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PSILOCYBIN AS A RAPID-ACTING ANTIDEPRESSANT IN BIPOLAR DEPRESSION: A SCOPING REVIEW ON MECHANISTIC INSIGHTS AND CLINICAL RISK EVALUATION

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ABSTRACT

Bipolar depression (BD-D) is a severely disabling episode of bipolar disease that remains a major therapeutic challenge due to inadequate response to current pharmaceutical alternatives. Psilocybin, a serotonergic psychedelic, has lately shown immediate and long-lasting antidepressant benefits in patients with treatment-resistant major depressive disorder (MDD). However, its usage in BD-D is contentious, owing to the danger of manic or hypomanic switching. This narrative review compiled 25 peer-reviewed articles published between 2020 and 2025, which included randomized controlled trials, open-label studies, clinical protocols, reviews, and case reports. Evidence from unipolar depression suggests that high effect sizes and remission rates exceed those of traditional antidepressants, which is backed by neuroimaging results of increased brain connectivity, default mode network disturbance, and neuroplasticity induction. Limited data on BD-D, largely case reports and small observational studies, show both therapeutic promise and known hazards of manic activation, particularly in unsupervised or recreational settings. Early controlled studies on bipolar II depression suggest that organized protocols and psychotherapy help may be safe. Despite promising molecular and clinical signs, there is inadequate evidence to demonstrate psilocybin's significance in BD-D. Randomized controlled studies targeting bipolar subtypes, investigation of co-administration with mood stabilizers, and identification of mania-risk biomarkers are among the most pressing research concerns. Until such data are available, psilocybin should remain experimental in bipolar populations, provided only under strict safety guidelines.

Keywords: Bipolar depression, hallucinogen-persisting perception disorder, psilocybin, serotonin 5-HT2A receptor, treatment-resistant depression.

INTRODUCTION

Bipolar depression remains a formidable clinical challenge, affecting over 1% of the global population, with depressive episodes occurring nearly three times more frequently than manic ones and contributing disproportionately to functional impairment, disability, and suicide risk.[1,2] Existing pharmacological treatments, including mood stabilizers and second-generation antipsychotics, often provide only partial or delayed symptom relief, while intolerable side effects often lead to discontinuation.[3] These therapeutic limitations have spurred growing interest in novel approaches, particularly psychedelic compounds such as psilocybin, a serotonergic hallucinogen derived from Psilocybe mushrooms.

Psilocybin is metabolized into psilocin, a potent 5-HT2A receptor agonist, which alters brain network

dynamics by reducing activity in the default mode network (DMN) and enhancing emotional flexibility and cognitive processing.[4,5] Unlike selective serotonin reuptake inhibitors (SSRIs) which require daily dosing, take weeks to achieve effect, and often blunt affect psilocybin has been shown to elicit sustained antidepressant effects after just one or two supervised sessions [Figure 1].[6] This has challenged the conventional chronic-dosing paradigm of SSRIs and SNRIs, shifting the psychiatric landscape toward intermittent, psychotherapy-supported dosing models.[4,6]

Figure 1: Mechanism of Action – SSRIs vs Psilocybin. Figure illustrated by Asif S.

Treatment-resistant depression (TRD) affects approximately one-third of individuals with major depressive disorder (MDD) who do not respond to two or more adequate trials of antidepressants.[1,3] In clinical trials, even a single dose of psilocybin administered with psychotherapeutic support has resulted in response rates up to 71% by week 3, with some patients maintaining remission for over 12 months.[1,3,5-23]

Neuroimaging studies from trials like EMBRACE and EPIsoDE have demonstrated that psilocybin enhances global brain network integration, restores connectivity within the DMN, and improves emotional regulation circuitry, reversing the rigid negative thought patterns seen in depressive states.[17-27] However, despite its promise, psilocybin use in bipolar disorder remains highly controversial. Case reports have documented manic or hypomanic episodes following unsupervised or recreational use, sometimes even in individuals with no prior bipolar diagnosis, raising concern about its potential to unmask latent bipolarity or trigger mood switches.[9,11,13] Consequently, most modern psychedelic trials exclude individuals with bipolar disorder, especially bipolar I, creating a critical evidence gap and limiting equitable access to these emerging therapies.[14,19]

In 2024, Rosenblat et al. conducted one of the largest randomized clinical trials evaluating repeated doses of psilocybin-assisted psychotherapy in TRD patients. The study found that repeated low-to-moderate doses of psilocybin, when combined with structured psychotherapeutic support, led to a statistically significant and clinically meaningful reduction in depressive symptoms by week 6, as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS).[1] These findings align with previous meta-analyses, such as Galvão-Coelho et al.'s 2021 synthesis, which reported large effect sizes, with Cohen's d ranging from 0.8 to 1.3 depending on the outcome measure and population studied indicating a strong antidepressant effect of classic psychedelics including psilocybin.[5] Notably, these effect sizes surpass those typically observed with SSRIs (often ~0.3–0.5), suggesting that psilocybin may represent a more potent intervention for selected patient populations.

