ROLE OF PSYCHEDELIC DRUGS IN MENTAL HEALTH CARE: A NARRATIVE REVIEW

Tamara Trajbarič

Faculty of Health Sciences, University of Maribor, Slovenia received: 29.8.2024; revised: 15.10.2024; accepted: 1.12.2024

SUMMARY

Good mental health is foundational for individual and societal well-being, enabling resilience, personal growth, and active community engagement. Despite the availability of pharmacological and non-pharmacological treatments, many individuals experience partial or non-response, delayed therapeutic effects, and adverse side effects. Increasingly, individuals are exploring the use of psychedelics for self-guided psychotherapy beyond clinical settings, highlighting their potential for transformative mental health benefits. However, the definition and application of psychedelics vary across contexts, underscoring the need for nuanced understanding and cautious use. While earlier prohibition was driven by exaggerated perceptions of harm, modern evidence recognizes psychedelics as powerful substances capable of eliciting profound positive and negative outcomes. Safety remains a paramount concern, and current research is constrained by methodological limitations. Addressing these gaps is essential to advancing the therapeutic potential of psychedelics, ensuring their responsible integration into mental health care while mitigating risks.

Key words: psychedelic drugs, mental health care, psychedelic-assisted therapy.

INTRODUCTION

Good mental health is essential for the holistic well-being of individuals and society, as it enables effective coping with life's challenges, the development of potential and active contribution to the community. Individuals facing mental health issues encounter obstacles that impact their lives, potentially resulting in poorer educational outcomes, higher unemployment rates, and deteriorating physical health (The Organization for Economic Cooperation and Development [OECD] 2022; World Health Organization [WHO] 2022). Mental health is not merely the absence of disorders but encompasses a broad spectrum and various levels of distress (WHO 2022). Notably, mental illnesses rank among the top ten most common causes of limitations in daily life, posing significant social and economic challenges and placing a burden on societal and economic structures (Eurostat 2021).

Current treatments, including pharmacotherapies such as selective serotonin reuptake inhibitors, first- and second-generation antipsychotics, lithium, benzodiazepines ect. (Khan, 2020), as well as nonpharmacological approaches like cognitive behavioral therapy, electroacupuncture, and psychomotor therapy (Guedes de Pino et al., 2024), benefit many patients. However, high rates of partial or no response, delayed therapeutic effects, and undesirable side effects remain significant challenges (Menke, 2018). Kopra et al. (2023) says that more people are turning to psychedelics for personal psychotherapy outside formal

clinical settings. How we define psyhedelics is dependent on the context.

Heal et al. (2018) examines and contrasts definitions from the Oxford English Dictionary, the Merriam-Webster Medical Dictionary, and the MediLexicon Medical Dictionary. The Oxford English Dictionary describes "psychedelic" as referring to substances, particularly lysergic acid diethylamide (LSD), that induce hallucinations and seemingly expand consciousness. The Merriam-Webster Medical Dictionary characterizes psychedelics as drugs, such as LSD, that can cause unusual psychological effects, including hallucinations and occasionally psychotic states. Meanwhile, the MediLexicon Medical Dictionary defines the term more broadly, associating it with a loosely defined category of drugs that primarily act on the central nervous system and are believed to enhance or amplify consciousness, including substances like LSD, hashish, mescaline, and psilocybin. These varying interpretations highlight the absence of a consistent definition for "psychedelic." However, a shared emphasis across the definitions is the capacity of these substances to induce profound shifts in perception, thought processes, and emotions (van Elk & Yaden 2022).

For instance, psilocybin is a psychedelic compound in certain mushrooms, which have been used in sacred ceremonies among indigenous peoples in Mexico and elsewhere for centuries. Other psychedelic compounds, such as mescaline and DMT (N,N-dimethyltryptamine), have likewise been used for hundreds or thousands of years in ritual contexts. The psychedelic LSD (lysergic acid diethylamide), which the Swiss chemist Albert Hofmann synthesized in 1938, led to innovations in understanding serotonin pharmacology and, eventually, to the development of therapeutics that modulate serotonin function such as selective serotonin reuptake inhibitors (Yaden et al. 2021). The earliest recorded medical use of a classical psychedelic in Western medicine dates back to 1895, when Prentiss and Morgan documented the ceremonial use of peyote cactus buttons by Central American indigenous communities (Prentiss & Morgan 1895). MDMA, also recognized as ecstasy in recreational contexts, was once widely employed in psychotherapy, particularly in couples therapy, where it was termed "empathy" for its ability to enhance emotional connection (Sessa & Nutt 2015). Ketamine, a well-established dissociative anesthetic, has more recently been repurposed in lower doses for pain relief and is also used recreationally for its mind-altering, psychedelic-like properties (Lener et al. 2017).

