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REVIEW ARTICLE

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# Psychedelic therapy in depression and substance use disorders

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## Abstract

Psychoactive substances obtained from botanicals have been applied for a wide variety of purposes in the rituals of different cultures for thousands of years. Classical psychedelics from N,N′-dimethyltryptamine, psilocybin, mescaline and various lysergamides cause specific alterations in perception, emotion and cognition by acting through serotonin 5-$HT_{2A}$ receptor activation. Lysergic acid diethylamide, the first famous breakthrough in the field, was discovered by chance by Albert Hoffman in the Zurich Sandoz laboratory in 1943, and studies on its psychoactive effects began to take place in the literature. Studies in this area were blocked after the legislation controlling the use and research of psychedelic drugs came into force in 1967, but since the 1990s, it has started to be a matter of scientific curiosity again by various research groups. In particular, with the crucial reports of psychotherapy-assisted psilocybin applications for life-threatening cancer-related anxiety and depression, a new avenues have been opened in the treatment of psychiatric diseases such as treatment-resistant depression and substance addictions. An increasing number of studies show that psychedelics have a very promising potential in the treatment of neuropsychiatric diseases where the desired efficiency cannot be achieved with

**Abbreviations:** 5-HT, 5-hydroxytryptamine; 5-$HT_{2A}$R, 5-hydroxytryptamine 2A receptor; AUD, alcohol use disorder; BMD, bone mineral density; DMN, default mode network; DMT, dimethyltryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; FDA, Food and Drug Administration; fMRI, functional magnetic resonance imaging; GPCR, G-protein-coupled receptor; IBS, irritable bowel syndrome; LSD, lysergic acid diethylamide; LTD, long-term depression; LTP, long-term potentiation; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDMA, 3,4-methylenedioxymethamphetamine; Nac, nucleus accumbens; NRIs, norepinephrine reuptake inhibitors; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; SERT, serotonin transporter; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; SUD, substance use disorders; TRD, treatment-resistant depression; vmPFC, ventral medial prefrontal cortex; VTA, ventral tegmental area.

conventional treatment methods. In this context, we discuss psychedelic therapy, encompassing its historical development, therapeutic applications and potential treatment effects—especially in depression, trauma disorders and substance use disorders—within the framework of ethical considerations.

**KEYWORDS**
anxiety, depression, neurobiology, psychedelics, substance disorders

## 1 | INTRODUCTION

Although the use of psychedelic substances in modern medicine spans a little more than half a century, their complex history and use in other fields goes back to earlier periods. It is known that psychedelics have been used in the rituals of religious, spiritualist, pagan and cult groups as well as in music and art to increase creativity (Tupper, 2009). In addition to limited use in medicine, these group of drugs are frequently found in the postmodern world in psychonaut, eccentric, party cultures.

### 1.1 | Brief history of psychedelic

It is difficult to say that the existence and effect of neurochemistry was understood in psychiatry until the 1950s. When the literature is examined, it is seen that visual phenomena and their effects on time perception, as a result of the use of mescaline sulphate, entered the literature with the 'experimental psychosis model' research conducted by Knauer and Maloney, who worked as researchers in Kraepelin's clinic. 'Personal experiment' methods, which were widely used in past research, have paved the way for many drug studies. 'Personal experimentation' methods, which were widely used in past research, paved the way for many drug studies (Knauer & Maloney, 1913; Nichols & Walter, 2021; Nielson & Guss, 2018).

Furthermore, French psychiatrists reported the antipsychotic effect of chlorpromazine in 1955. However, delving deeper into history, it can be found that Albert Hoffman discovered the first psychedelic drug at the Zurich Sandoz laboratory in 1943. The psychoactive effects of lysergic acid diethylamide (LSD) were serendipitously discovered, with Werner Stoll publishing the first scientific paper on LSD in 1947 at the University of Zurich. Despite its lack of mainstream acceptance until the last decade, research in this field is believed to have rapidly expanded following the groundbreaking work of these pioneers (Cade, 1949; Delay & Deniker, 1955; Hofmann, 2013; Kuhn, 1957; Nichols, 2018; Stoll, 1947). Examining the literature from that era, it can be notably deducted that a remarkable increase in psychiatric publications, with 100 articles in 1951 and over 100 articles in 1961. Noteworthy among these publications are studies on schizophrenia, post-traumatic stress disorder (PTSD), alcohol addiction and psychotherapy, all contributing to the development of current classification systems (Dyck, 2005; Nichols & Walter, 2021). Transitioning to the 1960s, two distinct therapeutic approaches emerged: Psycholytic and Psychedelic therapies, with LSD use and its forms gaining prominence in both Europe and America. Records indicate that approximately 7000 patients underwent treatment using psycholytic methods between 1953 and 1968 (Faillace, 1966; Passie, 1997).

