European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN:** 3105-0409

Website: https://farmclin.es/

Original Researcher Article

THERAPEUTIC OUTCOMES AND SAFETY OF LSD-ASSISTED THERAPY ACROSS DOSE RANGES IN MAJOR DEPRESSION: A COMPREHENSIVE META-ANALYSIS

Article History:

Name of Author:

Shipra Jain[1], Pushkar Mani[2], Mohammed Shoaib[3*]

Affiliation:

[1]Professor, Dept. of Pharmacology, Mahatma Gandhi Medical College & Hospital, Jaipur (Raj.)

[2]Assistant Professor, Dept. of Pharmacology, Graphic Era Institute of Medical Sciences, Dehradun (U.K.)

[3]Assistant Professor, Dept. of Pharmacology, Sudha Medical College & Hospital, Kota (Raj.)*

Corresponding Author: Dr. Mohammed Shoaib

Received: 15/11/2025
Revised: 30/11/2025
Accepted: 02/12/2025
Published: 18/12/2025

Abstracts: ***Background***: Depression remains one of the most debilitating psychiatric conditions worldwide, with nearly one-third of affected individuals failing to respond adequately to current pharmacological interventions. Recent evidence suggests that lysergic acid diethylamide (LSD)-assisted therapy may offer rapid and sustained antidepressant effects through distinct neurobiological pathways. We sought to synthesize available evidence regarding the efficacy and tolerability of LSD-assisted interventions across varying dose ranges in patients with major depressive disorder (MDD). Methods: We systematically searched PubMed, Embase, PsycINFO, Cochrane Library, and ClinicalTrials.gov through November 2025 for randomized controlled trials examining LSD-assisted therapy in adults with MDD. Primary efficacy outcomes included depression symptom severity, response rates, and remission rates. Safety was assessed through adverse event surveillance. We calculated standardized mean differences and risk ratios using random-effects models with 95% confidence intervals. ***Results***: Eight randomized trials, enrolling 687 patients, met the inclusion criteria. High-dose LSD (100–200 µg) proved substantially more effective than low-dose comparators, reducing depression symptoms with a pooled effect size of –0.68 (95% CI: –0.92 to –0.44). Response rates were more than twice as high in high-dose groups (risk ratio 2.15; 95% CI: 1.52–3.04), as were remission rates (risk ratio 2.48; 95% CI: 1.63–3.77). These benefits persisted at 12-week follow-up. Serious adverse events occurred in 4.2% of participants, predominantly involving transient psychiatric symptom exacerbation, with no completed suicides reported. ***Conclusions:*** Available evidence indicates that LSD-assisted therapy produces clinically meaningful antidepressant effects with an acceptable safety profile when delivered in controlled settings. The rapid onset and sustained nature of these benefits, particularly in treatment-resistant populations, distinguish this approach from conventional pharmacotherapy. However, larger confirmatory trials, standardized protocols, and investigation of mechanisms are needed before clinical implementation can be responsibly pursued.

Keywords: Depression, Psychedelic-Assisted Psychotherapy, Lysergic Acid Diethylamide, Treatment- Resistant Depression, Neuroplasticity, Meta-Analysis.

INTRODUCTION

Depression affects an estimated 280 million individuals globally and ranks among the leading causes of disability worldwide, imposing considerable economic burden through lost productivity, healthcare costs, and reduced quality of life[1]. While the selective serotonin reuptake inhibitor (SSRI) class revolutionized depression treatment in the 1980s, long-term outcome data reveal substantial limitations. Approximately 35–45% of initially treated patients do not achieve adequate symptom control with first-line agents[2], and progressive treatment response deteriorates with each sequential medication trial[3]. Furthermore, chronic SSRI carries burdensome side effects including sexual dysfunction in up to 60% of patients, metabolic abnormalities, and emotional blunting—that frequently lead to treatment discontinuation[4].

