



Psychedelic-Assisted Therapy: A Review of Current Evidence and Future Directions

Sharma M¹, Sharma VL² and Alam P^{*3}

¹Assistant Professor, Department of Psychiatry, Rajmata Vijaya Raje Scindia Medical College, India

²Consultant Obstetrician and Gynecologist, Urban CHC Kota, India

³Senior Resident, Department of Psychiatry, Lady Hardinge Medical College, India

***Corresponding author:** Parvaiz Alam, Senior Resident, Department of Psychiatry, Lady Hardinge Medical College, Delhi, India, Tel: 9915835329; Email: parvaizalam987@gmail.com

Received Date: February 05, 2024; **Published Date:** February 23, 2024

Abstract

Psychedelic substances are well known for their abuse but now-a-days Psychedelic-assisted therapy is gaining attention as a promising modality for treating various mental health conditions. Various psychedelic substances such as psilocybin, MDMA, and LSD are used in the treatment of depression, anxiety disorders, post-traumatic stress disorder (PTSD), addiction, and existential distress. In this review article we will be giving a comprehensive overview of the current evidence surrounding psychedelic-assisted therapy, including its historical context, therapeutic applications, safety considerations, and future directions.

Keywords: Psychedelic-assisted Therapy; PTSD; MDMA

Abbreviations: PTSD: Post-Traumatic Stress Disorder; MDMA: Methylenedioxy Methamphetamine; LSD: Lysergic Acid Diethylamide.

Introduction

In 1957, Humphrey Osmond coined the term psychedelic that means to have a mind-manifesting capability, revealing useful or beneficial properties of the mind [1]. They have their effect by altering mind's perception and mood changes. The historical use of psychedelics in therapeutic and spiritual contexts dates back centuries, with indigenous cultures utilizing substances such as psilocybin mushrooms, peyote, and ayahuasca for healing and ceremonial purposes [2]. Psychedelic-assisted therapy that uses psychedelic substances in therapeutic settings has a rich historical context and has experienced its notable resurgence in recent years [3]. However, psychedelics gained prominence in Western therapeutic settings in the mid-20th century.

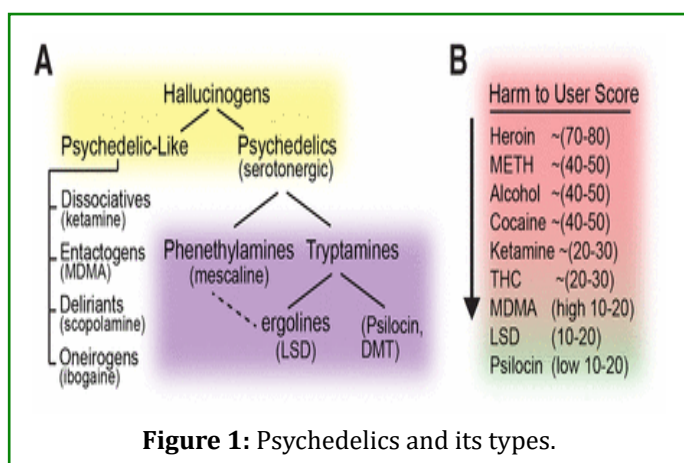


Figure 1: Psychedelics and its types.

The classical psychedelic substances are described as mind-manifesting drugs which have hallucinogenic effects via activation of serotonin 2A receptors [4]. The psychedelic-like compounds can be categorized as- dissociative anaesthetics

(the NMDAR antagonist ketamine), entactogens (i.e. the 5-HT releaser 3, 4-methylenedioxymethamphetamine, also known as MDMA or “ecstasy”), and deliriants (like, the anticholinergic drug scopolamine) (Figure 1) [4].

The pioneering work of figures like Albert Hofmann- the discoverer of LSD, and others like Timothy Leary, Richard Alpert and Stanislav Grof, played a major role in making the early field of psychedelic therapy. Through extensive studies over 40 years, Stanislav Grof has explored and defined various experiences with psychedelics to understand phenomena of near death and rebirth experiences, utility as psychotherapy and promoting spiritual growth [5]. His tremendous work to understand human consciousness through the use of psychedelics helped to establish the relationship between the individual ego and the cosmos. This has opened doors to understand spiritual emergency and the role of the psyche and its relationship to physical reality [5].

Scientific advancements have shed light on the neurobiological mechanisms of psychedelics, revealing their potential to induce profound and transformative experiences. Also, shifting societal attitudes towards mental health and alternative therapies have fostered an environment of increased openness and acceptance [6]. This is one of the reasons that transpersonal psychology has become the fourth force in psychology [5]. A growing body of evidence from clinical trials and studies has demonstrated promising outcomes in treating mental health disorders such as depression, anxiety, post-traumatic stress disorder (PTSD), addiction, and existential distress. Notable studies on psilocybin-assisted therapy for depression and MDMA-assisted therapy for PTSD have garnered attention and support [7-9].