### 1.2 | Overview of psychedelic usage in medicine

Classical psychedelics such as LSD, dimethyltryptamine (DMT), mescaline and psilocybin heralded a new era in the treatment of mental illness and psychiatric research. Among these, especially the use of LSD and psilocybin in psychedelic-assisted therapy in disorders such as depression, anxiety and substance use disorders (SUDs) constitutes a strong research area (Carhart-Harris et al., 2016; Davis et al., 2021; Gasser et al., 2015; Griffiths et al., 2016). In addition, clinical trials with psilocybin showed remarkable symptom relief effects in cancer-related anxiety, treatment-resistant depression (TRD) and major depressive disorder (MDD) and substance abuse treatment (Davis et al., 2022). Moreover, with increasing research interest, the focus of psychedelic studies has moved beyond psychiatric diseases to include the examination of other neurological diseases such as headache and migraine (Schindler et al., 2021). Although an increasing number of studies on psilocybin dosing have been conducted on patients in recent years with Phase 1 and Phase 2 studies, pharmacokinetic data are still limited (Griffiths et al., 2011; Hirschfeld & Schmidt, 2021; Madsen et al., 2019). However, LSD dosing response and pharmacokinetics are relatively well elucidated (Holze et al., 2019). Because psychedelic substances induce altered states of consciousness that include altered

perception of space and time, the self, altered patterns of thoughts and behaviour, the goal of their use with psychotherapy is to experience positive mental and perceptual changes and to create affirmative emotions; in short, this kind of personal experience is called 'good trip'. The positive response induced in this way is thought to have longer-lasting therapeutic effects (Prugger et al., 2022; Roseman et al., 2017). Doses that generally produce a psychedelic experience are studied under various headings as full effect doses, ego-dissolving doses or experiential doses. However, psychedelics are also used in microdoses that do not show acute effects, and they are attracting increasing interest in scientific research (Holze et al., 2021; Kuypers et al., 2019). Negative subjective experiences observed under the full dose concept are called 'bad trips'. It is more common in vulnerable individuals in unsuitable environmental conditions that are generally not under expert control (Barrett et al., 2016). When all these data are examined, it is seen that dose information is very important in the use of psychedelic substances for therapeutic purposes; therefore, microdosing will be emphasized separately.

In this context, the aim of this review is to examine the supportive and therapeutic use of psychedelic substances in the treatment of mental disorders and to discuss their potential effects especially in depression, anxiety and trauma disorders and even SUD.

## 1.3 | Psychedelic substances in the treatment of depression

It is known that more than 300 million people worldwide suffer from depression, which is a global public health problem (Organization, 2016). According to studies, the risk of death in depressed people is approximately 1.7 times higher than in non-depressed people (Walker et al., 2015). In addition to individual suffering, it is thought that the annual expenditure burden on the US economy is 210 billion dollars (Greenberg et al., 2015). A wide variety of pharmacotherapies and psychotherapies have been developed in the treatment of depression (Cuijpers et al., 2014). Although actual methods have relative efficacy, many patients with depression experience relapse (Morilak & Frazer, 2004), and approximately 30% of these patients are diagnosed with TRD (Nemeroff, 2007). According to a 2013 report, TRD increases medical care costs by 40–50% compared with treatment-responsive depression (Rizvi et al., 2014). Conventional first-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) generally show a latency of at least 2 weeks during treatment besides having various side effects that limit the treatment process (e.g., sexual dysfunction or decreased bone mineral density [BMD]) (Patacchini & Cosci, 2021; Tsapakis et al., 2012). It is necessary to develop new approaches to reduce the limitations of current treatments and to provide more effective treatment. For this reason, with increasing interest, psychedelic substances are showing promise in therapeutic use in the treatment of psychiatric diseases, especially depression, by offering a new generation approach (Grunder & Jungaberle, 2021).

Among the psychedelic substances that stand out for this purpose, psilocybin attracts the most attention due to its rapid effect, low toxicity and addiction tendency (Patra, 2016). Psilocybin shows a faster response of 2–6 h after clinical administration compared to LSD and mescaline (6–8 and 8–20 h, respectively) (Passie et al., 2002). Psilocybin is a natural psychedelic found in fungi of the genus *Psilocybe*. When metabolized in the bloodstream by alkaline phosphatases, it is converted to its active form, psilocin (Dinis-Oliveira, 2017). The chemical structures of psilocin and all other tryptamines are similar to serotonin, and all these classic psychedelics bind predominantly to the serotonin 2A receptor (Patra, 2016).

