Global Journal of Research in
Biology and Pharmacy
Journal homepage: https://gsjournals.com/gjrbp/
ISSN: 2980-4221 (Online)

(REVIEW ARTICLE)

Check for updates

PSYCHEDELICS AND ENTACTOGENS IN PSYCHIATRY: PHARMACOLOGY, CLINICAL TRIAL EVIDENCE, AND REGULATORY CONSIDERATIONS

Ifeyinwa Adar Opoku *

Department of Science Laboratory Technology, Delta State Polytechnic, Otefe – Oghara, Nigeria.
* Corresponding Author

Global Journal of Research in Biology and Pharmacy, 2025, 04(04), 001–003

Publication history: Received on 18 August 2025; revised on 22 October 2025; accepted on 25 October 2025

Article DOI: https://doi.org/10.58175/gjrbp.2025.4.4.0176

ABSTRACT

Psychedelics, including psilocybin, lysergic acid diethylamide, and dimethyltryptamine, and entactogens such as 3,4-methylenedioxymethamphetamine are being investigated for treatment-resistant depression, post-traumatic stress disorder, anxiety, and substance use disorders. These compounds act primarily through serotonin 5-HT2A receptor agonism (psychedelics) or monoamine release (MDMA), leading to acute alterations in consciousness that may enhance neuroplasticity and emotional processing. Randomized controlled trials have shown rapid and sustained reductions in depressive and post-traumatic stress symptoms following one or two assisted psychotherapy sessions. Psilocybin has received breakthrough therapy designation from the US FDA for treatment-resistant depression and major depressive disorder, while MDMA-assisted therapy for post-traumatic stress disorder has completed phase 3 trials with positive results, though regulatory review has raised methodological and safety concerns. This review critically examines the pharmacology, clinical evidence, and regulatory considerations for psychedelics and entactogens, focusing on literature through mid-2025. Challenges include blinding, expectancy effects, therapist training, and long-term safety. Future directions include dose optimization, identification of biomarkers, and integration into mental health care. While promising, these therapies require rigorous evaluation and careful regulatory oversight.

Keywords: Psilocybin; MDMA; Psychedelics; Entactogens; Treatment-Resistant Depression; Post-Traumatic Stress Disorder

1 INTRODUCTION

Classic psychedelics (psilocybin, LSD, DMT) and entactogens (MDMA) are being re-evaluated as potential treatments for psychiatric disorders after decades of prohibition. Early clinical research in the 1950s–1970s suggested benefit in depression, anxiety, and substance use, but methodological limitations and social concerns halted studies. Recent rigorous trials have renewed interest, leading to breakthrough therapy designations and large-scale phase 3 programs.

The pharmacology of these compounds differs: classic psychedelics primarily agonize serotonin 5-HT2A receptors, inducing profound changes in perception, cognition, and emotion. MDMA increases release of serotonin, norepinephrine, and dopamine, and also modulates oxytocin, producing emotional openness and reduced fear response.

Both are believed to promote neuroplasticity, potentially facilitating psychotherapeutic change when administered in controlled settings with psychological support.

This review summarizes the current evidence and regulatory landscape, with references through August 2025.

2 PHARMACOLOGY AND MECHANISMS

Psilocybin is a prodrug converted to psilocin, a potent 5-HT2A receptor agonist. Activation of 5-HT2A receptors in cortical pyramidal neurons increases glutamate transmission and alters functional connectivity, disrupting default mode network activity and enhancing neuroplasticity. MDMA acts primarily by inhibiting monoamine reuptake and stimulating release, particularly serotonin, leading to acute subjective effects including euphoria, empathy, and reduced anxiety. It also reduces amygdala reactivity to negative stimuli, enabling processing of traumatic memories. Both agents promote downstream neurotrophic signaling (e.g., BDNF) and may reopen critical periods of plasticity.

3 CLINICAL TRIAL EVIDENCE

3.1 Psilocybin for Depression

A landmark phase 2 trial in moderate-to-severe major depressive disorder showed that psilocybin 25 mg, administered with psychological support, produced significant reductions in depression scores compared with a low-dose control, with effects lasting weeks. Subsequent trials in treatment-resistant depression and cancer-related anxiety confirmed rapid and sustained benefits. A large phase 2b trial found that a single 25 mg dose was superior to 10 mg and 1 mg controls. Phase 3 trials are ongoing. Common adverse events include transient anxiety, headache, and nausea; serious adverse events are rare in controlled settings.