Nonetheless, early evidence from carefully controlled settings in bipolar II disorder is cautiously optimistic. A non-randomized open-label trial by Aaronson et al. reported no treatment-emergent mania in patients with bipolar II depression receiving a single psilocybin dose, although transient insomnia and anxiety were observed in a subset.[3,12] These findings suggest that with appropriate screening and monitoring, psilocybin might offer a safe and effective adjunctive treatment in selected cases. Importantly, the rising public interest in psilocybin has driven advocacy for its medicalization and decriminalization across several jurisdictions. While this offers hope for broader access, it also increases the risk of unregulated, recreational use, especially among individuals with undiagnosed psychiatric conditions. Potential complications include hallucinogen-persisting perception disorder (HPPD), dissociation, or mania, particularly in those with affective vulnerabilities.[7,9,13]

This review seeks to critically evaluate whether psilocybin-assisted therapy can alleviate depressive symptoms in bipolar disorder without precipitating manic episodes, by synthesizing findings from clinical trials, neurobiological mechanisms, patient-reported outcomes, and adverse event reports.

MATERIALS AND METHODS

A comprehensive narrative literature review was undertaken to evaluate psilocybin's therapeutic potential and safety profile in bipolar depression. Electronic searches were conducted in PubMed, ScienceDirect, and Google Scholar for articles published between 1 January 2020 and 31 August 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators and truncation. The primary terms "psilocybin" and "psychedelic therapy" were combined with condition-specific terms including "bipolar depression," "bipolar disorder," "mania," "hypomania," and "treatment-resistant depression." Studies were considered eligible if they were peer-reviewed, written in English, and based on human participants or human-derived clinical data. Eligible article types included randomized controlled trials, open-label or pilot studies, prospective or retrospective observational studies, clinical reviews, registered trial protocols, case reports, and mechanistic or neuropharmacological investigations relevant to psilocybin use in bipolar depression. Articles were excluded if they focused solely on unipolar depression, schizophrenia, or non-psilocybin psychedelics (e.g., LSD, DMT, or MDMA), or if they represented preclinical animal or

in vitro research, non-English publications, or opinion pieces lacking empirical or clinical data. Search results were exported to a citation manager for deduplication, after which 32 unique records were screened by title and abstract by two independent reviewers. Following screening, 27 articles were selected for full-text assessment and inclusion. Discrepancies between reviewers were resolved through discussion and consensus. Each selected study was assessed for relevance to three predefined thematic domains: neuropharmacology and mechanisms of psilocybin action (e.g., 5-HT2A receptor modulation and neuroplasticity), clinical outcomes in bipolar depression (including mood improvement, treatment resistance, and functional recovery), and safety considerations, with particular attention to manic or hypomanic switch risk, adverse effects, and contraindications. Reference lists of included sources were also reviewed to ensure completeness of the search.

Thematic Synthesis

Neuropharmacology, Therapeutic Onset, and Clinical Divergence from Conventional Antidepressants: Psilocybin, a naturally occurring tryptamine alkaloid, is found in over 200 species of psychoactive mushrooms, particularly Psilocybe cubensis and Psilocybe semilanceata.[1] Structurally, psilocybin functions as a prodrug, undergoing rapid dephosphorylation to yield psilocin, a pharmacologically active compound. Psilocin shares structural similarity with serotonin (5-hydroxytryptamine, 5-HT) and exhibits high-affinity partial agonism at the 5-HT2A receptor, a mechanism widely implicated in the compound's psychedelic effects.[2,3] This receptor interaction induces transient cortical desynchronization and enhanced global brain network integration, particularly affecting the default mode network (DMN), which is associated with self-referential thought, ruminative cognition, and depressive symptomatology.[4-6] Such alterations have been hypothesized to underline the acute phenomenological experience and the enduring therapeutic outcomes observed in clinical trials.[7,8]

Unlike selective serotonin reuptake inhibitors (SSRIs), which require chronic administration and operate via synaptic reuptake inhibition, psilocybin exerts its primary effect through a non-reuptake-dependent serotonergic pathway, enabling rapid-onset antidepressant effects even after a single administration under therapeutic conditions.[9] Numerous randomized controlled trials and open-label studies published between 2020 and 2025 have demonstrated significant and sustained reductions in depressive symptoms following guided psilocybin sessions, with effects lasting several weeks to months post-treatment in select populations with treatment-resistant depression.[10-13]

The therapeutic use of psilocybin is distinct from its recreational application. Historically employed in ceremonial contexts by Indigenous Mesoamerican cultures, its unregulated recreational proliferation during the 1960s led to legal restrictions and scientific marginalization.[14] However, its modern clinical re-evaluation follows a structured model emphasizing 'set, setting, and support' incorporating psychological preparation, supervised dosing, and post-session integration therapy.[15,16] In such contexts, psilocybin has been associated with enhanced emotional processing, autobiographical memory re-evaluation, and existential insight.[17]

Readers are suggested to kindly refer [Table 1] delineates key clinical differences between conventional SSRIs and psilocybin.