Studies conducted in recent years have found that psilocybin-assisted therapy is effective in alleviating the symptoms of depression (Agin-Liebes et al., 2020; Griffiths et al., 2016). In a double-blind randomized study conducted in 2016, it was shown that depressive symptoms decreased up to 6 months after psilocybin administration in a population with cancer-related depression and anxiety (Griffiths et al., 2016). In a study reported in 2017, it was found that depression symptoms decreased for up to 3 months after psilocybin administration to patients with TRD (Carhart-Harris et al., 2018). In the first randomized controlled study conducted in 2020, it was noted that after the administration of psilocybin to patients with depression, symptoms decreased to a great extent, with approximately 54% of them in remission 1 month later (Agin-Liebes et al., 2020). In a recent clinical study by Carhart-Harris et al., depressed patients were divided into two separate groups and administered psilocybin and an SSRI escitalopram for 6 weeks. When the depression scores were examined at the end of the study, there was no significant difference between psilocybin and escitalopram among the positive results in the first phase; however, SSRI side effects such as dry mouth, decreased emotional responsiveness and sexual dysfunction were not seen in the psilocybin group. This result shows that psilocybin can be at least as effective as an antidepressant (Carhart-Harris et al., 2021). In a Phase 2 double-blind, randomized study published in 2022, a

single dose of psilocybin (25 mg, 10 mg and 1 mg as a control) was administered to TRD patients in the presence of 6–8 h of therapy, and 3 weeks later, the groups were examined with the Montgomery–Åsberg Depression Rating Scale (MADRS), a depression severity scale. According to the results obtained, the significant improvement in the depression symptoms was observed in the group of 25 mg of psilocybin but not 10-mg received group compared with 1-mg group. However, in 25-mg group, it was shown some adverse side effects in the comparison of 10-mg group and control. Therefore, to understand the comprehensive impact of the behaviour and neural circuits functions needs to done further studies (Goodwin et al., 2022).

## 1.4 | Psychedelic substances in the treatment of SUDs

SUD directly and significantly affects patients and their relatives and indirectly affects public health and the social environment. Notably, excessive alcohol and drug consumption are associated with substantial morbidity, disability, mortality and costs (Friedmann et al., 1998). Although counselling and other behavioural therapies are important for the addiction treatment, they are not effective solely (Abuse, 1999). Also, approximately 50% of pharmacological approaches to the treatment of alcohol use disorder (AUD) are relapsed (Moos & Moos, 2006). Therefore, innovative approaches are needed. Data from studies show that psychedelic-assisted psychotherapy is a promising approach for the treatment of addiction (Reiff et al., 2020). The first studies on SUD done in the 1950s consisted of LSD applications and showed positive results in abstinence from most substances. However, it should be taken into account that these early studies included inappropriate standards in scientific methodology (Dyck, 2006). Two promising scientific studies have recently shown that psilocybin administration has beneficial effects of up to 6 months in nicotine and AUD (Bogenschutz & Pommy, 2012; Weinstein et al., 2014). There are currently ongoing clinical trials (NCT04620759, NCT04410913, NCT04141501, NCT01943994, NCT02037126) investigating the therapeutic effects of psychedelic substances on SUD. In summary, it can be said that there are no well-established pharmacotherapies for addiction (Saitz, 2007); however, there are many promising studies in progress.

One of the most important problems encountered in the treatment process is to determine the appropriate dose of the drug to be administered. Microdosing, which is a promising approach in the literature, has an important place in this context.

## 1.5 | Microdosing application areas of psychedelic substances

According to the literature, microdosing is a drug dose of 1% of the pharmacologically active dose, representing a maximum dose of 100 μg. In this context, for psychedelic microdosing, for example, the amount of microdose for LSD is 6–20 μg, whereas for psilocybin, microdoses typically range from 0.1 to 0.5 g of dried mushroom material, with 0.1 g roughly equating to approximately ≈4.6 μg of LSD (Prochazkova et al., 2018; Szigeti et al., 2021). However, variations in psilocin content may be observed between doses of dried mushrooms due to differences between individual fungi within a species; additionally, these amounts are about 5–10% of the usual psychoactive dose (Kuypers, 2020; Polito & Liknaitzky, 2022; Use, C.f. M.P.f.H, 2004). The inclusion of the concept of microdosing in the use of psychedelic substances has gained popularity in recent years. In studies conducted by certain groups, it is noted that after the microdosing experience, people reported minimal side effects and positive returns to their general health status (Polito & Stevenson, 2019). Moreover, the dose comparisons are the records obtained by researching on healthy subjects in a controlled clinical setting (Table 1). It should be considered that these data may produce different results in patients with neuropsychiatric disorders or in consumption in an inappropriate environment (Barrett & Preller, 2022). Besides, there are anecdotal reports that microdosing has positive effects on the emotions of the participants without causing hallucinations that limit daily life in trials conducted by taking approximately 10% of the dose taken recreationally two or three times a week. However, it should be noted that this concept, which has been brought to the agenda as an alternative to the use of psychedelic in recent years, has not yet been created universal protocols, and data such as dose, frequency and duration of use differ between studies (Kuypers et al., 2019). Therefore, there is a need for meta-analysis and scientific publications that include dose adjustment according to appropriate formal standards.