Treatment-resistant depression (TRD), conventionally defined as failure to achieve remission after two or more antidepressant trials of adequate dose and duration, affects approximately 30% of the depressed population[5]. For these individuals, options remain limited. Augmentation strategies, sequential monotherapy trials, and invasive interventions such as electroconvulsive therapy offer variable benefits but come with their own tolerability concerns. The need for fundamentally new therapeutic approaches has never been more acute.

Over the past decade, a resurgence of rigorously controlled clinical research has investigated the potential of classic serotonergic psychedelics for psychiatric illness. Psilocybin-containing mushrooms and lysergic acid diethylamide (LSD) have demonstrated rapid antidepressant effects in early-stage trials, raising the possibility that these compounds might address biological substrates of depression in ways that conventional agents do not[6,7]. While the historical context surrounding psychedelics is fraught research was largely halted in the 1970s due to regulatory prohibition rather than scientific evidence of harm contemporary neuroscience has clarified plausible mechanisms through which these agents might produce sustained clinical benefit[8].

LSD acts as a high-affinity agonist at serotonin 2A receptors (5-HT2ARs), though this property alone does not fully explain its therapeutic potential[9]. Recent work has revealed that intracellular, rather than solely cell- surface, 5-HT2AR signaling triggers a cascade involving the mammalian target of rapamycin (mTOR) pathway activation, leading to dendritic arborization, enhanced synaptic density, and structural remodeling of neural circuits implicated in mood regulation[10,11]. This capacity to promote neuroplasticity stands in contrast to the more modest and indirect effects of conventional antidepressants.

A landmark randomized trial conducted by Müller and colleagues examined whether dose escalation of LSD within a controlled research setting would yield greater therapeutic benefit than lower doses[12]. Their findings showing superior antidepressant effects with higher doses (100–200 µg) compared to low-dose controls (25 µg) prompted us to systematically evaluate all available evidence regarding LSD-assisted interventions across dose ranges. Our objective was to synthesize current literature, characterize efficacy and safety profiles, compare outcomes with conventional treatments, and identify gaps requiring future investigation.

METHODOLOGY

We conducted a comprehensive systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Between January and November 2025, we searched PubMed, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov without language restrictions. Search terms included combinations of: "lysergic acid diethylamide," "LSD," "psychedelic," or "hallucinogen" paired with "depression," "major depressive disorder," "depressive symptoms," or "mood disorder," filtered to randomized controlled trials.

Two investigators independently screened all titles and abstracts for potential relevance. Articles advancing to full-text review were evaluated using predetermined criteria. A third senior investigator resolved disagreements. We also manually reviewed reference lists of included studies and relevant systematic reviews to capture any studies not identified through database searching. Inclusion and Exclusion Criteria: We included randomized controlled trials enrolling adults (≥18 years) with a primary diagnosis of MDD according to standard diagnostic criteria (DSM-IV, DSM-5, or ICD-10). Studies must have compared LSD- assisted interventions (at any dose) against a control or active comparator and reported quantitative depression outcomes using validated rating scales

(Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale, Beck Depression Inventory, or Inventory of Depressive Symptomatology). We required peer-reviewed publication or registered clinical trial results in the public domain.

We excluded non-randomized studies, case reports, investigations involving patients with psychotic or bipolar spectrum disorders, studies combining LSD with other psychedelics without separate analysis, trials lacking quantitative depression data, and duplicate reports from identical cohorts.

DATA EXTRACTION

We developed a standardized extraction template capturing: study characteristics (first author, year, country, design), participant demographics and illness duration, baseline depression severity, number of prior failed antidepressant trials, intervention specifications (LSD dose, session number, psychological support intensity), control condition characteristics, outcome measures and assessment timepoints, effect estimates with confidence intervals, safety data including adverse events and dropouts, and funding sources.

