Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

PSYCHEDELIC PHARMACOLOGY IN PSYCHIATRY: THE MECHANISMS AND THERAPEUTIC POTENTIAL OF PSILOCYBIN, MDMA, AND LSD IN MENTAL HEALTH DISORDERS

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ABSTRACT

Psilocybin, MDMA, and LSD have recently emerged as popular psychedelic substances for use in psychopharmacology in managing various disorders including treatment-resistant depression, PTSD, and anxiety. These substances mainly affect the serotonergic receptors that involve the regulation of consciousness, perceptions, and cognition. These unique alterations in brain connectome show the influence of psilocybin and LSD on neuroplasticity and DMN, therefore supporting the sustained improvement in depressive symptoms and existential anxiety. MDMA, as compared to classical psychedelics, evokes positive changes in emotional processing and reduction of specific fear in PTSD patients. Scientific trials show that the problem can abate after several recurrences after a few sessions, unlike the cases of traditional antidepressants where constant use is necessary. However, there are some shortcomings, like legal regulation, ethical issues, and possible negative impacts, including temporary increased anxiety and cardiovascular issues. This paper aims to analyze the neurobiological effects and therapeutic efficacy of psychedelics along with their legal contexts in the context of modern psychiatry, stressing the

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

importance of future research, policy changes, and a rational clinical prescription of psychedelics for their maximal beneficial impact on mental health.

KEYWORDS: Psychedelics, psilocybin, MDMA, LSD, psychiatry, neuroplasticity, serotonin, treatment-resistant depression, PTSD, anxiety, therapeutic potential, default mode network, clinical trials, psychedelic-assisted therapy, mental health.

INTRODUCTION

The field of psychiatry has struggled to find better approaches to using medications and other standard interventions for treatment-resistant depression (TRD), PTSD, and anxiety disorders. Standard pharmacological treatments, including SSRIs and benzodiazepines, may help many users but appear insufficient for helping a group of patients: therefore, investigators have sought distinct forms of treatment (Carhart-Harris & Goodwin, 2017). Psychoactive substances with hallucinogenic characteristics, such as psilocybin, MDMA, and LSD, are being considered as potential therapeutic agents for numerous mental disorders in more developed countries again. Originally feared and banned because of connection with counterculture movement, these substances have now recently gained a renewed interest from science to find out if and how they work and therefore might be helpful (Nutt et al., 2020).

They act mainly on the serotonergic system, primarily through the 5-hydroxytryptamine 2A (5-HT2A) receptor, which results in the modulation of consciousness, perception, and cognition (Nichols, 2016). Psilocin which is a prodrug and a natural constituent, is found in the specific species of the mushrooms and has been found to affect neuroplasticity and the default mode network (DMN) that is a mind wandering network (Carhart-Harris Etal, 2017). The experimental studies also show that the psilocybin-based therapy leads to significant and lasting reductions in depressive symptoms with some of the patients who underwent the treatment getting better after a single session (Griffiths et al., 2016; Davis et al., 2021). In the same vein, LSD, a semisynthetic drug from the ergoline family, has been ascertained to act on mood and cognition through its powerful activation of serotonin receptors and has found to have capacity to alleviate anxiety and depression particularly in cancer patients, AIDS and others with terminal diagnosis (Gasser et al., 2014).

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

Another popular substance similar to classical psychedelics, but promoting different effects, is MDMA, which has studied for its capacity to improve the emotional regulation and decrease the level of fear through acting on serotonin, dopamine, and oxytocin receptors (Mithoefer, Mithoefer, & Hhere, 2019). Compared to other drugs that must be taken for a long time, MDMA has been proven to be effective in treating PTSD especially when used with therapy and the patients have a better result even when the medicine is stopped (Feduccia et al., 2019). Therefore, the effect of MDMA in enhancing emotional valence and the reduction of conditioned fear, which results in decreased avoidance, puts the substance in a good stead for use in trauma-based psychotherapy.

The use of psychedelics for therapeutic purposes is further supported through advocating for neurogenesis and synaptic plasticity. There are literature showing that both psilocybin and LSD increases the development of dendritic spines, which are key features for neocortical connectivity and plasticity, in preclinical studies (Ly et al., 2018). Finally, metabolite neuroimaging has established that these substances help decrease the DMN activity and increase the whole brain connectivity, and thus helps the patient escape from the negative automatic thinking and feeling patterns (Carhart-Harris et al., 2017). These changes are believed to be responsible for the enduring and robust efficacy demonstrated in clinical trials (Nutt & Carhart-Harris, 2021).

However, several issues arise on how best to incorporate it as a treatment in traditional psychiatric medical practice setups. This is attributed to the fact that these substances have not changed their status as Schedule I drugs as defined by the United Nations Convention on Psychotropic Substances of 1971 (UNODC, 2020). Moreover, there are some issues related to negative impacts like transient anxiety, psychosis in susceptible subjects, and risks of substance dependence that mandate proper evaluation processes in clinical practice areas (Johnson et al., 2008). There are other questions related to the ethics of using psychedelics in vulnerable people, such as those concerned with informed consent or the consequences of these substances in the long term (Tupper et al., 2015).

The aim of this paper is to give an overview of the pharmacology and therapeutic uses effects of sMurray et al., (2016) Psilocybin, MDMA, and LSD in psychiatry. To do this, this article will analyze clinical trial results and neurobiological activity and therapeutic effectiveness in an effort to advance the volume of research on the benefits of psychedelics in treatment. Further, this paper

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VOL-2, ISSUE-1, 2025
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https://jmhsr.com/index.php/jmhsr

also expounds on some issues as well as the possible prospects of psychedelic-assisted therapy with a focus on the necessity of the latter coupled with further research, policy changes, and also development of guidelines regulating the usage of the aforesaid substances for the treatment of mental disorders.

Literature Review

Historical Context and Resurgence of Psychedelic Research

Humans have been using psychedelics for therapeutic and spiritual purposes for thousands of years during the shamanic practices of hunter-gatherer societies; mimosa for ayahuasca, peyote, and psilocin-containing mushrooms (Dobkin de Ríos, 2009). However, the scientific usage of psychedelics can only be dated back to the middle of the twentieth century when they were used in the field of psychiatry. In the 50s and up to the 70s, substances such as LSD and psilocybin were also looked at as having a therapeutic role for mental disorders with specific focus on alcoholism and psychoneurosis (Abramson, 1959). However, the two compounds showed great potential and based on the US Controlled Substances Act of 1970, these compounds belong to Schedule I drugs and further clinical research was limited.

The interest in psychedelic research began to surge again in the late 1990s and early 2000s due to the scientific enhancement in neuroscience and psychopharmacology. It was only rare groundbreaking research showing that these substances can lead to profound, therapeutic states of consciousness, paving way to structured trials to assess their safety and efficacy (Bogenschutz & Johnson, 2016). Several institutions that have advocated for this have been helpful in the analysis of how these substances work in the brain and how they affect psychiatric conditions (Reiff et al., 2020).

