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Psilocybin-Induced Neuroplasticity and Sustained Antidepressant Effects

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Abstract

Psilocybin-assisted interventions have shown rapid reductions in depressive symptoms in controlled clinical settings, raising questions about biological mechanisms supporting durability beyond the acute drug effect. [5,7] Mechanistic accounts increasingly focus on neuroplasticity as a candidate pathway linking transient serotonergic receptor activation to longer-lasting psychological and clinical change. [2,6] To synthesize evidence from the

publications regarding (1) antidepressant clinical outcomes after psilocybin-assisted interventions and (2) neuroplasticity-related biological findings that plausibly support sustained improvement. [2,3] Narrative review using only (clinical trials/secondary analyses and mechanistic animal/neuroimaging work). Evidence was summarized qualitatively; no meta-analysis was performed. [2,16] Randomized and open-label clinical studies report rapid symptom reduction and follow-up persistence in major depression and cancer-related depression/anxiety, including six-month outcomes in treatment-resistant depression (TRD) protocols with psychological support. [4,5,7,19] Preclinical work provides convergent evidence of plasticity-relevant change after psilocybin, including structural synaptic remodeling in frontal cortex and hippocampal plasticity-related outcomes in extinction learning paradigms. [3,8] Human neuroimaging work reports changes consistent with altered large-scale brain dynamics after psilocybin and TRD-related mechanistic findings on fMRI. [6,20] Across the uploaded dataset, psilocybin-assisted therapy is associated with rapid antidepressant effects and durability signals in selected samples, while convergent animal and human mechanistic findings support neuroplasticity as a biologically plausible contributor to sustained clinical improvement. [2,3]

Keywords: Psilocybin; Depression; Treatment-Resistant Depression; Neuroplasticity; Dendritic Spines; BDNF; Psychedelic Therapy; Functional Connectivity; SSRIs

Introduction

Introduction Major depressive disorder (MDD) remains highly prevalent and often recurrent, and a substantial proportion of patients experience incomplete response to standard treatments. [16] Psilocybin is evaluated not as a stand-alone drug exposure but as a psychologically

supported intervention delivered under structured monitoring and therapeutic preparation/integration. [5,7] A central mechanistic question is why clinical improvement may persist beyond acute intoxication. [2] A neuroplasticity-focused framework proposes that psychedelic serotonergic pharmacology may trigger downstream molecular and circuit-level adaptations that facilitate enduring changes in affective processing, learning, and self-related cognition. [2] This review synthesizes the clinical durability signals to plasticity-relevant mechanistic findings. [2,3] Direct mechanistic anchor (title-level quote): “Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo.”

Methods

Design Narrative review based exclusively on the references below. No external databases or internet sources were used.

Included evidence

Clinical antidepressant outcomes MDD randomized clinical trial (psilocybin-assisted therapy). [5] TRD protocols with psychological support and follow-up. [14,19] Cancer-related depression/anxiety randomized trials. [4,7] TRD with concomitant SSRI medication. [9] Comparative/adjacent trial framework vs escitalopram and related secondary analyses (affective bias, rumination/thought suppression, discontinuation). [12,15,18] Mechanistic and neuroplasticity-related evidence Structural plasticity in vivo (dendritic spines). [3] Extinction learning with hippocampal plasticity-related outcomes. [8] Human brain dynamics / network-level effects and TRD fMRI mechanisms. [6,20] Mechanistic reviews and translational synthesis. [1,2,16,17]

Results Table 1.

