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# Psilocybin and hallucinogenic mushrooms

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**Review**

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**Abstract**

Psilocybin therapy has recently emerged as a promising new treatment for depression and other mental health disorders. This chapter summarizes the most recent data on its safety and efficacy. The delivery of psilocybin therapy and its subjective effects are also presented. Furthermore, this chapter outlines our current understanding of psilocybin's pharmacology and neurobiological effects. Other similar psychedelic substances with encouraging therapeutic potential are briefly presented.

## Brief historical and anthropological perspective on the use of hallucinogenic mushrooms

### *Indigenous use of psilocybin mushrooms*

Psilocybin-containing mushrooms have been used in rituals by the Indigenous Peoples of Mesoamerica long before being consumed as recreational drugs or treatments in Western medicine, as evidenced by art from 3500 years ago.[1] Sculptures of "mushroom stones" with faces carved on their stalks, and other art pieces dating back centuries depict fungi in religious and ceremonial contexts.[1] The first written accounts suggesting psilocybin consumption were documented by 16th-century Spanish naturalists. Notably, the friar Bernardino de Sahagún studied the life and customs of the Aztecs and mentioned in his accounts *teonanacatl*, a Nahuatl term translated as "flesh of the gods." Sahagún recalled the use of *teonanacatl* for medicinal and spiritual purposes in rituals that induced intoxication, visions, and "sensuousness".[3] Diego Durán, another Spanish friar, described the mass consumption of mind-altering mushrooms at the coronation of Aztec emperor Montezuma II.[4] Francisco Hernández de Toledo, a naturalist and physician, also reported the ritualistic use of mushrooms that could induce "madness" and visions.[5] Beyond these early accounts, there is little documentation of the mysterious *teonanacatl*, likely due to cultural suppression by the Catholic Church and colonial authorities.[2,6]

Today, psilocybin is still used in ritual vigils (often called *veladas*) by multiple Indigenous Peoples including the Nahuas, Matlatzinca, Totanac, Mazatec, Zapotec, and Chatinos.[2] The rituals may serve a wide range of spiritual and therapeutic purposes, and their objective is not necessarily to provide a cure. Sometimes they aim to unravel the cause of a problem.[2,7,8] Understanding the original nature of these ceremonies is difficult since outside influences have inexorably reached these communities and altered their traditions. Even the earliest descriptions of *veladas* mentioned the presence of Christian symbolism in these ceremonies.[2,7] Since the early 1960s, rituals were further modified as they became tourist attractions for Westerners. Nonetheless, certain essential features of a *velada* can still be identified.[2] The ceremony is generally held at night after a period of fasting and abstinence. It is led by a shaman or an older experienced person who usually invites the participants to their house. The mushrooms are incensed with copal resin, then counted and offered in pairs. Throughout the experience, chants, poetry, and dances are often performed by the leader of the *velada*.[8,9]

While psilocybin-containing mushrooms are found all around the world, it is only in current-day Mexico that their traditional use has been documented with certitude. Limited archeological data may support their ethnobotanical use in parts of Africa, Columbia, or New Guinea.[2,10–13]

### *Introduction to Westerners*

Shortly before the Second World War, Austrian-born physician Blasius Paul Reko (who later adopted the name Blas Pablo) reported to Richard Evans Schultes and Robert J. Weitlaner that Mazatec Indians in Huautla de Jiménez were using mushrooms in religious ceremonies. Intrigued by this information and by the mysterious tales of early Spanish settlers, Schultes and Weitlaner traveled to the region of Oaxaca to collect fungi samples and to describe their traditional use.[14,15] In 1938, a group composed of Weitlaner, Jean Bassett Johnson, Irmgard Weitlaner-Johnson, Bernard Bevan, and Louise Lacaud were the first known Westerners to attend and describe a mushroom ceremony.[2,16]

Around 1952, New York banker Robert Gordon Wasson became intrigued by the works of Schultes and initiated a series of trips to Mexico with his wife Valentina Pavlovna Wasson. Accompanied by the photographer Allan Richardson, Wasson was allowed to participate in a mushroom *velada* with Mazatec *sabia* María Sabina during the summer of 1955. To be allowed access to the *velada*, Wasson deceived the community by pretending he worried about the well-being of his son back home.[17] Shortly after, their experience was narrated in the photo essay "Seeking the Magic Mushroom" published in *Life* magazine, which brought widespread attention to this phenomenon.[7]

In 1957, Wasson and his wife were accompanied on a follow-up expedition by French mycologist Roger Heim, who correctly identified several of the mushrooms as species of *Psilocybe*. Heim cultivated the mushrooms in France and sent a sample of dried *Psilocybe mexicana* to Swiss chemist Albert Hofmann.[18] Hofmann used paper chromatography to separate the different components of the fungi. The paper chromatogram was cut into pieces that Hofmann and several colleagues voluntarily ingested to identify the active fraction. Hofmann successfully characterized psilocybin and invented a synthesis process that led to its commercialization by Sandoz under the name Indocybin.[19]

Revealing the secret of psilocybin mushrooms came with devastating consequences for the Mazatec. Without María Sabina's consent, Wasson disclosed her identity and location.[16,20] The popularity of his work brought a surge of Westerners to Oaxaca seeking psychedelic trips, which profoundly disrupted the local community. Sabina was blamed for the actions of intoxicated foreigners, while the Mexican police suspected her of being a drug dealer.[20] She was ostracized, her house burned down, and her son was murdered. Regretful, María Sabina later died in poverty.[20,21] Many regret how the Mazatec traditional knowledge was commodified and profited from.[22] Indigenous communities from Mexico do not profit from the lucrative commercialization of psilocybin.[23,24]

### *Occidental research on psilocybin*

The 1960s ushered in a wave of research investigating the pharmacology and the psychological effects of psychedelics such as psilocybin, LSD, and mescaline. Prominent and charismatic figures such as Timothy Leary, Richard Alpert, and Ralph Metzner were at the vanguard of this movement. Trials were performed using psychedelic substances in an eclectic array of situations. Many investigated their power to facilitate psychodynamic-oriented therapies.[25] The Concord Prison Experiment explored psilocybin's effect on convicted inmates in the hopes of reducing recidivism.[26] In the Marsh Chapel Experiment (also known as the Good Friday Experiment), the entheogen power of psilocybin was studied on students of Harvard Divinity School. Unethical projects such as the CIA-led MK-Ultra investigated the use of psychedelics for psychological torture, brainwashing, and forcing confessions during interrogations.[27] Many concerns were raised about the ethics and the scientific validity of research conducted during this period. While psychedelic substances were widely used recreationally, psilocybin research became tied with the counter-culture movement of the 1960s.