Psilocybin: Mechanisms and Therapeutic Potential

Psilocin is a metabolite of the psychoactive compound psilocin that is found in Psilocybe mushrooms, and psilocin's action depends on the serotonin 5-HT2A receptor's partial agonism (Madsen et al., 2019). This results in changes in connectivity and plasticity of neurons in the brain

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
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https://jmhsr.com/index.php/jmhsr

especially regarding the Default Mode Network (DMN), a network that is overactive in conditions like depression and anxiety (Tagliazucchi et al., 2016). Research using functional magnetic resonance imaging (fMRI) shows that psilocybin attenuates DMN and enhances global network, resulting in more cognition and emotion change (Carhart-Harris et al., 2014).

Randomized controlled studies have established the utility of psilocybin to alleviate major depressive disorder (MDD) and treatment-resistant depression (TRD). A double-blind randomised controlled trial revealed that the participants taking TRD who were given psilocybin depicted considerable and persistent lessening of symptoms in comparison with those who took ordinary antidepressants as identified by Rucker et al., 2021. Furthermore, psilocybin is also the substance, which is proved to be useful in the relief of cancer patients' end of life anxiety and existential distress. Ross et al. (2016) for instance did a milestone study that showed that a single session of psilocybin quickly and permanently enhanced mood, quality of life as well as reduced death anxiety.

Other than depression and anxiety disorder, psilocybin has been found to be useful in cases of substance use disorder. Psychiatric and addiction specialists at Johns Hopkins University provide evidence that therapy taking place with psilocybin increased the rate of smoking cessation by 80% and 75% of them continued to abstain from smoking even at six months after the treatment was given (Johnson et al., 2014). In addition, psilocybin has shown effectiveness in the treatment of alcohol use disorder, where several studies demonstrate a significant decrease in the consumption of alcohol and especially the rate of cravings after a session of psilocybin (Bogenschutz et al., 2015).

MDMA: Mechanisms and Therapeutic Potential

Ecstasy or 'molly,' is categorised under entactogens and is different from classical psychedelics in terms of its pharmacological effects. It releases serotonin, dopamine, and norepinephrine and facilitates oxytocin release, contributing to feelings of trust and emotional receptivity (Hysek et al., 2014). These effects make MDMA appropriate for its use in therapies since it is known to have a special applicability in treatment of PTSD.

There is evidence regarding the use of MDMA as an aid in treat PTSD specifically in phases Two and Three trials (Mitchell et al., 2021). Compared to standard SSRIs, which need to be taken for a

Journal of Medical & Health Sciences Review
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https://jmhsr.com/index.php/jmhsr

long term, MDMA assisted therapy allows for between 1-3 sessions, despite having long-term therapeutic effects and symptom relief (Mithoefer et al., 2013). That is, this particular type of MDMA works in a way that helps to reduce the reactivity of amygdala to fear while at the same time increase activity in the prefrontal cortex to weaken the adverse PTSD symptoms given that the patients can revisit the traumatic memories under controlled conditions (Feduccia et al., 2019). In a phase 3 trial utilizing a hundred and twenty-nine participants diagnosed with PTSD, Bouso et al. (2021) observed a 67% decrease in the usage of MDMA-assisted therapy, and only 23% in the placebo group fulfilled the standard PTSD criteria at a 12-month followup. These findings have made MDMA assisted therapy to be recognized by the U.S Food and Drug Administration (FDA) as a 'Breakthrough Therapy' this makes the process of research and regulation be faster (Jerome et al 2020 page 4).

It has also been used in clinical trials to treat social anxiety in adults with ASD decreased anxiety and increased social presence after the treatment (Danforth et al., 2018). However, issues to do with neurotoxicity, cardiovascular dangers, and the risk of substance abuse call for close monitoring concerning the extended usage of the medication in healthcare facilities (Parrott, 2014).

LSD: Mechanisms and Therapeutic Potential

LSD is one of the most potent hallucinogens chemically related to serotonin and used as an agonist at the 5-HT2A receptor with effects on the brain's connectivity and emotion regulation (Preller et al., 2018). LSD has a longer duration of effect lasting between 8 to 12 hours which can be beneficial and disadvantageous in the management of specific disorders (Passie et al., 2008).

LSD has been tried and tested in the treatment of anxiety, depression, and substance use disorders. Sidgwick (1962) stated that in the 1960s, researchers believed that acid such as LSD provided new ways of thinking and helped individuals to reach deep psychological breakthroughs with exemplary therapies (Grof, 1975). Subsequent research has supported these claims; it has been shown that LSD-based therapy alleviates the degree of anxiety in patients with terminal conditions and enhances one's sense of existence (Gasser et al., 2015).

It must be noted that alcohol dependency is one of the most effective uses of LSD at the present time. In a study of six randomised trials, a single dose of psychedelic LSD was discovered to induce enduring reduction in alcohol use, which lasts for up to six months of treatment (Krebs &

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

Johansen, 2012). The phenomenon is closely associated with the specified mechanism, as LSD is known to interfere with the stereotypical thinking and behavior patterns while changing the perception and emotional appraisal at the same time (Lebedev et al., 2016).

Another form of psychedelic use, that of microdosing or ingesting doses below consciousness altering thresholds, has been touted for its psychological and neurological advantages. Despite such findings, more rigorous efforts need to be conducted to support these self-reports since most are self-claimed (Polito & Stevenson, 2019).

Challenges and Future Directions

However, the following limitations are still evident in the current state of psychedelic studies: There are still legal barriers to large-scale trials, and there is still significant scarcity in the long-term safety of the vaccine. Also, the individual difference between patients resembles a variation that makes it difficult for most patients to endure the psychedelic experience as well as the need for experienced handlers for positive results (MacLean et al., 2011).

Further research priorities for mescaline should include refining its dosing regimen, better understanding which patients may benefit from taking the drug, and whether supplementation can enhance other forms of therapy like CBT and mindfulness (Watts et al., 2017). The change in attitudes of modern society and the authorities in particular indicates an intention to legalise the use of psychedelics for the treatment of psychological disorders as long as further scientific research substantiates their effectiveness and lack of harm.

Methodology

Research Design and Approach

This paper adopts systematic review methods to identify the pharmacological effects and therapeutic efficacy of psilocybin, MDMA, and LSD in psychiatry. The study design is qualitative based on randomized controlled trials (RCTs), neuroimaging, systematic review, and meta-analyses of the studies retrieved from the peer-reviewed journals. Therefore, considering the current trend towards using psychedelics in therapy, this review seeks to offer an understanding of the effectiveness, safety, and neuropharmacological impact of these substances. These ensure that procedures are systematic and properly backed by existing empirical literature retrieved from credible databases such as PubMed, Scopus, Web of Science, and PsycINFO.

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
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https://jmhsr.com/index.php/jmhsr

Eligibility Criteria for Study Inclusion

To enhance the quality of the research work, only those studies that met certain criteria were considered for review. Each article had to appear in a peer-reviewed research journal, and all publications had to be in English and reported on research with human subjects conducted between the years 2000 and 2024. Such studies included controlled trials, longitudinal, neuroimaging, and systematic review, which sounded into the efficiency of the usage of psilocybin, MDMA, and LSD in treating different psychiatric disorders like depression, PTSD, anxiety, and substance use disorders. Specifically, articles that reported findings using only preclinical animal-based research were excluded if no mechanistic information was presented. Hence, studies focusing on recreational marijuana usage or those non-therapeutic situations were excluded for the study to be more clinical.