## 1.6 | Effect of microdosing on LSD tolerance

In the double-blind controlled study, participants were randomly assigned doses of LSD (13 and 26 μg) and placebo to three groups and applied in four repeated sessions. When mood tasks were evaluated, a moderate stimulant effect was observed in the 26-μg LSD group, but no difference was found in emotional and psychomotor tasks. Although repeated LSD applications at low

**TABLE 1** Dose comparison of different classical psychedelic substances.

| | LSD[a] [μg] | Psilocybin [mg] | Mescaline[b] [mg] | DMT[c] [mg i.v.] |
|---|---|---|---|---|
| Microdoses | <10 | <2.5 | <75 | NA |
| Low dose | 25–50 | 5–10 | 10–100 | 15 |
| Intermediate dose | 100 | 20 | 500 | 25 |
| Ego-dissolution dose | 200 | 30–40 | 1000 | 30 |

[a]100-μg LSD base corresponds to a tartrate of approximately 146-μg LSD.
[b]This is the dose indicated for the hydrochloride form of mescaline.
[c]This is the indicated dose for the DMT fumarate form.
*Source*: This table has been edited from Barrett and Preller (2022), Disruptive Psychopharmacology (75).

doses were shown to be reliable in this study, no significant increase in mood and cognitive performance was observed in the low LSD group. On the other hand, it is claimed, due to tolerance, that the LSD-like effects experienced on the first day during the administration period are not observed to the same degree in the following days in individuals in the low dose group (de Wit et al., 2022).

It is possible that psychedelics, which are frequently used in microdose increase cognitive performance or for hedonistic purposes, may cause tolerance even with microdosing, and it has not yet been clarified. Although the majority of studies in the literature show that microdosing may be beneficial in reducing dose-related side effects and may have curative effects, it should be considered that there is a real risk of commodification that would encourage people to routinely use drugs and cause individuals to experience unpredictable negative physical and mental experiences, suitable for widespread use by people alone without a therapist. Therefore, much more scientific research is needed to elucidate the phenomenon of microdosing.

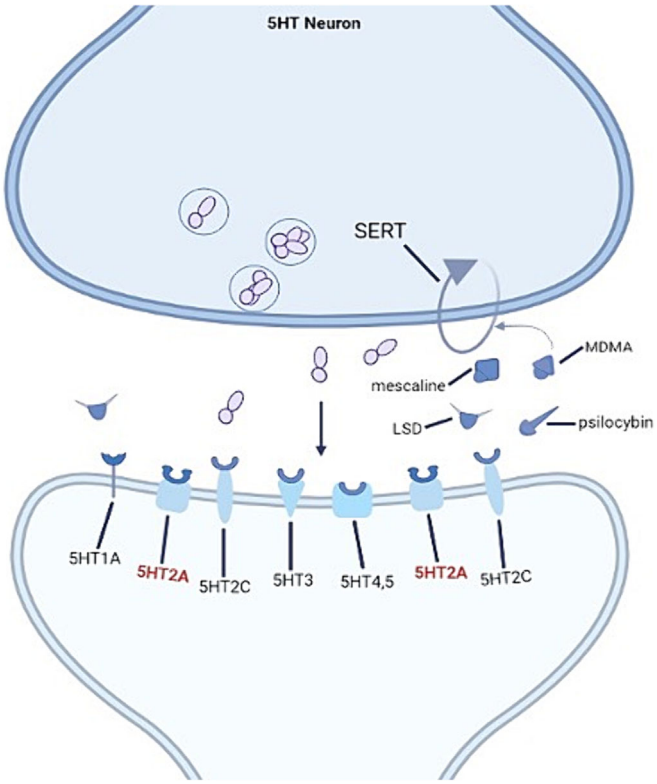


**FIGURE 1** Mechanism of psychedelics at $5HT_{2A}$ receptors. (This figure has been edited from Stahl's Essential Psychopharmacology Neuroscientific Basis and Practical Applications 5th Edition and was created with BioRender.com, Stahl, 2021.)

## 2 | NEUROBIOLOGY OF PSYCHEDELICS

Psychedelics or serotonergic hallucinogens are substances that are 5-HT receptor agonists; the most well known are DMT, psilocybin, mescaline and various lysergamides (Nichols, 2016). Psychedelics are agents that act at serotonin synapses in the reward system (Figure 1). They trigger changes in sensory perception, triggering visual illusions and hallucinations. They can also induce the phenomenon of intoxication characterized by increased attention to external stimuli and heightened awareness of internal thoughts and stimuli, called trips.