Psychedelics have inspired new hope for treating brain disorders due to their unique ability to produce sustained therapeutic effects after a single administration, offering broad potential for conditions like depression, PTSD, anxiety, addiction, and psychological distress associated with end-of-life experiences (Menke 2018; Vargas et al. 2021). Despite their long history, they remain a contentious topic in Western culture, as their highly context-dependent effects necessitate carefully controlled studies in supportive environments supervised by trained professionals (Menke 2018). The Food and Drug Administration (FDA) ruled to reject MDMA for assisted psychotherapy for PTSD, citing insufficient evidence and the need for more research. The ruling is consistent with a letter APA sent the FDA earlier this year that stated that a of the literature on MDMA-assisted psychotherapy by a multidisciplinary panel of experts determined that there is insufficient evidence to be able to recommend MDMA-assisted psychotherapy for patients with PTSD (Stinger 2024). For decades, psychiatric treatments have experienced limited advancements. Emerging research on psychedelics suggests they could offer promising new therapeutic options for a range of psychiatric disorders (Yaden et al. 2021).

This narrative review examines the role of psychedelic drugs in modern mental health care, focusing on their therapeutic potential, effectiveness, and challenges. The importance of this research lies in its potential to uncover innovative approaches for treating mental health conditions that often resist traditional therapies. By exploring the historical context, analyzing recent clinical studies, and understanding how psychedelics affect the brain and emotional well-being, this review provides a comprehensive synthesis of existing knowledge. Using the PIO framework, it identifies theoretical foundations,

key findings, and gaps in the research. This exploration offers promising insights and could pave the way for breakthroughs in addressing complex psychological challenges through the effects, risks, and therapeutic applications of psychedelics.

MECHANISM OF ACTION OF PSYCHEDELIC DRUGS

Serotonin is widely recognized as a neurotransmitter that influences neural activity and plays a crucial role in various neuropsychological Medications designed to interact with serotonin receptors are commonly utilized in the fields of psychiatry and neurology (Berger et al. 2009; Lv & Liu 2017). Building on this foundation, psychedelic drugs exert their distinctive effects primarily by interacting with the brain's serotonin (5-HT) neurotransmission system. Specifically, these compounds act as partial agonists at the 5-HT2A receptors, which are critically involved in the regulation of mood, perception, and cognitive processes (Bamalan et al., 2024). These receptors are particularly abundant in brain regions such as the medial prefrontal cortex and the visual cortex, which are integral to emotional and sensory processing (van Elk & Yaden, 2022). Upon activation, 5-HT2A receptors stimulate cortical layer 5 pyramidal neurons, triggering Gq protein-coupled signaling cascades. This process leads to intracellular calcium release and the activation of various kinases, influencing neuronal dynamics in ways that produce the characteristic altered states of consciousness associated psychedelics (Hatzipantelis & Olson, 2024). The central role of 5-HT2A receptors in psychedelic effects has been demonstrated through experiments showing that drugs like ketanserin, a receptor antagonist, block these effects, while genetic models that lack 5-HT2A receptors fail to respond to hallucinogenic compounds altogether (López-Giménez & González-Maeso, 2017; van Elk & Yaden, 2022). Notably, not every compound that targets these receptors induces hallucinations. This distinction is explained by the concept of biased agonism, wherein hallucinogenic compounds activate both the Gq/11 and Gi/o signaling pathways, whereas non-hallucinogenic agonists engage only the Gq/11 pathway. Such intricate interactions at the receptor level highlight the complex mechanisms underlying the differentiation between hallucinogenic and potentially therapeutic effects of 5-HT2A-targeting compounds (López-Giménez González-Maeso, 2017).

Research into psychedelics was effectively halted for decades due to societal and political factors rather than a lack of scientific interest. The 1960s and 1970s saw a wave of public concern and media-driven panic regarding the widespread use of psychedelics, culminating in the enactment of restrictive laws like the 1970 Controlled Substances Act. These regulations imposed severe

limitations on clinical research, making it nearly impossible for scientists to conduct studies during this period (Nichols, 2016).