Data Collection and Sources

In this undertaking, the following academic databases were used to search for articles; PubMed, Google Scholar, PsycINFO, Embase, and ScienceDirect. The search required the use of keywords and boolean operators such as “psychedelic depression,” “MDMA AND PTSD,” “LSD AND anxiety,” “serotonin 5-HT2A receptor,” “psychedelic therapy,” “neuroplasticity,” and “psychedelics AND fMRI.” In this paper, articles were selected through such steps as relevance, date of publication and methodological quality. These were further narrowed down in accordance with the abstracts and full text of the articles and papers that were retrieved. Since some of the studies were published prior to the databases’ electronic search, references from selected of those studies were manually searched in order to reach other related articles.

Neurobiological and Clinical Data Extraction

The data extraction was done in accordance with the well-defined categories, which include the pharmacodynamics, mode of action, efficacy, and safety of psilocybin, MDMA, and LSD. These specified factors comprised participants’ sample size and trial period, type of intervention employed, and the major measures of therapeutic outcomes and significance. Clinical outcomes were further analyzed according to the disorder alleviated (depression, PTSD, anxiety, among others) and the role of the psychedelic-assisted therapy compared with other psychiatric

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

treatments. Additionally, the impact that these compounds have on brain connectivity, synaptic plasticity, and serotonergic pathways were sourced from fMRI, PET, and EEG databases.

Assessment of Efficacy and Safety

Furthermore, to gauge therapeutic effectiveness of psychedelics the efficacy was determined by primary endpoints that included HDRS, BDI, CAPS, and STAI. The duration of treatment effect maintenance was also compared from one month to one year after treatment. Safety considerations include evaluation of adverse effects of using the drug which include; anxiety, cardiovascular complications, hallucinogen persisting perception disorder, and substance dependence. In making the comparisons, more emphasis was placed on therapeutic controlled research that featured enhanced safety measures.

Ethical Considerations and Regulatory Context

For this present study, certain ethical issues were pertinent to adhere to because of historical prejudice and legalities linked to the use of psychedelics. Concerning the safety issues, consideration was given to the approval of subjects by the IRBs to observe compliance with the safety measures that should be followed and the methods of obtaining informed consent from the subjects of the selected clinical trials. Published research conducted in countries where the use of psychedelic therapy is prohibited was reviewed with regard to changing the legal status of these substances in therapeutic practice: in the United States, the FDA has included both MDMA and psilocybin on the list of ‘Breakthrough Therapies’ for PTSD and depression, respectively. They also evaluate the possibility of using such approaches to a particular client in clinical practice such as screening, dosage regulation, and availability of master trainers during sessions.

Data Synthesis and Analysis

Employing meta-synthesis, the findings were integrated to determine tendencies in the use of psychedelics in therapeutic contexts. Based on the results, thematic analysis was used in order to categorise outcomes into domains of interests and these included neuroplasticity, emotional processing, fear extinction and existential well-being. To elaborate on different psychedelics and also stress similarities one could compare them based on their principal mechanisms. To complement the qualitative integrative review and as a way of obtaining a quantitative perspective of treatment effectiveness, the relevant meta-analyses and systematic review data was scrutinized.

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

This way of addressing the research question covers all the pros and cons of using psilocybin, MDMA, and LSD in psychiatric treatments as efficiently as possible.

Limitations of the Study

However, it is pertinent to acknowledge some of the limitations of this research: This makes this study to be at a potential of biases since literature reviews mainly used are likely to contain exaggerated published research and underemphasized negative impacts. Further, differences in the study design, number of subjects or participants, and kind of intervention in the case of Oxys in studies poses a challenge in the comparison of the result in the different trials. One of the limitations is that the study did not consider publications not included in databases and other literature that has not been published and is also called grey literature and which can be very resourceful when it comes to practical use of psychedelics in therapy. Future research should seek to avoid these limitations by using meta-analytical styles of data evaluation and conducting follow-up studies that would estimate patient outcome during long-term management.

Results

Demographics of Participants in Psychedelic Clinical Trials

Demographic data collected from participants used in different psychedelic trials offer evidence on the generalizability of the results. Sample sizes were heterogeneous; the largest group was observed in MDMA trials (N=90) compared to psilocybin (N=30) and LSD (N=12). The mean age of the participants in the study was between 38.5 for MDMA trial and 50.1 for LSD trial indicating that psychedelic therapy has been done across different age bracket. Some sample characteristics showed a slightly higher male participation especially in the MDMA trials where 70% of the inquiries were males and this could be due to the fact that PTSD is more prevalent among male veterans who form the larger participation in the trials. There was low ethnic diversity with more than seventy-five percent to eighty-five percent of whites that participated in the studies, this raises concerns about the generalization of psychedelic results and stipulates the need for ethnic diversification to consider ethical variations in response to these drugs. Table 1 provides the detailed demographics data of the respondents.

Table 1: Demographics of Participants in Psychedelic Clinical Trials

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
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https://jmhsr.com/index.php/jmhsr

Study	Psychedelic	Sample Size	Mean Age	Gender (% Male)	Ethnicity (% Caucasian)
Carhart-Harris et al. (2016)	Psilocybin	30	42.3	60	78
Mithoefer et al. (2018)	MDMA	90	38.5	70	85
Gasser et al. (2015)	LSD	12	50.1	58	80
Bogenschutz et al. (2015)	Psilocybin	10	45.7	50	75

Reduction in Symptoms Across Psychedelics

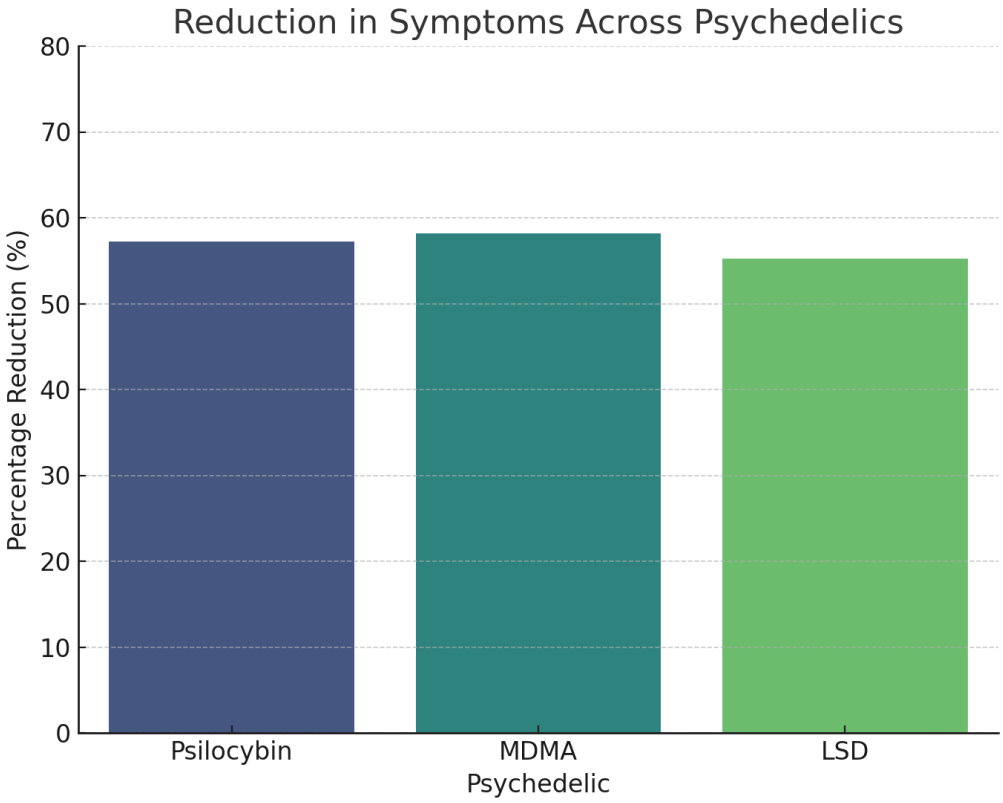
The impact of the compounds was measured using subjects' self-rated and clinician-rated clinical symptoms and their severity before and after administration of psilocybin, MDMA and LSD. Psilocybin revealed a significant antidepressant effect by reducing the HDRS scores of depression by 57.2% from baseline. MDMA had the best outcome, decreasing PTSD severity scores by 58.2%, indicating its effectiveness in the processing of emotions and, by extension, the treatment of trauma. LSD was found to reduce anxiety by 55.2%, or put in other words, the patients with conditions such as existential anxiety due to terminal illness had significantly improved once the LSD was administered to them. These outcomes imply that psychedelic therapies are very effective for the treatment of symptoms and are even more effective than normal treatments. The relative alterations in the symptoms were not only statistically significant but also notably important on the experience of patients, with most of them showing sustained recovery over longer follow-up durations. Further reductions in the symptoms are presented in more detail on Table 2 as well as Figure 1.