Psychedelic is the term for the subjective experience in which one's perceptions expand through increased sensory awareness, a kind of mystical experience in which one feels in harmony with the universe. Psychotomimetic, on the other hand, is the triggering of a psychotic state by the experience of substance use (Stahl, 2021). According to studies, psychedelics may exhibit their antidepressant effect by increasing glutamate release (Chruscicka-Smaga et al., 2023). Additionally, it has been shown that they also demonstrate potent agonist effects against $5\text{-}HT_{2A}R$, a G-protein-coupled receptor (GPCR) highly effective in anxiolytic and antidepressant treatments (Vollenweider & Kometer, 2010). However, the findings regarding the relationship between

the antidepressant effects of classical psychedelics such as LSD and DMT and the 5-$HT_{2A}$ receptor are controversial and are still unclear (Cameron et al., 2023; Qu et al., 2023). According to the findings of the experiment conducted on mice, it was shown that the antidepressant-like effects of psilocybin did not disappear when the agent that blocked the 5-$HT_{2A}$ receptor was administered to mice (Hesselgrave et al., 2021). Findings from other studies (Sekssaoui et al., 2024) (Hashimoto, 2024; Hesselgrave et al., 2021) suggest that 5-$HT_{2A}$ agonists may exert their antidepressant-like effects independently of their psychedelic effects, but ongoing studies aim to clarify the involvement of the 5-$HT_{2A}$ receptor in the antidepressant effects of psychedelics.

The main action of psychedelic substances such as LSD, mescaline, psilocybin and DMT is agonism to $5HT_{2A}$ receptors. Psychedelics may also have additional effects on other serotonin receptors (especially $5HT_{1A}$ and $5HT_{2C}$) and other neurotransmitter systems. For example, N-methyl-3,4-methylenedioxyamphetamine (MDMA), which is not classified in the classic psychedelic group, has potent serotonergic psychoactive effects and specifically blocks the serotonin transporter (SERT) (Stahl, 2021). Agonism of the 5-HT receptor group is associated with neuroplastic changes potentially reducing depression and anxiety symptoms (Gill et al., 2020). The 5-HT receptor group also plays a significant role in the gut-brain axis and is associated with the pathophysiology of irritable bowel syndrome (IBS), a chronic functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits, through dysregulated serotonin signalling (Bonetto et al., 2021; Pretorius & Smith, 2020). Receptor affinity studies have shown that high and low affinity states affect different intracellular pathways in GPCRs. While the high affinity $G_{\alpha i1}$-protein pathway is activated, at low affinity, the canonical $G_{\alpha q/11}$-protein pathway exerts a functional effect (Lopez-Gimenez et al., 2001). The data show that 5-$HT_{2A}$R agonists bind to GPCRs with high affinity, resulting in rapid receptor internalization, triggering lysosomal degradation and downregulation of the receptor (Gray & Roth, 2001). It has been shown that this 5-$HT_{2A}$R downregulation occurs temporarily. In recent studies, it is thought that this receptor downregulation triggers the formation of dendritic spine in presynaptic neuron, and thus, $5HT_{2A}$ agonists have a possible antipsychotic effect by modulating synaptic plasticity (Raval et al., 2021). Despite GPCRs are considered primary in the initiation of signal transduction, recent studies have shown that intracellular components have significant effects on GPCR signal (Vargas et al., 2023). Studies have shown that 5-$HT_{2A}$ receptors are localized in cortical neurons, especially in the Golgi (Ly et al., 2021). Furthermore, due to its chemical structure, serotonin cannot pass through the non-polar bilayer of the cell membrane by passive diffusion, like psychedelic substances (Kwan et al., 2022). Also, it is possible that psychedelics interacting with the 5-$HT_{2A}$ receptor in the intracellular compartment, which has an acidic microenvironment like the Golgi, may be protonated by the acidic environment, and this situation play an active role in neurogenesis process (Vargas et al., 2023). Based on recent studies, researchers hypothesize that psychedelics interact with intracellular 5-$HT_{2A}$ receptors to induce plasticity and exert a pronounced effect on cortical neurons (Ly et al., 2018; Olson, 2018; Vargas et al., 2023).

Upon the matter, all these data show that downregulation and desensitization of the 5-$HT_{2A}$ receptor play an active role in the improvement of symptoms related to depression and anxiety (Van Oekelen et al., 2003). In addition, recent data show that apart from 5-$HT_{2A}$ receptors localized on the membrane, the interaction of the intracellular 5-$HT_{2A}$ receptor and psychedelics may also have a significant effect on the signalling cascade, and this phenomenon may cause plasticity changes on the cell (Vargas et al., 2023).

Additionally, LSD acts as a partial agonist of 5-$HT_{2A}$R and primarily exerts its effects through agonism of 5-$HT_{1A}$R (Marek & Aghajanian, 1996; Rickli et al., 2016). Both LSD and SSRIs affect 5-$HT_{1A}$R by desensitizing post-synaptic receptors, leading to increased serotonin release. Moreover, the rationale behind the development and application of these tests is discussed. Behavioural effects akin to those of SSRIs, such as antidepressant-like effects, have been elicited by agonists targeting 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{2C}$, 5-$HT_4$, and 5-$HT_6$ receptors (Carr & Lucki, 2011). Further research is necessary to ascertain the specific roles of different 5-HT receptors, as each psychedelic drug necessitates distinct investigations.