Isomeric forms of psychedelics: Differences in effects and activity

Popik et al. (2022) investigated whether fast-acting antidepressants like ketamine and psilocybin influence time perception and whether this effect relates to their therapeutic action. While (S)-ketamine at high doses led to time underestimation alongside severe cognitive impairments, (R)-ketamine improved cognition without affecting time perception. Psilocybin and psilocin caused nonspecific behavioral changes but did not alter time perception. Thus, the study concluded that changes in time perception are not essential for antidepressant efficacy, as both (R)-ketamine and psilocybin remain clinically effective without this effect. In the same way, (±)-MDMA has shown promise in treating PTSD and other psychiatric disorders, yet its widespread use is limited by adverse effects. A potential solution is using its enantiomer R(-)-MDMA, which offers comparable therapeutic benefits with lower toxicity, hyperthermia, hypertension, and abuse potential. However, placebocontrolled human studies are still needed to confirm its safety. Further research could establish R(-)-MDMA as a safer alternative for psychiatric treatment (Pitts et al. 2018). It is essential to highlight LSD, a potent centrally acting drug, with only the d-isomer pharmacologically active. It selectively inhibits the brain's raphe system, stopping the spontaneous firing of serotonin-containing neurons in the dorsal and median raphe nuclei, making it an indirect serotonin antagonist. However, this inhibition alone does not explain LSD's hallucinogenic effects, as lisuride, a stronger raphe inhibitor, lacks psychedelic properties. This suggests that other mechanisms, such as glutamate or serotonin receptor interactions, play a role. Additionally, LSD may indirectly affect the cytoskeleton by reducing serotonin release from the raphe system (Jenkins & Gates 2020).

While isomers influence how psychedelic drugs work, some new compounds take a different approach. DLX-001, a novel orally active molecule, exhibits rapid and long-lasting antidepressant effects similar to ketamine and psilocybin. It enhances synaptic connectivity in the mPFC without inducing hallucinogenic effects, distinguishing it from psychedelics. Given its potential to provide antidepressant benefits without the drawbacks of ketamine or psilocybin, DLX-001 may represent a promising advancement in depression treatment (Rasmussen et al. 2024).

MENTAL HEALTH DISORDERS CAUSED BY PSYCHEDELIC DRUGS

Aday et al. (2020) identified 34 contemporary humansample studies on classic psychedelics, with most focusing on psilocybin and published within the last five years, documenting lasting changes in personality, attitudes, depression, spirituality, affect, mood, anxiety, wellbeing, substance use, meditative practices, and mindfulness. Commonly proposed mechanisms for these changes included mystical experiences, a sense of connectedness, emotional breakthroughs, and increased neural entropy. However, concerns have emerged regarding potential negative psychological effects, with 37.5% of participants in one study reporting psychiatric diagnoses after psychedelic use, including worsening anxiety symptoms in 87%. In-depth interviews revealed contributing factors such as unsafe environments, unpleasant acute effects, psychological vulnerabilities, high or unknown dosages, and youth, with approximately one-third of interviewees receiving new psychiatric diagnoses after use (Bremler et al. 2023). These findings underscore the importance of cautious use, particularly given the prevalence of substance-related health issues reported at rave parties, where around one-third of attendees seeking first aid attributed their problems to substances like ecstasy or alcohol, although lifethreatening incidents were rare (Krul et al. 2011). Similarly, microdosing, while generally associated with minor and short-lived negative effects such as anxiety, led some users to discontinue due to co-occurring psychological and physical impacts or a perceived lack of efficacy, often influenced by unrealistic media-driven expectations (Huten et al. 2019). Together, these studies highlight both the transformative potential and risks of psychedelic substances, emphasizing the need for careful consideration and responsible use.

Other studies challenge the notion that psychedelics pose significant risks to mental health, with evidence showing no consistent link between lifetime psychedelic use and negative outcomes such as psychological distress, mental health treatment, or disorder symptoms. Adjusted odds ratios demonstrate no elevated risk, and some findings suggest lower rates of mental health problems among users, potentially reflecting benefits or favorable baseline mental health (Nesvåg et al. 2015). While rare cases of prolonged negative psychological responses have been reported, they are often associated with specific factors like pre-existing personality disorders, emphasizing the need for individualized psychological support (Marrocu et al. 2024). Furthermore, documented cases of severe outcomes, including suicides or deaths directly linked to psychedelics, remain exceedingly rare and are often unsubstantiated (Johansen & Krebs 2015). Research has consistently demonstrated the relative safety of psychedelics, especially when administered with proper preparation, supervision, and integration, leading to lasting psychological benefits (Aday et al. 2020). The absence of neurotoxicity or addiction potential further supports their use in controlled therapeutic settings, where emerging evidence indicates significant and lasting improvements in psychological well-being, contrasting with earlier reports highlighting concerns over adverse effects (Schlag et al. 2022).