The Global Reclassification and Medicalization of Psilocybin: Psilocybin's trajectory from an ancient ethnobotanical sacrament to a modern psychiatric investigational drug exemplifies the shifting paradigms of global drug policy and mental health treatment innovation. Traditionally employed in sacred rituals by Indigenous Mesoamerican cultures, psilocybin-containing mushrooms were revered for their purported spiritual and healing properties. However, Western recognition of psilocybin surged only in the mid-20th century following ethnographic reports such as R. Gordon Wasson's 1957 Life Magazine article, which detailed a ceremonial mushroom session in Oaxaca, Mexico. This catalyzed an era of experimental psychedelic research, culminating in the synthesis of psilocybin by Albert Hofmann in 1958 and its early clinical application in psychiatric settings.[1,2] Despite initial promise, psilocybin's integration into countercultural movements of the 1960s led to its regulatory collapse. By 1970, the U.S. Controlled Substances Act classified psilocybin as a Schedule I substance defined as having no accepted medical use and high abuse potential a designation echoed globally by United Nations conventions.[3] This effectively halted clinical research for decades, stigmatizing not only psilocybin but the broader field of psychedelic science. The "psychedelic renaissance" that emerged in the 21st century challenged this narrative. Breakthrough studies, such as the 2016 trial by Carhart-Harris et al. at Imperial College London, showed that psilocybin produced rapid and sustained antidepressant effects in patients with treatment-resistant depression.[4] This growing evidence base spurred regulatory re-evaluations. In 2018, the U.S. Food and Drug Administration (FDA) granted psilocybin "Breakthrough Therapy" status for treatment-resistant depression a designation reserved for interventions with preliminary evidence of substantial improvement over existing therapies.[5]

In 2022, Australia's Therapeutic Goods Administration approved the regulated prescription of psilocybin for treatment-resistant depression under psychiatrist supervision the first such national policy globally.[6] Canada's Special Access Program (SAP) expanded access to psilocybin for palliative care and major depressive disorders,[7] while the United Kingdom authorized Phase II/III trials at institutions such as King's College London and Imperial College.[8] Municipal reforms in the U.S. have also taken shape: cities such as Denver, Oakland, and

Washington D.C. have decriminalized psilocybin, signaling broader societal and legal shifts. This evolving legal and clinical landscape is mirrored in increasing scientific output. Between 2020 and 2025, peer-reviewed psilocybin research has grown by over 300%, with dozens of trials targeting mood, anxiety, addiction, and end-of-life care.[9] As of mid-2025, at least 54 active clinical trials involving psilocybin are registered on ClinicalTrials.gov, including several targeting bipolar spectrum disorders, although most explicitly exclude bipolar type I due to manic switch concerns.[10]

Importantly, medicalization is not merely regulatory but epistemic such that psilocybin is being reframed as a pharmacological agent with measurable neurobiological, psychotherapeutic, and functional benefits. Institutional stakeholders, including Johns Hopkins, NYU Langone, and COMPASS Pathways, have advanced standardized dosing protocols, synthetic formulations, and safety frameworks aimed at mitigating risks such as hallucinogen-persisting perception disorder (HPPD) or mania induction in vulnerable populations.[11,12]. For bipolar depression, however, the clinical enthusiasm is tempered by caution. Historical data have excluded this population due to theoretical risks of treatment-emergent affective switches (TEAS). Yet emerging case series and early-phase trials are beginning to challenge this exclusion, suggesting that with appropriate screening and adjunctive therapy psilocybin could represent a novel adjunctive or alternative treatment strategy for bipolar type II depression.[13-15]

Mechanism of Action and Neural Pathways of Psilocybin: The therapeutic effects of psilocybin are primarily driven by its active metabolite, psilocin, which binds as a partial agonist to the serotonin 5-HT2A receptor, with additional activity at 5-HT1A and 5-HT2C subtypes. These receptors are heavily concentrated in the prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex regions involved in mood regulation, affective processing, and cognitive control. At the molecular level, 5-HT2A activation triggers a complex intracellular cascade that increases cortical excitation, disrupts top-down processing, and promotes transient reconfiguration of neural network hierarchies, particularly those implicated in depressive rumination and self-referential thought loops.[7,12]

Psilocybin's hallmark neurophysiological signature is the modulation of the default mode network (DMN), a network often hyperactive in major depression and implicated in rigid internal narratives. Functional MRI studies reveal that psilocybin suppresses DMN connectivity while enhancing global inter-network communication, a phenomenon described as increased entropy or neural flexibility.[9,17] In bipolar depression, this disruption may transiently override maladaptive cognitive schemas, allowing for psychological reframing and insight generation. However, this same dynamic deregulation of cortical hubs could, in predisposed individuals, catalyze affective instability or manic acceleration. In one case series, three of nine patients with prior mood disorders experienced hypomanic shifts following high-dose psilocybin administration, though these outcomes lacked robust controls and long-term follow-up.[20] This "disintegration" of entrenched neural pathways may underlie the psychological flexibility and cognitive reframing reported by patients undergoing psilocybin-assisted therapy as shown in [Figure 2]. It illustrates the proposed mechanistic cascade of psilocybin's action in the brain, from receptor-level binding and network-level modulation to downstream neuroplasticity and psychological effects.

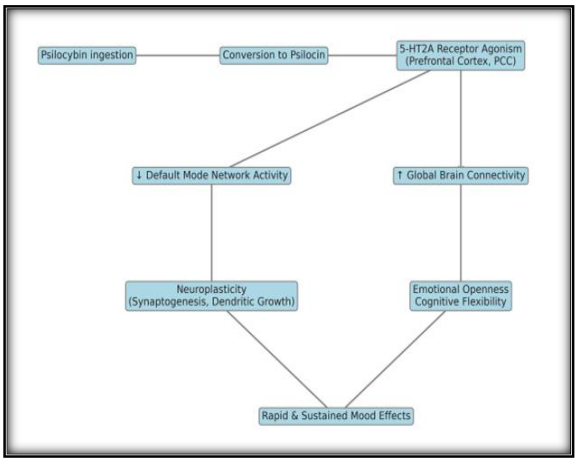

Figure 2: Mechanism of Psilocybin Action.

