered at therapeutic doses for the specified durations.

This standardization will help identify patients who require alternative or novel therapeutic approaches; thus, guiding the design of more effective clinical trials for TRBD (Figures 1 and 2).

While our definition of TRBD is structurally modeled on the framework used in treatment-resistant MDD—namely, the requirement of non-response to at least two adequate treatment trials—the types of treatments considered differ substantially due to the distinct pathophysiology and treatment paradigms of the two disorders. In treatment-resistant MDD, resistance is typically defined by failure to respond to at least two antidepressants. However, in bipolar depression, the use of antidepressants is more controversial and not uniformly recommended, particularly as monotherapy. As such, our definition of TRBD focuses on non-response to at least two approved treatments with demonstrated efficacy in acute bipolar depression, which primarily include atypical antipsychotics. This approach reflects the current evidence base and international treatment guidelines specific to bipolar disorder and ensures that our

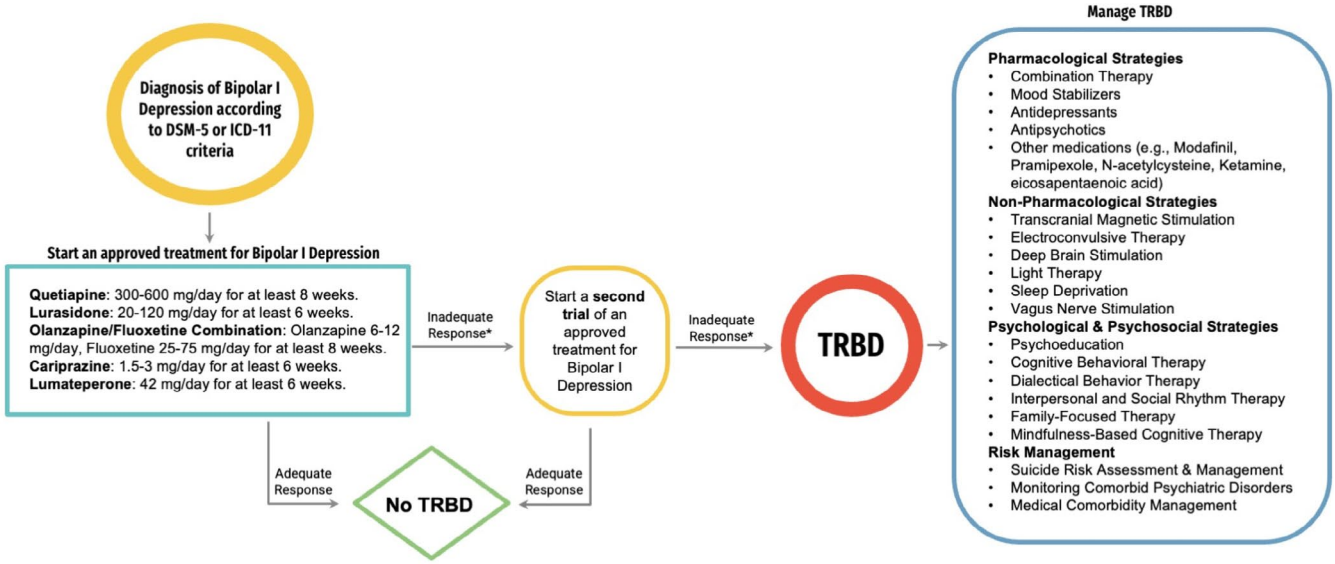

FIGURE 1 | Algorithm for diagnosis and management of TRBD—BDI.

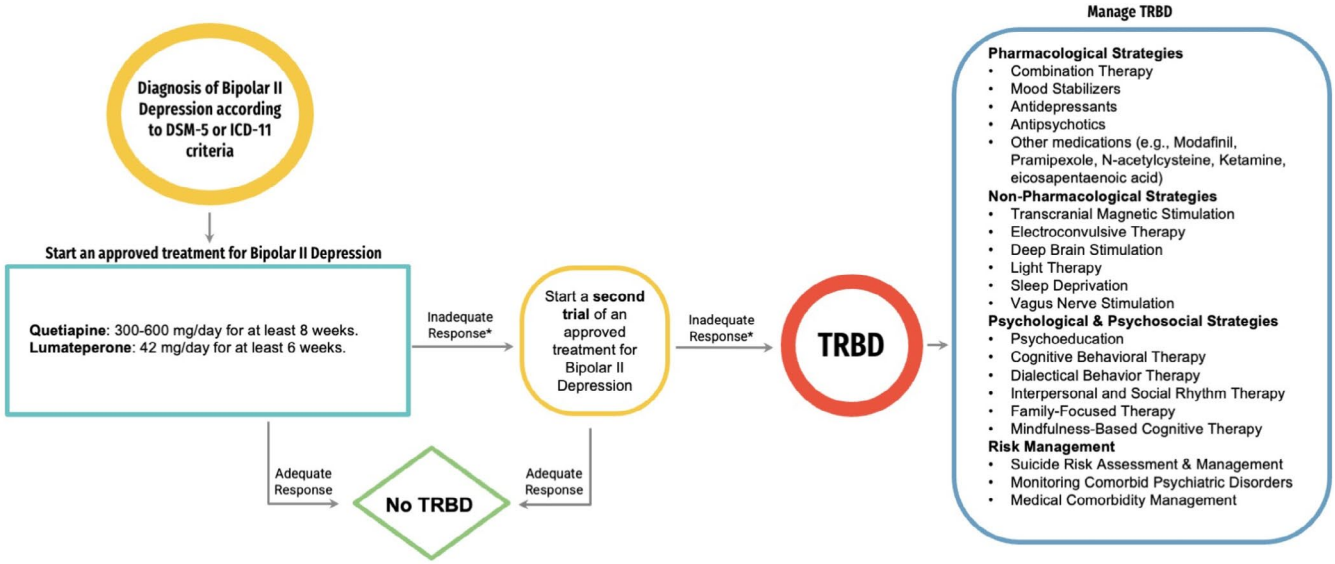

FIGURE 2 | Algorithm for diagnosis and management of TRBD—BDII.

operational criteria are both clinically relevant and consistent with regulatory standards.

6 | Management Options for TRBD

Management of TRBD requires a comprehensive, evidence-based approach tailored to its unique complexities. Before initiating TRBD-specific interventions, it is crucial to confirm the diagnosis using an operationalized definition, rule out contributing organic or medical comorbidities, and address co-occurring psychiatric conditions such as anxiety or substance use disorders. Given the heightened risk of suicide in TRBD, clinicians must consider the most appropriate treatment setting and implement effective risk reduction strategies.

Pharmacological options for TRBD often involve combining mood stabilizers like lithium with lamotrigine, which has demonstrated efficacy in recent studies [52]. Recent evidence shows that lithium has a critical role in reducing depression-related hospitalizations, while antidepressant monotherapy not only fails to reduce the risk of depression-related hospitalizations but is associated with a higher risk of mania-related hospitalizations, offering important insights for managing TRBD [53]. Other potential agents include modafinil, pramipexole, and tranylcypromine, which have shown benefits in smaller trials

[54, 55]. The International College of Neuropsychopharmacology (CINP) guidelines recommend a treatment algorithm encompassing agents such as lithium plus lamotrigine, modafinil, or pramipexole, while evidence is inconclusive for other treatments [24]. Adjunctive therapies, including *N*-acetylcysteine, omega-3 fatty acids, and supraphysiologic doses of levothyroxine, have shown promise in refractory or rapid cycling cases. Functional imaging studies suggest levothyroxine improves depressive symptoms by modulating anterior limbic network activity [56].