## 2.1 | Effects of psychedelics on neural networks

Data from neuroimaging studies show that the default mode network (DMN) is overactive in MDD. The DMN is the large-scale brain network that is active during introspection and self-reflective actions whereas shows deactivation during goal-directed cognitive tasks (Baliki et al., 2008; Husain et al., 2022). It has been found that especially the amygdala is abnormally activated in depressed individuals (Berman et al., 2011). Carhart-Harris et al. designed a study with functional magnetic resonance imaging (fMRI) during psilocybin administration, in which they showed reduced blood flow to the ventral medial prefrontal cortex (vmPFC) and thalamus

under psychedelic influences. This finding suggests that DMN, which is overactive in depression, can be normalized with psilocybin (Carhart-Harris et al., 2012). This dysconnectivity in DMN induced by psilocybin is also supported by additional neuroimaging studies. In magneto/electroencephalography imaging experiments, it has been shown that neuronal desynchronization occurs in the alpha band, and DMN connectivity decreases, especially in the posterior cingulate cortex (PCC), which is one of the main centres of the DMN, under the influence of psychedelic substances. It is assumed that the dysconnection in the mentioned DMN regions is effective in ego resolution and provides a more flexible and holistic state than a self-directed mind (Letheby & Gerrans, 2017; Muthukumaraswamy et al., 2013; Nour et al., 2016). These data showing the neural correlates of psychedelics in brain networks suggest that they may be promising in neuropsychiatric treatments, especially depression.

Continuing with psychedelic substances, LSD is a semi-synthetic product of naturally occurring lysergic acid found in the ergot fungus *Claviceps purpurea* growing on the rye. LSD was discovered by Swiss chemist Albert Hofmann in 1938, sparking interest in the field of mental health research and revealing the potential for a new treatment approach (Nichols & Walter, 2021). A recent review of clinical studies following the discovery of LSD noted that depression symptoms were relieved in approximately 79.2% of the patients after the LSD application. However, it should be considered that these early period studies have methodological shortcomings such as not being blind and without a control group (Rucker et al., 2016).

In a placebo-control, double-blind study conducted in 2020, resting state fMRI was performed after administering LSD (13 μg, this is a microdose, and the normal psychoactive dose is 100 μg) to healthy participants. In the results of the study examining the amygdala-seed connectivity, it was observed that the connectivity of the amygdala and superior temporal gyrus, which is known to show hyperactivity in depressed individuals in the literature (Groenewold et al., 2013), decreased with low dose LSD. In addition, the increase in amygdala-cerebellum connectivity, which is another finding, was found compatible with the positive mood scores of the participants (Bershad et al., 2020). At this point, it is worth noting that cerebellar-limbic circuit function is important for emotional regulation, and it is known from previous studies that the decreased connectivity of this circuit is normally correlated with negative mood in depressed individuals (Ramasubbu et al., 2014).

All these data show explicit consistency with previous results from literature with the application of psilocybin (Barrett et al., 2020; Kraehenmann et al., 2015). It is known that $5HT_{2A}$ receptors strongly targeted by psychedelic substances and these receptors are intensely expressed in the amygdala as well (Bombardi & Di Giovanni, 2013). Moreover, these findings clearly show that dysfunction in these areas, which are prominent in disorders such as depression and anxiety (Almeida et al., 2010), can be improved with the use of psychedelic substances in appropriate doses and under the guidance of an expert. Besides the potential therapeutic uses of psychedelic substances, they have also particular importance in elucidating the neural circuits and connectivity underlying the pathology of mental illness (De Gregorio et al., 2021).