PSYCHEDELIC DRUGS IN TREATMENT OF MENTAL HEALTH DISORDERS

Two studies (Bahji et al. 2020; Shahrour et al. 2024) have examined the impact of MDMA in psychotherapy, showing consistent benefits such as increased clinical response, higher remission rates, and reduced PTSD symptoms. This effectiveness may be attributed to MDMA's prosocial effects, including heightened feelings of empathy, connection, and sociability, which strengthen the therapeutic bond between therapists and patients and support the therapeutic process (Bahji et al. 2020). Additionally, MDMA promotes the extinction and consolidation of traumatic memories by restoring brainderived neurotrophic factor levels in key brain regions like the amygdala, vmPFC, and hippocampus. This mechanism facilitates memory consolidation and weakens fear-associated memories, reducing emotional reactivity (Shahrour et al. 2024). Preclinical studies further support these findings, showing that acute MDMA administration before extinction training significantly enhances long-term fear extinction in mice models (Young et al. 2015). These treatments, often referred to as drug-assisted psychotherapy, are complex and require significant therapist involvement. Patients must be adequately prepared for the profound effects of psychedelic sessions, typically through a dedicated preparatory session with a trained therapist or guide. This session educates patients about the rationale, purpose, and procedures of the treatment to ensure a safe and effective therapeutic experience (Nutt 2019).

Shahrour et al. (2024) highlights that there is no significant difference in the incidence of adverse events or suicidal tendencies between participants undergoing MDMA-assisted therapy and those in control groups, suggesting that the therapy is generally safe and well-tolerated when administered in controlled clinical settings. This finding supports the view that MDMA-assisted psychotherapy does not inherently increase the risk of severe adverse effects compared to other therapeutic interventions. Similarly, Bahji et al. (2020) reviewed multiple studies and found that the majority reported no MDMA-related serious adverse events, further supporting its safety profile. However, one study included in the review (Mithoefer et al. 2018) did document four serious adverse events, which included

increased depressive symptoms and suicidal ideation. It is important to note, though, that three of these events were determined to be unrelated to the study drug, indicating that while such events occurred, they may not have been directly caused by MDMA. Adverse events have also been noted in other systematic reviews of psychedelicassisted therapies. Graziosi et al. (2024) in their review on the potential therapeutic use of psychedelics in OCD and related disorders, reported an increase in adverse events associated with LSD use. Similarly, Maia et al. (2022), in their systematic review on the therapeutic potential of psychedelic-assisted therapies for symptom control in patients with serious illnesses, observed mild to moderate intensity adverse events. In 20% of studies, no complications were reported, while 55% noted mild to moderate, self-resolving adverse effects, both physical (e.g., nausea, headaches) and psychological (e.g., anxiety, hallucinations). Some studies reported distress under LSD without psychotherapy, with 50% needing intervention and 30% unwilling to repeat the experience. In 25% of studies, adverse effect data were not reported.

Studies on ayahuasca and other psychedelics consistently highlight their significant therapeutic potential for mood disorders, showing marked reductions in depression and anxiety symptoms alongside notable improvements in mood, self-transcendence, and quality of life (Jiménez-Garrido et al. 2020; Sarris et al. 2021; Yao et al. 2024). Yao et al. (2024), through a comprehensive systematic review and meta-analysis of 126 articles, identified substantial decreases in depression, anxiety, and negative mood. Among the psychedelics studied, psilocybin emerged as the most effective, demonstrating the strongest therapeutic impact, followed by ayahuasca, MDMA and LSD. Additionally, the study found emerging evidence supporting the use of psychedelics in addressing other conditions, including substance-use disorders, obsessive-compulsive disorder, PTSD, and eating disorders, highlighting their broader mental health applications. Importantly, adverse effects were minimal, with headaches being the most frequently reported, and nearly one-third of studies reported no lasting adverse