Non-pharmacological treatments like electroconvulsive therapy (ECT) remain a cornerstone for TRBD management, with superior response rates compared to algorithm-based pharmacotherapy [57]. Repetitive transcranial magnetic stimulation (rTMS), including accelerated protocols, has demonstrated efficacy and tolerability [58].

Psychological and behavioral interventions are essential components of TRBD management, especially for their impact on functional outcomes and relapse prevention. Psychoeducation has consistently demonstrated effectiveness in enhancing medication adherence, reducing relapse rates, and improving quality of life in BD, although direct evidence for TRBD is limited [59, 60]. Cognitive-behavioral therapy (CBT) and interpersonal and social rhythm therapy (IPSRT) are effective in managing depressive episodes and stabilizing mood in BD and should be adapted for TRBD contexts. Additionally, lifestyle modifications—focusing on exercise, structured sleep hygiene, and stress management—are important adjuncts to pharmacological therapy.

Emerging strategies like deep brain stimulation (DBS) hold the potential for complex, resistant forms of BD [61]. Other adjunctive approaches, including light therapy and sleep deprivation protocols, have shown some utility in managing depressive episodes; though specific evidence for TRBD remains sparse [62]. These non-pharmacological interventions highlight the importance of a multimodal approach, combining pharmacological and behavioral strategies to address the multifaceted challenges of TRBD.

7 | Innovations in the Pharmacological Management of Treatment-Resistant Bipolar Depression

Effective management of TRBD requires innovative approaches to overcome the limitations of conventional therapies. Recent research has explored the potential of novel agents such as psilocybin, ketamine derivatives, and other compounds to address TRBD, each with distinct mechanisms of action and varying levels of evidence.

Psilocybin, a naturally occurring psychedelic, has been evaluated in a 12-week open-label trial for its efficacy in treating depressive episodes in individuals with BD-II and treatment-resistant depression. In this trial, 19 participants received a single 25 mg dose of synthetic psilocybin combined with psychotherapy. Results showed significant reductions in depression severity (measured by MADRS scores) 3 weeks post-treatment, with sustained benefits observed at 12 weeks. Twelve participants met both response and remission criteria by the study's conclusion [63]. Additional open-label trials, including one with 31 participants, demonstrated similar positive effects on depression symptoms with psilocybin [64].

Ketamine and its derivative esketamine have also garnered attention for their rapid-acting antidepressant properties [65]. Ketamine, in particular, has shown promise as a treatment for TRBD in several studies. A randomized controlled trial (RCT) involving 41 participants compared ketamine to midazolam, an active placebo. Ketamine was associated with significant reductions in depressive symptoms, with cumulative benefits observed after multiple infusions [66]. In patients with TRBD, ketamine infusion has been found to offer rapid relief from depressive symptoms and anhedonia, with a study showing a 51% response rate after a single infusion [67]. However, the effects of multiple ketamine infusions appear transient, with symptom relief diminishing over time [68]. Esketamine, the S-enantiomer of ketamine, has been studied for its efficacy in TRBD [69], with real-world studies indicating significant reductions in depressive symptoms without increasing the risk of manic switches [70].

The aforementioned preliminary results are supported by real-world evidence data on its effectiveness [71]. Notably, ketamine and its s-enantiomer esketamine have shown rapid anti-suicidal effects in mood disorder patients, sometimes independently of their overall antidepressant effect [72, 73]. This anti-suicidal property is particularly relevant in TRBD, given the high suicide risk in this population. The limited evidence may also be indicative of an antisuicidal or antianhedonic effect of ketamine in bipolar depression, especially in patients presenting with unstable phenotypes of TRBD, such as those presenting with mixed episodes [74].

Other pharmacological approaches for TRBD include nitrous oxide, which has demonstrated rapid symptom reduction compared to midazolam but lacked lasting effects [75], and metformin, an insulin sensitizer, which showed improvements in depression scores and functioning in patients without insulin resistance [76]. Celecoxib, an anti-inflammatory drug, has also been explored as an adjunct to antidepressants, showing promise in reducing depressive symptoms and anxiety [77, 78]. In contrast, pentoxifylline failed to outperform a placebo in recent trials on TRBD [79], while cannabidiol demonstrated efficacy in a post hoc analysis and is currently being tested in a larger RCT [80].

Currently, ongoing clinical trials are exploring various treatments for individuals with BD, yet they define treatment resistance using different criteria, reflecting a lack of consensus. For instance, a trial (NCT06431386) is investigating the combination of esketamine with behavioral activation therapy in patients who have not responded to at least two antidepressant treatments. Another study (NCT05625555) is examining predictors of response to low-dose intravenous ketamine in treatment-resistant depression, with a focus on individuals who have failed at least two first-line treatments, such as mood stabilizers [14]. Long-term effects of ketamine are also being studied in TRBD, with a 12-week trial (NCT05339074) investigating the impact

of repeated sub-anesthetic doses on maintaining antidepressant effects. Similarly, psilocybin is being evaluated in a trial (NCT05029466) for individuals with MDD or BD-II who have not responded to at least two guideline-concordant pharmacological treatments.

Other ongoing studies focus on the safety and efficacy of newer agents, such as brexpiprazole, which is being tested for its ability to improve depressive symptoms and cognitive function in patients with BD (NCT04569448). Additionally, nutraceutical treatments, like mangosteen extracts [81] (ACTRN12616000028404), and mitochondrial-targeting therapies, such as trimetazidine [82, 83] (ACTRN12622000474752), are under investigation. Moreover, the angiotensin agent candesartan, supported by positive epidemiological findings, is being explored for its potential in TRBD treatment (ACTRN12620001095954). However, the varying definitions of TRBD across these trials highlight the ongoing challenge of establishing a standardized approach to defining treatment resistance, complicating comparisons between studies and the development of universally applicable treatment strategies. This challenge directly applies to efforts to develop treatment guidelines for BD-I and BD-II.

8 | TRBD Versus Insufficient Response in BD

TRBD is not the same as an insufficient response, also known as "partial response" or "inadequate response," and either concept implies a slightly different clinical challenge, a different indication, and, thus, a different clinical trial design. Insufficient response represents a situation where a patient does experience some improvement with treatment but does not achieve response or remission. This may involve symptomatic improvement that does not meet the $\geq 50\%$ response threshold or failure to achieve remission (e.g., MADRS score > 10 or HAM-D score > 7) despite adequate dose, duration, and adherence. This construct aligns with the literature on unipolar depression, where partial or inadequate response often indicates the need for augmentation rather than a shift in diagnosis [51]. This term is more general and can apply after the first or subsequent treatments. In MDD, FDA-approved agents for "insufficient response" are adjunctive lithium, T3, quetiapine, aripiprazole, brexpiprazole, cariprazine.

The EMA has only approved lithium, T3, and quetiapine, mostly because the trials with most antipsychotics did not follow their guidelines, failing to include a comparator and longer follow-up. The clinical trial design implications for this distinction in the context of BD are extremely relevant: for adjunctive treatment, studies should include patients with partial responses to other therapies; the investigational drug should be compared to placebo when added to the baseline treatment. Hence, most trials include patients with a history of at least one retrospective failure plus prospectively tested lack of response to another. Patients who have not responded to more than one prior approved treatment, administered at an adequate dose and duration, should be enrolled in TRBD studies. According to the FDA, patients should be randomized to either the new treatment or continue the compound to which they had failed to respond.

9 | Clinical Trial Design and Methodology for TRBD

To design an effective clinical trial for TRBD, a well-structured approach is crucial. First, trials must define TRBD with precise and consistent criteria. Specifically, treatment resistance should be characterized by the lack of significant improvement after at least two consecutive, approved pharmacological treatments for bipolar depression, administered at therapeutic doses for the recommended duration. We distinguish between "insufficient response"—defined as partial or inadequate response after a single adequate treatment—and treatment resistance. Patients with insufficient response may be appropriate for adjunctive or augmentation trials, consistent with FDA guidance that such designs often enroll participants after a single failed treatment. In contrast, patients meeting criteria for TRBD—defined by failure of two adequate trials of evidence-based bipolar depression treatments—are appropriate candidates for monotherapy trials or investigations of novel mechanisms. This differentiation ensures that our definition of TRBD is not simply a replication of treatment-resistant MDD but rather a tailored adaptation to the unique treatment context of BD.