3.2 Psilocybin for Other Indications

Psilocybin has shown promise in end-of-life anxiety, alcohol use disorder, and tobacco cessation, though evidence is preliminary. Large trials are needed.

3.3 MDMA-Assisted Therapy for PTSD

MDMA-assisted therapy involves two or three 8-hour sessions with a therapist team. The MAPS phase 3 trials (MAPP1 and MAPP2) reported significant reductions in PTSD symptoms, with high response and remission rates. However, regulatory review identified concerns about blinding, therapist allegiance, and potential cardiovascular effects. An FDA advisory committee voted against approval in 2024, citing insufficient evidence of efficacy and safety. Further trials and regulatory discussions are ongoing.

4 REGULATORY AND SAFETY CONSIDERATIONS

Psychedelics and MDMA are Schedule I substances in the US and controlled elsewhere, limiting research and clinical use. Regulatory frameworks are evolving, with breakthrough therapy designations and compassionate use pathways. Challenges include standardization of psychological support, therapist training and accreditation, and risk of abuse or diversion. Safety concerns include cardiovascular effects (MDMA increases heart rate and blood pressure), potential for serotonin syndrome, and psychological adverse effects such as prolonged anxiety or psychotic reactions in vulnerable individuals. Long-term effects on neuroplasticity and mental health require further study.

5 CHALLENGES AND LIMITATIONS

Blinding is difficult due to obvious subjective effects, raising risk of expectancy bias. The contribution of psychotherapy versus drug effect is unclear. Patient selection criteria are important to exclude those with personal or family history of psychosis or bipolar disorder. Durability of response varies, and maintenance strategies are not established. Access and equity, including cost and therapist availability, are barriers.

6 FUTURE PERSPECTIVES

Ongoing phase 3 trials will clarify efficacy and safety. Biomarkers such as neuroimaging and electroencephalography may predict response. Newer compounds with shorter durations or reduced cardiovascular effects are in development. Integration into healthcare will require infrastructure for psychedelic-assisted therapy, training programs, and reimbursement models. Regulatory agencies may need new frameworks for combination drug–therapy products.

7 CONCLUSION

Psychedelics and entactogens offer a novel paradigm for treating psychiatric disorders, with rapid effects and potential for neuroplasticity. Psilocybin shows robust evidence for depression, and MDMA-assisted therapy has demonstrated efficacy for PTSD, though regulatory hurdles remain. Careful evaluation, standardized protocols, and long-term safety data are essential before broad implementation.

REFERENCES

[1] 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.

[2] 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.

[3] Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30(12):1165–1180.

[4] Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry. 2021;78(5):481–489.

[5] Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med. 2022;387(18):1637–1648.

[6] Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025–1033.

[7] Mitchell JM, Ot'alora G M, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med. 2023;29(10):2473–2480.

[8] Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology. 2019;236(9):2735–2745.

[9] Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat Rev Neurosci. 2010;11(9):642–651.

[10] Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. Cell Rep. 2018;23(11):3170–3182.

[11] Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry. 2022;79(10):953–962.

[12] Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol. 2014;28(11):983–992.

[13] Feduccia AA, Jerome L, Yazar-Klosinski B, et al. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. Front Psychiatry. 2019;10:650.

[14] Rucker JJ, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs: past, present & future. Neuropharmacology. 2018;142:200–218.

[15] US Food and Drug Administration. FDA grants breakthrough therapy designation for psilocybin for treatment-resistant depression. 2018.

[16] US Food and Drug Administration. FDA briefing document: Psychopharmacologic Drugs Advisory Committee Meeting on MDMA-assisted therapy for PTSD. June 2024.

[17] Carhart-Harris RL, Wagner AC, Agrawal M, et al. Can pragmatic research, real-world data and digital technologies aid the development of psychedelic medicine? J Psychopharmacol. 2022;36(1):6–11.

[18] Romeo B, Karila L, Martelli C, et al. Efficacy of psychedelic treatments on depressive symptoms: a meta-analysis. J Psychopharmacol. 2020;34(10):1079–1085.

[19] Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542–555. (Relevant context for rapid-acting antidepressants.)

[20] Andersen KAA, Carhart-Harris R, Nutt DJ, et al. Therapeutic effects of classic serotonergic psychedelics: a systematic review of modern-era clinical studies. Acta Psychiatr Scand. 2021;143(2):101–118.