## 2.2 | Effects of psychedelics on plasticity

Studies have shown that in addition to the acute effects of psychedelics, they have emotional and cognitive effects that continue up to 4 weeks after use (Mason et al., 2019). Studies show that the neurobiological process underlying these effects is related to plasticity. Plasticity is the brain's capacity to change. The effects of these processes are manifested by structural changes when they occur in dendrites, by functional change via PFC circuits when they occur in layer 5 pyramidal neurons, and by epigenetic changes through the expression of neuroplasticity-related genes (Fuchs & Flugge, 2014). In rat studies, psychedelics have been observed to have a very similar effect like rapid antidepressants on behavioural outcomes. A single dose of LSD and psilocybin was found to produce antidepressant-like behaviour lasting up to 5 weeks in rat behavioural tests (Hibicke et al., 2020). In other studies, it has been shown that the fear memory of mice and rats administered a single dose of psychedelic substance, DMT (N,N-dimethyltryptamine), is erased and their anxiety decreases accordingly (Cameron et al., 2018; Zhang et al., 2013). Furthermore, in a DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, a non-indole 5-$HT_{2A}$ agonist)-induced model study in mice, it was demonstrated that psychedelics promote long-term plasticity and significant epigenetic changes. Another finding of the study is that this process of neuroplasticity and transcriptomic change occurs through 5-$HT_{2A}$ receptor dependent mechanisms. In the study, DOI was injected into two groups, one consisting of 5-$HT_{2A}$ receptor knockout and the other normal mice, in order to elucidate the effect of DOI on dendritic spine formation via the 5-$HT_{2A}$ receptor. As a result, a decreased dendritic spine development was observed in 5-$HT_{2A}R^{-/-}$ mice compared with the control group. This finding highlights the significance of the 5-$HT_{2A}$ receptor's function in dendritic morphology (de la Fuente Revenga

et al., 2021). Many factors are effective in shaping plasticity, such as cell ageing, developmental process and environmental factors. Therefore, state-dependency concept is mainly effective in shaping the cell's plasticity response. According to this approach, a dynamic occurring in a certain period directs the formation of long-term potentiation (LTP) and long-term depression (LTD) in later processes. LTP and LTD are at the root of synaptic plasticity. With LTP, synapses are strengthened, and the response of the postsynaptic neuron is reinforced in this way. On the other hand, the opposite is exhibited with LTD; the synapse weakens, the postsynaptic neuron is suppressed. Synaptic modulation is provided by the controlled processing of these two components (Lee, 2022).

If we return to state-dependence, which is an effective concept in the regulation of the cell's response to the plasticity, the concept of metaplasticity emerges. Metaplasticiy is a heterosynaptic activity in which LTP and LTD processes are regulated on a larger scale (Chiamulera et al., 2021; Wang & Wagner, 1999). Metaplasticity phenomenon is a neuroadaptation seen in drug abuse as well. In this process, a permanent drug memory is created depending on the drugs used chronically, and it leads to addictive behaviours such as drug seeking through severe dopamine release in the mesocorticolimbic circuit (Creed & Luscher, 2013). As it is known, nucleus accumbens (Nac) receives dopaminergic projections from the ventral tegmental area (VTA) and glutamatergic innervations from the cortex. Addictive behaviour patterns occur with synaptic plasticity processes triggered by chronic substance use by metaplastic effect of glutamate transmission on Nac (Chiamulera et al., 2021).

Taking these aforementioned points into consideration, it is thought that psychedelics have significant effects on molecular, cellular, and behavioural scales. In addition, another emphasis of the studies is that the concept of plasticity is not always positive for biological processes and has a characteristic depending on the situation, such as a critical period. Although studies suggest that these effects occur with neuroplasticity, additional studies are needed in this area.

## 3 | ETHICAL CONCERNS

Nevertheless psychedelics have entered a long path towards approval for the treatment of many diagnoses, Sandoz Pharmaceuticals stopped production of Delysid (LSD) in 1966 issuing the statement of 'unpredictable social reaction', despite many important and promising studies in the past. As a result of the 'War on Drugs' evaluations initiated by the Nixon Administration, on the grounds that it was used by demonstrators and hippies in the increasing anti-war movement and supposedly contributing to social unrest, all ongoing studies were stopped by the FDA.

As mentioned above, the use of psychedelics in modern medicine has been increasing in recent years. The fact that the 'banned' treatment option of a period is used in the treatment of many different nosologies, of course, brings with it some difficulties and debate. Although an attempt was made to standardize the appropriate doses to be administered in the treatment of some disorders, it is ethically necessary to evaluate many topics such as determining the people to be selected/excluded from the treatment, indications/contraindications of the treatment, the effect on other treatment options used in current practice and possible side effects. Here, we come across the famous phrase attributed to Hippocrates, 'Primum Non Nocere', meaning 'First Do No Harm'.

Delving further into the literature reveals research conducted by G. T. Stockings in the 1940s, where mescaline was employed as a means to gain insights into the essence of mental disorders (Stockings, 1940). This provided a suitable working ground for the Experimental Model of Schizophrenia. Although it can be said that the emergence of short-term psychotic experiences in healthy participants was an important step towards understanding the nature of the diseases at that time, it is not an ethically acceptable study design in today's medical world. Although it is an important issue, it still keeps a question mark in minds with a limited number of samples and limited number of studies that psychedelics can cause psychosis-like pictures in people who do not have psychiatric complaints before (Dos Santos et al., 2017). There are many definitions such as Psychotomimetics, psychotogens, hallucinogens and psychodysleptics have been used as a result of these experiences from past to present, in the last instance it has been termed *psychedelics* (mind-manifesting) by the British scientists Humphrey Osmond and John Smythies (Carhart-Harris et al., 2013; Hartogsohn, 2017, 2020; Johansen & Krebs, 2015; Langlitz, 2013).