This would standardize participant selection and improve comparability across studies. Starting with a novel treatment in a controlled manner can simplify initial evaluations, but incorporating adjunctive therapies for partial responders may offer a more personalized and potentially effective strategy. The trial should be randomized, double-blind, and placebo-controlled. For an indication of "inadequate response," prospective verification of that feature (e.g., less than 50% improvement in a depression severity scale versus baseline) and an adjunctive design would be preferred. Monotherapy designs are only appropriate for TRBD, not insufficient response.

However, to enable testing treatments with antidepressant properties but not necessarily antimanic effects, the proposed trial designs can be applied to patients who are already on long-term mood stabilizing therapy. This adds complexity to the studies but reflects the clinical reality that patients with BD are, most often, on polytherapy [84]. Women and men at childbearing age would not be included if on valproate, given the teratogenic risks [85, 86].

This approach allows for flexibility in managing varying degrees of resistance and may enhance overall treatment efficacy. Additionally, beyond just symptom reduction, integrating measures of functional outcomes and quality of life would provide a more comprehensive evaluation of treatment efficacy. Measures of functional outcomes, such as the Functional Assessment Short Test (FAST) [87], the Sheehan Disability Scale (SDS) [88], or the World Health Organization Disability Assessment Schedule (WHODAS-II) [89] are essential for capturing the real-world impact of depressive symptoms. At least one of these measures should be included alongside traditional scales like the HDRS or MADRS, which are sometimes suboptimal as they do not assess atypical symptoms such as hypersomnia and mixed states [90], to provide a comprehensive view of treatment effects. A clinician-friendly measure of severity such as the CGI-BP [91] is also advised. Considering emerging scales such as the Bipolar Depression Rating Scale (BDRS), which better

captures bipolar-specific phenotypes such as mixed states and atypical features that are common in the disorder [92, 93], and digital health tools for continuous monitoring can further refine outcomes.

Cognitive impairments, which persist in 50%–70% of patients and significantly impair socio-occupational function, quality of life, and prognosis, warrant particular focus. These impairments, linked to an increased risk of (hypo)manic relapse and psychiatric hospitalization, should be assessed even after symptomatic remission [94], as recommended by the ISBD Targeting Cognition Task Force [95]. Using a feasible cognitive screener, such as the Screen for Cognitive Impairment in Psychiatry (SCIP), is essential to capture this domain [96, 97].

A critical safety consideration is the standardized definition of "switch" to mania or hypomania, enhancing the comparability of studies and meta-analyses [98]. Patients experiencing a switch should not be classified as "responders," even if their depression severity scores improve. The primary outcome must be framed as improvement in one pole of the illness without exacerbation in the opposite pole, ensuring balanced efficacy and safety metrics.

A critical point is that lumateperone is not widely available in many regions, a limitation we acknowledge in the current definition; as discussed elsewhere, the Task Force aims to develop a more clinically relevant definition in the future of TRBD, which could include treatment failures with agents such as lithium or lamotrigine.

This approach acknowledges the multifaceted nature of TRBD, fostering meaningful progress in treatment strategies.

10 | Practical Clinical Considerations Arising From the TRBD Definition

Although the primary objective of this manuscript is to provide a consensus-based definition of TRBD, several clinical considerations emerge from the reviewed literature and expert discussions. These are not intended as formal clinical guidelines, but rather as potential implications that can support clinical decision-making in real-world settings (see Figures 1 and 2). A future publication from the ISBD Task Force will be dedicated to developing a more detailed consensus on the management of TRBD.

From a diagnostic standpoint, clinicians are advised to ensure diagnostic accuracy, ruling out bipolar spectrum misdiagnosis, psychiatric or medical comorbidities, and assessing adherence, dosage, and treatment duration before concluding treatment resistance. Psychosocial dimensions, including early trauma, psychosocial stressors, substance use, and lack of social support, should also be evaluated as part of a comprehensive assessment.

The operational definition of TRBD proposed here—nonresponse to at least two adequate trials of evidence-based treatments for bipolar depression—has implications for treatment sequencing. First-line pharmacological options (e.g., quetiapine, lurasidone, lithium) should be adequately trialed and optimized before moving to combination strategies. Additional pharmacological strategies may include adjunctive modafinil, pramipexole, or thyroid hormone. The use of antidepressants should be reserved for selected cases, particularly bipolar II depression, and always in combination with a mood stabilizer. The exclusion of mood stabilizers such as lithium, lamotrigine, and valproate from this trial-focused definition should not be interpreted as a negation of their clinical value but of the availability of relevant trial data. Rather, our aim is to provide an operational framework to support new discoveries and regulatory evaluation of novel treatments for acute bipolar depression. In parallel, the ISBD task force is currently working on a complementary manuscript that will propose a clinically oriented definition of TRBD, more in line with the concept of "difficult-to-treat bipolar depression," and grounded in real-world practice and aligned with international treatment guidelines. That forthcoming work will include more nuanced recommendations regarding treatment resistance, including the role of mood stabilizers, combination therapies, and maintenance strategies.

For individuals with severe symptomatology or acute suicidality, somatic treatments such as ECT should be considered. Although growing evidence supports the potential efficacy of rTMS in bipolar depression, including in treatment-resistant populations, it is important to note that rTMS remains off-label for this indication in many countries. Furthermore, access may be limited due to regulatory, geographic, or cost-related barriers. As such, while rTMS may represent a useful adjunctive option in select cases, its applicability varies widely and should be considered within the local clinical and regulatory context. Similarly, ketamine and esketamine, with emerging evidence for rapid antidepressant and anti-suicidal effects, may represent valid interventions in selected high-risk patients, although their accessibility remains limited.

Psychotherapeutic interventions, including cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and structured psychoeducation, play a key role in TRBD management. These should be accompanied by interventions targeting lifestyle factors—such as sleep hygiene, circadian rhythm regularity, physical activity, and substance use reduction—which may indirectly improve mood stability. Clinical formulation of the patient's profile can assist in choosing between the multitude of options.

Finally, clinical monitoring using validated instruments (e.g., MADRS, HAM-D) is essential for assessing treatment response over time. Suicide risk should be regularly evaluated; decisions about further treatment should be made in close collaboration with patients through shared decision-making.

An important ethical consideration is that clinicians and investigators must avoid the practice of intentionally cycling patients through treatment failures solely to meet research inclusion criteria for TRBD. The proposed definition is intended to support consistency in clinical trials and regulatory science—not to override individualized clinical decision-making. The use of this framework must always be guided by patient-centered care, shared decision-making, and the principle of therapeutic beneficence.