These findings are reinforced by Jiménez-Garrido et al. (2020), who conducted a longitudinal and cross-sectional study on the effects of ayahuasca on mental health and quality of life. In one part of the study, among ayahuascanaïve users, over 45% initially met diagnostic criteria for psychiatric disorders. However, following ayahuasca use, more than 80% experienced significant and lasting clinical improvements in depression psychopathology scores, which persisted for six months. In another part of the study, long-term ayahuasca users displayed lower levels of depression and higher scores in self-transcendence and quality of life compared to their peers who had never used ayahuasca. Sarris et al. (2021) further bolstered these insights in their cross-sectional study of 11,912 individuals who consumed ayahuasca,

including 1,571 participants with depression and 1,125 with anxiety. Among those with depression, 78% reported that their symptoms were either "very much" improved or "completely resolved". Similarly, among participants with anxiety, 70% reported significant improvements. Factors contributing to these positive outcomes included the intensity of mystical experiences, the number of ayahuasca sessions, and the depth of personal psychological insights experienced during treatment. However, 2.7% of participants with depression and 4.5% of those with anxiety reported worsening symptoms. It is important to note that this study is a cross-sectional analysis and cannot directly assess treatment efficacy. Additionally, potential selection bias may exist, as participants with favorable experiences might have been more likely to respond to the survey, skewing the results. Psychedelic drugs, particularly psilocybin, show promising potential in the treatment of obsessivecompulsive disorder (OCD) and related disorders. Graziosi et al. (2024) reviewed 23 articles, including

clinical trials, preclinical studies, and case reports, and found that psilocybin was generally well-tolerated, with no serious adverse events reported. Significant reductions in OCD symptoms were observed within 24 hours of treatment, though long-term efficacy remains uncertain due to limited follow-up data. Romeo et al. (2021) highlighted the importance of acute psychedelic experiences as predictors of response across psychiatric disorders but noted limited evidence specifically for OCD due to small study sizes.

An innovative method was chosen to present the results of the articles in the synthesis table (Table 4.1). Instead of standard numerical values, words and symbols were used. The symbol ↑ indicates an increase in a parameter (e.g., clinical response), while the symbol ↓ signifies a decrease (e.g., symptoms). If supervision showed no noticeable effect, the symbol − was used. This approach facilitates easier understanding of the key findings and the evaluation of supervision effectiveness for each article or study.

Table 1. Psychedelic-Assisted Therapies Research Overview

Research, country	Type of research	Sample	Intervention	Outcome
Bahji et al. (2020) Canada	A systematic review and meta-analysis	n = 5 randomized and quasirandomized clinical trials using MDMA- assisted psychotherapy for PTSD in comparison with other medications, placebo or no medication	Efficacy of MDMA-assisted psychotherapy for posttraumatic stress disorder	↑ clinical response ↑ remission rates ↓ PTSD symptoms ↑ adverse events
Yao et al. (2024) China	A systematic review and meta-analysis	n = 126 articles	Efficacy and safety of psychedelics for the treatment of mental disorders	↓ depression ↓ anxiety ↓negative mood
Graziosi, et al. (2024) USA	A systematic review	n = 23 articles (2 non- systematic reviews, 11 preclinical studies investigating the use of classic psychedelics or analogs in preclinical models of OCD, 8 case studies or case reports, and 2 clinical trials)	Potential therapeutic use of psychedelics in OCD and related disorders	↓ OCD symptoms ↑adverse events (LSD)
Romeo, et al. (2021) France	A systematic review	n = 20 studies investigating addictive disorder, treatment- resistant depression, obsessive-compulsive disorder and depressive and anxiety symptoms in patients with life- threatening cancer	Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders	↑ clinical response ↓ substance use behaviors ↓ depressive symptoms − no predictive effect identified in OCD
Maia et al. (2022)	A systematic review	n = 20 studies	Therapeutic Potential of Psychedelic-assisted Therapies for Symptom Control in Patients Diagnosed With Serious Illness	† symptom control † mild/moderate intensity adverse events
Shahrour et al. (2024) Jordan	A systematic review and meta-analysis of randomized controlled trials (RCTs)	n = 9 studies with a total of 297 participants with PTSD	MDMA-assisted psychotherapy for the treatment of PTSD	↑improving PTSD symptoms ↑ clinical response ↑ remission rates − treatment-emergent adverse events, severe adverse events, and suicidal ideation
Jiménez- Garrido et al. (2020) Spain	A longitudinal and crosssectional study combination	n = 63 participans	Effects of ayahuasca on mental health and quality of life in naïve users	↓ psychopathology scores ↓ depression, ↑ self-transcendence ↑ quality of life
Sarris et al. (2021) Australia	Cross-sectional study	n =11,912 consumers of ayahuasca with depression (n = 1571) or anxiety (n = 1125)	Ayahuasca use and reported effects on depression and anxiety symptoms	↓ depression ↓ anxiety