Mounting concerns and tensions lead to the abrupt end of this first era of psychedelic research. In 1966, the FDA demanded the shutdown of almost all psychedelic research programs. Soon after, the U.S. Congress criminalized the possession of psilocybin in a 320–2 vote. In 1970, the Controlled Substances Act was passed, which categorized psilocybin as a Schedule I substance, therefore supposing it has no medical use and high potential for abuse.[28] Around that time, many other countries adopted similar approaches to criminalize activities involving psychedelics. All these factors contributed to the long hiatus in psychedelic research.

Psychedelic research began to re-emerge in the late 1990s and early 2000s.[29] Organizations such as the Multidisciplinary Association for Psychedelic Studies (MAPS) and academic institutions such as Johns Hopkins University were among the first to reexplore the therapeutic potential of psychedelics. Contemporary research is now generally led with higher ethical standards and improved scientific methodology. Meanwhile, modern techniques in neuroscience allow for a better understanding of psilocybin's effects.

## Subjective experience propelled by hallucinogenic mushrooms or psilocybin

The ingestion of psilocybin or hallucinogenic mushrooms produces mighty modifications in perceptions, thoughts, and moods. Despite the ineffable quality of psychedelic journeys and although each experience is unique, we will do our best to summarize the complex and intertwined sensory, cognitive, and emotional manifestations that often characterize them. The importance of set and setting will be addressed in Section 4 on the delivery of psilocybin therapy (PT) and the duration of these experiences will be discussed in Section 5 with other notions of pharmacokinetics.

### *Sensory and perceptual alterations*

Characteristic visual manifestations are soon noticed after the ingestion of psilocybin or hallucinogenic mushrooms. Wavy or rhythmic moving patterns can be observed when contemplating objects or surfaces. Colors often appear brighter and more vivid, and flashes or streaks of light can be seen. Objects or body parts can appear smaller or larger than their actual size. Closing the eyes gives rise to visions of abstract patterns, geometric shapes, or complex scenes involving people, landscapes, and objects.[30] Psychedelic substances commonly produce audiovisual synesthesia, *that is* music inducing dynamic images, shapes, or colors.[31] Synesthesia can less commonly occur between other sensory modalities. Even though the term "hallucinogen" is often used to classify substances like psilocybin, LSD, DMT, and mescaline, they are unlikely to cause hallucinations such as those classically described in psychotic disorders.[30,32]

During the psychedelic experience, the perception of time is greatly altered. It might appear slower to some, while others will perceive its acceleration.[33] Feelings of "timelessness" or experiences of "eternity" have even been described by many.[34] Beyond these sensory alterations, the subjective experience of perception is often enhanced by a surge of curiosity and amazement. This typically translates into the adoption of a contemplative stance, through which the perception of beauty can be expanded.[33]

### *Changes in thoughts and cognition*

When attention is turned inward, subjects of psychedelic experiences can fall into a state of internal absorption where arising thoughts are often felt with a sense of deep and intuitive understanding. These internal phenomena can sometimes be felt as "more real than reality".[34] Akin to revelations of great importance, many consider these experiences with reverence and strive to remember their details. Culturally loaded terms such as "sacred" or "mystical" are often used to describe these subjective experiences.


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Thoughts and feelings of being united with something that transcends the personal self are cardinal features of many psychedelic experiences,[34,35] and terms such as "oceanic boundlessness" have been used to describe these profound experiences of connection with a larger whole. These experiences of unity may be characterized by a blurring of the boundary between the external environment and what is commonly considered the "I" or the "self." Some subjects may recall losing ownership of their body or surrendering their mind.[30] After the notion of "self" has been stripped of its familiar quality, usual ideas, and behaviors can often be considered with a renewed curiosity. Automatic or mindless thoughts and actions can seem puzzling and remarkable. Symbolic imagery such as archetypal themes can be brought to the forefront of consciousness, and identifying with some of these symbolic patterns can nourish a deeper reinterpretation of one's personal narrative.[30] Although thinking is generally less target-oriented, subjects may seek answers to existential and ontological questions.

### Changes in mood and affect

Most experiences with psilocybin are characterized by a heightened mood, although difficult or challenging psychological experiences of varying severity are not uncommon.

Many people experience joy or happiness, while some even recall feeling bliss or ecstasy. Psychedelics often produce spells of uncontrollable laughter. Overall, a sense of deep contentment often envelops the experience and its aftermath.[34,36]

Unfortunately, emotional hardship can be the cost of psychedelic-altered thought patterns. Deep alterations in the sense of "self" can come with the impression of losing control, becoming insane, or even dying. These distressful impressions can be felt with anxiety and panic.[37] Overinterpreting insignificant occurrences or events by giving them a personal meaning can also result in feelings of paranoia. Some also experience vivid recollections of personal conflicts or traumatic memories.[37] Facing difficult emotions, conflicts, or memories, rather than pushing them aside is often followed by a sensation of breakthrough, which can lead to feelings of relief or closure.[38]

## Efficacy of psilocybin therapy: state of the current knowledge & methodological challenges in research

Clinical studies have explored the therapeutic potential of psilocybin for a wide range of conditions. Owing to the encouraging results of prior trials, there is now considerable enthusiasm and momentum in favor of interventions using psilocybin, and the literature on this subject is rapidly expanding as many new studies are underway. We will briefly summarize current knowledge on the efficacy of psilocybin therapy (PT) for the treatment of mental health problems. Safety considerations and possible adverse events from these treatments will be reported in Section 6.

It must be noted that many studies were conducted on psilocybin and other psychedelic drugs during the 1960s and 1970s. While this pioneering work was of considerable importance, it often lacked the methodological or ethical standards required in today's research.[39] Therefore, the information we summarize will focus on clinical trials conducted since the rebirth of psychedelic research in the 2000s.

### Treatment of depressive episodes

Major depressive disorder (MDD) is a burdensome condition, and current treatment options are unfortunately ineffective in helping many patients who suffer from it.[40,41] Therefore, there is great interest and need for new treatments against MDD. In recent years, PT has emerged as a promising intervention and many studies have evaluated its efficacy.

A thorough review of the literature allowed us to identify published results for seven controlled trials and four open-label trials evaluating PT for MDD. Trials that solely recruited patients suffering from anxiety or depressive symptoms occurring in the context of a life-threatening medical illness will be discussed in Section 3.2. The main characteristics of these studies are presented in Table 1. Most recruited participants suffered from moderate to severe MDD, which was commonly defined by a score ≥ 17 on the Hamilton Depression Rating Scale (HAMD). Some studies recruited patients with treatment-resistant depression (TRD), meaning the patients' symptoms persisted despite prior antidepressant trials. All studies had a small sample size, the largest having only recruited 233 participants. The interventions varied significantly between clinical trials. Most offered around 10–30 mg of psilocybin on a fixed-dose regimen, while others calculated a weight-based dose. Protocols had between one to three medication administration sessions, and there was a wide variation in the type of psychological intervention offered. All studies reported short-term primary outcomes (from 1 to 6 weeks after PT), while only a few reported outcomes after a longer follow-up period (from 6 to 12 months after PT). By drafting funnel plots for psychedelic interventions in MDD or TRD and by performing Egger's test, some authors have suggested publication bias or small study effects that could also limit our current knowledge of the efficacy of psychedelic treatments.[42,43]

At short-term endpoints, most studies found that PT offered a meaningful reduction in depressive symptoms (with an average MADRS reduction between 13 and 23 points or with an average HAMD decrease between 7 and 15 points). The effect sizes were generally large as illustrated by Cohen's *d* commonly reported between 0.9 and 2.5. At short-term endpoints, these small studies found response rates ranging from 40% to 75%, while remission rates vary between 20% and 60%.

