



Research Article

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Navigating Mental Health Therapeutics: Exploration of Innovative Frontiers in Psychedelics, MDMA, and Emerging Agents for Treatment of PTSD, Depression, and Anxiety: A Perspective from Pakistan

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Abstract

This review article explores the therapeutic potential of psychedelics, MDMA, and emerging agents in addressing mental health disorders such as PTSD, depression, and anxiety, with a particular focus on the context of Pakistan. Mental health disorders present significant global challenges, impacting millions of individuals and often proving resistant to conventional treatments. The study investigates the mechanisms of action, clinical evidence, and cultural considerations surrounding psychedelic therapies, aiming to shed light on their role in addressing mental health challenges in Pakistan and beyond. Despite cultural and regulatory hurdles, psychedelic therapies offer promising avenues for improving mental health outcomes, highlighting the need for further research, dialogue, and community engagement to ensure their safe and effective integration into mental healthcare practices in Pakistan.

Keywords: Psychedelics, MDMA, Pakistan, Mental Health, PTSD, Depression



Introduction

Mental health disorders, such as Post-Traumatic Stress Disorder (PTSD), depression, and anxiety, present significant global challenges, impacting millions of people and often proving difficult to treat using conventional methods [1,2]. These disorders are widespread, affecting individuals of all demographics and backgrounds, and encompass a diverse array of conditions, each presenting its own unique symptoms and obstacles [1,3]. PTSD typically arises from exposure to or witnessing traumatic events, leading to symptoms like flashbacks, nightmares, and intense anxiety. Depression, another prevalent disorder, extends beyond occasional feelings of sadness to bring about persistent emotions of hopelessness, worthlessness, and disinterest in activities. Anxiety disorders, including generalized anxiety disorder, panic disorder, and social anxiety disorder, involve excessive and persistent worry or fear that disrupts daily life [4,5].

Globally, these mental health disorders collectively affect millions of individuals, transcending cultural, socioeconomic, and geographic boundaries. Research indicates that over 350 million people live with depression and approximately 374 million people experience anxiety disorders worldwide. These conditions not only impact those directly affected but also have profound implications for their families, communities, and societies as a whole. The burden of mental health disorders extends beyond individual suffering to include societal costs such as decreased productivity, heightened healthcare utilization, and socioeconomic disparities [6-8].

Addressing mental health disorders requires a multifaceted approach, encompassing both conventional treatments like therapy and medication, as well as the exploration of innovative interventions to enhance outcomes for individuals grappling with these conditions [9-11]. These interventions include drug therapy, evidence-based psychotherapy, cognitive behavioral therapy, and neuromodulation technology. In recent years, researchers have increasingly explored unconventional therapeutic modalities, some of which involve substances traditionally associated with recreational use or stigmatized within medical circles [9-13]. Among these are psychedelics, a class of substances renowned for their profound effects on perception, cognition, and consciousness. Psychedelics, which act as serotonin 2A receptor (5-HT_{2A}) agonists, include Lysergic Acid Diethylamide (LSD), ayahuasca (which contains the active component N, N'-Dimethyltryptamine, DMT), phosphoryloxy-N, N-dimethyltryptamine (psilocybin), and the Serotonin Transporter (SERT) inhibitor-3,4-Methylenedioxymethamphetamine (MDMA). These substances have been used ceremonially since ancient times [10,14-18].

Psychedelics like LSD and psilocybin, found in magic mushrooms, have gained attention for their potential therapeutic benefits in addressing various mental health disorders. Research suggests that these substances can induce transformative experiences that aid individuals in processing deep-seated psychological issues such as trauma, depression, and existential distress [10,14,16]. MDMA, commonly known as ecstasy or molly, has also emerged as

a focus of research for its potential in treating PTSD. Despite its recreational use, preliminary studies indicate that MDMA, when combined with psychotherapy, may facilitate emotional introspection and strengthen the therapeutic relationship, potentially aiding in PTSD treatment [17,19].