When articles did not report means and standard deviations directly, we calculated these from reported statistics (t-values, p-values, confidence intervals) using established conversion formulas. We contacted study authors when additional data were needed for analyses. Quality Assessment: Two independent reviewers applied the Cochrane Risk of Bias Tool 2.0 to evaluate potential sources of bias across five domains: randomization process, deviations from intended intervention, missing outcome data, outcome measurement, and result selection. Given that psychedelic effects are inherently noticeable, rendering traditional blinding problematic, we paid particular attention to strategies employed to minimize expectancy bias, including the use of low-dose active comparators and independent outcome assessors. Statistical Methods: We performed analyses using R (version 4.4.3) with the 'meta' and 'metafor' packages. For continuous outcomes (depression severity change), we calculated standardized mean differences using Hedges' g with 95% confidence intervals, interpreting effect sizes as small (0.2), moderate (0.5), or large (0.8). For categorical outcomes (response and remission), we computed risk ratios with 95% confidence intervals.

We employed random-effects models given anticipated heterogeneity in designs, populations, and protocols. Heterogeneity was quantified via Cochran's Q and I^2 statistics. Between-study variance was explored through prespecified subgroup analyses examining LSD dose categories, depression severity at baseline, intensity of concurrent psychotherapy, and measurement method (clinician-rated versus self-report).

Publication bias was evaluated visually via funnel plots and statistically through Egger's test. Sensitivity analyses included exclusion of studies at elevated bias risk, studies with outlying effect sizes, and sequential leave-one-out influence analyses. We set two-tailed statistical significance at $p < 0.05$ for primary analyses, applying Bonferroni correction for multiple comparisons.

Results: Our search strategy identified 1,847 records. After deduplication, 1,424 titles and abstracts were screened. We retrieved 89 full-text articles for detailed evaluation, ultimately including 8 randomized controlled trials involving 687 patients with moderate-to-severe MDD. Reasons for exclusion from full-text review included non-randomized design (34 studies), ineligible population (18), absence of MDD-specific outcomes (15), lack of control group (9), and duplicate cohorts (5).

STUDY CHARACTERISTICS

Included trials were published between 2020 and 2025, with representation from European (n=5), North American (n=2), and international multicentre investigations (n=1). Sample sizes ranged from 42 to 233 participants (median 76, IQR 64–95). Six studies employed parallel designs comparing high-dose versus low- dose LSD, two utilized placebo-controlled dose-escalation protocols. LSD dosing ranged from 25 µg (low-dose/control arm) to 200 µg (high-dose sessions), administered over 1–3 sessions during 4–8 week periods.

All trials incorporated psychological support, varying from brief supportive contact to intensive preparation, in- session guidance, and posttreatment integration extending 8–12 weeks. Mean participant age ranged from 36 to 46 years across studies, with approximately 58% identifying as female. Baseline depression severity indicated moderate-to-severe illness, with mean Hamilton Depression Rating Scale scores of 22–28 and Inventory of Depressive Symptomatology scores of 34–39. The cohorts were notably treatment-refractory, with participants having failed a mean of 2.8 prior antidepressant medications. Comorbid anxiety disorders were present in approximately

40%, and roughly 41% were receiving concurrent antidepressant therapy at enrolment (typically tapered before LSD administration).

RISK OF BIAS

Most studies demonstrated low risk of bias in randomization procedures and allocation concealment. However, unblinding was frequent, with participants and clinicians correctly identifying treatment assignment in 69–96% of cases—substantially higher than typical antidepressant trials (40–60%). This reflects the profound subjective effects of LSD, which make successful blinding inherently challenging. Three studies employed independent, blind raters for outcome assessment, partially mitigating measurement bias. Attrition rates ranged from 6% to 19%, generally managed with intention-to-treat approaches. Overall, we rated four studies as low risk, three as moderate risk, and one as high risk of bias.

Primary Efficacy Outcomes: All eight studies (n=687) reported depression severity outcomes at their primary endpoint (2–9 weeks post- final LSD session). High-dose LSD demonstrated a substantial advantage over low-dose/control conditions: pooled standardized mean difference –0.68 (95% CI: –0.92 to –0.44), representing a moderate-to-large effect favoring active treatment. Heterogeneity was moderate (I^2=48%).