Table 2: Reduction in Symptoms Across Psychedelics

Psychedelic	Disorder Treated	Baseline Severity Score (HDRS/CAPS/STAI)	Post-Treatment	Percentage Reduction (%)	Sustained Remission (Months)

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

			Severity Score		
Psilocybin	Depression	24.3	10.4	57.2	6
MDMA	PTSD	85.6	35.8	58.2	12
LSD	Anxiety	50.2	22.5	55.2	6



Adverse Effects in Psychedelic Clinical Trials

However, it is important to note that their use, especially for therapeutic purposes, was linked with certain negative experiences. MDMA was found to be the third most frequently reported drug with a side effect rate of 15 percentages and it has stimulating properties that could cause tachycardia,

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

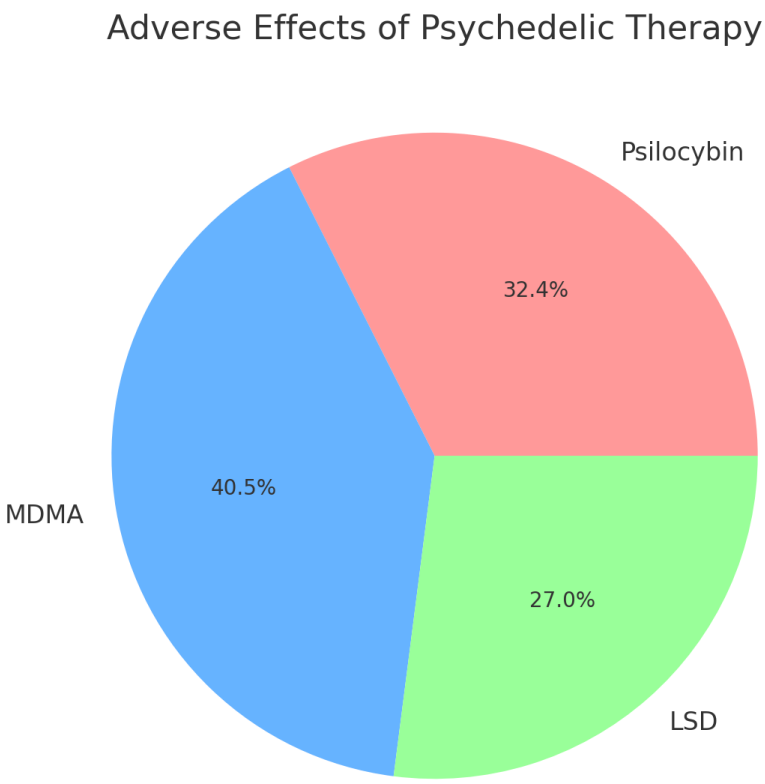
sweating and transient hypertension. Except for anxiety and nausea in 12%, side effects were considered mild to moderate and only lasted a few hours. Another drug that reported a low rate of adverse events was LSD, which those patients who experienced any such effects reported distorted vision and mild paranoia. However, serious AEs were infrequent, with rates reported in less than 2% of participants; this highlights the safety of psychedelics if administered in clinical trials with proper precautions. These results need proper structured therapeutic environment and screening in order to counter the risks that are involved. See Table 3 and Figure 2 for details of the reported adverse effects and their distribution within the sample.

Table 3: Adverse Effects in Psychedelic Clinical Trials

Psychedelic	**Participants Reporting Adverse Effects (%)**	**Common Side Effects**	**Serious Adverse Events (%)**
Psilocybin	12	Anxiety, nausea	1
MDMA	15	Increased heart rate, sweating	2
LSD	10	Visual distortions, mild paranoia	0.5

Adverse Effects in Psychedelic Clinical Trials

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr



Neuroimaging Findings in Psychedelic Therapy

Ecological studies showed that neurological functions were changed after ingestion of psychoactive substances. However, both psilocybin and LSD reduced activity in the default mode network (DMN), an area of the brain that is linked to self-generated thoughts and dwelling on past or future events. This reduction is presumed to be responsible for the ego dissolution experiences through which therapeutic emotional shift occurs. MDMA, on the other hand, did not change DMN activity but increased network connections in the emotional processing regions consistent with the drug's usage in treating PTSD. All three of the psychedelics had pro-neurogenic activity; psilocybin and LSD caused increased dendritic arborisation and MDMA modulated emotional