11 | Conclusion

Treatment Resistant Bipolar Depression remains a formidable challenge due to its complex nature and the variability in its definitions across studies. Despite the availability of various pharmacological and non-pharmacological treatments, a substantial subset of patients continues to experience persistent depressive episodes that are unresponsive to standard therapies. The proposed definition of TRBD, which emphasizes the failure to achieve a significant and sustained clinical response after two consecutive approved pharmacological treatments, aims to provide clarity and consistency across studies. This new definition is crucial for improving the comparability and conclusiveness of clinical trials and guiding the development of novel, more effective treatment strategies. By adopting this standardized approach, future research can better address the complexities of TRBD, leading to more robust and targeted clinical trials that can ultimately enhance patient outcomes. However, the ISBD TRBD Task Force also acknowledged that while a strict definition may aid in clinical trials, it may be too restrictive in clinical practice, where psychiatrists frequently rely on off-label treatments to manage TRBD. Also, lumateperone is not widely available in many parts of the world, and this can limit the correct application of the current definition of TRBD, especially for BD-II. It should be emphasized that, although the proposed definition of TRBD aligns with clinical and regulatory considerations, there is a paucity of empirical evidence demonstrating that failure of two sequential trials of atypical antipsychotics enhances the validity or prognostic utility of the diagnosis. Our recommendations should thus be viewed as a consensus-based operationalization intended to guide future research and clinical characterization, rather than as a definitively validated construct. Although lithium and lamotrigine are first-line treatments per CANMAT-ISBD guidelines, their exclusion from our definition reflects a pragmatic focus on approved acute-phase treatments with consistent evidence in bipolar depression. The role of these agents—particularly in maintenance and combination strategies—warrants further exploration and may be integrated into future models. One of the Task Force's key objectives moving forward will be to explore how this definition can be adapted to better reflect real-world clinical challenges, ensuring that it can be effectively applied in everyday practice to optimize patient care and treatment outcomes.

Affiliations

[1]Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain | [2]Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), Institut de Neurociències (UBNeuro), Barcelona, Spain | [3]Institut D'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain | [4]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain | [5]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada | [6]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, California, USA | [7]Department of Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Victoria, Australia | [8]Centre for Mental Health and Brain Sciences, Swinburne University of Technology, Melbourne, Victoria, Australia | [9]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, USA | [10]Neurocognition and Emotion in Affective Disorders, Psychiatric Centre, Mental Health Services in the Capital Region of Denmark, Copenhagen, Denmark | [11]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK | [12]Mood Disorders Clinic, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada | [13]Deakin University, IMPACT, the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Victoria, Australia | [14]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA | [15]Université de Paris Cité, Paris, France | [16]GHU Psychiatrie & Neurosciences, Paris, France | [17]Department for Bipolar Disorders, Clinic of Psychiatry, University Clinical Center of Serbia, Belgrade, Serbia | [18]Faculty of Medicine, University of Belgrade, Belgrade, Serbia | [19]Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland | [20]Department of Psychiatry & Behavioral Sciences, University of New Mexico, Albuquerque, New Mexico, USA | [21]University of São Paulo, São Paulo, Brazil | [22]University of British Columbia, Vancouver, British Columbia, Canada | [23]Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellin, Colombia | [24]Hospital Universitario Álava, BIOARABA, UPV/EHU, Álava, Spain | [25]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy | [26]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy | [27]Bipolar Collaborative Network, Bethesda, Maryland, USA | [28]Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, Houston, Texas, USA | [29]Department of Psychiatry and Psychotherapy, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany | [30]Department of Pharmacology & Toxicology, and Psychiatry, University of Toronto, Toronto, Ontario, Canada | [31]Experts by experience, Barcelona, Spain

Conflicts of Interest

Dr. Vieta has received grants and served as a consultant, advisor, or CME speaker for AB-Biotics, Abbott, AbbVie, Aimentia, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Casen-Recordati, Celon, Compass, Dainippon Sumitomo, Ethypharm, Ferrer, Gedeon Richter, GH Research, GSK, Idorsia, Janssen, Lundbeck, Novartis, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris. Dr. Fico has received grants and served as a paid consultant, adviser, or CME speaker for Angelini, Janssen, Lundbeck, and Sanofi-Aventis. Dr. Singh has received research grant support from Mayo Clinic, the National Network of Depression Centers (NNDC), Breakthrough Discoveries for Thriving with Bipolar Disorder (BD2), and NIH. He has received honoraria from Elsevier for editing a Clinical Overview on Treatment-Resistant Depression, and he is a KL2 Mentored Career Development Program scholar, supported by CTSA Grant Number KL2TR002379 from the National Center for Advancing Translational Science. Dr. Tohen has received honoraria or consulted for multiple entities, including Abbott, AbbVie, AstraZeneca, Alkermes, Biohaven Pharmaceuticals, Lilly, Johnson & Johnson, and others. He was formerly employed by Lilly, and his spouse was also employed at Lilly. Dr. Swartz has received honoraria or consulted for Intracellular Therapies, Physician Postgraduate Press, Medscape/WebMD, Mediflix, and Clinical Education Alliance. Dr. Ozerdem has received research grant support from TÜBİTAK and Mayo Clinic, and honoraria from Carnot Laboratories. Dr. Roger McIntyre has received research grant support from Global Alliance for Chronic Diseases/Canadian Institutes of Health Research (CIHR)/National Natural Science Foundation of China's Mental Health Team Grant; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, and AbbVie. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp. Dr. Hidalgo-Mazzei has received CME-related honoraria and served as

a consultant for Abbott, Angelini, Ethypharm Digital Therapy, and Janssen-Cilag. Dr. Gonzalez-Pinto has received grants and served as a consultant, advisor, or CME speaker for Janssen-Cilag, Lundbeck, Otsuka, Angelini, Novartis, and Takeda. Dr. Anmella has received CME-related honoraria or consulting fees from Adamed, Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Rovi, and Viatris. Dr. Cubala has received consultation or advisory fees from Alfred E. Tiefenbacher GmbH, COMPASS Pathfinder Ltd., GH Research, MedEd-Link Inc., Janssen-Cilag, and others, as well as speaking fees from Janssen-Cilag and Biogen. Dr. Bauer has received competitive grant support from Deutsche Forschungsgemeinschaft (DFG), Bundesministerium für Bildung und Forschung (BMBF), European Commission, Sächsische Aufbaubank (SAB), and served as an advisor to Alfred E. Tiefenbacher GmbH Co. KG, COMPASS Pathfinder Ltd., GH Research, MedEd-Link Inc., Janssen Global Services LLC, Livanova, Mindforce Game Lab AB, Novartis Switzerland, Sunovion, and has received lecture fees from MedTrix GmbH and Streamedup GmbH. Dr. Cubała received CME-related honoraria from Acadia, Angelini, Beckley Psytech, GH Research, HMNC Brain Health, IntraCellular Therapies, Janssen, MSD, Neumora, Novartis, Otsuka, Recognify Life Sciences. Honoraria: Angelini, Janssen, Novartis. Advisory Boards: Douglas Pharmaceuticals, GH Research, Janssen, MSD, Novartis. Dr. Van Rheenen was supported by an Al and Val Rosenstrauss Fellowship from the Rebecca L Cooper Medical Research Foundation (relationships reported within the last 3 years). The remaining authors declare no conflicts of interest related to the subject matter of this article.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. V. Oliva, G. Fico, M. De Prisco, X. Gonda, A. R. Rosa, and E. Vieta, "Bipolar Disorders: An Update on Critical Aspects," *Lancet Regional Health—Europe* 48 (2024): 101135, https://doi.org/10.1016/j.lanepe.2024.101135.

2. R. S. McIntyre, M. Alda, R. J. Baldessarini, et al., "The Clinical Characterization of the Adult Patient With Bipolar Disorder Aimed at Personalization of Management," *World Psychiatry* 21, no. 3 (2022): 364–387, https://doi.org/10.1002/WPS.20997.

3. S. Miller, B. Dell'Osso, and T. A. Ketter, "The Prevalence and Burden of Bipolar Depression," *Journal of Affective Disorders* 169, no. S1 (2014): S3–S11, https://doi.org/10.1016/S0165-0327(14)70003-5.

4. D. A. Dev, G. H. Le, A. T. H. Kwan, et al., "Comparing Suicide Completion Rates in Bipolar I Versus Bipolar II Disorder: A Systematic Review and Meta-Analysis," *Journal of Affective Disorders* 361 (2024): 480–488, https://doi.org/10.1016/J.JAD.2024.06.045.