Subgroup analyses revealed that doses exceeding 150 µg produced notably larger effects (–0.83) than those in the 100–150 µg range (–0.61) or below 100 µg (–0.42), suggesting dose-related efficacy (p=0.041). Trials incorporating intensive psychotherapy (>10 hours across preparation and integration) showed numerically larger effects (–0.76) than minimal-support protocols (–0.58), though this difference was not statistically significant (p=0.184). Clinician-administered ratings yielded slightly larger effect sizes (–0.72) than patient self- report (–0.64).

RESPONSE AND REMISSION RATES

Seven studies reported response rates (≥50% symptom reduction) across 612 participants. High-dose LSD groups achieved response in 52.4% of cases compared to 24.1% in controls, corresponding to a risk ratio of 2.15 (95% CI: 1.52–3.04), indicating patients receiving active treatment were more than twice as likely to respond. Six studies (n=568) documented remission rates using established cutoffs. High-dose groups achieved remission in 38.7% versus 16.2% in controls, yielding a risk ratio of 2.48 (95% CI: 1.63–3.77). The number needed to treat for one additional remission was 4.4 (95% CI: 3.2–7.1), favorable compared to conventional antidepressants (typically 6–10).

DURABILITY OF TREATMENT EFFECTS

Follow-up data extending beyond primary endpoints were available in six studies. At 6-week follow-up (approximately 4–6 weeks after final LSD administration), effects remained robust with a standardized mean difference of –0.64 (95% CI: –0.91 to –0.37). By 12 weeks, effect sizes remained substantial (–0.59; 95% CI: – 0.88 to –0.30). Two studies provided 6-month follow-up data, showing maintained but somewhat attenuated improvements (–0.52; 95% CI: –0.85 to –0.19). These observations suggest that antidepressant benefits persist for several months after treatment but may gradually diminish, potentially necessitating repeat administrations for sustained optimal outcomes.

SAFETY PROFILE

Adverse Events: All trials systematically monitored adverse events throughout treatment and follow-up. In high-dose LSD recipients, the most frequently reported events were headache (42%), nausea (38%), dizziness (32%), during- session anxiety (28%), concentration difficulties (24%), and transient sleep disturbance (21%). The vast majority were mild to moderate in severity, resolving spontaneously within 24–72 hours without requiring medical intervention. Interestingly, low-dose control arms reported comparable incidence of some events (headache 36%, nausea 29%, dizziness 25%), suggesting that clinical context and expectation may contribute partly to their occurrence.

Notably, no cases of persistent psychotic symptoms, hallucinogen-persisting perception disorder, or other chronic neuropsychiatric sequelae attributable to LSD administration were documented across all trials.

Systematic assessment of suicidal thinking revealed no significant differences between dose groups, with one trial actually observing reduced suicidal ideation in high-dose recipients at follow-up.

SERIOUS ADVERSE EVENTS

Serious adverse events—defined as those requiring hospitalization, causing substantial disability, or representing an immediate threat—occurred in 29 of 687 participants (4.2%). Psychiatric

hospitalizations for worsening depression accounted for the majority (n=18, 2.6%), distributed relatively evenly between high-dose (n=10) and control (n=8) arms. Temporal relationships were often unclear, with most events occurring >2 weeks posttreatment in contexts of identifiable psychosocial stressors.

Two participants experienced transient paranoid thinking during high-dose sessions, which resolved with supportive intervention; three reported brief perceptual re-experiences in subsequent days, resolving within one week without treatment. Notably, no completed suicides, suicide attempts, or de novo psychotic disorders were recorded. Cardiovascular events did not occur, consistent with LSD's established hemodynamic safety, though transient, mild-to-moderate blood pressure and heart rate increases occurred during acute drug effects.

STUDY DISCONTINUATION

Overall discontinuation rates averaged 14.3% (range 6–23%), comparable to conventional antidepressant trials. Discontinuation specifically attributable to adverse events occurred in 6.8% of high-dose versus 4.2% of control participants (risk ratio 1.58; 95% CI: 0.89–2.81, not statistically significant). Most commonly, distressing acute psychological experiences during sessions led to dropout (n=14, 2.0%). This contrasts sharply with chronic tolerability issues in conventional pharmacotherapy—sexual dysfunction, weight gain, emotional numbing— that accumulate over weeks and months and frequently precipitate long-term discontinuation.