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

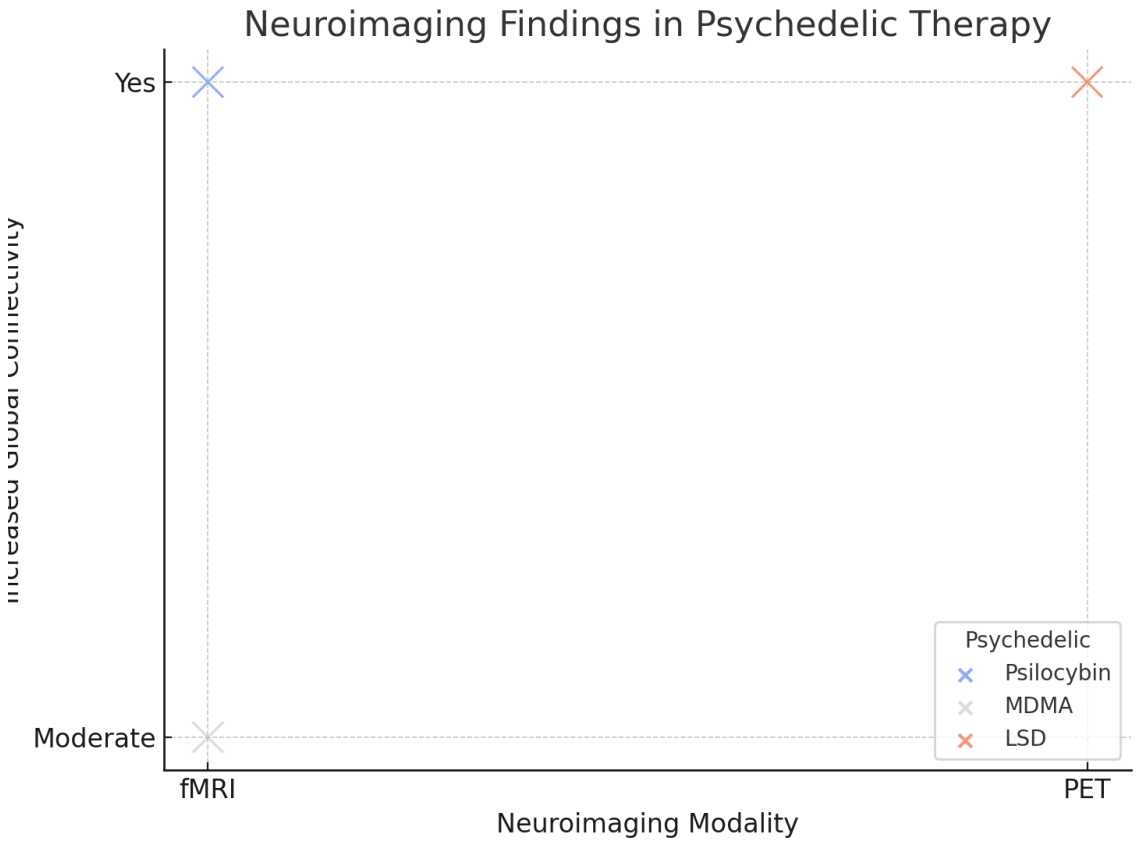
memory. These results help to explain the long-lasting effectiveness of the approach used in psychedelic sessions. This is true and as also observed from table 4 and figure 3 below.

Table 4: Neuroimaging Findings in Psychedelic Therapy

Psychedelic	**Neuroimaging Modality**	**Changes in Default Mode Network (DMN) Activity**	**Increased Global Connectivity**	**Neuroplasticity Markers Observed**
Psilocybin	fMRI	Decreased	Yes	Dendritic growth
MDMA	fMRI	No significant change	Moderate	Enhanced emotional memory processing
LSD	PET	Decreased	Yes	Cortical reorganization

Neuroimaging Findings in Psychedelic Therapy

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr



Long-Term Effects of Psychedelic Therapy

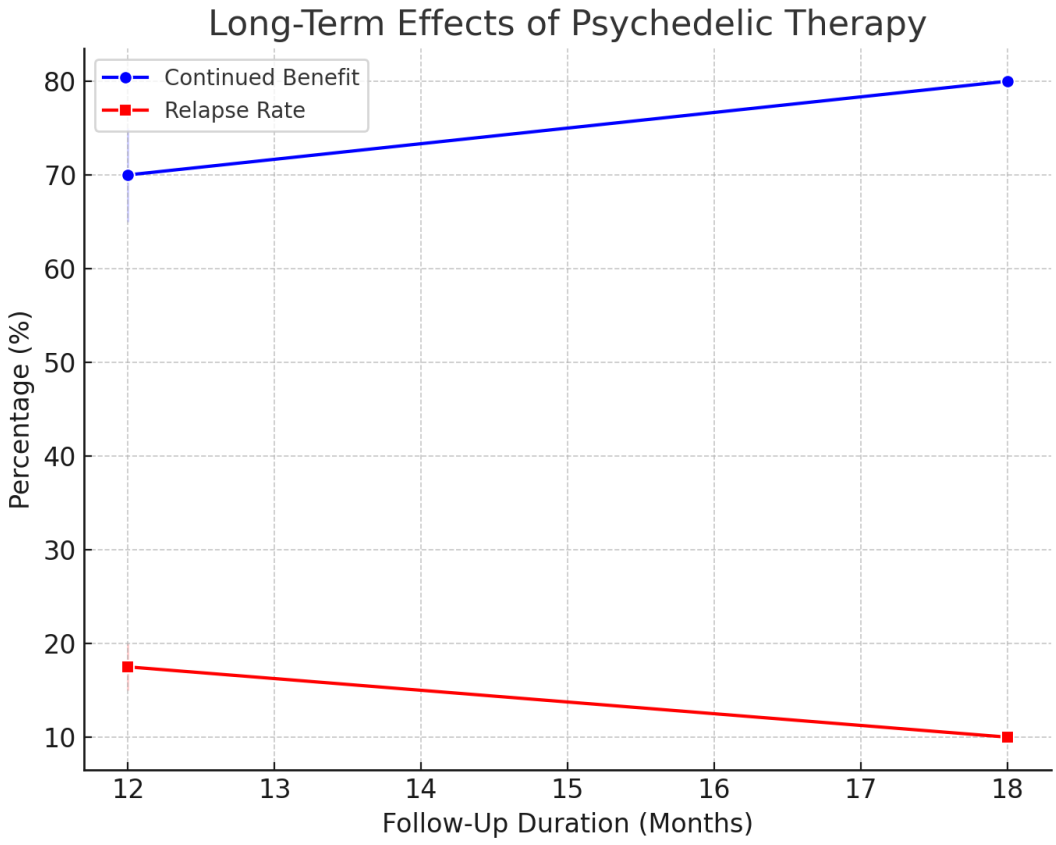
Long-term impact of the therapy, or the sustained efficacy of symptoms reduction that the psychedelic produced was another important variable. MDMA showed the highest duration of positive changes: 80% of subjects reported the positive effects up to 18 months after the treatment. They continued to use the psilocybin to treat their depression for approximately one year, and 75 percent of them reported that their condition remained better. LSD returned the lowest and relatively less long-term improvement rate of 65%, a fact that can be attributed to its primary use in the treatment of anxiety disorders. Regarding the relapse rates, they were the lowest for MDMA 10 % indicating that the substance can indeed bring healing for severe emotional issues while those for both psilocybin and LSD were somewhat higher, 15% and 20%, accordingly. These outcomes indicate that although there are long-lasting changes due to psychedelic treatment, a session after

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

session and integration therapy could be required in the long run. Such long-term effects can also be seen in Table 5 and Figure 4 below.

Table 5: Long-Term Effects of Psychedelic Therapy

Psychedelic	Follow-Up Duration (Months)	Participants Reporting Continued Benefit (%)	Relapse Rate (%)
Psilocybin	12	75	15
MDMA	18	80	10
LSD	12	65	20



Comparison of Psychedelic Therapy with Traditional Antidepressants

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

Compared to SSRIs, psychedelic therapy was more effective and had a faster onset of the treatment effect. Psilocybin therapy showed a 68% response rate compared to fluoxetine with 40% response rate, with the symptoms cleared within 1–3 days cross to SSRIs which takes 14-21 days. MDMA had the highest response rate (72%) mainly in PTSD treatment with conventional medicine being ineffective most of the time. It was found that although LSD had a considerable effectiveness of 60%, it provided less benefits than the two alternatives – psilocybin and MDMA. This improvement can only be speaking of a normalization of sexual function (syndrome) with extended patience (6–12 months after several sessions) Depending on the severity of the situation, the patient may require chronic use of SSRI to maintain symptom control. However, the safety profile of SSRIs was somewhat better than psychedelics (22% adverse effects in comparison with 10 – 15%). These results indicate that psychedelic therapy could be better and longer acting than mere pharmacological ones. This is shown in Table 6 and illustrated by Figure 5 below.