The long-term efficacy of PT has not yet been thoroughly described. A study by Gukasyan *et al.* reported 12 months of follow-up results for a cohort of 24 patients who initially suffered from moderate to severe MDD. This study showed a 75% response rate (>50% reduction in HAMD score) and a 58% remission rate (HAMD score ≤ 7) one year after a single psilocybin treatment.[49] Soon-to-be-published data from our laboratory also suggests that response and remission rates can remain high, even 12 months after PT. In a small sample of veterans suffering from moderate to severe TRD, sustained response was observed for 50% of participants, and persistent remission for 40% at a 12-month endpoint ($n = 10$).

Currently, PT has limited evidence as a treatment for depression in bipolar disorders. Aaronson *et al.* reported the safety and efficacy of psilocybin in 15 patients with type II bipolar disorder and a current depressive episode. In this study, all participants had a reduced MADRS score at week 3, with a mean improvement of 24 points on this scale. At the same study endpoint, 80% of participants met remission criteria. The intervention was well tolerated, and no manic or hypomanic episode was observed.[57] Four participants with type II bipolar disorder were also included in a recent study.[55]


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**Table 1.** Characteristics of Clinical Studies Evaluating PT for MDD or TRD

| Study | Clinical presentation | N | Study design | Intervention & control | Main study findings |
|---|---|---|---|---|---|
| Carhart-Harris et al., 2016[44] | Moderate–severe MDD, and treatment resistance (failure with ≥2 antidepressants) | N = 12 | Open-label | Two doses of psilocybin 10 mg → 25 mg + psychological support | After PT, depressive symptoms were markedly reduced at 1 week (mean QIDS difference − 11.8, Hedges' $g$ = 3.1) and 3 months (−9.2, Hedges' $g$ = 2.0). |
| Carhart-Harris et al., 2018[45] | Moderate–severe MDD, and treatment resistance (failure with ≥2 antidepressants) | N = 20 | Open-label | Two doses of psilocybin 10 mg → 25 mg + psychological support | Marked reductions in depressive symptoms were observed for the first 5 weeks post-treatment (Cohen's $d$ = 2.2 at week 1 and 2.3 at week 5). At week 5, 45% met the criteria for response and 20% for remission. Results remained positive at 3 and 6 months (Cohen's $d$ = 1.5 and 1.4, respectively). |
| Carhart-Harris et al., 2021[46] + Erritzoe et al., 2024[47] | Moderate–severe MDD | N = 59 (30 PT, 29 escitalopram) | Double-blind RCT | Two sessions with 25 mg psilocybin + psychological support. The control group received escitalopram 10–20 mg + similar psychotherapy. | Non-significant difference between QIDS score reduction at week 6 between PT vs escitalopram (average − 8.0 for PT vs −6.0 for escitalopram, $p$ = 0.17). PT seemed to allow a greater proportion of patients to achieve response (70% for PT vs 48% for escitalopram) and remission (57% for PT vs 28% for escitalopram), but analyses of secondary endpoints were not corrected for multiple comparisons. Erritzoe et al., 2024: 25 PT patients and 21 escitalopram patients participated in a 6-month follow-up. Both treatments led to sustained antidepressant response (QIDS score reduction) compared to baseline with a large effect size, but there was no between groups difference. PT led to greater improvement in some secondary outcomes (functioning, connectedness, and "meaning in life"). |
| Davis et al., 2021[48] + Gukasyan et al., 2022[49] | Moderate–severe MDD | N = 24 (13 immediate PT, 11 delayed PT) | Waitlist-controlled RCT | Two doses of psilocybin 20 mg → 30 mg + psychological support. Controlled by comparing immediate PT *vs* delayed PT after 8 weeks on the waitlist. | Significant HAMD decrease 1 week after PT vs controls on the waitlist (average − 14.9 vs +1.3, Cohen $d$ = 2.5) and 4 weeks after PT versus controls (average − 14.4 vs +1.0, Cohen $d$ = 2.6). Large decreases from baseline in HAMD scores were still observed after 6- and 12-month (Cohen $d$ = 2.6 and 2.4). At 12 months 75% met criteria for response, and 58% met criteria for remission. |
| Goodwin et al., 2022[a] [50] | Moderate–severe MDD, and treatment resistance (failure with 2–4 antidepressants) | N = 233 (79 PT 25 mg, 75 PT 10 mg, 79 control) | Double-blind, dose-finding, parallel-groups design | One dose of psilocybin 10 or 25 mg + psychological support. The control group received psilocybin 1 mg and similar psychotherapy. | At week 3, the mean MADRS change from baseline was −12.1 for 25 mg, −8.9 for 10 mg, and − 4.6 for 1 mg. At 3 weeks after 25 mg PT, the proportion of response (37%) and remission (29%) was significantly higher than with placebo ($p$ = 0.01). |
| von Rotz et al., 2023[51] | MDD with MADRS between 10 and 40 | N = 52 (26 PT, 26 placebo) | Randomised, double-blind, placebo-controlled, parallel-groups design | One dose of psilocybin 0.215 mg/kg + psychological counseling. The control group received an inert placebo + similar psychological intervention. | At week 2, patients who received psilocybin had a significant decrease in MADRS (mean − 13.0 points; Cohen $d$ = 0.97) and BDI (mean − 13.2 points, Cohen $d$ = 0.67) when compared to patients who received placebo. |
| Sloshower et al., 2023[52] | Moderate–severe MDD, and treatment resistance (failure with 1 antidepressant) | N = 19 (19 had placebo in 1st phase, then 15 had PT) | Placebo-controlled, within-subject, fixed-order study | One dose of psilocybin 0.3 mg/kg + ACT-inspired psychotherapy. Within-subject control comparing outcome from 1st session with inert placebo versus 2nd session with psilocybin. | A decrease in HAMD score was greater 2 weeks after psilocybin (mean − 7.5) than after placebo (mean − 5.1), but this was not statistically significant. All 15 participants who completed both dosing sessions achieved response by the end of week 6, with 33% responding after receiving placebo but prior to psilocybin, and 67% responding only after psilocybin. 20% attained remission after the placebo but prior to psilocybin, while 47% remitted only after receiving psilocybin. |
| Raison et al., 2023[a] [53] | Moderate–severe MDD | N = 104 (51 PT, 53 control) | Randomized controlled trial | One dose of psilocybin 25 mg + psychological support. The control group received niacin 100 mg + similar support. | After 6 weeks, MADRS was on average decreased by 19.1 points in the PT group, versus 6.8 points in the control group. After 6 weeks, 42% had responded after receiving PT versus only 11% in the control group. After 6 weeks, the remission proportion appeared greater with PT, but the difference was not statistically significant (25% for PT vs 9.1% for control). |
| Goodwin et al., 2023[a] [54] | Moderate–severe MDD, and treatment resistance (failure with 2–4 antidepressants) | N = 19 | Open-label | One dose of psilocybin 25 mg + psychological support | At week 3, the mean change from baseline in MADRS was −14.9. Response and remission were observed in 8 participants (42%). |