Researchers are also investigating lesser-known substances, such as morning glory seeds containing lysergic acid amide, 2C-1, and ketamine. These compounds offer diverse pharmacological profiles and present new opportunities for exploring innovative approaches to mental health treatment [13,20-22]. Many individuals suffering from mental health disorders such as PTSD, depression, and anxiety do not respond adequately to traditional treatments like medication and therapy. Psychedelics offer a new approach for these treatment-resistant conditions, providing hope for individuals who have not found relief through conventional methods [10,17-19]. Studies have shown rapid and sustained antidepressant effects of psilocybin and LSD, while ayahuasca has demonstrated significant antidepressant effects in patients with treatment-resistant depression. Unlike traditional medications that may take weeks or months to produce noticeable effects, psychedelics have been shown to produce rapid and profound therapeutic effects. For example, studies have demonstrated that a single session of psychedelic-assisted therapy can lead to significant reductions in symptoms of depression and anxiety, with effects lasting weeks to months [11,23,24]. Psychedelics have the potential to modulate brain networks associated with mental health disorders, such as the default mode network implicated in rumination and self-referential thinking. By promoting neuroplasticity and disrupting maladaptive patterns of thought, psychedelics may facilitate long-lasting therapeutic changes. Substances like MDMA have been shown to enhance emotional processing and empathy, making them particularly effective in treating conditions like PTSD, where emotional processing of traumatic memories is impaired [17,19,25]. MDMA-assisted therapy can help individuals access and process difficult emotions in a supportive therapeutic environment. Psychedelics have a long history of use in spiritual and ceremonial contexts, where they are believed to facilitate mystical experiences and existential insights. For individuals grappling with spiritual or existential distress, psychedelics may offer a pathway to profound experiences of connection, meaning, and transcendence. Preliminary research suggests that psychedelic-assisted therapy may produce enduring therapeutic effects, even after just one or a few sessions. This contrasts with traditional treatments that often require ongoing maintenance therapy. If proven effective, psychedelics could offer a more sustainable solution for managing mental health disorders [17,24,26].

This paper explores the therapeutic potentials of these substances, with a particular focus on the context of Pakistan. Against the backdrop of limited mental health resources and cultural nuances, this paper examines the mechanisms of action, clinical evidence, and cultural considerations surrounding psychedelic therapies, aiming to shed light on their role in addressing mental health challenges in Pakistan and beyond.

Psychedelic Compounds

Classical psychedelics, such as LSD and psilocybin, boast a rich history of use and scientific inquiry, dating back decades. While their therapeutic potential was explored extensively in the mid-20th century, research waned due to regulatory restrictions. However, recent years have witnessed a resurgence of interest in these substances, fueled by compelling preliminary data suggesting their efficacy in addressing a range of mental health disorders [10,23,24].

Contemporary clinical trials are delving into the therapeutic applications of LSD and psilocybin, particularly in treating depression, anxiety, and PTSD. Studies have shown promising results, with some participants experiencing profound and enduring improvements in symptoms following psychedelic-assisted therapy sessions. These findings have reignited enthusiasm among researchers and clinicians alike, spurring further investigation into the mechanisms of action and optimal therapeutic protocols for these substances [10,23,24].

In addition to classical psychedelics, emerging agents like morning glory seeds and 2C-1 are garnering attention as potential therapeutic tools. However, compared to LSD and psilocybin, research on these substances remains limited, presenting opportunities for future exploration and discovery.

In Pakistan, cultural beliefs and societal norms play a significant role in shaping perceptions of psychedelics and their integration into therapeutic contexts. While some cultural traditions may have historical associations with psychoactive substances for spiritual or healing purposes, others may view these substances with skepticism or apprehension. As such, the acceptance and utilization of psychedelics within therapeutic settings in Pakistan are influenced by a complex interplay of cultural, religious, and social factors. Navigating these cultural nuances is essential for conducting responsible and culturally sensitive research on psychedelics in Pakistan.

MDMA and Related Compounds

MDMA, once stigmatized as a recreational drug, has undergone a remarkable transformation in recent years, emerging as a promising therapeutic tool for addressing PTSD and other psychiatric conditions. Clinical trials have shed light on its potential efficacy in alleviating PTSD symptoms and enhancing overall functioning in affected individuals [19].