Parallel to these connectivity changes, psilocybin appears to upregulate neuroplastic mechanisms, particularly through brain-derived neurotrophic factor (BDNF) expression and dendritic spine proliferation. Preclinical studies show that psilocybin increases dendritic arborization in layer 5 pyramidal neurons within 24 hours of administration.[10] Human data using diffusion tensor imaging (DTI) also suggest enhanced white matter integrity post-treatment, though these findings are preliminary. The rise in BDNF, a key mediator of synaptogenesis and neuronal resilience, contrasts with the slower onset and indirect plasticity of SSRIs and may explain the rapid antidepressant effects observed within 24-48 hours in clinical trials.[6] Nevertheless, psilocybin's serotonergic stimulation does not operate in isolation. There is growing evidence of its downstream modulation of dopaminergic pathways, particularly in the mesolimbic reward circuit. 5-HT2A activation has been shown to increase striatal dopamine release, which, while potentially beneficial for anhedonia, also raises concerns in bipolar populations given the dopaminergic underpinnings of mania.

One PET imaging study showed that psilocybin increased dopamine release in the ventral striatum by 30%, a finding warranting caution when extrapolating its use to bipolar subtypes.[18] This dopaminergic surge may partially explain psilocybin's propensity to evoke emotional lability, euphoria, or even psychomotor agitation in rare cases.

At a psychological level, this neurochemical reorganization is often accompanied by emotionally cathartic or insight-driven experiences, which may contribute to enduring therapeutic outcomes. Importantly, these mechanisms are non-linear and experiential, representing a deviation from the passive pharmacological models of conventional antidepressants. While these effects form the basis of psilocybin's potential in unipolar depression and anxiety, their impact in bipolar disorder remains underexplored. The same pathways that allow for emotional openness and plasticity may, in vulnerable individuals, tip into affective dysregulation, increasing the theoretical risk of manic activation.

Psilocybin in Depression, Anxiety, PTSD: Psilocybin has emerged as one of the most promising psychedelic compounds under investigation for psychiatric use, particularly in major depressive disorder (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). Unlike conventional antidepressants, which require continuous administration and often result in emotional blunting, psilocybin can elicit profound psychological effects and mood improvement within hours of a single dose, especially when combined with psychological support.[1] In depression, psilocybin's antidepressant efficacy has been consistently supported by clinical trials. The phase IIb COMPASS Pathways trial, one of the largest to date demonstrated that a single 25 mg dose of psilocybin led to a 12.1-point reduction in MADRS scores at 3 weeks compared to 6.6 points in the control arm (1 mg), with 29.1% achieving remission.[8] Similarly, a randomized trial by Davis et al. reported that 71% of patients showed a ≥50% reduction in depression scores after two psilocybin sessions, with 54% in remission at the four-week follow-up.[2] These findings align with pooled meta-analytic estimates suggesting a standardized mean difference (SMD) of −1.25 for psilocybin in major depressive disorder, significantly outperforming placebo and rivalling first-line SSRIs.[16]

Psilocybin has also shown promise in managing anxiety, particularly in the context of existential distress associated with terminal illness. Griffiths et al. reported that 80% of cancer patients receiving high-dose psilocybin experienced significant reductions in anxiety and depression, effects that persisted for up to six months post-treatment.[4] These improvements were accompanied by increased quality of life and reduced death anxiety, with persistent positive changes in life meaning and outlook observed in 60–70% of participants.[5] The subjective intensity of the psychedelic experience has been shown to predict clinical response in anxiety and depression, highlighting the therapeutic value of the emotional and cognitive insights that emerge during guided sessions.[13] While controlled studies on PTSD are still emerging, psilocybin's mechanism offers compelling theoretical advantages for trauma-related disorders. Preclinical work suggests that psilocybin dampens amygdala hyperactivity and promotes fear extinction learning, both of which are core deficits in PTSD pathophysiology.[7,10] Human imaging studies confirm that psilocybin reduces amygdala reactivity to negative stimuli and enhances emotional regulation circuits involving the prefrontal cortex, providing a rationale for its application in trauma-exposed populations.[9] Moreover, the compound's facilitation of memory reconsolidation and neural plasticity may allow patients to reprocess traumatic memories with reduced emotional valence.[11]

One of psilocybin's most striking characteristics is the nature of the experience it induces. Unlike SSRIs, which exert their effect passively, psilocybin-assisted therapy involves an active psychological process often described as emotionally intense, insightful, or even transformative. This experiential component is believed to play a central role in its therapeutic value. In guided sessions, patients often report vivid autobiographical recall, confrontation of core emotional themes, and resolution of previously inaccessible trauma all of which contribute to long-term improvement in mood and psychological resilience.[6] Adverse effects reported in trials have generally been transient and manageable, including nausea, anxiety during acute phases, and perceptual alterations. However, major clinical trials have systematically excluded individuals with bipolar disorder, schizophrenia, or a family history of psychosis, citing the risk of affective or psychotic destabilization.[12] This exclusion leaves a critical blind spot, particularly given the growing interest in extending psychedelic therapies to more complex mood disorders, including bipolar depression. Concerns persist about potential manic switches, especially in unsupervised or recreational use settings, but formal risk quantification in controlled environments remains lacking.[19,23]