**Table 1.** *Continued*

| Study | Clinical presentation | N | Study design | Intervention & control | Main study findings |
|---|---|---|---|---|---|
| Rosenblat et al., 2024[55] | Depressive episode (87% MDD & 13% BDII) and treatment resistance (failure with ≥2 antidepressants) | N = 30 (16 immediate PT, 14 delayed PT) | Waitlist-controlled RCT | One session with 25 mg psilocybin + psychological support. Controlled by comparing immediate PT to delayed PT after 2 weeks on the waiting list. After the primary endpoint, patients could receive a 2nd or even a 3rd course of PT. | After 2 weeks, MADRS was reduced on average by 9.6 points after PT, versus by 3.0 points among patients on the waitlist (Hedge's $g = 1.07$). After the primary endpoint, repeated doses were associated with further reductions in MADRS. |
| Ellis et al., 2024[56] | Moderate–severe MDD, and treatment resistance (failure with ≥5 antidepressants or current episode duration >2 years) | N = 15 | Open-label | One dose of psilocybin 25 mg + psychological support | Total MADRS scores significantly decreased between baseline and week 3, with a mean change of −23.0 points (Cohen's $d = 2.2$). At week 3, 60% met response criteria, and 53% met remission criteria. At 12 weeks, 47% of participants maintained a response, and 40% maintained remission. |

[a]Industry-sponsored trials. PT, psilocybin therapy; MDD, major depressive disorder; TRD, treatment-resistant depression; QIDS, Quick Inventory of Depressive Symptomatology; RCT, randomized controlled trial; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; BDI, Beck Depression Inventory.

We reviewed clinical practice guidelines for the treatment of depression published across the United States, Canada, Europe, and Asia-Pacific. None has yet recommended PT for the treatment of MDD or TRD. Because of limited data regarding its efficacy, methodological limitations in published studies (that will be discussed further), and challenges surrounding its implementation, PT remains an investigational treatment.[40,58]

### Treatment of psychological distress in patients with life-threatening illness

The mainstream rebirth of psychedelics research was initially sparked by seminal works on PT to relieve anxiety and depressive symptoms in patients with advanced cancer. We were able to find 4 studies (some having led to multiple publications) comprising a total of 104 patients with psychological distress related to cancer. The main characteristics of these small studies are presented in Table 2.

These studies demonstrated that PT can remarkably improve depressive symptoms, anxiety, sense of life meaning, and fear of death in some patients. Large effect sizes were generally reported for these outcomes. Remarkably, one study explored long-term follow-up until an average of 4.5 years after treatment and showed sustained response in approximately three-quarters of patients.[62] Because of limited clinical data and implementation challenges, no clinical practice guideline has yet recommended PT to alleviate psychological distress among oncology patients.

### Alcohol use disorder

Two recent studies ($n = 105$) could be found for PT against alcohol use disorder. The characteristics of these small studies are detailed in Table 3. These promising results suggest a meaningful reduction in alcohol consumption after PT, but these interventions have currently not made their way into clinical practice because of very limited data on their efficacy and innocuity.

### Other conditions

Results from exploratory studies suggest that PT might be versatile in treating a wide array of disorders. A small but rapidly expanding literature supports the promising potential of psilocybin for tobacco addiction (2 studies, $n = 30$),[67,68] obsessive-compulsive disorder (1 study, $n = 9$),[69] anorexia nervosa (1 study, $n = 10$),[70] headaches (2 studies, $n = 24$)[71,72] and body dysmorphic disorder (1 study, $n = 12$).[73] Much research is still needed before affirming the efficacy of PT in these clinical contexts. Many registered clinical trials are currently evaluating PT's therapeutic potential in other conditions: substance use disorders (opioid, stimulant, or cannabis), post-traumatic stress disorder, chronic Lyme disease, functional neurological disorder, post-concussive symptoms, and chronic pain.

### Limitations in clinical studies on psilocybin therapy

Designing and conducting clinical trials on PT is remarkably challenging, and limitations can be identified in the current literature.

Functional unblinding has rightly been identified as a serious limitation while interpreting results from recent PT trials. Because psilocybin produces powerful and easily recognizable alterations of perceptions, mood, and thoughts, most participants in RCTs can


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**Table 2.** Characteristics of Clinical Studies Evaluating PT for Anxiety and Depressive Symptoms in Cancer Patients