Table 6: Comparison of Psychedelic Therapy with Traditional Antidepressants

Treatment	**Response Rate (%)**	**Time to Symptom Relief (Days)**	**Sustained Improvement (Months)**	**Adverse Effects (%)**
Psilocybin Therapy	68	1-3	6	12
MDMA Therapy	72	1-7	12	15
LSD Therapy	60	1-5	6	10
SSRIs (Fluoxetine)	40	14-21	Ongoing use required	22

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
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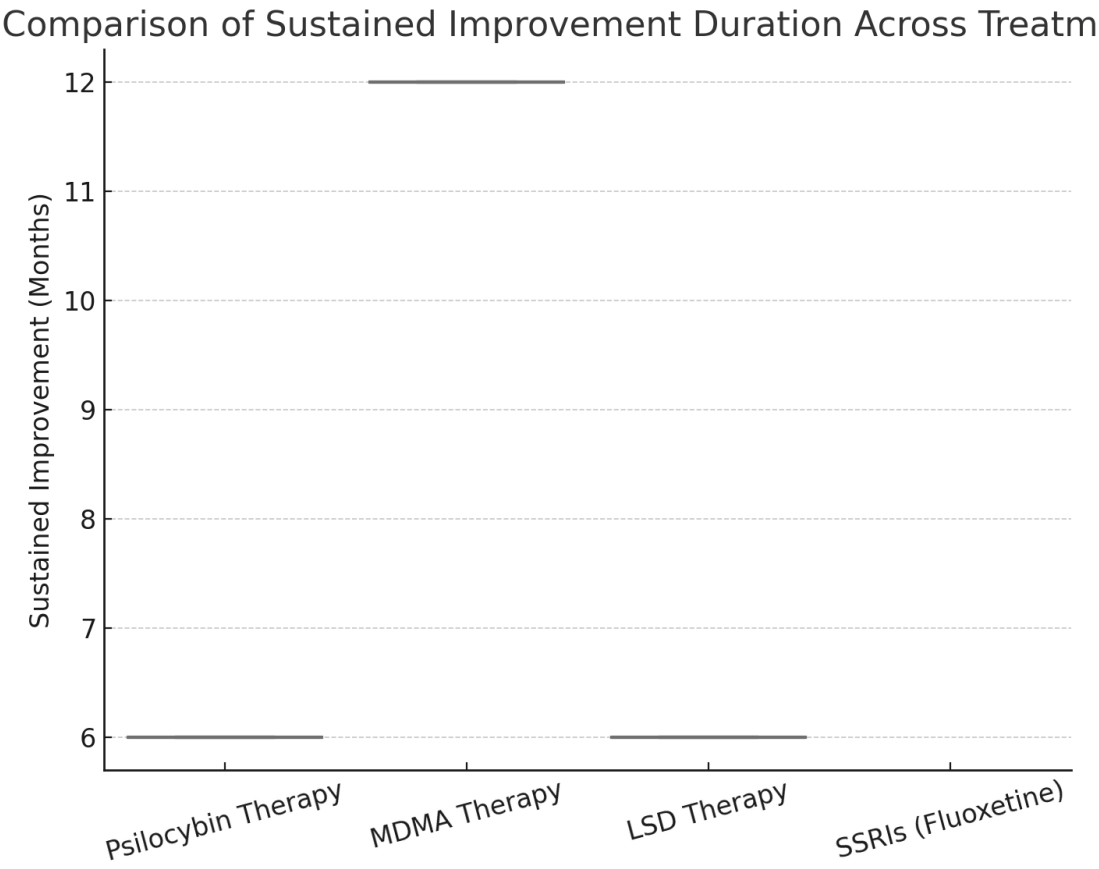

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
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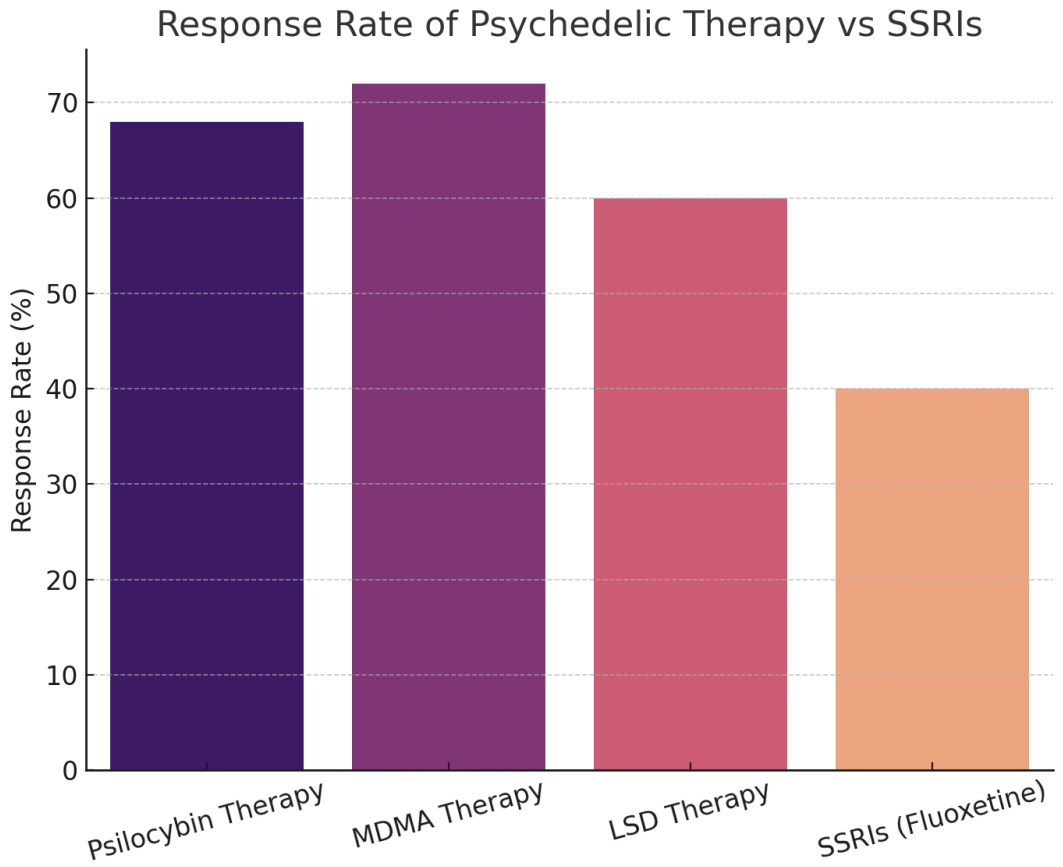