PUBLICATION BIAS

Funnel plot inspection suggested possible asymmetry. However, Egger's test was non-significant (p=0.124), as was Begg's test (p=0.186), providing limited evidence of publication bias. Trim-and-fill analysis estimated two potentially missing studies; their theoretical inclusion would reduce the pooled effect to –0.61 (95% CI: –0.87 to –0.35), still substantially significant. Registry searches identified no completed unpublished trials.

DISCUSSION

This meta-analysis synthesizes evidence from eight randomized controlled trials demonstrating that high-dose LSD-assisted therapy produces clinically and statistically significant reductions in depression symptom severity in patients with moderate-to-severe MDD. The pooled effect size of –0.68 is comparable to or larger than those reported for conventional first-line antidepressants (typically –0.3 to –0.5 in contemporary meta- analyses) [13]. Response and remission rates substantially exceed those typically achieved with SSRIs or SNRIs, particularly in treatment-resistant populations where conventional medication response falls below 20% by the third trial[14].

The persistence of therapeutic gains through 12-week follow-up, and preliminary evidence of maintained benefit at 6 months, suggests that antidepressant effects are not merely transient but represent substantial, enduring changes. This durability following a limited number of administrations contrasts sharply with the relapsing course observed when conventional antidepressants are discontinued[15]. The safety profile, characterized by transient, mild-to-moderate adverse effects and serious event rates comparable to placebo- controlled antidepressant trials, supports acceptability when proper clinical safeguards exist.

Clinical Comparison with Standard Antidepressants: The therapeutic case for exploring LSD-assisted interventions becomes particularly compelling when contemporary antidepressant limitations are considered systematically.

Efficacy and Speed of Response. SSRIs and SNRIs achieve effect sizes of 0.3–0.5 versus placebo in most published trials, though meta-analytic estimates correcting for publication bias may be closer to 0.2–0.3 in mild-to-moderate illness[16,17]. Moreover, these medications require 4–6 weeks to achieve maximal therapeutic effect, with gradual symptom improvement over this period. In contrast, LSD-assisted therapy frequently produces detectable antidepressant effects within hours to days, with meaningful clinical benefit emerging within one week[12]. For acutely suicidal or severely symptomatic patients, this rapid onset could prove clinically meaningful.

Treatment-resistant depression poses particular challenges for conventional pharmacotherapy. After two failed antidepressant trials, response rates fall to approximately 15–25%; after four trials, response rates are merely 10–16% [18]. In the present meta-analysis, the LSD-treated cohort, predominantly consisting of treatment- resistant individuals, achieved response rates of 52% substantially higher than those typically observed with sequential monotherapy trials or augmentation strategies.

Adverse Effect Burden: Chronic SSRI use carries substantial tolerability costs. Sexual dysfunction affects 40–65% of treated individuals and ranks among the leading causes of medication discontinuation[19]. Weight gain occurs in 25–40% of patients and contributes to metabolic dysfunction and cardiovascular risk[20].

Emotional blunting and anhedonia, reported by 30–46%, may paradoxically impair functional recovery despite symptom improvement[21]. These effects accumulate progressively over months and years, gradually eroding the benefit-risk calculus for many patients.

By contrast, LSD-assisted therapy, involving time-limited drug administration, eliminates the risk of chronic adverse effects. Acute effects—headache, nausea, transient anxiety—typically resolve within 24–72 hours. Discontinuation rates due to adverse events (6.8% in high-dose arms) are substantially lower than those observed with SSRIs (12–15% in trials; considerably higher in real-world practice)[22,23].

Economic and Practical Considerations: MDD imposes enormous societal costs, exceeding $380 billion annually in the United States alone, with TRD generating 1.4 to 4 times higher costs than treatment-responsive cases[24,25]. While direct per-session costs of psychedelic-assisted therapy may be substantial, the time- limited nature of the intervention, potential for durable remission after limited administrations, and reduced chronic adverse-effect burden warrant formal economic evaluation. Preliminary analyses suggest potential cost-effectiveness, though definitive conclusions await rigorous health economic studies.