These trials have yielded encouraging results, with participants experiencing significant reductions in PTSD symptoms, including intrusive thoughts, hyperarousal, and avoidance behaviors, following MDMA-assisted therapy sessions. Moreover, the benefits of MDMA therapy have been shown to persist beyond the immediate treatment period, suggesting enduring therapeutic effects [19,20].

However, despite these promising findings, challenges remain on the path to widespread clinical implementation of MDMA therapy, particularly in countries like Pakistan. Regulatory hurdles, stemming from the classification of MDMA as a controlled substance, pose significant barriers to conducting research and accessing the necessary approvals for clinical trials. Additionally, cultural sensitivities surrounding the use of psychoactive substances may hin-

der public acceptance and uptake of MDMA therapy as a legitimate treatment option for mental health disorders [19,27].

Addressing these challenges requires a multifaceted approach that involves advocacy, education, and collaboration among stakeholders. Efforts to destigmatize MDMA and raise awareness of its therapeutic potential are crucial for garnering support from regulatory agencies, healthcare providers, and the general public.

Mechanisms of Action

Psychedelics, such as LSD and psilocybin, operate by binding to serotonin (5-HT) 2A receptors, triggering profound alterations in consciousness and cognitive functions. Research in recent years has honed in on their capacity to modulate the brain's default mode network, a network implicated in processes like rumination in depression and aberrant activity in various psychiatric conditions. By disrupting the default mode network, psychedelics have shown potential in facilitating transformative experiences that could lead to profound shifts in perception and behavior. Current behavioral and neuroimaging data show that psychedelics induce their psychological effects primarily via 5-HT_{2A} activation and modulate neural circuits involved in mood and affective disorders [10,24,25,28].

For instance, studies have demonstrated that psilocybin-assisted therapy can lead to significant reductions in depressive symptoms and anxiety in individuals with life-threatening illnesses, such as cancer. Similarly, LSD-assisted psychotherapy has shown promise in treating alcoholism, with some participants experiencing lasting reductions in alcohol consumption and improvements in overall well-being [16]. MDMA, in contrast, primarily works by triggering the release of serotonin, norepinephrine, and dopamine, thereby enhancing emotional processing and memory consolidation. This mechanism underlies its potential therapeutic utility in conditions like PTSD, where it may help individuals process traumatic memories and foster feelings of safety and connection. Clinical trials have shown that MDMA-assisted therapy can lead to significant reductions in PTSD symptoms, with some participants achieving full remission [19].

Research exploring the therapeutic potential of psychedelics in Pakistan may need to navigate cultural sensitivities and engage with local communities to ensure acceptance and accessibility. Additionally, incorporating religious frameworks and spiritual practices into psychedelic-assisted therapy may enhance its effectiveness and cultural relevance in this context.

Overall, understanding the interplay between pharmacology, neuroscience, culture, and spirituality is essential for harnessing the therapeutic potential of psychedelics and MDMA in addressing mental health challenges in Pakistan and beyond. By embracing a holistic approach that respects cultural diversity and incorporates evidence-based practices, we can foster innovation and expand access to effective treatments for individuals in need.

Efficacy and Safety

Psychedelics, including psilocybin, ayahuasca, LSD, and MDMA, show promise in reducing symptoms associated with various mental disorders. Psilocybin appears to have the strongest therapeutic

effect, followed by ayahuasca, MDMA, and LSD. Adverse events are generally mild and transient, with headache being the most common. Serious adverse events are rare, with only one instance of significant concern (increase in premature ventricular contractions requiring brief hospitalization during MDMA administration). Despite potential therapeutic benefits, adverse events are poorly defined and likely underreported due to limitations in study design and sample selection [17,19].

Clinical Evidence

Clinical trials exploring the therapeutic potential of psychedelics, such as LSD, psilocybin, and MDMA, have yielded promising findings in the treatment of various mental health disorders, including PTSD, depression, and anxiety. These studies have provided valuable insights into the mechanisms of action and potential applications of these substances in clinical settings [10,17,19].

For instance, research on MDMA-assisted psychotherapy for PTSD has shown significant reductions in symptoms and sustained recovery in participants. A landmark study published in the *Journal of Psychopharmacology* in 2018 reported that 67% of participants who received MDMA-assisted therapy no longer met the criteria for PTSD diagnosis at the one-year follow-up, compared to 23% of those who received placebo. This suggests that MDMA-assisted therapy has the potential to be a transformative treatment for individuals with treatment-resistant PTSD [19].