Table 1. Summary of key clinical studies

Study (population)	Design	Intervention context	Main outcome domain	Durability window reported
Davis et al. (MDD) [5]	Randomized clinical trial	Psilocybin-assisted therapy with psychological support	Depressive symptom reduction	Follow-up within trial window reported [5]
Griffiths et al. (cancer distress) [4]	Randomized, double-blind trial	PsCT setting with structured support	Depression/anxiety reduction	Sustained decreases reported at follow-up [4]
Ross et al. (cancer distress) [7]	Randomized controlled trial	Psychological support + psilocybin session	Anxiety/depression reduction	"rapid and sustained symptom reduction" (title-level wording) [7]
Carhart-Harris et al. TRD (acute + follow-up) [14,19]	Open-label/clinical follow-up	Psychological support (TRD protocol)	Depressive symptom change	Six-month follow-up reported [19]
Goodwin et al. (TRD + concomitant SSRI) [9]	Clinical study	Psilocybin while continuing SSRI medication	TRD symptom outcomes + feasibility	Follow-up as reported in study [9]

Becker et al. (healthy volunteers) [10]	Randomized, crossover	Escitalopram vs placebo pretreatment then psilocybin	Acute effects / interaction	Acute outcomes (not long-term clinical) [10]
Psilocybin vs escitalopram secondary outcomes [12,15,18]	Trial/secondary analyses	Comparator framework including escitalopram	Rumination/thought suppression; negative affective bias; discontinuation effects	As reported per analysis [12,15,18]

Summary of key clinical studies in the uploaded dataset Study (population) Design Intervention context Main outcome domain Durability window reported Davis et al. (MDD) [5] Randomized clinical trial Psilocybin-assisted therapy with psychological support Depressive symptom reduction Follow-up within trial window reported [5] Griffiths et al. (cancer distress) [4] Randomized, double-blind trial PsCT setting with structured support Depression/anxiety reduction Sustained decreases reported at follow-up [4] Ross et al. (cancer distress) [7] Randomized controlled trial Psychological support + psilocybin session Anxiety/depression reduction “rapid and sustained symptom reduction” (title-level wording) [7] Carhart-Harris et al. TRD (acute + follow-up) [14,19] Open-label/clinical follow-up Psychological support (TRD protocol) Depressive symptom change Six-month follow-up reported [19] Goodwin et al. (TRD + concomitant SSRI) [9] Clinical study Psilocybin while continuing SSRI medication TRD symptom outcomes + feasibility Follow-up as reported in study [9] Becker et al. (healthy volunteers) [10] Randomized, crossover Escitalopram vs placebo pretreatment then psilocybin Acute effects / interaction Acute outcomes (not long-term clinical) [10] Psilocybin vs escitalopram secondary outcomes [12,15,18] Trial/secondary analyses Comparator framework including escitalopram Rumination/thought suppression; negative affective bias; discontinuation effects As reported per analysis [12,15,18] 3.1 Clinical antidepressant outcomes and durability signals 3.1.1 Major depressive disorder In a randomized clinical trial of psilocybin-assisted therapy for MDD, the intervention produced substantial symptom reduction within the controlled therapeutic protocol. [5] The paper’s design and follow-up support claims of improvement persisting beyond the dosing day(s) within the observation window. [5] 3.1.2 Depression/anxiety in life-threatening cancer Two randomized controlled trials in cancer-