| Study | Clinical presentation | N | Study design | Intervention & control | Main study findings |
|---|---|---|---|---|---|
| Grob et al., 2011[59] | Advanced-stage cancer + adjustment disorder or anxiety disorder | N = 12 | Randomized, double-blind, placebo-controlled, cross-over trial | One session with psilocybin 0.2 mg/kg + psychological support. Within-subject control by offering all participants one session with placebo (niacin 250 mg) + similar psychological support. | BDI scores decreased on average by 7 points in the first 2 weeks after PT, while there was no change after sessions with a placebo. BDI scores were decreased on average by 8 points 1 month after PT, by 5 points after 3 months (N = 12), and by 10 points after 6 months (N = 8). There was also a small and sustained decrease in "trait anxiety" on the STAI. |
| Griffiths et al., 2016[60] | Life-threatening cancer + symptoms of depression and/or anxiety | N = 51 | Randomized, double-blind, placebo-controlled, cross-over trial | One session with psilocybin 22 or 30 mg/70 kg + psychological support. Within-subject control by offering one session with very low dose psilocybin (1–3 mg) + similar psychological support. | At 5 weeks, HAMD was decreased on average by 12.3 points after PT versus by 3.8 points after placebo. At 6 months, HAMD was on average decreased by 16.0 points. Comparable improvements were observed with BDI, HADS, and HAM-A. Many patients also reported significant and persistent improvements in quality of life, death acceptance, life meaning, and optimism. "Mystical experience" during PT mediated the effect on therapeutic outcomes. |
| Ross et al., 2016[61] + Agin-Liebes et al., 2020[62] + Ross et al., 2021[63] | Cancer + related anxiety or depression | N = 29 | Randomized, double-blind, placebo-controlled, cross-over trial | One session with psilocybin 0.3 mg/kg + psychological support. Within-subject control by offering all participants one session with placebo (niacin 250 mg) + similar psychological support. | Ross et al., 2016: Compared to the control group, there was a rapid and significantly greater improvement after PT for all primary outcomes (HADS depression & anxiety, BDI, and STAI) at 7 weeks. The Cohen's *d* effect sizes were large across all primary outcome measures at 1 day, 2 weeks, 6 weeks, and 7 weeks after PT, and these improvements remained significant at 6.5 months. There was a rapid and sustained decrease in cancer-related demoralization and hopelessness, while spiritual well-being and quality of life were improved. Agin Liebes et al., 2020: At long-term follow-up, MMRM analyses indicated sustained reductions for HADS, BDI, and STAI around 3.2 years after PT (N = 15) and around 4.5 years after PT (N = 14). Cohen's *d*-effect size ranged from 0.9 to 2.0 for all anxiety and depression outcomes at long-term follow-up. Ross et al., 2021: In a subset of patients with suicidal ideation (N = 11), PT led to a rapid within-group reduction in suicidal ideation that persisted for 6.5 months after PT. |
| Lewis et al., 2023[64] | Cancer (any) + depressive symptoms (PHQ–9 ≥ 10) | N = 12 | Open-label | 3 group preparatory sessions, one high-dose (25 mg) group psilocybin session, and 3 group integration sessions | 2 weeks after PT, there was a substantial decrease in HAMD scores (average decrease −15.8 points, Cohen's *d* = 1.7). This improvement in HAMD persisted after 6 months (average decrease −18.1 points, Cohen's d = 1.3). "Mystical experience" during PT was associated with HAMD improvement. |

PT, psilocybin therapy; BDI, Beck Depression Inventory; STAI, State–Trait Anxiety Inventory; HAMD, Hamilton Depression Rating Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Scale; MMRM, Mixed models for repeated measures; PHQ-9, Patient Health Questionnaire-9.

**Table 3.** Characteristics of Clinical Studies Evaluating PT for Alcohol Use Disorder

| Study | Clinical presentation | N | Study design | Intervention and control | Main study findings |
|---|---|---|---|---|---|
| Bogenschutz et al., 2015[65] | Active alcohol dependence (DSM-IV) | N = 10 | Open-label | 2 psilocybin sessions (0.3–0.4 mg/kg) + psychotherapy (7 sessions of motivational interviewing, 3 preparation sessions, 2 integration sessions) | 5–12 weeks after baseline, there was a significant decrease in the percentage of drinking days (mean difference − 27.2%) and heavy drinking days (mean difference − 26.0%). Effect sizes are large, with Cohen's *d* ranging from 0.75 to 1.38. Meaningful improvements were observed in secondary outcomes (perception of drinking consequences, craving, self-efficacy, and motivation). |
| Bogenschutz et al., 2022[66] | Alcohol dependence (DSM-IV) and at least 4 heavy drinking days in the last month | N = 95 (49 PT, 46 controls) | Double-blind RCT | 2 sessions with psilocybin (25–40 mg/70 kg) + psychotherapy on motivational interviewing & CBT framework. The control group received diphenhydramine 50–100 mg + similar psychotherapy. | During weeks 5 to 36, participants who received psilocybin had a lower percentage of heavy drinking days (mean 9.7%) than controls (mean 23.6%) The mean difference was therefore −13.9, and the effect size was medium-large (Hedges' g = 0.52). Participants who received psilocybin were more likely to be abstinent, and to have a 2-level reduction in WHO risk level during weeks 5 to 36. NNT for these outcomes ranged from 4 to 8. |

PT, psilocybin therapy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; RCT, randomized controlled trial; CBT, Cognitive behavioral therapy; WHO, World Health Organization; NNT, Number needed to treat.

easily deduce if they have received psilocybin or placebo. Similarly, most therapists in RCTs can also recognize the allocation of each participant, which might consciously or unconsciously affect the psychotherapeutic intervention they offer. Unfortunately, studies with inadequate blinding of participants or clinicians are likely to overestimate the efficacy of treatments.[74,75] Limitations stemming from the unblinding of study participants are further amplified by the highly positive expectations of many patients enrolling in psilocybin clinical studies. Indeed, abundant media coverage has led to premature expectations about the efficacy of psychedelic interventions, and many enroll in trials with high hopes. If participants with hopeful expectations receive psilocybin and recognize its effects, psychosomatic factors will likely heighten their treatment response.[76] On the contrary, participants with high expectations are randomized to receive a placebo, their disappointment may lead to clinical worsening or a nocebo effect.[77]

In short, high treatment expectancies and functional unblinding of participants likely synergize to inflate the results from PT studies.[76,78] Some possible solutions have been proposed to mitigate these concerns,[79] although each has its limitations. It has been suggested to systematically monitor participants' expectations before therapy and to use questionnaires measuring the extent of patients' and therapists' unblinding. Using consciousness-altering placebos has also been suggested to confound the study participants, although the effectiveness of this measure is still being explored. Some have even proposed to administer psilocybin to patients under general anesthesia,[80] which would potentially solve the problem of blinding and expectancy bias. If this unusual measure was applied, it would cancel the effects of the subjective psychedelic experience, psychotherapy intervention, set, and setting. The results of such an experiment could also be confounded by the neuro-pharmacological effects of the anesthetics.

The necessity of psychotherapy in conjunction with psilocybin is still debated, and research trying to optimize these therapeutic interventions is still in its infancy. In studies involving psilocybin, psychotherapy interventions are heterogeneous and often poorly described. Although some research groups have published their psychotherapy protocols with reasonable detail,[61,81–83] the largest industry-sponsored trials have failed to disclose the exact nature of their psychotherapeutic interventions.[50,53] Extensive studies are needed to assess the role of psychotherapy in PT, and specific protocols may be required for different conditions such as mood disorders, anxiety disorders, and substance abuse. Trials with a factorial design could help differentiate the drug efficacy from the effect of psychotherapy.[79] Head-to-head comparisons of different psychotherapy models and component studies are also needed to define the essential elements of these interventions. Before such trials are conducted, we can only speculate on important questions. To what extent (if any) does psychotherapy contribute to the efficacy of PT? What are the most effective and most efficient ways of conducting psychotherapy in synergy with psilocybin?