Although psychotic experiences related to psychedelics are phenomenologically differentiated from positive psychotic symptoms seen in schizophrenia, this needs to be proven by other studies. People who use ayahuasca (psychedelic combination made by boiling two herbs containing harmala alkaloids and DMT and used for ritual and curative purposes by Amazonian Indians for centuries) have reported reliving memories of past events and may therefore be at risk of re-traumatization if these past events are traumatic in nature (Kaasik & Kreegipuu, 2020; Leptourgos et al., 2020; Nielson & Megler, 2014). Another important aspect is that

psychedelics may facilitate the emergence of mystical experiences as well as their therapeutic effects. Experiences of immaterial ultimate reality, transcending the time–space distinction, seem to be the triggers that invoke non-naturalistic metaphysics. Despite subjective experience varies, it can be considered that usage of psychedelics in a therapeutic manner may offer a comforting opportunity to the palliative care patients who have end-stage cancer, from destructive and potentially life-threatening realities (like depression or suicide); that the mystical experience is felt as if it is real; or that the delusions continue in a controlled manner under psychedelic treatment but save the person That is an important issue or controversy at the end of life that this delusion or hallucination is whether better. Although subjective experiences can vary, it is hypothesized that offering palliative care patients with end-stage cancer a comforting illusion via mystical experiences, or a controlled dissociation from reality through psychedelic therapy, may provide a respite from their challenging and life-threatening conditions. However, the ethical implications of inducing a truly dissociative psychedelic experience still require careful consideration. The need for an ethical discussion arises due to the potential consequences of such experiences, which may distance the individual from reality and create a sense of detachment that could have adverse effects on their psychological and emotional well-being. Therefore, it is important to examine the potential benefits and risks of these approaches before implementing them in clinical settings.

In other words, the balance of epistemic harm and the psychological benefit of a delusion remains an ethically controversial area (Fink, 2022; Lyvers & Meester, 2012; Roseman et al., 2017; Ross et al., 2016; Vickers, 2017). Because of many such causalities, the use of psychedelics in medicine and ethics will continue to be a topic of pre-clinical and clinical discussions for the foreseeable future.

## 4 | CONCLUSION

The use of psychedelic substances in the treatment of depression and SUDs has been studied with increasing interest in recent years. The use of psychedelic bioactive substances in medical treatment attracts even more attention, especially when the mortality and morbidity rates of these diseases and the economic burden they cause socially are considered. There are many research groups showing that the use of tryptamine derivatives, especially LSD, psilocybin, is beneficial in the treatment of anxiety, PTSD, mood disorders and addiction (Griffiths et al., 2016; Moreno et al., 2006; Whelan & Johnson, 2018). In line with the satisfactory results from the studies, especially promising in the treatment of depression, psilocybin has been approved by the Food and Drug Administration (FDA) as a 'breakthrough therapy' (Meir et al., 2023). The FDA also granted 'breakthrough therapy' status in 2017 to 3,4-methylenedioxymethamphetamine (MDMA) for the treatment of PTSD (Emerson et al., 2014). MDMA is one of the classical psychedelics that create an empathogenic effect, and it produces significant non-repeatable improvements, especially in PTSD, both through the activation of the 5-$HT_{2A}$ receptor and the release of oxytocin it triggers (Inouye & Wolfgang, 2022; van Wel et al., 2012). In clinical studies, psychedelics, especially psilocybin and MDMA, its applications with therapy show very positive results, and it is indicated in studies that its therapeutic use in clinical settings under medical control has potential benefits in the treatment of other psychiatric diseases such as eating disorder and addiction (Garcia-Romeu et al., 2014; Gukasyan et al., 2022; Mithoefer et al., 2016).

Despite their increasing interest, the biological mechanisms and possible therapeutic effects of psychedelic substances are not yet fully known. When the literature is reviewed, it is seen that unfortunately, very few of the studies are controlled and randomized. In particular, the distance from objectivity and the use of uncontrolled variables in the questionnaire scores, which consist of subjective answers in most of the studies, also limit the value of the studies in this field. In addition, the fact that participants know that they will use psychedelic in most of the studies may play a role in increasing the positive results with the effect of placebo in the experimental group. Therefore, more double-blind, randomized clinical studies are needed.

All in all, to understand the importance of the psychedelics' impact on neuronal circuits functions and plasticity will pave the way to identify reformist and powerful therapeutic approaches for the treatment of psychiatric diseases and disorders.

### AUTHOR CONTRIBUTIONS

**Nur Damla Korkmaz:** Conceptualization; writing—original draft; writing—review and editing. **Ugur Cikrikcili:** Supervision; writing—review and editing. **Merve Akan:** Writing—review and editing. **Emrah Yucesan:** Conceptualization; writing—review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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