Therapeutic Applications of Psychedelics

The mind-altering substances have been majorly studied for the various mental illnesses, among which common are depression, anxiety, emotional crisis/ distress and other addictive disorders.

Psilocybin-Assisted Therapy for Depression and Anxiety: Psilocybin, a naturally occurring psychedelic compound extracted from mushrooms, has gained significant attention as a potential therapeutic tool for the treatment of depression and anxiety. Psilocybin-assisted therapy combines the administration of psilocybin in a controlled setting with therapeutic support to induce transformative experiences that may alleviate symptoms and promote long-term well-being [7]. A randomized controlled trial conducted by Griffiths, et al. [9] evaluated psilocybin-assisted therapy in individuals with life-threatening cancer and associated depression and anxiety. The study reported sustained reductions in depressive symptoms and anxiety,

with improvements persisting at a six-month follow-up. Similar positive outcomes have been observed in studies exploring psilocybin-assisted therapy for treatment-resistant depression and anxiety-related existential distress [9]. Also, psilocybin-assisted therapy is not solely reliant on its pharmacological effects; but it requires a supportive therapeutic framework, including- pre-session preparation, therapeutic guidance during the experience, and post-session integration to maximize the potential therapeutic benefits and minimize adverse reactions [10].

MDMA-Assisted Therapy for PTSD and Trauma: Methylenedioxy-methamphetamine (MDMA)- assisted therapy has emerged as a promising treatment modality for post-traumatic stress disorder (PTSD) and trauma-related acute crisis. MDMA acts primarily by increasing the release of serotonin, dopamine, and norepinephrine, while also affecting oxytocin and cortisol levels. These neurochemical changes induce a state of heightened empathy, increased emotional openness, and reduced fear response. The unique pharmacological profile of MDMA provides a conducive environment for psychotherapeutic interventions by promoting emotional connection, facilitating the processing of traumatic memories, and enhancing the therapeutic alliance [11]. MDMA-assisted therapy typically consists of three phases:-

- Preparation,
- MDMA-assisted session(s), and
- Integration.

The preparation phase involves building rapport, establishing safety, and setting therapeutic goals. During the MDMA-assisted session, a carefully guided and supportive environment is created, allowing individuals to explore and process traumatic memories and emotions. The therapist provides guidance and support throughout the session, helping individuals navigate challenging experiences and facilitating healing. The integration phase focuses on the incorporation of insights gained during the MDMA session into daily life, promoting sustained therapeutic benefits [8]. Multiple clinical trials have demonstrated the efficacy of MDMA-assisted therapy in reducing PTSD symptoms and improving overall well-being.

Notable studies, such as the ground-breaking Phase 2 trials conducted by Mithoefer, et al. [11], reported significant reductions in PTSD symptoms following MDMA-assisted therapy. Long-term follow-up studies have shown sustained improvements and increased quality of life in participants. The positive outcomes observed in these trials have led to expanded research and on-going Phase 3 trials, further validating the therapeutic potential of MDMA-assisted therapy for PTSD. The unique effects of MDMA, including increased empathy, reduced fear response, and enhanced emotional processing, contribute to its therapeutic benefits

in PTSD treatment. MDMA-assisted therapy can facilitate the exploration and processing of traumatic memories, promote emotional healing, enhance self-compassion, and strengthen the therapeutic alliance. The integration of these experiences can lead to significant reductions in PTSD symptoms, increased emotional resilience, and an improved sense of well-being.

LSD-Assisted Therapy for Addiction and Existential Distress: LSD-assisted therapy has emerged as a potentially effective treatment modality for addressing addiction and existential distress. This scientific note explores the use of LSD (lysergic acid diethylamide) in combination with psychotherapy to target these challenging conditions. By delving into the therapeutic potential of LSD, the neurobiological effects, and the available evidence, a promising role of LSD-assisted therapy in facilitating transformative experiences and promoting psychological well-being is noted [12].

- **LSD-Assisted Therapy for Addiction:** LSD-assisted therapy has shown promise in treating addiction by providing individuals with new perspectives and insights. The unique pharmacological properties of LSD, which primarily involve agonistic effects on serotonin receptors, facilitate profound shifts in consciousness, leading to enhanced self-awareness, increased emotional openness, and decreased attachment to addictive patterns. LSD-assisted therapy aims to break the cycle of addiction by helping individuals confront underlying psychological issues, gain clarity, and develop healthier coping mechanisms [12].
- **LSD-Assisted Therapy for Existential Distress:** Existential crisis often arises from profound questions about the meaning and purpose of life, resulting in emotional and psychological challenges. LSD-assisted therapy can help individuals explore existential issues by facilitating expanded states of consciousness, transcendent experiences, and deep introspection. The profound and transformative nature of LSD-assisted sessions allows individuals to confront existential concerns, gain insights, and experience a sense of interconnectedness, potentially alleviating distress and fostering personal growth [12,13].