related distress report rapid reductions in depression/anxiety measures and sustained benefit at longer follow-up in a substantial portion of participants. [4,7] These studies are central to the "limited dosing, durable effect" clinical pattern described in the dataset. [4] Direct quote (title-level wording): "Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer." [4] 3.1.3 Treatment-resistant depression (TRD) and follow-up TRD-focused protocols with psychological support report symptom reduction and durability signals, including longer follow-up reporting at six months in the uploaded set. [14,19] These papers reinforce the observation that clinical improvement may persist well beyond acute pharmacological exposure. [19] 3.1.4 Concomitant SSRI medication and acute SSRI–psilocybin interaction Real-world implementation often involves patients taking SSRIs. A TRD study in the uploaded set specifically evaluates psilocybin in patients taking concomitant SSRI medication, providing feasibility and outcome data under that condition. [9] Separately, a randomized crossover study in healthy participants tested psilocybin after escitalopram or placebo pretreatment, informing controlled understanding of acute interaction effects. [10] 3.2 Neuroplasticity-related evidence supporting a durability mechanism 3.2.1 Structural synaptic plasticity (frontal cortex dendritic spines) The clearest direct neuroplasticity evidence in the dataset is the in vivo demonstration of rapid and persistent dendritic spine growth in frontal cortex following psilocybin exposure. [3] Structural synaptic remodeling is widely interpreted as a cellular substrate of longer-term circuit adaptation, providing a plausible biological bridge between acute receptor activation and durable behavioral/clinical effects. [2,3] 3.2.2 Learning/extinction processes linked to hippocampal plasticity A mouse study reports facilitated fear extinction and links this behavioral effect to hippocampal neuroplasticity-related findings. [8] While fear extinction is not itself a depression endpoint, it models learning processes relevant to maladaptive affective and stress-related patterns, offering an additional mechanistic bridge from acute dosing to durable behavioral change. [8] Direct quote (title-level wording): "Psilocybin facilitates fear extinction in mice by promoting hippocampal neuroplasticity." [8] 3.2.3 Human brain-level mechanistic findings Human neuroimaging and brain-dynamics work in the uploaded set supports mechanistic discussion at the systems level, including altered brain activity dynamics after psilocybin and TRD-related fMRI-measured brain mechanisms. [6,20] These findings are compatible with the idea that psilocybin can transiently perturb large-scale networks in a way that may enable subsequent reorganization, though causal durability mechanisms cannot be proven from these studies alone. [2,20]

Clinical antidepressant outcomes and durability signals

Major depressive disorder

In a randomized clinical trial of psilocybin-assisted therapy for MDD, the intervention produced substantial symptom reduction within the controlled therapeutic protocol. [5] The paper's design and follow-up support claims of improvement persisting beyond the dosing day(s) within the observation window. [5]

Depression in life-threatening cancer

Two randomized controlled trials in cancer-related distress report rapid reductions in depression/anxiety measures and sustained benefit at longer follow-up in a substantial portion of participants. [4,7] These studies are central to the "limited dosing, durable effect" clinical pattern described in the dataset. [4] In a rigorous randomized double-blind cross-over trial involving 51 cancer patients with depression or anxiety symptoms, researchers compared a very low placebo-like dose of psilocybin with a moderately high dose. Participants were randomized to receive either the low dose first then the high dose, or vice versa, with sessions separated by five weeks and follow-up lasting six months. The low dose served as a placebo control, and instructions minimized expectancy effects while psychological support was provided throughout. High-dose psilocybin produced large reductions in clinician- and self-rated depression and anxiety scores. Patients also reported increases in quality of life, life meaning and optimism, and decreases in death anxiety. At the six-month follow-up, about 80% of participants still showed clinically significant reductions in depression and anxiety. Participants attributed improvements in attitudes toward life, mood, relationships and spirituality to the high-dose experience. More than 80% reported enhanced well-being or life satisfaction. Observers from participants' communities also noted corresponding positive changes in mood and behavior. Together, these results suggest that psilocybin-assisted therapy can provide rapid and enduring relief for psychological distress in cancer patients, meriting further large-scale trials. [4]

Treatment-resistant depression (TRD) and follow-up

TRD-focused protocols with psychological support report symptom reduction and durability signals, including longer follow-up reporting at six months in the uploaded set. [14,19] These papers reinforce the observation that clinical improvement may persist well beyond acute pharmacological exposure. [19]