5. R. S. McIntyre and J. R. Calabrese, "Bipolar Depression: The Clinical Characteristics and Unmet Needs of a Complex Disorder," *Current Medical Research and Opinion* 35, no. 11 (2019): 1993–2005, https://doi.org/10.1080/03007995.2019.1636017.

6. C. Henry and L. Berkovitch, "Mixed Features in Mood Episodes: Mismatch Between Intensity and Valence in Emotional Responses," *European Neuropsychopharmacology* 87 (2024): 13–15, https://doi.org/10.1016/j.euroneuro.2024.06.009.

7. A. C. Altamura, M. Buoli, A. Caldiroli, et al., "Misdiagnosis, Duration of Untreated Illness (DUI) and Outcome in Bipolar Patients With Psychotic Symptoms: A Naturalistic Study," *Journal of Affective Disorders* 182 (2015): 70–75, https://doi.org/10.1016/j.jad.2015.04.024.

8. G. Fico, G. Anmella, M. Gomez-Ramiro, et al., "Duration of Untreated Illness and Bipolar Disorder: Time for a New Definition? Results From a Cross-Sectional Study," *Journal of Affective Disorders* 294 (2021): 513–520, https://doi.org/10.1016/j.jad.2021.07.062.

9. C. De Dios, E. Ezquiaga, A. Garcia, B. Soler, and E. Vieta, "Time Spent With Symptoms in a Cohort of Bipolar Disorder Outpatients in Spain: A Prospective, 18-Month Follow-Up Study," *Journal of Affective Disorders* 125, no. 1–3 (2010): 74–81, https://doi.org/10.1016/J.JAD.2009.12.006.

10. R. S. McIntyre, "In Vivo Phenotyping, Mechanism-Informed Treatments, Domain-Based Psychopathology and Nomological Networks: A Strategy for Treatment Discovery and Development in Bipolar Depression," *Bipolar Disorders* 22, no. 7 (2020): 657–659, https://doi.org/10.1111/bdi.13026.

11. M. Tohen, H. Katagiri, S. Fujikoshi, and S. Kanba, "Efficacy of Olanzapine Monotherapy in Acute Bipolar Depression: A Pooled Analysis of Controlled Studies," *Journal of Affective Disorders* 149, no. 1–3 (2013): 196–201, https://doi.org/10.1016/J.JAD.2013.01.022.

12. G. Fico and E. Vieta, "Antidepressant Use in Bipolar Disorder: Shifting Focus From "Whether" to "Whom"," *European Neuropsychopharmacology* 84 (2024): 1–2, https://doi.org/10.1016/J.EURONEURO.2024.04.004.

13. N. Gottlieb and A. H. Young, "Antidepressants and Bipolar Disorder: The Plot Thickens," *American Journal of Psychiatry* 181, no. 7 (2024): 575–577, https://doi.org/10.1176/APPI.AJP.20240411.

14. K. Keramatian, N. K. Chithra, and L. N. Yatham, "The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence," *Focus* 21, no. 4 (2023): 344–353, https://doi.org/10.1176/appi.focus.20230009.

15. G. S. Malhi, D. Bassett, P. Boyce, et al., "Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders," *Australian and New Zealand Journal of Psychiatry* 49, no. 12 (2015): 1087–1206, https://doi.org/10.1177/0004867415617657.

16. N. Verdolini, D. Hidalgo-Mazzei, A. Murru, et al., "Mixed States in Bipolar and Major Depressive Disorders: Systematic Review and Quality Appraisal of Guidelines," *Acta Psychiatrica Scandinavica* 138, no. 3 (2018): 196–222, https://doi.org/10.1111/acps.12896.

17. J. Mendlewicz, I. Massat, S. Linotte, et al., "Identification of Clinical Factors Associated With Resistance to Antidepressants in Bipolar Depression: Results From an European Multicentre Study," *International Clinical Psychopharmacology* 25, no. 5 (2010): 297–301, https://doi.org/10.1097/YIC.0b013e32833c4ceb.

18. C. Datto, W. J. Pottorf, L. Feeley, S. LaPorte, and C. Liss, "Bipolar II Compared With Bipolar I Disorder: Baseline Characteristics and Treatment Response to Quetiapine in a Pooled Analysis of Five Placebo-Controlled Clinical Trials of Acute Bipolar Depression," *Annals of General Psychiatry* 15 (2016): 9, https://doi.org/10.1186/s12991-016-0096-0.

19. A. Aguglia, G. Giacomini, C. F. De Michiel, et al., "Characterization of Bipolar Disorder I and II: Clinical Features, Comorbidities, and Pharmacological Pattern," *Alpha Psychiatry* 25, no. 4 (2024): 472–479, https://doi.org/10.5152/alphapsychiatry.2024.241474.

20. I. E. Bauer, J. C. Soares, S. Selek, and T. D. Meyer, "The Link Between Refractoriness and Neuroprogression in Treatment-Resistant Bipolar Disorder," *Modern Trends in Pharmacopsychiatry* 31 (2017): 10–26, https://doi.org/10.1159/000470803.

21. Y. K. Liu, S. Ling, L. M. W. Lui, et al., "Prevalence of Type 2 Diabetes Mellitus, Impaired Fasting Glucose, General Obesity, and Abdominal Obesity in Patients With Bipolar Disorder: A Systematic Review and Meta-Analysis," *Journal of Affective Disorders* 300 (2022): 449–461, https://doi.org/10.1016/j.jad.2021.12.110.

22. C. A. Macneil, M. K. Hasty, P. Conus, and M. Berk, "Is Diagnosis Enough to Guide Interventions in Mental Health? Using Case Formulation in Clinical Practice," *BMC Medicine* 10 (2012): 111, https://doi.org/10.1186/1741-7015-10-111.

23. R. S. McIntyre, M. Alsuwaidan, B. T. Baune, et al., "Treatment-Resistant Depression: Definition, Prevalence, Detection, Management, and Investigational Interventions," *World Psychiatry* 22, no. 3 (2023): 394–412, https://doi.org/10.1002/WPS.21120.

24. K. N. Fountoulakis, L. N. Yatham, H. Grunze, et al., "The CINP Guidelines on the Definition and Evidence-Based Interventions for Treatment-Resistant Bipolar Disorder," *International Journal of Neuropsychopharmacology* 23, no. 4 (2020): 230–256, https://doi.org/10.1093/ijnp/pyz064.

25. O. H. Elsayed, M. Ercis, M. Pahwa, and B. Singh, "Treatment-Resistant Bipolar Depression: Therapeutic Trends, Challenges and Future Directions," *Neuropsychiatric Disease and Treatment* 18 (2022): 2927–2943, https://doi.org/10.2147/NDT.S273503.

26. A. A. Nierenberg, M. J. Ostacher, J. R. Calabrese, et al., "Treatment-Resistant Bipolar Depression: A STEP-BD Equipoise Randomized Effectiveness Trial of Antidepressant Augmentation With Lamotrigine, Inositol, or Risperidone," *American Journal of Psychiatry* 163, no. 2 (2006): 210–216, https://doi.org/10.1176/appi.ajp.163.2.210.

27. G. S. Sachs, "Treatment-Resistant Bipolar Depression," *Psychiatric Clinics of North America* 19, no. 2 (1996): 215–236, https://doi.org/10.1016/S0193-953X(05)70285-9.

28. L. N. Yatham, J. R. Calabrese, and V. Kusumakar, "Bipolar Depression: Criteria for Treatment Selection, Definition of Refractoriness, and Treatment Options," *Bipolar Disorders* 5, no. 2 (2003): 85–97, https://doi.org/10.1034/J.1399-5618.2003.00019.X.