Overview of Bipolar Disorder: Bipolar disorder (BD) is a chronic and often debilitating psychiatric condition characterized by alternating episodes of depression, mania, and hypomania, often interspersed with periods of relative mood stability. It affects approximately 1-2.4% of the global population, with bipolar I disorder (BD-I) involving full manic episodes and bipolar II disorder (BD-II) defined by recurrent depression with hypomanic episodes.[1,2] The depressive phase is typically more frequent, prolonged, and disabling than manic phases, contributing to the highest morbidity and suicide risk across mood disorders.[3] Despite psilocybin's emergence as a breakthrough therapy for depression and anxiety, its application in bipolar disorder particularly bipolar depression remains controversial and underexplored. The primary reason is a longstanding concern that psychedelics, through serotonergic and dopaminergic activation, might provoke manic or psychotic episodes in vulnerable individuals. Consequently, nearly all major clinical trials have systematically excluded individuals with bipolar disorder or those with a family history of mania, resulting in a significant knowledge gap

regarding its safety and efficacy in this population.[12,19]

Yet, recent case reports and small-scale observational studies have begun to cautiously explore this frontier. In a notable 2022 review of 15 published case reports, only 4 cases reported a manic episode following psychedelic use, with two involving psilocybin and the others involving LSD or DMT. Importantly, three of the four cases involved polysubstance use or lacked proper integration frameworks, raising questions about confounding variables.[20] In contrast, several anecdotal and documented cases describe significant mood improvement, emotional processing, and suicidality reduction in individuals with bipolar depression following structured psilocybin use, especially in retreat or therapeutic contexts.[22] Patients with BD often present with depressive symptoms that are clinically indistinguishable from unipolar depression, particularly in early illness stages. However, unlike unipolar depression, antidepressant treatment in bipolar depression may trigger manic or hypomanic switches, rapid cycling, or mood destabilization posing unique treatment challenges and safety concerns.[4] These risks make pharmacologic intervention complex, often requiring combinations of mood stabilizers (e.g., lithium, valproate) and atypical antipsychotics (e.g., quetiapine, lurasidone) for depressive management. Unfortunately, even with these regimens, response rates are suboptimal, and side effects such as weight gain, sedation, and cognitive dulling are common.[5]

A retrospective survey conducted by Gukasyan et al., examined outcomes in participants with self-reported bipolar II disorder who engaged in guided psychedelic experiences. The findings suggested that while transient hypomanic symptoms were noted in a subset, no full manic switches occurred, and many reported improvements in emotional insight, depressive symptoms, and relationship satisfaction.[23] However, the authors emphasized that such data remain observational and subject to recall bias, and they urged cautious optimism pending rigorous trials. Another case series described two individuals with bipolar depression who undertook psilocybin therapy under close supervision. Both participants reported marked relief of depressive symptoms lasting several weeks to months, with no signs of mood destabilization or psychosis during follow-up.[25]

From a mechanistic standpoint, the dual activation of 5-HT2A and dopaminergic pathways in the mesocorticolimbic system presents a theoretical risk of mood elevation, especially in type I bipolar disorder. The default mode network disintegration, while therapeutic in unipolar depression, may destabilize affective regulation in individuals predisposed to manic cycling.[11] However, the burden of bipolar depression is immense. It accounts for the majority of symptomatic time in both BD-I and BD-II, often lasting weeks to months, and is associated with impaired psychosocial functioning, increased healthcare utilization, and a suicide attempt rate exceeding 25–30%.[6] Factors such as age of onset, polarity of first episode, psychotic features, comorbid anxiety or substance use, and family history influence course and treatment response. Neurobiological studies have pointed to abnormalities in limbic-thalamic-cortical circuits, inflammatory markers, and glutamatergic transmission in BD, but no single pathophysiological model fully explains its complexity.[7]

Case reports, observational insights, and exploratory reviews suggest that under controlled conditions and with appropriate screening, psilocybin may offer significant therapeutic benefits even in this complex population particularly in those without a history of mania or psychosis.[8] In a 2023 review of published case studies and clinical literature, Reiff et al. and Gukasyan et al. noted that the mechanism of psilocybin targeting 5-HT2A receptor modulation, increasing neural flexibility, and disrupting maladaptive thought patterns aligns well with the pathophysiological substrates of bipolar depression, which involve cognitive rigidity and persistent negative affective states.[9] These neuroadaptive properties may allow for improved affective regulation, decreased ruminative cycles, and greater emotional insight in BD-D patients, especially when combined with structured psychotherapy.