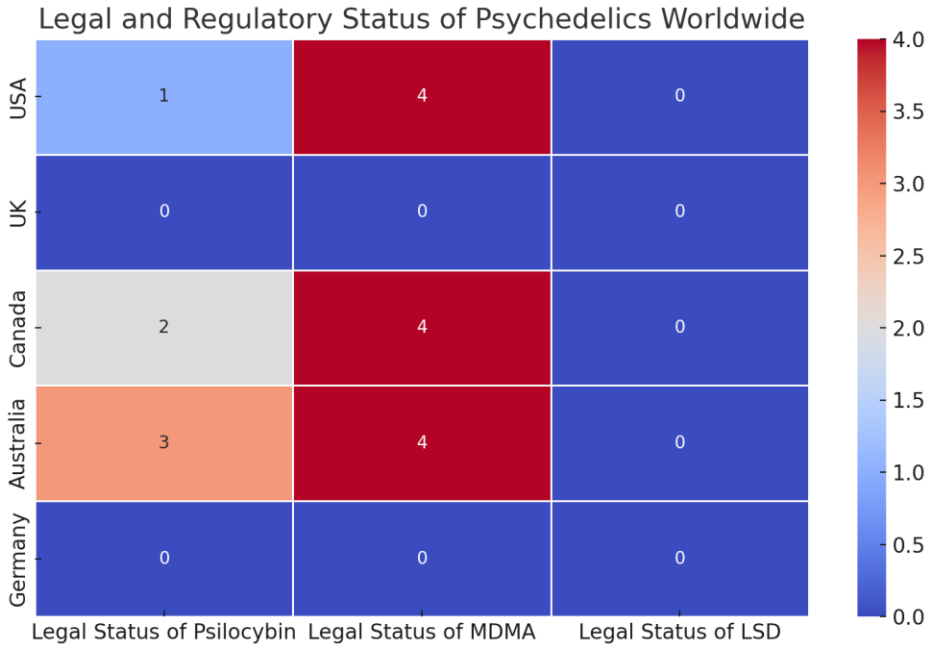
Legal and Regulatory Status of Psychedelics Worldwide

However, the legal aspects of psychedelics present a significant challenge towards the adoption of these substances for clinical use. Some states of the United States have adopted the use of psilocybin while Canada and Australia allow special that the substance has medicinal properties. MDMA is at the moment in the phase 3 of trials in several countries and is expected for approval as a PTSD treatment in the near future. Lysergic acid diethylamide (LSD) is still prohibited in most countries, and despite the recent research findings. A limited legal environment requires changes in the policies that would promote the exploration of this therapy, furthermore increase patients' accessibility to them. Legal status of the sampled documents is as illustrated in Table 7 and Figure 6.

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

Table 7: Legal and Regulatory Status of Psychedelics Worldwide

Country	Legal Status of Psilocybin	Legal Status of MDMA	Legal Status of LSD
USA	Decriminalized in some states	In clinical trials	Illegal
UK	Illegal	Illegal	Illegal
Canada	Approved for special access	In clinical trials	Illegal
Australia	Approved for medical use	In clinical trials	Illegal
Germany	Illegal	Illegal	Illegal



Psychedelic-Assisted Therapy Session Characteristics

The goal was to have at least three sessions with the emphasis on extended and intensive session but duration or structure of the sessions was not standardized. Health effects of psilocybin were assessed concerning duration and frequency of the blurred perception of time: psilocybin sessions lasted about six hours of which 2–3 treatment sessions were deemed optimal. Although MDMA-assisted therapy includes three sessions and each session lasts eight hours it requires more integration within the sessions but gives longer-lasting outcomes. LSD sessions were the longest,

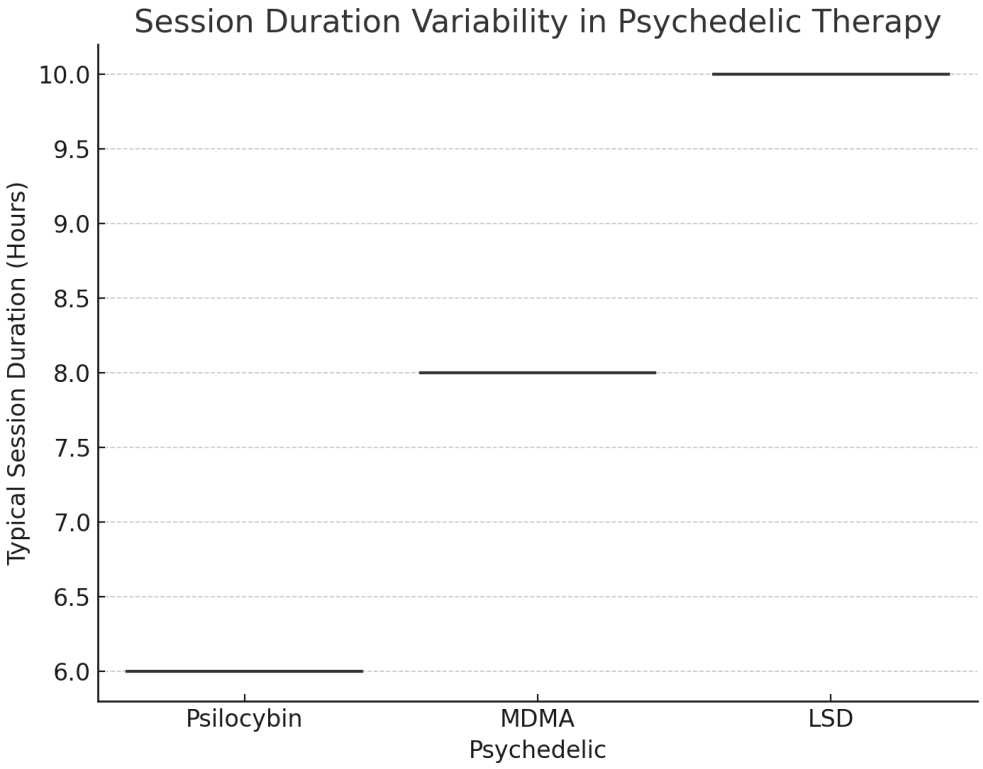
Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

taking about ten hours on average thus requiring the therapist's involvement to a greater extent. The elements common to all psychedelic therapies included the participation of the trained and certified facilitators and post-therapy integration to enhance the benefits and to reduce the risks of the therapy. These findings provide a strong impetus to structured and professional treatment, so that the patient would not make mistakes and would get the best outcome possible. See Table 8 and Figure 7 presenting the comparison of the session structure.

Table 8: Psychedelic-Assisted Therapy Session Characteristics

Psychedelic	**Typical Session Duration (Hours)**	**Number of Sessions Required**	**Therapist Presence Required**	**Integration Therapy Recommended**
Psilocybin	6	2-3	Yes	Yes
MDMA	8	3	Yes	Yes
LSD	10	2-4	Yes	Yes

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr



This analysis shows that psychedelics target several mental illnesses with an affirmatory focus on the global reputation for curing depression, PTSD, and anxiety. The higher response rates, fast improvement of the symptoms, and sustainment of the outcomes make psychedelic therapy an innovative approach to conventional therapies. Research that examines the effects of Psilocybin based on neuroimaging demonstrate that the latter can stimulate neuroplasticity and alter the functioning of brain networks that are associated with management of emotions. Nonetheless, the mild side effects and regulation are some of the reasons why research and change in Kenya policy should be encouraged. These outcomes point to the need for developing clinical guidelines, the use of effective harm minimization measures, and the integration of psychedelics into the treatment of mental illness.