29. M. Gitlin, "Treatment-Resistant Bipolar Disorder," *Molecular Psychiatry* 11, no. 3 (2006): 227–240, https://doi.org/10.1038/sj.mp.4001793.

30. P. Gajwani, "Treatment-Refractory Bipolar Disorder: Classification to Aid in Clinical Management," *Expert Opinion on Pharmacotherapy* 10, no. 12 (2009): 1907–1915, https://doi.org/10.1517/14656560903064170.

31. I. Pacchiarotti, L. Mazzarini, F. Colom, et al., "Treatment-Resistant Bipolar Depression: Towards a New Definition," *Acta Psychiatrica Scandinavica* 120, no. 6 (2009): 429–440, https://doi.org/10.1111/j.1600-0447.2009.01471.x.

32. N. Lipsman, R. S. McIntyre, P. Giacobbe, C. Torres, S. H. Kennedy, and A. M. Lozano, "Neurosurgical Treatment of Bipolar Depression: Defining Treatment Resistance and Identifying Surgical Targets," *Bipolar Disorders* 12, no. 7 (2010): 691–701, https://doi.org/10.1111/j.1399-5618.2010.00868.x.

33. G. S. Malhi, D. M. Bargh, E. Cashman, M. A. Frye, and M. Gitlin, "The Clinical Management of Bipolar Disorder Complexity Using a Stratified Model," *Bipolar Disorders* 14, no. s2 (2012): 66–89, https://doi.org/10.1111/j.1399-5618.2012.00993.x.

34. D. Hidalgo-Mazzei, M. Berk, A. Cipriani, et al., "Treatment-Resistant and Multi-Therapy-Resistant Criteria for Bipolar Depression: Consensus Definition," *British Journal of Psychiatry* 214, no. 1 (2019): 27–35, https://doi.org/10.1192/bjp.2018.257.

35. M. Hamilton, "A Rating Scale for Depression," *Journal of Neurology, Neurosurgery, and Psychiatry* 23 (1960): 56–62, https://doi.org/10.1136/jnnp.23.1.56.

36. S. A. Montgomery and M. Åsberg, "A New Depression Scale Designed to Be Sensitive to Change," *British Journal of Psychiatry* 134, no. 4 (1979): 382–389, https://doi.org/10.1192/bjp.134.4.382.

37. H. Akil, J. Gordon, R. Hen, et al., "Treatment Resistant Depression: A Multi-Scale, Systems Biology Approach," *Neuroscience and Biobehavioral Reviews* 84 (2018): 272–288, https://doi.org/10.1016/J.NEUBIOREV.2017.08.019.

38. C. Fabbri, F. Corponi, D. Souery, et al., "The Genetics of Treatment-Resistant Depression: A Critical Review and Future Perspectives," *International Journal of Neuropsychopharmacology* 22, no. 2 (2019): 93–104, https://doi.org/10.1093/ijnp/pyy024.

39. Q. S. Li, C. Tian, and D. Hinds, "Genome-Wide Association Studies of Antidepressant Class Response and Treatment-Resistant Depression," *Translational Psychiatry* 10 (2020): 360, https://doi.org/10.1038/s41398-020-01035-6.

40. P. Jiang, Z. Huang, S. Allegra, et al., "ABCB1 Gene Is Associated With Clinical Response to SNRIs in a Local Chinese Han Population," 10 (2019): 761, https://doi.org/10.3389/fphar.2019.00761.

41. J. D. Allen and J. R. Bishop, "A Systematic Review of Genome-Wide Association Studies of Antipsychotic Response," *Pharmacogenomics* 20 (2019): 291–306, https://doi.org/10.2217/pgs-2018-0163.

42. M. Veldic, A. T. Ahmed, C. J. Blacker, et al., "Cytochrome P450 2C19 Poor Metabolizer Phenotype in Treatment Resistant Depression: Treatment and Diagnostic Implications," *Frontiers in Pharmacology* 10 (2019): 83, https://doi.org/10.3389/FPHAR.2019.00083.

43. M. Herrera-Rivero, M. Adli, K. Akiyama, et al., "Exploring the Genetics of Lithium Response in Bipolar Disorders," *International Journal of Bipolar Disorders* 12 (2023): 20, https://doi.org/10.1186/s40345-024-00341-y.

44. A. M. Díaz-Zuluaga, J. I. Vélez, M. Cuartas, et al., "Ancestry Component as a Major Predictor of Lithium Response in the Treatment of Bipolar Disorder," *Journal of Affective Disorders* 332 (2023): 203–209, https://doi.org/10.1016/J.JAD.2023.03.058.

45. L. Hou, U. Heilbronner, F. Degenhardt, et al., "Genetic Variants Associated With Response to Lithium Treatment in Bipolar Disorder: A Genome-Wide Association Study," *Lancet* 387, no. 10023 (2016): 1085–1093, https://doi.org/10.1016/S0140-6736(16)00143-4.

46. J. Houenou, J. Frommberger, S. Carde, et al., "Neuroimaging-Based Markers of Bipolar Disorder: Evidence From Two Meta-Analyses," *Journal of Affective Disorders* 132, no. 3 (2011): 344–355, https://doi.org/10.1016/j.jad.2011.03.016.

47. M. L. Phillips and H. A. Swartz, "A Critical Appraisal of Neuroimaging Studies of Bipolar Disorder: Toward a New Conceptualization of Underlying Neural Circuitry and a Road Map for Future Research," *American Journal of Psychiatry* 171, no. 8 (2014): 829–843, https://doi.org/10.1176/appi.ajp.2014.13081008.

48. L. Schmaal, E. Pozzi, T. Ho, et al., "ENIGMA MDD: Seven Years of Global Neuroimaging Studies of Major Depression Through Worldwide Data Sharing," *Translational Psychiatry* 10(1):172 (2020): 172, https://doi.org/10.1038/s41398-020-0842-6.

49. S. Cakir, R. Tasdelen Durak, I. Ozyildirim, E. Ince, and V. Sar, "Childhood Trauma and Treatment Outcome in Bipolar Disorder," *Journal of Trauma & Dissociation* 17, no. 4 (2016): 397–409, https://doi.org/10.1080/15299732.2015.1132489.

50. G. B. Parker and R. K. Graham, "Clinical Characteristics Associated With Treatment-Resistant Bipolar Disorder," *Journal of Nervous and Mental Disease* 205, no. 3 (2017): 188–191, https://doi.org/10.1097/NMD.0000000000000517.

51. M. Tohen, E. Frank, C. L. Bowden, et al., "The International Society for Bipolar Disorders (ISBD) Task Force Report on the Nomenclature of Course and Outcome in Bipolar Disorders," *Bipolar Disorders* 11, no. 5 (2009): 453–473, https://doi.org/10.1111/J.1399-5618.2009.00726.X.

52. T. Maruki, T. Utsumi, M. Takeshima, et al., "Efficacy and Safety of Adjunctive Therapy to Lamotrigine, Lithium, or Valproate Monotherapy in Bipolar Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *International Journal of Bipolar Disorders* 10, no. 1 (2022): 24, https://doi.org/10.1186/S40345-022-00271-7.

53. C. Ermis, H. Taipale, A. Tanskanen, et al., "Real-World Effectiveness of Pharmacological Maintenance Treatment of Bipolar Depression: A Within-Subject Analysis in a Swedish Nationwide Cohort," *Lancet Psychiatry* 12, no. 3 (2025): 198–207, https://doi.org/10.1016/S2215-0366(24)00411-5.

54. A. Tundo, S. Betro', R. de Filippis, et al., "Pramipexole Augmentation for Treatment-Resistant Unipolar and Bipolar Depression in the Real World: A Systematic Review and Meta-Analysis," *Life* 13, no. 4 (2023): 1043, https://doi.org/10.3390/life13041043.