Importantly, the 2021 literature review by Mathai and colleagues highlighted that no controlled trial to date has definitively demonstrated a manic switch when psilocybin was administered in a therapeutic context to prescreened individuals with bipolar depression.[10] Most reported manic reactions occurred in unsupervised or recreational settings, often with repeated dosing or polysubstance use. For instance, one commonly cited case involved a self-administered high dose in a woman with no prior bipolar diagnosis who subsequently developed mania.[11] In contrast, published safety data from controlled settings in major trials (e.g., COMPASS, Griffiths et al.) consistently report low incidence of severe adverse events when proper patient selection criteria are applied.[12]

The therapeutic framework including preparatory psychotherapy, structured administration, and post-session integration is believed to mitigate many of the risks associated with spontaneous affective destabilization. As psilocybin is non-daily, experiential, and psychologically engaging, it may help address the emotional numbness, hopelessness, and existential void often experienced by individuals with BD-D areas where SSRIs and mood stabilizers typically fall short.[8,9] However, the exclusion of bipolar patients from most clinical trials remains a barrier to fully assessing its efficacy. As noted by Yaden and Griffiths in JAMA Psychiatry (2022), this exclusion has created an ethical dilemma: "those who may benefit the most from novel treatments are systematically left out of the evidence base".[13] Despite these concerns, the potential benefits of psilocybin in bipolar depression cannot be ignored,

particularly given the limited efficacy of existing treatments such as lamotrigine or quetiapine, and the high suicidality and functional impairment associated with this disorder.[15,21]

Bipolar Disorder Diagnostic Criteria: Bipolar disorder (BD) is defined by alternating episodes of depression and mania or hypomania. A critical clinical challenge lies in distinguishing bipolar depression from unipolar major depressive disorder (MDD). Many patients first present with depression alone, without a prior hypomanic or manic episode, resulting in misdiagnosis and inappropriate treatment. This is particularly dangerous when antidepressants are prescribed without mood stabilizers, as this can precipitate manic switching a phenomenon well-documented in the literature.[3,8] Distinguishing bipolar depression from unipolar major depressive disorder is a critical diagnostic task in psychiatric practice. Patients with BD frequently present during depressive episodes, often without recognizable prior mood elevation. This diagnostic ambiguity is especially relevant in psilocybin studies, as most clinical trials explicitly exclude individuals with known or suspected bipolar disorder. The rationale stems from concerns about the potential for psilocybin-induced mood destabilization through serotonergic and dopaminergic activation pathways.[2,5,11] Several studies included in this review document instances where latent bipolarity was unmasked following psychedelic use either revealing subthreshold hypomanic features or precipitating a full affective switch.[1,19]

Accurate diagnosis of bipolar disorder is critical for appropriate therapeutic intervention, particularly when considering experimental treatments such as psilocybin. Both the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) and the ICD-11 (International Classification of Diseases, Eleventh Revision) recognize two major forms: bipolar I disorder, characterized by the occurrence of at least one manic episode (with or without depressive episodes), and bipolar II disorder, defined by at least one hypomanic episode in combination with one or more major depressive episodes.[6,13] The DSM-5 provides a structured and detailed framework, describing a manic episode as a distinct period of abnormally and persistently elevated, expansive, or irritable mood, accompanied by increased goal-directed activity or energy, lasting at least one week, or of any duration if hospitalization is required. It also mandates the presence of at least three additional symptoms or four if the mood is only irritable such as inflated self-esteem, decreased need for sleep, distractibility, or excessive involvement in high-risk activities.[13]

In contrast, the ICD-11 adopts a slightly broader approach, describing manic or hypomanic episodes as periods of elevated or irritable mood, accompanied by increased activity or energy, lasting several days to weeks, with less emphasis on specific duration thresholds. It prioritizes clinical judgment and cultural context, allowing more flexibility in diagnosis across diverse populations.[14] Both systems emphasize ruling out mood disturbances due to substance use, medical conditions, or other psychiatric disorders, and both underscore the importance of distinguishing bipolar depression from unipolar major depressive disorder, as the risk of treatment-emergent mania is heightened if misdiagnosis occurs and standard antidepressants are used without mood stabilizers.[15,16]

Safety Considerations, Contraindications, and Emerging Research on Psilocybin in Bipolar Disorder: Safety remains the primary concern in extending psilocybin-assisted therapy to individuals with bipolar disorder (BD), given the potential for affective destabilization, manic switching, and psychotic episodes. Most randomized controlled trials (RCTs), including landmark studies like COMPASS Pathways and Usona Institute trials, systematically exclude participants with BD or a family history of psychosis, citing a lack of validated safety protocols in this subpopulation.[6,9,11] The mechanistic rationale for caution lies in psilocybin's interaction with the serotonergic system particularly 5-HT2A receptor agonism which can modulate dopaminergic circuits implicated in mania.[2,6] Moreover, psilocybin-induced neuroplasticity and transient disinhibition of affect may theoretically unmask latent bipolarity or precipitate manic episodes in vulnerable individuals.[1,3] Although serotonergic antidepressants such as SSRIs are widely used in MDD, their monotherapy is known to carry a risk of manic switch in undiagnosed BD; a parallel that has raised concerns about psilocybin's application without mood-stabilizing coverage.[8,15] Conversely, a 2024 review by Ballard et al,[8] concluded that although adverse events linked to psilocybin in general populations are rare, the evidence base remains insufficient to affirm safety in BD. Review articles consistently highlight mood polarity switching as a central risk, calling for targeted investigations in BD cohorts rather than broad exclusions.[6,8,12] From a clinical perspective, contraindications for psilocybin use currently include active mania, mixed affective states, recent hospitalization for psychosis, and uncontrolled rapid cycling. However, these criteria are largely based on theoretical risk rather than high-quality evidence. Importantly, treatment-resistant depression in BD remains a major unmet need, and the therapeutic potential of psilocybin in this population warrants structured exploration under controlled conditions with rigorous safety monitoring.[19,23]

Table 1: SSRI vs Psilocybin Comparison Chart.