An open-label feasibility study at Imperial College London treated 20 patients with severe, treatment-resistant major depression using two sessions of psilocybin (10 mg and 25 mg one week apart), combined with psychological support. Depression severity, measured primarily by the self-rated QIDS-SR16 scale, decreased markedly: effect sizes at week 1 and week 5 were very large (Cohen's d ≈ 2.2 and 2.3, respectively), with nine patients meeting response criteria and four achieving remission at week 5. These improvements persisted at three and six months (effect sizes ≈ 1.5 and 1.4), and patients generally did not seek conventional antidepressant treatments in the early weeks following psilocybin. Treatment was well tolerated, with only transient anxiety or headaches during the dosing sessions, and no serious adverse events were reported; reductions in depressive symptoms correlated with the quality of the acute psychedelic experience. Although the open-label design limits definitive conclusions, the combination of rapid, sustained symptom relief and good tolerability suggests that psilocybin-assisted therapy is a promising avenue for addressing treatment-resistant depression, warranting further research in controlled trials.[1]

Concomitant SSRI medication and acute SSRI–psilocybin interaction

Real-world implementation often involves patients taking SSRIs. A TRD study in the uploaded set specifically evaluates psilocybin in patients taking concomitant SSRI medication, providing feasibility and outcome data under that condition. [9] Separately, a randomized crossover study in healthy participants tested psilocybin after escitalopram or placebo pretreatment, informing controlled understanding of acute interaction effects. [10]

Neuroplasticity-related evidence supporting a durability mechanism

Structural synaptic plasticity (frontal cortex dendritic spines)

The clearest direct neuroplasticity evidence in the dataset is the in vivo demonstration of rapid and persistent dendritic spine growth in frontal cortex following psilocybin exposure. [3]

Structural synaptic remodeling is widely interpreted as a cellular substrate of longer-term circuit adaptation, providing a plausible biological bridge between acute receptor activation and durable behavioral/clinical effects. [2,3]A single dose of psilocybin rapidly increases dendritic spine density and size in the mouse frontal cortex, with effects lasting for at least a month. These changes mainly arise from heightened formation of new spines, many of which persist and stabilize over time. Psilocybin also reduces stress-related behaviors and increases excitatory neurotransmission, suggesting strengthened glutamatergic signaling. Notably, blocking 5-HT_2A receptors with ketanserin eliminates the typical head-twitch response but does not prevent psilocybin's structural effects, implying partial independence from this receptor subtype. These findings place psilocybin among rapid-acting antidepressants that induce enduring synaptic rewiring, potentially providing a biological basis for long-term therapeutic benefits.[12]

Learning/extinction processes linked to hippocampal plasticity

A mouse study reports facilitated fear extinction and links this behavioral effect to hippocampal neuroplasticity-related findings. [8] While fear extinction is not itself a depression endpoint, it models learning processes relevant to maladaptive affective and stress-related patterns, offering an additional mechanistic bridge from acute dosing to durable behavioral change. [8]

Direct quote (title-level wording): "*Psilocybin facilitates fear extinction in mice by promoting hippocampal neuroplasticity*." [8]

Human brain-level mechanistic findings

Human neuroimaging and brain-dynamics work in the uploaded set supports mechanistic discussion at the systems level, including altered brain activity dynamics after psilocybin and TRD-related fMRI-measured brain mechanisms. [6,20] These findings are compatible with the idea that psilocybin can transiently perturb large-scale networks in a way that may enable subsequent reorganization, though causal durability mechanisms cannot be proven from these studies alone. [2,20]

Discussion

Principal synthesis

Across the uploaded clinical studies, psilocybin-assisted protocols delivered with psychological support are associated with rapid symptom improvement and follow-up persistence in selected populations (MDD, cancer distress, TRD). [4,5,7,19] Convergent preclinical evidence demonstrates plasticity-relevant biological change after psilocybin exposure, including structural synaptic remodeling and hippocampal plasticity-linked learning effects. [3,8] Mechanistic reviews in the dataset provide an integrative account connecting serotonergic receptor action to downstream plasticity pathways, offering a coherent explanatory frame for durability signals observed clinically. [2,16]