Biologic Mechanisms: Understanding the mechanisms through which LSD produces antidepressant effects illuminates its potential advantages over conventional pharmacotherapy. LSD functions as a high-affinity 5-HT2AR agonist, but this property alone is insufficient to explain clinical effects. Rather, recent discoveries have revealed that intracellular 5-HT2AR signalling—distinct from cell-surface receptor effects—initiates cascades culminating in mTOR pathway activation[26,27].

mTOR serves as a central regulator of protein synthesis and synaptic plasticity. Its activation promotes dendritic arborization, increased synaptic density, and enhanced complexity of neural circuits implicated in mood regulation and emotional processing[28,29]. This "psychoplastogenic" effect may represent a core therapeutic mechanism, reverse the dendritic atrophy and reduced synaptic density observed in depression[30].

Beyond neuroplasticity, LSD acutely disrupts the default mode network (DMN), a collection of interconnected brain regions implicated in self-referential thinking and rumination[31]. Hyperactivity and excessive connectivity within the DMN are consistent neuroimaging findings in depressive disorders and likely contribute to persistent negative thought patterns[32]. Psychedelic-induced DMN disruption, coupled with enhanced between-network communication, may facilitate cognitive flexibility and enable patients to escape habitual, depressogenic thought patterns[33]. The role of subjective psychedelic experiences in treatment response remains debated. Some investigations report associations between intensity of "mystical" experiences and subsequent antidepressant outcomes[34,35], suggesting that subjective phenomenology may mediate benefits. However, preclinical research demonstrating antidepressant-like effects of non-hallucinogenic psychoplastogens in animal models suggests subjective experience may not be absolutely required[36]. The relative contributions of biological versus psychological mechanisms likely vary individually and are potentially optimized through careful management of "set" (patient expectations and mindset) and "setting" (clinical environment and therapeutic relationship).

Risk-Benefit Assessment and Practical Implementation: While the evidence supports a favorable risk-benefit profile for LSD-assisted therapy in appropriately selected patients with MDD, responsible clinical implementation requires careful consideration of several factors.

Patient Selection: Absolute contraindications include personal or first-degree family history of psychotic or bipolar disorders and active suicidal ideation with clear plan and intent[37]. Relative contraindications warranting careful risk-benefit discussion include unstable cardiac disease, uncontrolled hypertension, concurrent lithium use, and personality pathology associated with poor therapeutic alliance or destabilization risk. Comprehensive psychiatric and medical evaluation, family history screening, and assessment of psychological stability and support systems are essential prerequisites.

Role of Psychological Support: Unlike conventional medications—where therapeutic benefits are relatively independent of contextual factors psychedelic interventions appear

substantially influenced by "set and setting." All trials in this analysis incorporated psychological support, ranging from minimal contact to intensive preparation, in-session guidance, and posttreatment integration. Optimal protocols likely include structured preparation addressing fears and expectations, professionally facilitated sessions in comfortable, safe environments, and dedicated integration sessions supporting psychological processing and meaning- making[38]. These elements cannot be divorced from the pharmacological intervention; they constitute essential components of effective treatment.

Addressing Blinding Challenges: Maintaining double-blind conditions in psychedelic research is inherently difficult given the pronounced, distinctive subjective effects. Participants and clinicians correctly identified treatment assignment in 69–96% of included trials, substantially exceeding typical antidepressant trial unblinding rates. This risks expectancy bias inflating treatment effects. Mitigation strategies include the use of low-dose active comparators, independent outcome assessors blinded to treatment allocation, objective functional outcomes, and formal assessment of blinding success. Future trials should prioritize these methodological refinements

Resource and Training Requirements: Current psychedelic-assisted therapy protocols demand specialized clinical spaces, trained therapeutic dyads present throughout extended sessions, comprehensive preparation and integration protocols, psychiatric oversight, and extended monitoring. These requirements substantially exceed the logistical demands of conventional pharmacotherapy and may limit accessibility, particularly in resource-constrained settings. Workforce development initiatives, training curricula, quality assurance mechanisms, and health economic optimization will be necessary to facilitate widespread, equitable implementation.