n = nubmer of sample; ↑ increase; ↓ decrease; − no noticeable effect

DISCUSSION

Safety is a critical consideration in the use of psychedelics for therapeutic purposes. Although the prohibition of these substances was largely based on exaggerated claims of harm, it is clear that psychedelics are potent mind-altering substances that can create both deeply positive and negative experiences (Carbonaro et al. 2016). One major clinical challenge involves patients who are on medications, such as antidepressants, that interfere with the effects of psychedelics. Medications like quetiapine and olanzapine completely block psilocybin's interaction with 5-HT2A receptors, rendering it ineffective, while SSRIs reduce the psychedelic response by desensitizing these receptors. To allow for effective treatment, patients often need to discontinue these medications gradually and carefully to avoid withdrawal symptoms or exacerbation of depression (Nutt 2019). Furthermore, psychedelics are not suitable for individuals with a predisposition to or family history of psychotic disorders or bipolar mood disorders. They are also contraindicated for people with cardiovascular issues, as these substances can elevate heart rate and blood pressure (Wsół 2023).

Psychedelic research in the US has evolved over more than 20 years, transitioning from its early resurgence to a more advanced and established stage. The field's future remains unclear, with the potential to either revert to prohibition and stagnation or advance toward broader acceptance and clinical use. Achieving the best possible outcomes will depend on upholding rigorous standards in both research and clinical applications (Yaden et al. 2021). Current research on psychedelic therapies and related interventions is limited by several factors that must be addressed in future studies. Firstly, the findings often rely on small sample sizes, which reduces statistical power and limits the generalizability of results (Bahji et al. 2020; Yao et al. 2024). Furthermore, heterogeneity in study designs, dosing regimens, and outcome measures complicates comparisons and meta-analyses (Shahrour et al. 2024; Yao et al. 2024). The exclusion of non-English publications and gray literature restricts cross-cultural insights and the inclusion of diverse perspectives (Graziosi et al. 2024). Additionally, challenges such as publication bias, functional unblinding, and placebo effects raise concerns about the reliability of current evidence (Yao et al. 2024).

Future research should prioritize large-scale, placebocontrolled randomized trials to ensure robust and replicable findings (Yao et al. 2024). Standardized protocols for assessment methods, treatment regimens, and long-term follow-up are necessary to enhance reliability and comparability across studies (Shahrour et al. 2024). Efforts to include diverse populations and address biases in participant demographics are essential to ensure broader applicability (Maia et al. 2022). Research should also expand into underexplored areas, such as the effects of psychotherapeutic methods on psychedelic efficacy and their potential applications for related disorders (Romeo et al. 2021; Graziosi et al. 2024).

Psychedelics must prove their deliverability and costeffectiveness to gain acceptance as established treatments. Many therapies fail to meet these criteria. In practical healthcare settings, psychedelic treatments are likely to be costly compared to other interventions, reinforcing the view that their investigation should focus on addressing socioeconomically burdensome psychiatric conditions, like treatment-resistant depression, where more affordable, conventional therapies have failed (Rucker et al. 2018).

CONCLUSION

Psychedelics show significant potential in advancing mental health care, with research highlighting their effectiveness in treating conditions such as depression, anxiety, PTSD, and OCD. Therapies like MDMA- and psilocybin-assisted psychotherapy hold promise for addressing treatment-resistant psychiatric disorders but require a thoughtful approach, including trained therapists, preparatory sessions, and controlled administration. While the risk of severe side effects appears low, challenges remain in understanding long-term impacts, interactions with other medications, and the development of clear clinical guidelines.

Open questions include how to optimize dosing and therapy protocols, assess long-term efficacy, and enhance accessibility and cost-effectiveness. Future research must focus on larger, more standardized studies and prioritize diversity in study populations to ensure broader applicability of these treatments.

These findings mark a significant step forward for the field, offering new treatment avenues, reducing the burden of mental illness, and providing hope for improved outcomes in cases where traditional approaches have fallen short. For the wider public, they represent the potential for advanced and more effective treatment options, while emphasizing the need for education and regulation to ensure safe integration into clinical practice.