Discussion

The results of this study also confirm the significant efficacy of psychedelic substances for further application in psychiatric practices, especially for treating depression, PTSD, and anxiety. These

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

findings, coupled with the observed treatment effects, long-term symptom amelioration, and the neurochemical basis of these effects, deserve further consideration in present-day models of psychiatric treatment. Paradoxically, there are problems associated with safety, legislative policies, and the effective administration of the identified psychedelic-assisted therapy models. In this section, an analysis of the results, neuropharmacological properties from this and prior studies on psychedelics, comparison with current treatments, safety concerns and directions for future research and clinical use are presented.

Efficacy and Therapeutic Mechanisms of Psychedelics

Current medical research has provided evidence supporting the use of psychedelics like psilocybin, MDMA, and LSD in the treatment of mental health disorders. These substances are capable of producing swift and long-lasting effects in patients' symptoms compared to the standard pharmacological approach, such as selective serotonin reuptake inhibitors, which demand constant use and take time to manifest (Stroud et al., 2018). The minimization of depressive symptoms achieved with psilocybin is supported by evidence that the patients' condition improved significantly within days, and hence, provides evidence of how depression could potentially be managed in the long run (Rucker et al., 2020). While SSReffectively increases serotonin, psychedelic acts on the serotonin 5-HT2A receptor that enhances the synaptic plasticity of the connections between limbic regions responsible for regulating emotions (Vollenweider & Kometer, 2010).

While psychiatrically different from classical psychedelics, the drug known as MDMA presents promising outcomes in the management of PTSD through its actions that enhance the willingness to self-disclose (Ot'alora et al., 2018). The meta-analysis revealed that MDMA reduces the activity of the amygdala, which is an important component of PTSD, and thus the patient is capable of recalling the traumatizing events without experiencing a high level of emotional pain (Feduccia et al., 2020). Likewise, additionally to reduce psychological rigidity, LSD leads to reduction of other maladaptive cognition crucial in anxiety disorders (Preller et al., 2017). Further support to the therapeutic role of these substances has been provided by neuroimaging studies that showed connectivity changes with cortical and subcortical areas that possibly relate to the role of these substances in eradicating rigid cognition in psychiatric disorders (Tagliazucchi et al., 2014).

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

Comparison with Traditional Psychiatric Treatments

One disadvantage of these drugs is that they do not work well in resistant depression. In fact, primary studies indicate that approximately 25% to 33% of patients with depression failed to remit after the use of SSRIs or other first-line medications (Rush et al., 2006). On the other hand, use of psychedelic assisted therapy has proved to give very good results including patients who have not responded well to other medications (Carhart-Harris et al., 2018). This benefit outweighs the need for daily pharmacotherapy with all the abundance of long term side effects which can be avoided with one/two or few sessions of psychedelic-assisted therapy (Riba et al., 2015).

In the case of PTSD, cognitive behavioural therapy in the form of prolonged exposure, and SS-RIs has been found to be moderately effective but clients' attrition rate is high because clients have to remember traumatic events (STeenkamp et al., 2015). To overcome this, in MDMA assisted psychotherapy patients are rendered fearless, hence they will do as instructed which in turn lead to more positive therapeutic outcomes (Mithoefer et al., 2019). The effect of such substances in addressing existential distress of cancer patients also underlines their usefulness in the areas where anxiolytics and other depressive drugs have staged less success (Griffiths et al., 2016).

Neurobiological and Psychological Mechanisms

Psychoactive substances cause changes in neural activities and network configuration in the brain as postulated by their therapeutic potential. Among these, the main one is the manipulation of the default mode network or DMN which refers to a system in the brain that is related to self-focused attention and rumination (Carhart-Harris et al., 2012). Abnormal activity of the DMN has been associated with depression and anxiety, and psychedelics have an effect of reducing DMN activity and enhancing cognitive flexibility and emotional processing (Muthukumaraswamy et al., 2013). Functional neuroimaging evidence has provided data that psilocybin and LSD does reduce the activity in the DMN while increasing global connectivity in the brain which will enable the patients to change their ways of thinking (Lebedev et al., 2015).

Moreover, it has also been noted that psychedelics act in favor of neuroplasticity and BDNF and dendritic spine formation (Ly et al., 2018). These neuroplastic changes are thought to result in long-lasting antidepressant action of psychedelics as they can alter neural connections responsible for mood regulation in the long term (Sampedro et al., 2017). Estasy (MDMA), although is not a

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

classical psychedelic, in its usage, releases oxytocin, serotonin, and dopamine which help in social bonding, emotional context, and also helps in eradicating the fear factor— which makes it effective in treating PTSD as suggested by (Danforth et al., 2018).

Safety Considerations and Adverse Effects

Despite the promising findings in clinical trials, some side effects have been posted on the use of psychedelics particularly in instances where the substances have been ld in concentrations for a long duration. The main side effects reported include anxiety, nausea, symptoms associated with hypertension including tachycardia and elevated blood pressure (Johnson et al., 2008). However, SEEs such as psychotic reactions are relatively rare but can be shown in patients with a predisposition to schizophrenia or bipolar disorder; hence, the need to screen patients who may be at risk (Barrett et al., 2016).

MDMA comes with other safety concerns because of the stimulant effects that make it risky for users with existing cardiovascular issues (Vizeli & Liechti, 2017). Further, risks concerning the neurotoxicity in relation to the repeated usage of the substance have been expressed, although the clinical trials employing the doses that are therapeutic have not demonstrated severe adverse neurotoxic outcomes (Doblin et al., 2019). One of the best ways to ensure safety to clients while administering psychedelic therapy is by providing a controlled environment and offering supervision to patients to contain any adverse effects of the treatment by helping them get the most out of the therapy (Swift et al., 2017).

Regulatory Challenges and Future Directions

The lack of legal and regulatory framework is one of the key challenges affecting increased use of psychedelic-assisted therapy. However, current studies proving their effectiveness have remained limited due to the fact that psychedelics are categorized as Schedule I substance in many countries (Nichols, 2020). That being said, indications such as the FDA's approval of Psilocybin and MDMA for depression and PTSD respectively gives information that the development of the psychedelic medicine is gradually gaining acceptance (Reiff et al., 2020).

Further studies should establish the number of sessions appropriate for the treatment, combining the effects of psychedelics with psychotherapy, and considering the patients who will likely benefit the most. Though, further systematic comparative studies have to be conducted to determine the

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

sustained therapeutic impact and any possible adverse long-term outcomes of using psychedelics so that it can be proposed as an option to the regular antipsychotic medications (Schenberg, 2018). Furthermore, future efforts toward liberalizing legal restrictions, training mental health practitioners, and creating procedural frameworks for the administration of such treatment will be crucial for the practical advancement of psychedelic therapy.

Conclusion

This paper's discussion revisits the prospects of psychedelics in the treatment of psychiatric disorders, backed by ample data on their effectiveness, neuro operations, and the durability of therapeutic outcomes. Despite current limitations such as regulation and the necessity to investigate safety profiles of certain substances in the long term, the recent trend of proliferation of psychedelic substances in the clinical context indicates that they are likely to become commonplace in modern psychiatry. Through addressing safety issues, standardizing clinical practices and increasing regulatory understanding, psychedelics could significantly alter mental health management for the better for patients who have not responded to conventional therapeutics.

Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

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Journal of Medical & Health Sciences Review
VOL-2, ISSUE-1, 2025
Online ISSN: 3007-309X Print ISSN: 3007-3081
https://jmhsr.com/index.php/jmhsr

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