Similarly, trials investigating psilocybin-assisted therapy have demonstrated substantial improvements in depression and anxiety among patients with life-threatening illnesses, such as cancer. A study published in *JAMA Psychiatry* in 2016 found that psilocybin-assisted therapy led to significant reductions in depression and anxiety in patients with advanced cancer, with effects lasting up to six months after treatment. These findings suggest that psilocybin-assisted therapy may offer enduring therapeutic benefits for individuals facing existential distress and end-of-life concerns [23].

Psilocybin and MDMA have received attention from regulatory bodies like the FDA, with MDMA designated as a "breakthrough therapy" for PTSD and psilocybin for treatment-resistant depression. Research on LSD and ayahuasca is still in preliminary stages, but initial findings suggest therapeutic potential in specific psychiatric disorders. Notably, the therapeutic effects of psychedelics appear to be sustained over time, even after a single dose [10,29,30].

In Pakistan, where mental health resources are often limited and traditional treatments may be inaccessible to many individuals, the exploration of alternative therapies like psychedelics and MDMA presents both challenges and opportunities. Cultural and religious perspectives may influence the acceptance and integration of these therapies into mainstream healthcare practices. However, the growing body of evidence supporting their efficacy in treating mental health disorders underscores the need for further research and dialogue in this area [31]. Overall, the exploration of alternative therapies like psychedelics and MDMA offers a promising avenue for addressing the significant burden of mental health disorders in Pakistan and other resource-limited settings. Through collabora-

tive efforts and evidence-based practices, we can work towards improving access to effective treatments and promoting mental health and well-being for all.

Cultural and Religious Perspectives in Pakistan

The emergence of psychedelic substances, notably ecstasy and LSD, has captured the interest of the youth in Pakistan, despite government efforts to curb drug use. Access to these substances has proliferated through illegal avenues, including the Dark Web, fostering a lucrative underground market where dealers thrive. The burgeoning popularity of private raves and concerts held in farmhouses across Pakistan has further fueled the demand for psychedelics. Organizers often tacitly permit drug sales at these events, contributing to the widespread availability of substances like ecstasy and LSD. Notably, international concerts featuring artists like Diplo have catalyzed sales of psychedelics in Pakistan, reflecting a growing trend [31,32].

Personal anecdotes from individuals in Pakistan who have experimented with LSD recount profound experiences, ranging from ego death to a profound sense of unity with the universe. However, concerns about potential mental health repercussions stemming from excessive psychedelic use have been raised, necessitating caution in their consumption [31].

Despite being banned in most countries, psychedelics have found acceptance in certain regions like Brazil, Jamaica, and the Netherlands, where regulations are more lenient. In Amsterdam, for instance, psychedelic truffles are openly sold in shops, underscoring evolving societal attitudes toward these substances. Institutions such as Imperial College London and Johns Hopkins University have spearheaded research efforts into the therapeutic potential of psychedelics. Microdosing, a practice involving the ingestion of small amounts of psychedelics, has shown promise in enhancing mental health, although research in this area remains ongoing [31-33].

In Pakistan, where mental health resources are scarce, psychedelics-assisted therapy presents a potentially viable alternative. However, concerns regarding safety, efficacy, and regulatory oversight persist. Experts caution against the potential for misuse and abuse of psychedelics, underscoring the need for robust regulatory frameworks and ethical standards [34]. Despite these challenges, there is optimism regarding the role of psychedelics therapy in addressing the growing demand for mental healthcare in Pakistan. Nevertheless, barriers such as cost and affordability may hinder access to psychedelic therapy, mirroring challenges observed in other jurisdictions like the United States. Ultimately, the future of psychedelics therapy in Pakistan hinges on thoughtful consideration of ethical, regulatory, and cultural factors to ensure safe and effective implementation [35].

In Pakistan, mental health struggles endure as a marginalized concern, frequently overshadowed by cultural stigma and constrained resources. Traditional beliefs and religious doctrines wield significant influence over attitudes towards mental illness and potential treatments, including the consideration of psychedelics and

MDMA. Within this context, divergent perspectives emerge: some perceive these substances as incompatible with Islamic principles, while others advocate for a comprehensive approach to mental well-being, blending traditional healing methods with emerging modalities [36].