LITERATURE

- Aday JS, Mitzkovitz CM, Bloesch E, Davoli CC & Davis AK: Long-term effects of psychedelic drugs: a systematic review. Neurosci Biobehav Rev 2020;113:179-89.
- 2. Bahji A, Forsyth A, Groll D & Hawken ER: Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: a systematic review and meta-analysis.

- Prog Neuropsychopharmacol Biol Psychiatry 2020;96:109735.
- 3. Bamalan OA, Moore MJ & Al Khalili Y: Physiology, Serotonin. Treasure Island (FL): StatPearls Publishing; 2024.
- Berger M, Gray JA & Roth BL: The expanded biology of serotonin. Annu Rev Med 2009;60:355– 66.
- 5. Bremler R, Katati N, Shergill P, Erritzoe D & Carhart-Harris RL: Case analysis of long-term negative psychological responses to psychedelics. Sci Rep. 2023;13:15998.
- Carbonaro TM, Bradstreet MP, Barrett FS, MacLean KA, Jesse R, Johnson MW & Griffiths RR: Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. J Psychopharmacol 2016;30(12):1268-78.
- 7. van Elk M & Yaden DB: Pharmacological, neural, and psychological mechanisms underlying psychedelics: a critical review. Neurosci Biobehav Rev 2022;140:104793.
- 8. Eurostat. Mental health and related issues statistics [Internet]. 2024 [cited 2024 Apr 24]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mental_health_and_relat ed_issues_statistics#Mental_healthcare
- Graziosi M, Rohde JS, Tiwari P., Siev J & Yaden DB: Psychedelics, OCD and related disorders: a systematic review. J Obsessive Compuls Relat Disord 2024;41:100873.
- Guedes de Pinho L, Fronseca C, Gaweda L, Lopes M & Schneider BC: Editorial: Nonpharmacological interventions for mental disorders. Front Psychol 2024;15:1363348.
- 11. Hatzipantelis CJ & Olson DE. The effects of psychedelics on neuronal physiology. Annu Rev Physiol 2024;86(1):27-47.
- 12. Heal DJ, Gosden J & Smith SL: Evaluating the abuse potential of psychedelic drugs as part of the safety pharmacology assessment for medical use in humans. Neuropharmacology 2018;142:89-115.
- 13. Hutten RPWN, Mason LN, Dolder CP & Kuypers PCK: Motives and side-effects of microdosing with psychedelics among users. Int J Neuropsychopharmacol 2019;22(7):426-34.
- 14. Jenkins AJ & Gates MJ: Hallucinogens and Psychedelics. In Levine BS & Kerrigan S(eds): Principles of Forensic Toxicology, 467–489. Springer, 2020.
- 15. Jiménez-Garrido DF, Gomez-Sousa M, Ona G, Dos Santos RG, Hallak JEC, Alcazar-Corcoles MA & Bouso JC: Effects of ayahuasca on mental health and quality of life in naïve users: a longitudinal and cross-sectional study combination. Sci Rep 2020;10(1):4075.
- 16. Johansen PØ & Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a

- population study. J Psychopharmacol. 2015;29(3):270-9.
- Khan E: Medications used for mental health illness.
 In: Hood P, Khan E (eds): Understanding Pharmacology in Nursing Practice, 367–392.
 Springer Cham, 2020.
- 18. Kopra EI, Ferris JA, Winstock AR, Kuypers KP, Young AH & Rucker JJ: Investigation of selftreatment with lysergic acid diethylamide and psilocybin mushrooms: findings from the global drug survey 2020. J Psychopharmacol 2023;37(7):733-48.
- 19. Krul J, Blankers M & Girbes AR: Substance-related health problems during rave parties in The Netherlands (1997-2008). PLoS One 2011;6(12):e29620.
- 20. Lener MS, Kadriu B & Zarate CA: Ketamine and beyond: investigations into the potential of glutamatergic agents to treat depression. Drugs 2017;77(4):381-401.
- 21. López-Giménez JF & González-Maeso J: Hallucinogens and serotonin 5-HT2A receptormediated signaling pathways. Curr Top Behav Neurosci 2017;36:45-73.
- 22. Lv J & Liu F: The role of serotonin beyond the central nervous system during embryogenesis. Front Cell Neurosci 2017;11:1–9.
- 23. Maia LO, Beaussant Y & Garcia ACM: The therapeutic potential of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness: a systematic review. J Pain Symptom Manage 2022;63(6):e725-38.
- 24. Marrocu A, Kettner H, Weiss B, Zeifman RJ, Erritzoe D & Carhart-Harris RL: Psychiatric risks for worsened mental health after psychedelic use. J Psychopharmacol 2024;38(3):225-35.
- 25. Menke A: Precision pharmacotherapy: psychiatry's future direction in preventing, diagnosing, and treating mental disorders. Pharmacogenomics Pers Med 2018;11:211-22.
- 26. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, Holland J et al.: 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. Lancet Psychiatry 2018;5(6):486-97.
- 27. Nesvåg R, Bramness JG, & Ystrom E: The link between use of psychedelic drugs and mental health problems. J Psychopharmacol 2015;29(9):1035-40.
- 28. Nichols DE: Psychedelics. In Rang HP & Dale MM (eds): Pharmacological Reviews, 264-355.