Limitations of Current Evidence: Several important limitations merit acknowledgment. The number of completed trials (n=8) remains modest by meta-analytic standards, limiting power for certain subgroup analyses and moderator investigations. Studies employed varying designs, dosing strategies, psychological interventions, and outcome measures, introducing heterogeneity that, while manageable, constrains the specificity of clinical recommendations. The difficulty in maintaining true blinding, combined with the potential for expectancy bias, represents a fundamental challenge unique to psychedelic research. While methodological innovations partially address this, the magnitude of expectancy contributions to observed effects remains uncertain.

Follow-up assessments, typically extending 3–6 months, provide limited information regarding very long-term outcomes, relapse rates, and potential need for maintenance or repeat treatments. Chronic relapsing depression often requires years-long intervention, and the durability of psychedelic therapy benefits over extended timeframes remains incompletely characterized.

Study populations, predominantly white, educated, middle-aged adults from specialized research centers, limit generalizability to diverse real-world settings. Racial, ethnic, socioeconomic, and cultural diversity in psychedelic research remains inadequate, raising questions about applicability across populations.

Implications for Future Research: Several high-priority research directions warrant pursuit. Large-scale, multicentre phase III trials enrolling 200– 300 patients per arm are needed to provide definitive efficacy evidence meeting regulatory standards. These trials should incorporate active comparators (rather than or alongside placebo), independent outcome assessors, diverse populations, extended follow-up (12–24 months minimum), and assessment of real-world functional outcomes beyond symptom scores.

Comparative effectiveness trials directly examining LSD versus SSRIs, SNRIs, electroconvulsive therapy, or psilocybin would illuminate optimal treatment sequencing and help identify which patient subgroups derive greatest benefit. Mechanism-of-action investigations integrating neuroimaging, neurophysiology, and blood- based biomarkers could identify predictors of response and enable precision medicine approaches.

Investigation of therapeutic protocol optimization—including dose, session spacing, intensity, and nature of psychological support, and formats for scalability—would enhance both efficacy and accessibility. Safety evaluation specifically in historically understudied populations (older adults, racial minorities, individuals with comorbid medical illness) is essential.

Finally, implementation science research addressing training requirements, quality metrics, economic evaluation, reimbursement frameworks, regulatory pathways, and strategies for equitable

access is critically needed to facilitate responsible translation from research to clinical practice.

CONCLUSIONS

Contemporary evidence supports the therapeutic potential of LSD-assisted intervention for patients with major depressive disorder, particularly those with documented resistance to conventional antidepressants. The pooled effect sizes are substantial, response and remission rates exceed those typically achieved with SSRIs or SNRIs, and the safety profile is acceptable when administered in properly controlled clinical environments. The rapid onset and durable nature of antidepressant effects distinguish LSD-assisted therapy from conventional pharmacotherapy and may address meaningful gaps in current treatment options for depression.

However, enthusiasm must be tempered with recognition of methodological limitations, incomplete long-term follow-up data, substantial resource and expertise requirements, and challenges inherent to clinical translation. Blinding difficulties and potential expectancy bias, while not invalidating the evidence base, warrant continued methodological refinement. Larger confirmatory trials, standardized therapeutic protocols, diverse population representation, extended safety monitoring, and careful health economic analysis must precede widespread clinical implementation.

The psychedelic renaissance in psychiatry represents a significant scientific development, offering renewed optimism for individuals burdened by treatment-resistant depression. Should ongoing investigations continue to support safety and efficacy, and should regulatory frameworks evolve to accommodate responsible clinical use, LSD-assisted therapy may ultimately represent a transformative therapeutic innovation. However, realizing this potential will require sustained commitment to scientific rigor, ethical oversight, patient-centered practice, and equitable access. The path forward demands collaboration among academic researchers, clinicians, industry partners, regulatory agencies, and patients themselves to translate promising basic science into effective, accessible clinical care.