55. N. A. Nunez, B. Singh, F. Romo-Nava, et al., "Efficacy and Tolerability of Adjunctive Modafinil/Armodafinil in Bipolar Depression: A Meta-Analysis of Randomized Controlled Trials," *Bipolar Disorders* 22, no. 2 (2020): 109–120, https://doi.org/10.1111/bdi.12859.

56. M. Bauer, S. Berman, T. Stamm, et al., "Levothyroxine Effects on Depressive Symptoms and Limbic Glucose Metabolism in Bipolar Disorder: A Randomized, Placebo-Controlled Positron Emission Tomography Study," *Molecular Psychiatry* 21, no. 2 (2016): 229–236, https://doi.org/10.1038/mp.2014.186.

57. H. K. Schoeyen, U. Kessler, O. A. Andreassen, et al., "Treatment-Resistant Bipolar Depression: A Randomized Controlled Trial of Electroconvulsive Therapy Versus Algorithm-Based Pharmacological Treatment," *American Journal of Psychiatry* 172, no. 1 (2015): 41–51, https://doi.org/10.1176/appi.ajp.2014.13111517.

58. K. Li, A. Bichlmeier, C. DuPont, et al., "Fast Depressive Symptoms Improvement in Bipolar I Disorder After Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT): A Two-Site Feasibility and Safety Open-Label Trial," *Journal of Affective Disorders* 365 (2024): 359–363, https://doi.org/10.1016/j.jad.2024.08.087.

59. F. Colom, E. Vieta, J. Sanchez-Moreno, et al., "Group Psychoeducation for Stabilised Bipolar Disorders: 5-Year Outcome of a Randomised Clinical Trial," *British Journal of Psychiatry* 194, no. 3 (2009): 260–265, https://doi.org/10.1192/bjp.bp.107.040485.

60. È. Valls, J. Sánchez-Moreno, C. M. Bonnín, et al., "Effects of an Integrative Approach to Bipolar Disorders Combining Psychoeducation, Mindfulness-Based Cognitive Therapy and Functional Remediation: Study Protocol for a Randomized Controlled Trial," *Revista de Psiquiatria y Salud Mental* 13, no. 3 (2020): 165–173, https://doi.org/10.1016/j.rpsm.2020.05.005.

61. M. Bioque, J. Rumià, P. Roldán, et al., "Deep Brain Stimulation and Digital Monitoring for Patients With Treatment-Resistant Schizophrenia and Bipolar Disorder: A Case Series," *Revista de Psiquiatria y Salud Mental* 18, no. 1 (2023): 13–16, https://doi.org/10.1016/j.rpsm.2023.05.001.

62. F. Benedetti, R. Riccaboni, C. Locatelli, S. Poletti, S. Dallaspezia, and C. Colombo, "Rapid Treatment Response of Suicidal Symptoms to Lithium, Sleep Deprivation, and Light Therapy (Chronotherapeutics) in Drug-Resistant Bipolar Depression," *Journal of Clinical Psychiatry* 75, no. 2 (2014): 133–140, https://doi.org/10.4088/JCP.13m08455.

63. S. T. Aaronson, A. van der Vaart, T. Miller, et al., "Single-Dose Synthetic Psilocybin With Psychotherapy for Treatment-Resistant Bipolar Type II Major Depressive Episodes," *JAMA Psychiatry* 81, no. 6 (2024): 555, https://doi.org/10.1001/jamapsychiatry.2023.4685.

64. J. D. Rosenblat, S. Meshkat, Z. Doyle, et al., "Psilocybin-Assisted Psychotherapy for Treatment Resistant Depression: A Randomized Clinical Trial Evaluating Repeated Doses of Psilocybin," *Medicus* 5, no. 3 (2024): 190–200.e5, https://doi.org/10.1016/j.medj.2024.01.005.

65. S. Alberich, M. Martínez-Cengotitabengoa, P. López, et al., "Eficacia y Seguridad de la Ketamina en Depresión Bipolar: Una Revisión Sistemática," *Revista de Psiquiatria y Salud Mental* 10, no. 2 (2017): 104–112, https://doi.org/10.1016/j.rpsm.2016.05.005.

66. J. L. Phillips, S. Norris, J. Talbot, et al., "Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial," *American Journal of Psychiatry* 176, no. 5 (2019): 401–409, https://doi.org/10.1176/appi.ajp.2018.18070834.

67. J. K. Rybakowski, A. Permoda-Osip, and A. Bartkowska-Sniatkowska, "Ketamine Augmentation Rapidly Improves Depression Scores in Inpatients With Treatment-Resistant Bipolar Depression," *International Journal of Psychiatry in Clinical Practice* 21, no. 2 (2017): 99–103, https://doi.org/10.1080/13651501.2017.1297834.

68. C. Zhuo, F. Ji, H. Tian, et al., "Transient Effects of Multi-Infusion Ketamine Augmentation on Treatment-Resistant Depressive Symptoms in Patients With Treatment-Resistant Bipolar Depression—An Open-Label Three-Week Pilot Study," *Brain and Behavior: A Cognitive Neuroscience Perspective* 10, no. 8 (2020): e01674, https://doi.org/10.1002/BRB3.1674.

69. B. Dell'Osso and G. Martinotti, "Exploring the Potential of Esketamine in the Treatment of Bipolar Depression," *European Neuropsychopharmacology* 77 (2023): 21–23, https://doi.org/10.1016/J.EURONEURO.2023.08.498.

70. G. Martinotti, B. Dell'Osso, G. Di Lorenzo, et al., "Treating Bipolar Depression With Esketamine: Safety and Effectiveness Data From a Naturalistic Multicentric Study on Esketamine in Bipolar Versus Unipolar Treatment-Resistant Depression," *Bipolar Disorders* 25, no. 3 (2023): 233–244, https://doi.org/10.1111/BDI.13296.

71. F. Fancy, N. B. Rodrigues, J. D. Di Vincenzo, et al., "Real-World Effectiveness of Repeated Ketamine Infusions for Treatment-Resistant Bipolar Depression," *Focus (Madison)* 21, no. 4 (2023): 420–429, https://doi.org/10.1176/appi.focus.23021022.

72. D. De Berardis, C. Tomasetti, M. Pompili, et al., "An Update on Glutamatergic System in Suicidal Depression and on the Role of Esketamine," *Current Topics in Medicinal Chemistry* 20, no. 7 (2020): 554–584, https://doi.org/10.2174/1568026620666200131100316.

73. D. De Berardis, M. Fornaro, A. Valchera, et al., "Eradicating Suicide at Its Roots: Preclinical Bases and Clinical Evidence of the Efficacy of Ketamine in the Treatment of Suicidal Behaviors," *International Journal of Molecular Sciences* 19, no. 10 (2018): 2888, https://doi.org/10.3390/IJMS19102888.

74. R. S. McIntyre, O. Lipsitz, N. B. Rodrigues, et al., "The Effectiveness of Ketamine on Anxiety, Irritability, and Agitation: Implications for Treating Mixed Features in Adults With Major Depressive or Bipolar Disorder," *Bipolar Disorders* 22, no. 8 (2020): 831–840, https://doi.org/10.1111/BDI.12941.

75. W. S. H. Kim, M. K. Dimick, D. Omrin, et al., "Proof-Of-Concept Randomized Controlled Trial of Single-Session Nitrous Oxide Treatment for Refractory Bipolar Depression: Focus on Cerebrovascular Target Engagement," *Bipolar Disorders* 25, no. 3 (2023): 221–232, https://doi.org/10.1111/BDI.13288.