Concerns have been raised regarding the generalizability of the results so far published. Recent PT trials were generally conducted on small samples of demographically homogenous participants. White and educated individuals from high-income countries have formed most of these samples.[84–86] It is therefore unknown if these results could be replicated for patients with more diverse demographic characteristics or those in developing countries. Also, patients with substance use disorders, personality disorders, psychotic illness, or a history of suicide attempts were largely excluded from studies, even though patients with MDD or TRD often suffer from these comorbidities in real-world settings.[84] Also, PT studies generally have a long list of medical exclusion criteria (*e.g.* uncontrolled cardio-vascular condition, seizure disorder, BMI > 35 or < 17, *etc.*). All these exclusion criteria might reduce the generalizability of available results. Since psychiatric or medical comorbidities are associated with treatment resistance, the efficacy of PT in naturalistic settings could be less favorable.

## How is psilocybin therapy conducted?

Although significant variations exist in the way PT is conducted among clinicians and researchers, some general principles seem common in most settings.[25] As illustrated in Figure 1, PT protocols typically involve a sequence of preparation sessions, single or multiple medication administration session(s), and integration sessions. Rather than being a comprehensive guide for the delivery of PT, the following section offers a brief overview of typical interventions at its core. The summarized material presented here was extracted


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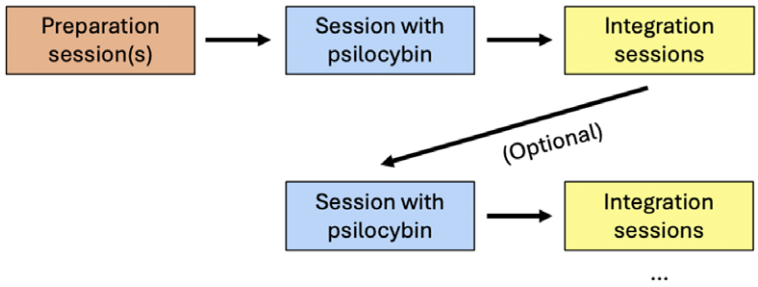


**Figure 1.** Structure of a typical PT protocol.

**Figure 2.** Design of the therapy room used for psychedelic studies at the Exploratory Therapeutics Laboratory, Stanford University.

from published treatment manuals[61,81–83] and reviews on the subject.[25,87–90]

### General considerations

It has long been recognized that psychedelics can produce iatrogenic and unpleasant effects if they are administered in a stressful environment or without proper support.[91,92] Therefore, much consideration is given to the *set* and the *setting* in which PT is offered.[93] The *set* refers to the states of mind carried by the patient and the therapists, which notably includes their respective expectations, motivations, and beliefs about PT. The *setting* refers to the actual physical and interpersonal environment in which treatment is delivered. It includes for example the design and atmosphere of the room, the music, and the behavior of the therapists. Components of set and setting are important to promote the safety and efficacy of psychedelic therapy.[94,95]

Therapists should have received specialized training in PT, and they should be in good standing with their regulatory or licensing agency. They should meet the highest standards of ethical integrity and professionalism. Furthermore, therapists must be capable of building and maintaining a sound therapeutic alliance. They should be welcoming, and they should treat patients with compassion, dignity, and respect. Therapists must be mindful of the increased suggestibility elicited by psychedelic substances, and they should be watchful of their countertransference.

In almost all studies published to date, PT was conducted by a dyad of therapists. They are usually encouraged to work in teams to


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ensure that the patient is always accompanied by at least one person, even if someone must briefly leave the room during the long medication administration session. Dyads could also provide greater safety for participants, diminish the risk of boundary violation, help manage transference and countertransference, and offer learning opportunities from the co-therapist.[79,82] Other models are being explored, including a hub-and-spoke system where one therapist is with the patient, while another supervises multiple simultaneous dosing sessions.

### Preparation sessions

A few hours of preparation are first offered, often spanning over two to three weeks. As discussed below, informed consent should be obtained, although patients have the right to withdraw consent at any step. The preparatory period allows for medical clearance, and screening for possible contraindications to PT. At this time, it is standard to taper medications that could interact with psilocybin or that might interfere with the effectiveness of PT (*e.g.* antipsychotics, antidepressants, benzodiazepines, etc.).

During the preparation sessions, therapists get a better understanding of the patient's history and current situation, which helps build trust and alliance. A collaborative process is initiated to define meaningful and realistic treatment goals. Therapists should encourage patients to adopt an engaged and proactive stance since PT is neither miraculous nor effortless.

Preparation also requires thorough explanations about the possible effects of psilocybin, and prior experiences with altered states of consciousness can be explored. Patients should be warned about possible reactions of anxiety, panic, or paranoia, and stress inoculation techniques can be practiced. Breathwork, body scan, and other grounding techniques are commonly taught or reviewed at this stage. Patients are encouraged to welcome rather than resist challenging emotions, imagery, or thoughts. Importantly, there should be a discussion about the potential application of supportive touch (*e.g.* holding hands or laying a hand on the shoulder) if challenging experiences arise during therapy. If the patient consents to receive supportive touch, clear boundaries must be set and recognized, as to avoid any inappropriate, sexual, or intimate physical contact.

Patients should also be informed about the logistics and structure of the psilocybin session. It is common practice to discuss music and to visit the room where the psychedelic experience will be lived. Patients can be advised to bring comfortable clothes and meaningful items. At the end of the experiential session, patients will be escorted by a companion that should be designated beforehand. If needed, the companion can be met by the therapy team before the dosing day. Finally, the patients' questions must be addressed during the preparatory period.

### Experiential session with psilocybin

On the day of the psilocybin administration session, the patient is welcomed in a comfortable and confidential setting. The room should ideally be calm and demedicalized (see example from Figure 2). The setting typically contains a bed or futon to recline, music, flowers, artwork, snacks, and soft drinks. Some participants may choose to bring significant or symbolic objects. The environment should be safe, and potentially dangerous objects (*e.g.* sharp edges, high balconies or unsafe windows, glass objects, *etc.*) should be avoided. Distracting items such as telephones should be removed. Throughout the session, the therapists will demonstrate their benevolent presence and ensure safety.

A dose of around 25 mg of psilocybin is typically offered, after which the patient is invited to relax. The substance typically starts producing its psychedelic effects 20 to 30 minutes after being ingested, at which point the patient is invited to bring his attention to the unfolding present-moment experience. The experiential session should mainly be an unrushed and inner-directed process. Wearing a blindfold can help focus on internal phenomena such as thoughts and affects, while the music can intensify the experience by offering a sense of guidance and evocating emotions or mental imagery.[96]

All internal states, whether pleasant or challenging, should be welcomed and observed with openness and curiosity. Rather than avoiding difficult internal phenomena, patients are encouraged to adopt a non-resisting stance. If the patient expresses the feeling of being stuck, the therapists can foster curiosity about perceived resistance, allow and encourage the patient to express himself or herself, or offer reassurance and encourage the deeper exploration of threatening mental states. If the patient shows signs of intense suffering or dissociation, therapists must stay present and should find a balance between alleviating versus tolerating and validating the patient's suffering. If the patient has consented to it, a supportive touch can also be offered. Many challenging experiences can be appeased by changing position, distracting, changing the music, doing breathwork, or applying other grounding techniques. In extreme situations, rescue medication such as benzodiazepine or antipsychotic can be proposed.