 American Society for Pharmacology and Experimental Therapeutics, 2016.
- Nutt D: Psychedelic drugs—a new era in psychiatry? Dialogues Clin Neurosci. 2019;21(2):139-47.

- 30. Pitts EG, Curry DW, Hampshire KN, Young MB & Howell LL: (±)-MDMA and its enantiomers: potential therapeutic advantages of R(-)-MDMA. Psychopharmacology 2018;235:377–392.
- 31. Popik P, Hogendorf A, Bugno R, Khoo SYS, Zajdel P, Malikowska-Racia N et al.: Effects of ketamine optical isomers, psilocybin, psilocin and norpsilocin on time estimation and cognition in rats. Psychopharmacology 2022;239:1689–1703.
- 32. Rasmussen K, Chytil M, Agrawal R, Leach P, Gille D, Mungenast A, Vancutsem P et al.: Preclinical Pharmacology of DLX-001, a Novel Non-Hallucinogenic Neuroplastogen With the Potential for Treating Neuropsychiatric Diseases. Biological Psychiatry 95(10): s80;2024
- 33. Romeo B, Hermand M, Petillion A, Karila L & Benyamina A: Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: a systematic review. J Psychiatr Res 2021;137:273-82.
- 34. Rucker JJH, Iliff J & Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology 2018;142:200-18.
- 35. Sarris J, Perkins D, Cribb L, Schubert V, Opaleye E, Bouso JC, Scheidegger M et al.: Ayahuasca use and reported effects on depression and anxiety symptoms: an international cross-sectional study of 11,912 consumers. J Affect Disord Rep 2021;4:100098.

- 36. Schlag AK, Aday J, Salam I, Neill J & Nutt DJ: Adverse effects of psychedelics: from anecdotes and misinformation to systematic science. J Psychopharmacol 2022;36(3):258-72.
- 37. Sessa B & Nutt D. Making a medicine out of MDMA. Br J Psychiatry 2015;206(1):4-6.
- 38. Shahrour G, Sohail K, Elrais S, Khan MH, Javeid J, Samdani K, Mansoor H et al.: MDMA-assisted psychotherapy for the treatment of PTSD: a systematic review and meta-analysis of randomized controlled trials (RCTs). Neuropsychopharmacol Rep 2024; 44(4):672-681.
- 39. Stringer H: The emergence of psychedelics as medicine. Monitor Psychol 2024;55(5):50.
- Vargas MV, Meyer R, Avanes AA, Rus M & Olson DE: Psychedelics and other psychoplastogens for treating mental illness. Front Psychiatry 2021;12:727117.
- 41. Wsół A: Cardiovascular safety of psychedelic medicine: current status and future directions. Pharmacol Rep 2023;75(6):1362-80.
- 42. Yaden DB, Yaden ME & Griffiths RR: Psychedelics in psychiatry-keeping the renaissance from going off the rails. JAMA Psychiatry. 2021;78(5):469-70.
- 43. Yao Y, Guo D, Liu FL, Huang SH, Diao MQ, Li SX, Zhang WJ et al.: Efficacy and safety of psychedelics for the treatment of mental disorders: a systematic review and meta-analysis. Psychiatry Res 2024;335:115886.
- 44. Young MB, Andero R, Ressler KJ & Howell LL: 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. Transl Ps

Correspondence:

Tamara Trajbarič, dipl.m.s., RN, BN, Faculty of Health Sciences, University of Maribor, Žitna ulica 15, 2000 Maribor, Slovenia tamara.trajbaric@student.um.si