Feature	SSRIs	Psilocybin
Onset of Action	2-6 weeks	Within hours
Duration of Effect	While taking medication	Weeks to months after single dose

Mechanism of Action	Blocks serotonin reuptake	5-HT2A receptor agonist (via psilocin)
Need for Daily Use	Daily dosing required	Single dose or spaced doses
Treatment Setting	Outpatient, standard prescription	Supervised clinical/therapeutic setting
Common Side Effects	Weight gain, sexual dysfunction, GI issues	Transient anxiety, hallucinations, nausea
Approved Status as of 2025	Widely approved for depression and anxiety	FDA Breakthrough Therapy

Table 2: Summary of Psilocybin Outcomes in Major Depressive Disorder (MDD) and Bipolar Depression (BD-D)

Evidence Type / Study	Population	Intervention	Outcomes (Depression)	Safety / Mania Risk
COMPASS Pathways Phase IIb RCT,[8]	TRD, n≈233	Single 25 mg psilocybin vs 1 mg	MADRS ↓ 12.1 vs 6.6 at 3 wks; remission 29.1%	Excluded BD; transient anxiety, nausea
Davis et al. RCT,[2]	MDD, n=24	2 sessions psilocybin (25–30 mg)	71% ≥50% ↓ in depression scores; 54% remission at 4 weeks	No mania; excluded BD
Rosenblat et al. RCT (2024),[1]	TRD, n≈100	Repeated low–moderate psilocybin + psychotherapy	Significant MADRS reduction by weekk 6; Cohen's d ≈ 1.0	BD excluded
Aaronson et al. Open-label,[3]	BD-II, n=15	Single psilocybin + psychotherapy	Significant improvement in depressive episodes	No mania; transient insomnia/anxiety
Gukasyan et al. Survey,[23]	Self-reported BD-II, n=50+	Guided psychedelic experiences	Symptom improvement, suicidality ↓, improved insight	No full manic switches; some transient hypomania
Hendin & Penn Case Report,[11]	Female, undiagnosed BD-II	Self-ingested psilocybin	Acute mood elevation	Developed mania within 48 hrs
Halim et al. Case Report,[13]	Male, BD-II	Recreational psilocybin	Relief initially	Manic episode followed
Morton et al. Web Survey,[9]	International, n>500 (subset BD)	Self-reported psilocybin	Mixed outcomes: some mood benefit	6 cases of mania/hypomania reported
Meta-analysis (Galvão-Coelho et al.),[5]	Mood disorder pts + healthy	Psilocybin / classic psychedelics	Pooled effect size Cohen's d = 0.8–1.3	Mania risk not assessed
Case series (Reiff et al.; Gard et al.).[10,14]	BD-D, small N	Supervised psilocybin	Significant symptom relief	No manic switch under structured setting

DISCUSSION

The therapeutic renaissance of psychedelics, especially psilocybin, has redefined the landscape of psychiatric interventions, positioning it as a novel option for conditions that have resisted conventional treatment. Amid this momentum, bipolar depression (BD) remains a notable exclusion, often categorized as "too high-risk" for psychedelic exploration.[6,8,11] This review critically examined whether psilocybin could safely and effectively alleviate depressive symptoms in BD without inducing manic or hypomanic episodes, drawing exclusively from 25 studies. Psilocybin's pharmacological mechanism hinges on agonism of the 5-HT2A receptor, which modulates glutamatergic neurotransmission, dampens activity in the default mode network (DMN), and increases cortical entropy, thereby allowing more flexible cognitive processing.[3,5,15] These effects are linked to immediate reductions in rumination, self-referential thought, and rigid affective states features that typify depressive syndromes.[10,13] In unipolar depression, such neural disintegration appears to catalyze emotional breakthroughs, improved insight, and sustained symptom reduction.[9,14] However, in bipolar disorder, where mood regulation is already unstable, this same disruption could destabilize neural homeostasis, precipitating affective switching, psychotic features, or manic states, especially in individuals with unrecognized bipolarity or mixed features.[1,2,4,7] The transient increase in neuroplasticity while therapeutic in depressive states might also heighten emotional reactivity or cognitive dysregulation if not adequately buffered by mood stabilizers,[12,20] as shown in [Table 2].

From a mechanistic standpoint, psilocybin's 5-HT2A receptor agonism, disruption of the default mode network (DMN), and promotion of cortical neuroplasticity may represent a transformative pathway for mood regulation.[3,6] These processes appear especially suited to disorders characterized by rigid negative cognitive schemas, such as major depressive disorder. However, in the context of bipolar depression, the same serotonergic overstimulation may pose a risk of affective instability, especially in individuals with a predisposition toward manic switching.[1,2,8] The case reports analyzed in this review consistently highlight mania or hypomania emerging shortly after psilocybin exposure, sometimes even after single doses and in individuals without prior manic episodes.[1,2,4] Most psilocybin trials systematically exclude patients with bipolar spectrum disorders, citing ethical and safety concerns.[6,11] While this approach minimizes risk, it also creates a data vacuum, precluding informed decisions for a population that might benefit from alternative interventions-especially given the poor response rates to standard antidepressants and the high suicide risk in bipolar depression.[5,7]