At the height of the psychedelic experience, the patient should not be urged to understand or interpret everything happening on the spot. The integration sessions are typically the preferred moment to analyze the experience. Therapists can discretely take notes to record meaningful observations, which may later be shared with the patient.

At the end of the session, the effects of psilocybin gradually subside, and patients often express the urge to talk about their psychedelic experience. Curiosity about the experience should be fostered, and it can be reiterated that "understanding" everything is not the current objective. If manifested, early insights or feelings of emotional breakthroughs should be acknowledged. Some patients may require support intervention if they experience distress linked to their psychedelic journey or the return of everyday life concerns.

If the patient has returned to his baseline psychological and physiological state, he can be safely discharged in the presence of a companion. Without attempting to perform therapy, the companion should find the right balance between respecting the patient's privacy and offering support. Some therapists encourage their patients to write about their experiences. Rest is typically encouraged on the night after the experiential session.

### Integration sessions

The integration process is prompted by a reunion with therapists on the day after each session with psilocybin. Other integration sessions are often offered over the following weeks. During these encounters, therapists can foster curiosity for internal phenomena, listen to the patient's narrative, and raise questions about its interpretation. Self-reflective practices such as journaling, dream analysis, and active imagination[97] can be suggested to revitalize insight and meta-cognition. Increased cognitive flexibility[98] and new insights may translate into a modified perception of oneself and the environment.[33,99] These new ways of thinking and


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perceiving can help surpass prior obstacles or facilitate grieving and acceptance of difficult situations. Cultivating mindfulness and attending to the present moment is encouraged during the integration process. Therefore, formal and informal meditative practices can be suggested. Some patients may also benefit from expressing themselves through arts such as writing, dancing, or painting.[88,90]

It is important to note that the integration process should not be restricted to a fruitless intellectual process. Rather, concrete and tangible change in behavior is hoped for. Changes outside the therapy setting such as behavioral activation, increased socialization, or use of more efficient coping strategies should be applauded. Patients should cultivate a sense of agency, and PT should not be seen as effortless. Statements like "*psilocybin may have opened a door, but you have to walk through it*" may encourage the patient's efforts and commitment.

Integration can continue long after the last meeting with therapists. Some have also pointed out that this process could be nonlinear, meaning that patients may sometimes experience a short period of stagnation or regression before reaching an improved state. Patience is therefore required to determine if a patient might have benefited from PT. Finally, it must be remembered that we are currently unable to describe the most effective way of conducting the integration process since many different theoretical frameworks have inspired a wide range of interventions. Heterogenous practices stemming from psychodynamics, existential therapy, or ACT have, for example, been tried.[61,81,83,100]

## Pharmacology and neurobiology

### *From hallucinogenic mushrooms to purified psilocybin*

Many species of mushrooms naturally synthesize tryptamine alkaloids that can produce psychedelic effects. These psychotropic mushrooms are distributed worldwide and belong to many genera, notably *Psilocybe*, *Panaeolus*, *Pluteus*, *Gymnopilus*, *Pholiotina*, *Galerina*, and *Inocybe*.[101] Although the exact adaptive function of these psychoactive compounds remains elusive, it has been hypothesized that their presence may offer an evolutionary advantage to these mushrooms by altering the behavior of mycophagous species.[102] Two opposing theories have been proposed: some believe that tryptamine alkaloids benefit the mushrooms by reducing mycophagy,[103] while others have suggested these molecules could increase mycophagy and insect-vectored spore dispersal.[104]

The mechanisms by which these mushrooms produce their psychedelic effects are complex. Psilocybin and psilocin are likely responsible for most of their psychedelic properties in humans, but these fungi also contain smaller amounts of chemically related compounds such as norbaeocystin, baeocystin, and aeruginascin.[101] These molecules have a chemical structure analogous to psilocin or psilocybin, and their effects on humans have not been fully characterized. Interestingly, a recent study identified that *Psilocybe* mushrooms can synthesize β-carbolines, which could potentially inhibit the degradation of psilocin by monoamine oxidase (MAO).[105] The significance of this pharmacokinetic interaction remains uncertain, considering the small concentrations of β-carbolines. Moreover, some psychedelic mushrooms contain phenylethylamine, which has amphetamine-like properties that could produce psychostimulant effects and a more pronounced cardiovascular activation.[106,107]

The concentrations of tryptamine alkaloids in hallucinogenic mushrooms can vary tremendously between species and between individual mushrooms, which has an impact on their psychotropic potency. Some species such as *P. cyanescens*, *P. cubensis*, and *P. mexicana* tend to contain relatively high amounts of psilocin and psilocybin, which means they are regarded as medium or high-potency species. Specific strains of these species are widely sold under names such as "Golden teacher" (a cultivar of *P. cubensis*) or "Blue meanie" (a cultivar of *P. cyanescens*). On the contrary, species from other genera such as *Inocybe* or *Panaeolus* are seldom used recreationally, because they tend to contain low amounts of psychoactive compounds.[101]

The fruiting bodies of the mushrooms are composed of a cap and a stipe. The concentration of tryptamines in caps is generally about two-fold higher, although the variability between each mushroom is considerable.[108] For example, a high-performance liquid chromatography-mass spectrometry analysis revealed that psilocybin concentration can vary from 2.3 to 13.8 mg/g in dry mass between samples of *P. cyanescens*.[101] The development stage, climatic conditions, and substrate composition can also contribute to this inconsistency. Furthermore, these concentrations can also be influenced by the processing and storage of the mushrooms after their harvest. Degradation of psilocybin happens quickly in lyophilized or frozen fresh fungi, while it can remain unaltered after many years in samples of dried whole mushrooms.[101,108]

Because fungi contain unpredictable concentrations of psychoactive tryptamines, clinical studies conducted in recent years have used pure psilocybin, either synthesized or extracted from natural sources.[109,110] These products have the advantage of containing a known and stable dose of psychoactive tryptamines, and no other compounds that may cause pharmacokinetic or pharmacodynamic interactions. If psilocybin is approved for clinical use in the future, good manufacturing practices will ensure the quality and reliability of the prescribed product.