Ketamine for Depression: The psychedelics response to mental illness treatment as gained the FDA's "breakthrough therapy" designation; following which the FDA granted Ketamine approval for treatment of treatment-resistant depression (2013). Also, later in 2017, MDMA got its approval for the management of post-traumatic stress disorder (PTSD), and in 2019- psilocybin was approved for treatment-resistant depression. In 2019, Esketamine nasal spray was granted FDA approval for treatment-resistant depression and is known for its best results as "breakthrough therapy" of the three to be FDA approved [14,15].

Safety Considerations

Among the various recreational agents, psychedelics are known to have the lowest harm-to-user scores and are considered to be relatively safe. For example, harm-to-user scores for heroin are 70-80, METH, alcohol and cocaine are 40-50; while, ketamine scores are 20-30 and, MDMA, LSD and psilocybin are 10-20 [4]. Despite having low harm-to-user scores the impact of psychedelics on mental cognition and emotions a caution is needed.

- **Clinical Protocols and Guidelines:** To maximize safety and optimize therapeutic outcomes, the development of comprehensive clinical protocols and guidelines is essential. These protocols outline the screening process for participants, dosing considerations, preparation and integration procedures, and measures to ensure the physical and psychological well-being of participants. They serve as a framework to standardize the delivery of psychedelic-assisted therapy and guide practitioners in creating a safe therapeutic environment. Study by Mithoefer, et al. [16] outlines the clinical protocols and guidelines used in a phase 2 clinical trials investigating MDMA-assisted psychotherapy for post-traumatic stress disorder (PTSD) in military veterans, firefighters, and police officers. The article provides insights into the screening process, dosing considerations, preparation and integration procedures, and safety measures employed to ensure participant well-being during therapy sessions [16].
- **Risk Management and Potential Adverse Effects:** Psychedelic substances can induce intense psychological experiences, which may carry inherent risks. Adequate risk management strategies are crucial to minimize potential adverse effects. This includes thorough participant screening to identify contraindications, monitoring vital signs during sessions, and implementing appropriate psychological support and interventions. Informed consent processes should also address potential risks and ensure participant autonomy and understanding. Potential adverse effects may include anxiety, challenging emotions, and temporary psychological distress. Rarely, some individuals may experience more serious reactions. Close monitoring and supportive care by trained therapists can help mitigate such risks and provide necessary support during the session [11].

Challenges and Ethical Considerations

There are the following ethical considerations:

- **Regulatory Barriers and Legal Status:** One of the major challenges facing psychedelic-assisted therapy is the regulatory barriers and legal restrictions surrounding the use of psychedelic substances. These

substances are classified as Schedule I drugs in many countries, limiting their availability for therapeutic use. The legal status presents obstacles for researchers, clinicians, and individuals seeking access to psychedelic-assisted therapy. Overcoming these barriers necessitates policy changes, regulatory reforms, and evidence-based advocacy to facilitate safe and legal access to these treatments [17].

- **Integration of Mystical Experiences and Spirituality:** Psychedelic experiences can induce profound and mystical states that often incorporate spiritual or transcendent elements. The integration of these experiences into therapeutic frameworks raises ethical considerations regarding the incorporation of spirituality in a clinical context. Clinicians must strike a balance between respecting individuals' spiritual beliefs and maintaining a secular and inclusive therapeutic environment. The development of guidelines and training programs can assist therapists in navigating these complex issues, ensuring a respectful and culturally sensitive approach to spirituality in psychedelic-assisted therapy [18].
- **Equity, Access, and Cultural Considerations:** Psychedelic-assisted therapy must address issues of equity, access, and cultural considerations to ensure that this therapeutic approach is accessible to a diverse range of individuals. Achieving equitable access involves addressing barriers related to cost, geographic location, socioeconomic disparities, and cultural beliefs. Cultural sensitivity and awareness are vital to avoid perpetuating historical inequalities and to tailor therapeutic approaches to diverse cultural contexts. Collaboration with communities and stakeholders is essential in developing inclusive and culturally appropriate psychedelic-assisted therapy models [18].

Future Directions and On-going Research

Integration of Psychedelic-Assisted Therapy into Mainstream Mental Healthcare is one of the primary future aspects that need consideration. As the evidence-based literature continues to grow and regulatory barriers are addressed, there is increasing recognition of the therapeutic potential of psychedelics and their applicability. This includes efforts to develop treatment guidelines, training programs for therapists, and the establishment of specialized treatment centres. Integration into mainstream mental healthcare will increase accessibility, acceptance, and standardization of psychedelic-assisted therapy.