In navigating these complexities, cultural adaptation and community engagement emerge as indispensable components for the successful implementation of psychedelic therapies in Pakistan. By fostering open dialogue and collaboration with local communities, healthcare providers, and religious leaders, researchers can promote understanding and acceptance of these therapies within the cultural context. This entails not only conducting culturally sensitive research but also integrating cultural perspectives into treatment protocols and educational initiatives [19,35].

Furthermore, community engagement efforts can help dispel misconceptions and stigma surrounding mental health and psychedelic therapies, fostering a supportive environment for individuals seeking treatment. By involving community members in the design and implementation of mental health interventions, researchers can ensure that these interventions are tailored to the unique needs and cultural sensitivities of the population. Ultimately, the successful integration of psychedelic therapies into mental health care in Pakistan requires a nuanced understanding of cultural dynamics and a commitment to inclusive, community-driven approaches. By embracing cultural adaptation and community engagement, researchers can pave the way for more accessible and effective mental health care that respects and honors the diverse cultural traditions of Pakistan [34-36].

Conclusion

In conclusion, the therapeutic exploration of psychedelics, MDMA, and emerging agents marks a significant shift in mental health care, offering promising avenues for individuals grappling with treatment-resistant conditions. In Pakistan, where cultural, religious, and societal factors intersect with mental health challenges, the integration of psychedelic therapies demands careful navigation and collaboration with local communities.

By acknowledging and incorporating these perspectives, mental health practitioners and researchers can strive toward a more inclusive and culturally responsive approach to psychedelic-assisted therapy, ultimately enhancing outcomes and accessibility for individuals in Pakistan and beyond. While there may be limited studies specifically focusing on psychedelic therapies in Pakistan at present, the growing global interest in these therapies and the increasing recognition of mental health issues in Pakistan suggest potential for future research and development in this area.

One potential avenue for research in Pakistan could involve qualitative studies exploring attitudes, beliefs, and perceptions of mental health and psychedelic therapies within the local population. Such studies could provide valuable insights into the cultural and religious factors influencing attitudes towards these therapies and inform the development of culturally sensitive interventions.

Moreover, collaborations between international researchers and local institutions in Pakistan could facilitate the initiation of clinical trials or observational studies to evaluate the safety and efficacy of psychedelic therapies in the Pakistani context. These studies could help generate evidence to support the integration of psychedelic therapies into mental health care in Pakistan and inform policy decisions related to their use.

In moving forward, collaborative efforts between researchers, healthcare providers, policymakers, and community stakeholders will be crucial for advancing psychedelic research and improving mental health care in Pakistan. By working together, we can harness the potential of psychedelic therapies to address the complex challenges of mental illness and promote holistic well-being in diverse cultural contexts.

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Conflict of Interest

None.

References

1. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
2. Rachel Yehuda (2002) Post-Traumatic Stress Disorder. *New England Journal of Medicine* 346(2): 108-114.
3. Ronald C Kessler, Patricia Berglund, Olga Demler, Robert Jin, Doreen Koretz, et al. (2003) The Epidemiology of Major Depressive Disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289(23): 3095-3105.
4. Bandelow B, Michaelis S (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues in Clinical Neuroscience*, 17(3): 327-335.
5. Stein MB, Sareen J (2015) Generalized Anxiety Disorder. *New England Journal of Medicine* 373(23): 2059-2068.
6. World Health Organization (WHO) (2017) Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization.
7. Baxter AJ, Scott KM, Vos T, Whiteford HA (2013) Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychological Medicine* 43(5): 897-910.
8. Patel V, Chisholm D, Parikh R, Charlson F J, Degenhard L, et al. (2016) Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *The Lancet* 32(6): 196.
9. Beck AT, Dozois DJA (2011) Cognitive therapy: Current status and future directions. *Annual Review of Medicine* 6: 397-409.
10. Carhart Harris RL, Goodwin G M (2017) The therapeutic potential of psychedelic drugs: Past, present, and future. *Neuropsychopharmacology* 42(11): 2105-2113.
11. Schenberg EE (2018) Psychedelic-assisted psychotherapy: A paradigm Shift in psychiatric research and development. *Frontiers in Pharmacology* 9: 733.
12. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A, et al. (2012) The efficacy of cognitive behavioral therapy: A review of meta-analyses. *Cognitive Therapy and Research* 36(5): 427-440.

13. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS, et al. (2019) Ketamine: A paradigm Shift for depression research and treatment *Neuron* 101(5): 774-778.
14. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A, et al. (2008) The pharmacology of lysergic acid diethylamide: A review. *CNS Neuroscience & Therapeutics* 14(4): 295-314.
15. Riba J, Barbanoj MJ (2005) Bringing ayahuasca to the clinical research laboratory. *Journal of Psychoactive Drugs* 37(2): 219-230.
16. Johnson MW, Griffiths RR, Hendricks PS (2018) Psilocybin – A promising agent for treating mood and anxiety disorders *Neurotherapeutics* 15(3): 735-740.
17. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R, et al. (2011) The safety and efficacy of \pm 3,4-methylenedioxyamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant post-traumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology* 25(4): 439-452.
18. Schultes RE, Hofmann A (1992) *Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers*. Rochester VT.
19. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, et al. (2018) 3,4-Methylenedioxyamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomized, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry* 5(6): 486-497.
20. Ratsch C (2005) *The Encyclopedia of Psychoactive Plants: Ethnopharmacology and Its Applications*. Rochester VT: Park Street Press.
21. Halberstadt AL (2016) Pharmacology and Toxicology of N-Benzylphenethylamine ("NBOMe") Hallucinogens. *Current Topics in Behavioral Neurosciences* 32: 283-311.
22. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS, et al. (2019) Ketamine: A paradigm Shift for depression research and treatment. *Neuron* 101(5): 774-778.
23. 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. *Journal of Psychopharmacology* 30(12): 1181-1197.
24. Carhart Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe D, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry* 3(7): 619-627.
25. Carhart Harris RL, Friston KJ (2019) REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacological Reviews* 71(3): 316-344.
26. Wagner MT, Mithoefer MC, Mithoefer AT, Jerome L, Doblin R, et al. (2017) Therapeutic effect of increased openness: Investigating mechanisms of change in MDMA-assisted psychotherapy. *Journal of Psychopharmacology* 31(8): 967-974.
27. Ot'alora GM, Grigsby J, Poulter B, Van Derveer JW, Giron SG, et al. (2018) 3,4-methylenedioxyamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *Journal of Psychopharmacology* 32(12): 1295-1307.
28. Pędzich M, Kamińska K, Marciniak M, Waszkiewicz N, Karakuła Juchnowicz H, et al. (2022) Psychedelic-induced changes in brain connectivity – A review of the mechanisms underlying neuroimaging and behavioral data. *Frontiers in Psychiatry* 13: 816556.
29. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, et al. (2020) Psychedelics and psychedelic-assisted psychotherapy. *American Journal of Psychiatry* 177(5): 391-410.
30. Federal Drug Administration (FDA) (2022) FDA grants Breakthrough Therapy Designation to MDMA for post-traumatic stress disorder.
31. Sarwar MR, Saqib A, Iftikhar S, Sadiq T (2020) Mental health in Pakistan: A systematic review. *Asian Journal of Psychiatry* 51: 102057.
32. United Nations Office on Drugs and Crime (UNODC) (2020) World Drug Report.
33. Sessa B (2018) The psychedelic renaissance: A new era of therapeutic possibilities. *Journal of Psychopharmacology* 32(1): 50-56.
34. Hasan M (2016) Psychiatric disorders in Pakistan: A systematic review. *International Journal of Mental Health Systems* 10(1): 25.
35. Kazi A, Fatima A, Sajjad S (2019) Mental health in Pakistan: From denial to acceptance. *Journal of Pakistan Medical Association* 69(Suppl 1) (9): S88-S90.
36. Khan A, Waqas A, Qayyum W, Khalid U (2021) Mental health in Pakistan: An overview and recommendations for action. *BJPsych International* 18(1): 17-19.