76. C. V. Calkin, K. N. R. Chengappa, K. Cairns, et al., "Treating Insulin Resistance With Metformin as a Strategy to Improve Clinical Outcomes in Treatment-Resistant Bipolar Depression (the TRIO-BD Study): A Randomized, Quadruple-Masked, Placebo-Controlled Clinical Trial," *Journal of Clinical Psychiatry* 83, no. 2 (2022): 21m14022, https://doi.org/10.4088/JCP.21m14022.

77. A. Halaris, A. Cantos, K. Johnson, M. Hakimi, and J. Sinacore, "Modulation of the Inflammatory Response Benefits Treatment-Resistant Bipolar Depression: A Randomized Clinical Trial," *Journal of Affective Disorders* 261 (2020): 145–152, https://doi.org/10.1016/j.jad.2019.10.021.

78. S. Murata, M. Murphy, D. Hoppensteadt, J. Fareed, A. Welborn, and A. Halaris, "Effects of Adjunctive Inflammatory Modulation on IL-1β in Treatment Resistant Bipolar Depression," *Brain, Behavior, and Immunity* 87 (2020): 369–376, https://doi.org/10.1016/j.bbi.2020.01.004.

79. M. Tam, M. Tam, and S. Tn, "Efficacy of Pentoxifylline for the Treatment of Bipolar I/II Patients With Treatment-Resistant Depression: A Proof-Of-Concept, Randomized, Double-Blind, Placebo-Controlled Trial," *Brain Research Bulletin* 216 (2024): 111047, https://doi.org/10.1016/J.BRAINRESBULL.2024.111047.

80. J. V. Pinto, J. A. S. Crippa, K. M. Ceresér, et al., "Cannabidiol as an Adjunctive Treatment for Acute Bipolar Depression: A Pilot Study: Le Cannabidiol Comme Traitement D'appoint de la Dépression Bipolaire

Aiguë: Une Étude Pilote," *Canadian Journal of Psychiatry* 69, no. 4 (2024): 242–251, https://doi.org/10.1177/07067437231209650.

81. M. M. Ashton, M. Berk, C. H. Ng, et al., "Efficacy of Adjunctive *Garcinia mangostana* Linn (Mangosteen) Pericarp for Bipolar Depression: Study Protocol for a Proof-Of-Concept Trial," *Brazilian Journal of Psychiatry* 41, no. 3 (2019): 245–253, https://doi.org/10.1590/1516-4446-2018-0114.

82. C. C. Bortolasci, S. Kidnapillai, B. Spolding, et al., "Use of a Gene Expression Signature to Identify Trimetazidine for Repurposing to Treat Bipolar Depression," *Bipolar Disorders* 25, no. 8 (2023): 661–670, https://doi.org/10.1111/bdi.13319.

83. S. Khanra, P. Reddy, A. Giménez-Palomo, et al., "Metabolic Regulation to Treat Bipolar Depression: Mechanisms and Targeting by Trimetazidine," *Molecular Psychiatry* 28, no. 8 (2023): 3231–3242, https://doi.org/10.1038/s41380-023-02134-8.

84. B. Singh, A. K. Yocum, R. Strawbridge, et al., "Patterns of Pharmacotherapy for Bipolar Disorder: A GBC Survey," *Bipolar Disorders* 26, no. 1 (2024): 22–32, https://doi.org/10.1111/BDI.13366.

85. G. Anmella and E. Vieta, "Teratogenicity of Valproate: Further Reasons for Action," *European Neuropsychopharmacology* 80 (2024): 25–26, https://doi.org/10.1016/J.EURONEURO.2023.11.008.

86. J. Christensen, B. B. Trabjerg, and J. W. Dreier, "Valproate Use During Spermatogenesis and Risk to Offspring," *JAMA Network Open* 7, no. 6 (2024): e2414709, https://doi.org/10.1001/JAMANETWORKOPEN.2024.14709.

87. A. R. Rosa, C. Franco, A. Martinez-Aran, et al., "Functional Impairment in Patients With Remitted Bipolar Disorder," *Psychotherapy and Psychosomatics* 77, no. 6 (2008): 390–392, https://doi.org/10.1159/000151520.

88. K. H. Sheehan and D. V. Sheehan, "Assessing Treatment Effects in Clinical Trials With the Discan Metric of the Sheehan Disability Scale," *International Clinical Psychopharmacology* 23, no. 2 (2008): 70–83, https://doi.org/10.1097/YIC.0B013E3282F2B4D6.

89. T. B. Üstün, S. Chatterji, N. Kostanjsek, et al., "Developing the World Health Organization Disability Assessment Schedule 2.0," *Bulletin of the World Health Organization* 88, no. 11 (2010): 815–823, https://doi.org/10.2471/BLT.09.067231.

90. D. Byrne, F. Doyle, S. Brannick, et al., "Evaluating the Psychometric Structure of the Hamilton Rating Scale for Depression Pre- and Post-Treatment in Antidepressant Randomised Trials: Secondary Analysis of 6843 Individual Participants From 20 Trials," *Psychiatry Research* 339 (2024): 116057, https://doi.org/10.1016/J.PSYCHRES.2024.116057.

91. M. K. Spearing, R. M. Post, G. S. Leverich, D. Brandt, and W. Nolen, "Modification of the Clinical Global Impressions (CGI) Scale for Use in Bipolar Illness (BP): The CGI-BP," *Psychiatry Research* 73, no. 3 (1997): 159–171, https://doi.org/10.1016/S0165-1781(97)00123-6.

92. M. Berk, G. S. Malhi, P. B. Mitchell, et al., "Scale Matters: The Need for a Bipolar Depression Rating Scale (BDRS)," *Acta Psychiatrica Scandinavica* 110, no. s422 (2004): 39–45, https://doi.org/10.1111/j.1600-0447.2004.00412.x.

93. M. Berk, G. S. Malhi, C. Cahill, et al., "The Bipolar Depression Rating Scale (BDRS): Its Development, Validation and Utility," *Bipolar Disorders* 9, no. 6 (2007): 571–579, https://doi.org/10.1111/j.1399-5618.2007.00536.x.

94. T. E. Van Rheenen, K. E. Lewandowski, I. E. Bauer, et al., "Current Understandings of the Trajectory and Emerging Correlates of Cognitive Impairment in Bipolar Disorder: An Overview of Evidence," *Bipolar Disorders* 22, no. 1 (2020): 13–27, https://doi.org/10.1111/bdi.12821.

95. K. W. Miskowiak, K. E. Burdick, A. Martinez-Aran, et al., "Methodological Recommendations for Cognition Trials in Bipolar Disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force," *Bipolar Disorders* 19, no. 8 (2017): 614–626, https://doi.org/10.1111/BDI.12534.

96. O. Pino, G. Guilera, J. E. Rojo, et al., "Spanish Version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S): Psychometric Properties of a Brief Scale for Cognitive Evaluation in Schizophrenia," *Schizophrenia Research* 99, no. 1–3 (2008): 139–148, https://doi.org/10.1016/J.SCHRES.2007.09.012.

97. Google Acadèmic, "Purdon: The Screen for Cognitive Impairment in Psychiatry—Google Acadèmic," (2024), https://scholar.google.com/scholar_lookup?title=The%20screen%20for%20cognitive%20impairment%20in%20psychiatry%20(SCIP):%20instructions%20and%20three%20alternate%20forms&author=SE%20Purdon&publication_year=2005&.

98. G. S. Leverich, L. L. Altshuler, M. A. Frye, et al., "Risk of Switch in Mood Polarity to Hypomania or Mania in Patients With Bipolar Depression During Acute and Continuation Trials of Venlafaxine, Sertraline, and Bupropion as Adjuncts to Mood Stabilizers," *American Journal of Psychiatry* 163, no. 2 (2006): 232–239, https://doi.org/10.1176/APPI.AJP.163.2.232.