Candidate mediators and cognitive-affective processes

Beyond symptom scores, secondary analyses in the uploaded set address cognitive-affective targets plausibly relevant to depression maintenance (e.g., rumination/thought suppression and negative affective bias) in comparator frameworks involving psilocybin and escitalopram. [15,18] Additional TRD work in the dataset examines emotion-related processing (e.g., emotional face recognition; emotional empathy) in relation to psilocybin with psychological support. [11,14] These outcomes support the broader hypothesis that psilocybin-assisted therapy may shift affective processing styles that maintain depressive symptomatology. [11,15]

SSRI discontinuation vs continuation: what the uploaded set can (and cannot) conclude

The uploaded dataset includes evidence relevant to both (a) psilocybin administration under concomitant SSRI use and (b) experimental escitalopram pretreatment in healthy participants. [9,10] It also includes an analysis focused on discontinuation of serotonergic antidepressants prior to psilocybin therapy versus escitalopram for major depression. [12] However, broad clinical generalization requires caution because protocols, populations, and endpoints differ across these papers. [9,12]

Conclusions Psilocybin-assisted interventions show rapid antidepressant effects with durability signals in controlled clinical settings (MDD, cancer distress) and in TRD protocols with psychological support, including longer follow-up reporting. [4,5,19] Convergent preclinical

work demonstrates neuroplasticity-relevant effects after psilocybin (structural synaptic remodeling; hippocampal plasticity-linked extinction learning). [3,8] Together with mechanistic reviews and human neuroimaging findings, the dataset supports neuroplasticity as a biologically plausible contributor to sustained improvement in depressive symptoms following brief psilocybin exposure. [2,6,20]Mechanistic reviews and human neuroimaging also support a plasticity-based model. For instance, recent reviews characterize psychedelics as **"psychoplastogens"** that acutely induce a period of heightened neuroplasticity, explaining why single or few doses can yield lasting psychological improvements. In depressed patients, post-psilocybin brain imaging shows enduring functional changes: Carhart-Harris et al. observed that therapeutic response was associated with post-treatment decreases in amygdala blood flow and specific connectivity shifts (increased default-mode network coherence) predictive of clinical benefit. In sum, the collective data from clinical trials, animal studies, and brain imaging converge on the idea that brief psilocybin exposure triggers plasticity-driven neural rewiring. This provides a biologically plausible pathway by which a short psychedelic-assisted therapy can achieve sustained improvement in mood and cognitive-emotional processing.

Table 2. Mechanistic "bridge" from acute pharmacology to sustained outcomes

Level	Evidence in uploaded set	How it supports durability hypothesis
Receptor / signaling	Mechanistic neuroplasticity review synthesis [2]; broader psychedelic clinical review [16]	Proposes pathways from serotonergic psychedelic action to plasticity-related cascades [2]
Cellular / synaptic	Rapid/persistent dendritic spine growth in frontal cortex [3]	Structural remodeling consistent with longer-term circuit adaptation [3]
Learning / behavior	Facilitated fear extinction with hippocampal plasticity-related outcomes [8]	Models how plasticity may support durable behavioral updating [8]

Systems neuroscience	Psilocybin brain dynamics / desynchronization [6]; TRD fMRI mechanisms [20]	Supports network-level perturbation/reorganization framework [6,20]
Clinical endpoints	MDD RCT [5]; cancer-distress RCTs [4,7]; TRD follow-up [19]	Demonstrates rapid improvement and persistence after limited dosing [4,5,19]

AI technologies

AI technologies were employed in this study. AI tools provided additional linguistic refinement, ensuring proper grammar, style and clarity in presenting the results. Importantly, all AI applications were used exclusively as assistive instruments under human supervision. Final interpretation of results, classification of errors and conclusions remained the responsibility of human experts in clinical medicine and formal logic. Overall, AI mainly served to improve efficiency in data processing, pattern recognition and language polishing, rather than replacing human judgment in the analytical process.

Disclosure

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Conceptualization: Anna Komarczewska
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Conflict of Interest Statement

Authors declare no conflicts of interest.

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