While much of the current research focuses on conditions such as PTSD, depression, and addiction, future directions in psychedelic-assisted therapy involve expanding the range of indications. On-going studies are exploring the

efficacy of psychedelics in various mental health disorders, including anxiety disorders, obsessive-compulsive disorder, eating disorders, and existential distress. Thus expansion of indications will provide a broader understanding of the therapeutic potential of psychedelics and diversify treatment options for individuals with different mental health needs.

Conclusion

Psychedelic-assisted therapy holds significant promise as a transformative approach in mental healthcare. The accumulating evidence suggests its efficacy in treating various mental health conditions, offering new avenues for individuals who have not responded to traditional treatments. However, further research is needed to establish long-term safety, optimize effect protocols, and address adverse event regulatory challenges. With careful consideration of ethical and practical concerns, psychedelic-assisted therapy has the potential to reshape the field of mental health and contribute to improved patient outcomes.

References

1. Nichols DE (2016) Psychedelics. *Pharmacol Rev* 68(2): 264-355.
2. Bosch OG, Halm S, Seifritz E (2022) Psychedelics in the Treatment of Unipolar and Bipolar Depression. *Int J Bipolar Disord* 10: 18.
3. Tupper KW, Wood E, Yensen R, Johnson MW (2015) Psychedelic Medicine: A Re-emerging Therapeutic Paradigm. *CMAJ* 187(14): 1054-1059.
4. Grieco SF, Castren E, Knudsen GM, Kwan AC, Olson DE, et al. (2022) Psychedelics and Neural Plasticity: Therapeutic Implications. *J Neurosci* 42(45): 8439-8449.
5. Grof S (1995) Implications of Holotropic Consciousness Research for Psychiatry: Observations from Psychedelic Therapy and Holotropic Breathwork. *Jahrbuch Fur Transkulturelle Medizin und Psychotherapie /Yearbook of Cross Cultural Medicine and Psychotherapy* 1995: 55-74.
6. Nichols DE, Johnson MW, Nichols CD (2017) Psychedelics as Medicines: An Emerging New Paradigm. *Clin Pharmacol Ther* 101(2): 209-219.
7. Carhart Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, et al. (2016) Psilocybin with Psychological Support for Treatment-Resistant Depression: An Open-label Feasibility Study. *Lancet Psychiatry* 3(7): 619-627.
8. Oehen P, Traber R, Widmer V, Schnyder U (2013) A Randomized, Controlled Pilot Study of MDMA

- (\pm 3,4-Methylenedioxymethamphetamine)-Assisted Psychotherapy for Treatment of Resistant, Chronic Post-Traumatic Stress Disorder (PTSD). *J Psychopharmacol* 27(1): 40-52.
9. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, et al. (2016) Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-blind Trial. *J Psychopharmacol* 30(12): 1181-1197.
 10. Johnson MW, Griffiths RR (2017) Potential Therapeutic Effects of Psilocybin. *Neurotherapeutics* 14(3): 734-740.
 11. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R (2011) The Safety and Efficacy of \pm 3,4-Methylenedioxymethamphetamine-Assisted Psychotherapy in Subjects with Chronic, Treatment-Resistant Posttraumatic Stress Disorder: The First Randomized Controlled Pilot Study. *J Psychopharmacol* 25(4): 439-452.
 12. Fuentes JJ, Fonseca F, Elices M, Farre M, Torrens M (2019) Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials. *Front Psychiatry* 10: 943.
 13. Rosenbaum D, Boyle AB, Rosenblum AM, Ziai S, Chasen MR, et al. (2019) Psychedelics for Psychological and Existential Distress in Palliative and Cancer Care. *Curr Oncol* 26(4): 225-226.
 14. Nichols DE, Walter H (2021) The History of Psychedelics in Psychiatry. *Pharmacopsychiatry* 54(4): 151-166.
 15. Gasser P, Kirchner K, Passie T (2015) LSD-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Disease: A Qualitative Study of Acute and Sustained Subjective Effects. *J Psychopharmacology* 29(1): 57-68.
 16. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, et al. (2018). 3, 4-Methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy for Post-traumatic Stress Disorder in Military Veterans, Firefighters, and Police Officers: A Randomised, Double-Blind, Dose-Response, Phase 2 Clinical Trial. *The Lancet Psychiatry* 5(6): 486-497.
 17. Schenberg EE (2018) Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. *Front Pharmacol* 9: 733.
 18. Nour MM, Evans L, Carhart-Harris RL (2017) Psychedelics, Personality and Political Perspectives. *J Psychoactive Drugs* 49(3): 182-191.