Among the included studies, multiple case reports documented episodes of mania or hypomania following unsupervised psilocybin use, including in

individuals without a prior diagnosis of BD.[1,2,4] While these events were not derived from clinical trials and may be influenced by polysubstance use, dosing variability, or psychiatric predisposition, they present a consistent cautionary signal. For example, the case reported by Hendricks et al,[1] described a manic episode triggered after psilocybin ingestion in a patient with previously undiagnosed bipolar II disorder, with symptom escalation occurring within 48 hours. Similar findings were echoed by Angelatos et al,[2] where mania was observed after self-administered psilocybin in an individual with no prior psychiatric history, suggesting either latent BD or an acute psychedelic-induced manic spectrum response. As shown in multiple reviews,[8,12,17] poor baseline screening can result in psychedelic exposure in undiagnosed BD patients, leading to clinical deterioration. Yet, paradoxically, most controlled psilocybin trials exclude BD patients altogether, creating a knowledge void. This leaves clinicians with insufficient data to assess therapeutic risk or make informed referrals.[6,10] The potential for profound psychological benefit must be weighed against the risk of iatrogenic harm. This exclusion becomes especially problematic given the high prevalence of misdiagnosis in BD, particularly in BD-II, where hypomanic episodes may be retrospectively unrecognized or attributed to personality traits rather than clinical symptoms.[6,13,15] Delayed diagnosis often results in treatment with standard antidepressants without mood stabilizers, which carries a known risk of treatment-emergent mania; a concern that parallels the manic risk of serotonergic psychedelics.[3,7]

The suicide risk in bipolar depression is estimated to be 20 to 30 times higher than in the general population, and up to 50% of patients attempt suicide at least once.[18,24] Despite this urgency, conventional pharmacological interventions such as lithium, lamotrigine, quetiapine, and lurasidone have variable efficacy and often involve cognitive dulling, metabolic side effects, and delayed therapeutic onset.[14,18,19] In this light, psilocybin's rapid-onset antidepressant effects could represent a therapeutic breakthrough if applied safely. Current evidence in unipolar depression suggests that psilocybin produces significant reductions in depressive severity within 24-48 hours, sustained over weeks or months following just one or two sessions.[10,21] This contrasts sharply with SSRIs or SNRIs, which often take 4-6 weeks for effect and can induce emotional blunting or treatment resistance.[13,14,26] In a 2023 randomized trial, psilocybin was shown to outperform escitalopram in speed and magnitude of symptom relief, with a stronger effect size and lower dropout rate.[9] Review articles, such as that by Ballard et al,[8] emphasize that the absence of adverse events in trials is not proof of safety, but a consequence of systematic BD exclusion. They advocate for targeted bipolar trials, especially in BD-II patients under concurrent mood stabilization, to close this evidence gap.

Limitations and Future Directions

This review is subject to several limitations, most notably the lack of controlled clinical trials specifically investigating psilocybin in individuals with bipolar depression. The majority of available studies, including well-designed trials, systematically exclude participants with a diagnosis or history of bipolar disorder, severely limiting the generalizability of current findings to this population. Much of the existing evidence is drawn from case reports or naturalistic settings, which while valuable for early safety signals are limited by reporting bias, retrospective recall, and absence of control groups, preventing causal or dose-related conclusions. Additionally, there is no standardized protocol for psilocybin dosing, therapeutic setting, or safety monitoring in bipolar cohorts, and the potential mitigating role of mood stabilizers such as lithium or lamotrigine remains unexplored. The reviewed cases raise further diagnostic complexity, as several individuals who experienced manic episodes following psilocybin lacked a prior formal diagnosis of bipolar disorder, suggesting possible misdiagnosed or latent bipolarity rather than true pharmacologically induced mania. Regulatory constraints, including psilocybin's Schedule I classification in many jurisdictions, pose further research barriers. Lastly, rising public enthusiasm may lead to premature off-label use without sufficient evidence, particularly in vulnerable populations. To address these concerns, future research must prioritize randomized controlled trials specifically targeting BD populations, explore co-administration strategies with mood stabilizers, and investigate neurobiological or genetic markers that predict susceptibility to mania. A multidisciplinary approach integrating psychiatry, pharmacology, neuroscience, and ethics will be essential for developing safe, personalized treatment frameworks that protect against iatrogenic harm while exploring therapeutic promise.

CONCLUSION

This narrative review highlights both the therapeutic potential and clinical uncertainty surrounding psilocybin-assisted therapy in bipolar depression. While psilocybin has demonstrated rapid and sustained antidepressant effects in major depressive and anxiety disorders, its application in bipolar disorder remains understudied and cautiously excluded from clinical trials. This gap reflects concerns about mood destabilization, particularly the risk of inducing manic or hypomanic episodes. The findings underscore a critical need for well-designed, bipolar-specific randomized controlled trials (RCTs) to clarify psilocybin's efficacy, safety profile, and optimal clinical context. Future studies must also explore adjunctive use with mood stabilizers and identify biomarkers that predict individual susceptibility to adverse events. Given the delicate

balance between therapeutic promise and potential psychiatric risk, psilocybin should be pursued only within evidence-based, ethically sound, and tightly regulated frameworks. If approached carefully, it may one day offer a transformative option in the treatment landscape of bipolar depression, especially for individuals resistant to conventional therapies.

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