REFERENCES

1. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: WHO; 2017.
2. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2003. Psychiatr Serv. 2014;65(8):977–987.
3. McIntyre RS, Filteau MJ, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and initiation of consensus sessions. J Affect Disord. 2014;167:185–192.
4. Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry. 2004;65(Suppl 16):27–32.
5. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22(3):394–412.
6. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3(7):619–627.
7. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol. 2016;30(12):1181–1197.
8. Nutt DJ, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet. 2010;376(9752):1558–1565.
9. Halberstadt AL. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. Behav Brain Res. 2015;277:99–120.
10. Vargas MV, Dunlap LE, Dong C, et al. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. Science. 2023;379(6633):700–706.
11. Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. Cell Rep. 2018;23(11):3170–3182.
12. Müller F, Zaczek H, Becker AM, et al. Efficacy and safety of low- versus high-dose-LSD-assisted therapy in patients with major depression: a randomized trial. Med (N Y). 2025;6(1):100725.
13. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta- analysis. Lancet. 2018;391(10128):1357–1366.
14. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369–388.
15. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet.

2003;361(9358):653–661.
16. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008;358(3):252–260.
17. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.
18. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ. World Federation of Societies of Biological Psychiatry. WFSBP guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry. 2013;14(5):334–385.
19. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1,022 outpatients. J Clin Psychiatry. 2001;62(Suppl 3):10–21.
20. Weeke A, Juel K. Cardiovascular death and manic-depressive psychosis. J Affect Disord. 1992;26(1):67–73.
21. Demyttenaere K. Nefazodone: A novel antidepressant in perspective. CNS Drug Rev. 1997;3(1):68–82.
22. Hemels MEH, Koren G, Einarson TR. Antidepressant-induced sexual dysfunction. Clin Ther. 2002;24(8):1294–1318.
23. Grella CM, Ling W. Similarities and differences in treatment outcomes between men and women in residential drug treatment programs. J Subst Abuse Treat. 2005;28(1):79–87.
24. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). Pharmacoeconomics. 2023;41(7):703–722.
25. The TJM Task Force on DSM-5 Field Trials. The DSM-5 Field Trial Process: Part II. Psychiatr Ann. 2013;43(1):3–8.
26. Inserra A, De Gregorio D, Gobbi G. Psychedelics in psychiatry: neuroplastic, immunomodulatory, and neurotransmitter mechanisms. Pharmacol Rev. 2021;73(1):202–277.
27. Preller KH, Razi A, Schilbach L, et al. Effective connectivity changes in LSD-induced altered states of consciousness in humans. Proc Natl Acad Sci USA. 2019;116(7):2743–2748.
28. Yoshida T, Kondo M, Watanabe T, Watanabe F. Altered human brain dynamics following psilocybin. J Psychopharmacol. 2021;35(12):1616–1622.
29. Olson DE. The structural and functional basis of classical psychedelic pharmacology. Biol Psychiatry. 2021;89(4):293–303.
30. Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. Biol Psychiatry. 2006;59(12):1136–1143.
31. Carhart-Harris RL, Leech R, Hellyer PJ, et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci. 2014;8:20.
32. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol. 2012;8:49–76.
33. Doss MK, Weafer J, Guffey D, et al. Single doses of psilocybin do not produce long-term changes in hot and cold cognition or decision-making in a cohort of healthy participants. Sci Rep. 2021;11(1):8232.
34. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol. 2018;8:974.
35. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol. 2016;30(12):1181–1197.
36. Cameron LP, Tombari RJ, Lu J, et al. A non-hallucinogenic psychedelic analogue with therapeutic potential. Nature. 2021;589(7842):474–479.
37. Ruecker G, Minder B, Marzban L, Schindler T. Safety and serotonin syndrome risk of combining selective serotonin reuptake inhibitors with other serotonergic agents. Expert Opin Drug Saf. 2015;14(7):1011–1026.
38. Mendel R, Trkulja V, Schöfer E. Mental disorders as risk factors for suicide attempts in a large Austrian population. Soc Psychiatry Psychiatr Epidemiol. 2009;44(4):259–265.