### *Pharmacokinetics*

Psilocybin is an alkaloid zwitterion containing a positively charged amine group and a negatively charged phosphate[111], which makes it more soluble in water but reduces its ability to penetrate cell membranes and the blood–brain barrier[111]. Psilocybin is rapidly dephosphorylated into psilocin by alkaline phosphatases and non-specific esterases[112]. Due to its increased lipophilicity, psilocin is readily absorbed from the upper gut[113] and then undergoes first-pass metabolism. After ingestion, its average absolute bioavailability is around 53%.[114] It first appears in the plasma within 20–30 minutes,[115,116] and the time to peak drug concentration is approximately 120 minutes.[117] In PK studies and clinical trials, patients typically fast between 2–4 hours to allow for more predictable kinetics,[114] since food in the stomach may delay absorption, reduce peak concentration, and reduce its bioavailability.

Psilocybin demonstrates linear pharmacokinetics in standard dose ranges,[115,118] which means that doubling its dose would lead to a two-fold increase in the plasma concentration of psilocin. Because of its high lipophilicity and extensive distribution into body tissues, it can be calculated that psilocin has a large volume of distribution.[118] Contemporary findings indicate that body weight does not significantly influence the subjective effects of psilocybin, nor does it influence plasma concentrations of psilocin.[118–120] Therefore, fixed-dose regimens were given in recent clinical studies, in contrast to the weight-based dosing protocols of earlier studies.

The metabolism of psilocin is summarized in Figure 3. Briefly, nearly 80% of psilocin is metabolized into psilocin-O-glucuronide by UGT enzymes, while the residual fraction is degraded into 4-HTP


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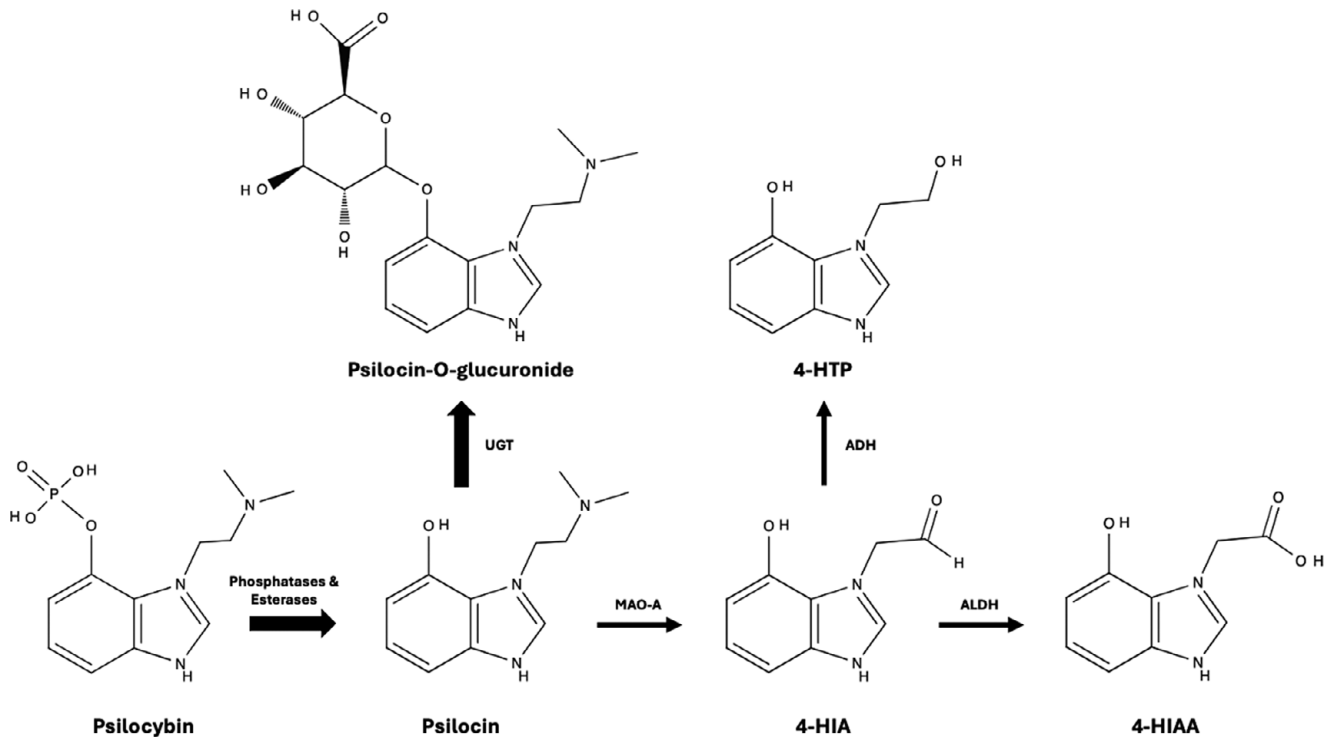


**Figure 3.** Metabolism of psilocybin and psilocin in humans.

and 4-HIAA through a minor pathway involving MAO-A.[121–123] The cytochrome P450 system has a minor role in psilocin's metabolism, and individuals with variations of CYP activity do not differ in their response to psilocin.[112] Psilocin has a dose-independent half-life of about 2–4 hours.[114–116,124,125] There is currently no evidence suggesting that psilocin's metabolites have any significant psychoactive effects.[112] About 80–85% of metabolites are excreted in the urine (mostly psilocin-O-glucuronide), while the remainder 15–20% is excreted through the biliary system.[121,126] Renal function has a minimal impact on the drug's elimination process. Therefore, dose adjustments may be unnecessary for patients with renal impairment, although limited data is available in this population.[118,127] Psilocybin has no significant effect on liver function or creatinine clearance in healthy individuals.[128]

## *Receptology and downstream signaling*

Serotonin and psilocin are tryptamine analogues and share an indole ring structure, which is crucial for binding to 5-$HT_{2A}$ receptors. Like other classic psychedelics such as LSD and mescaline, psilocin is an agonist of the 5-$HT_{2A}$ receptor. Good evidence supports the crucial role of 5-$HT_{2A}$ receptor activation in mediating its psychotropic effects: 5-$HT_{2A}$ receptor occupancy correlates with the subjective effects of classic psychedelics,[129,130] and pre-treatment with 5-$HT_{2A}$ receptor antagonist ketanserin blocks most of psilocybin's effects.[29,131,132] Upon their activation by psilocin, 5-$HT_{2A}$ receptors initiate complex cascades of downstream signaling. The activation of both canonical $G_{q/11}$ and β-arrestin-2 seems necessary to produce psychedelic effects,[133] and so is the coactivation of $G_{i/o}$ and Src tyrosine kinase.[134] These specific pathways are thought to differentiate 5-$HT_{2A}$ receptor agonists with psychedelic properties from other agonists of the same receptor such as ergoline and lisuride that do not have hallucinogenic effects. Many mysteries are yet to be unraveled, as exemplified by the recent discovery that psilocin could activate intracellular 5-$HT_{2A}$ receptors, which results in sustained neuronal growth and structural neuroplasticity.

Although strong evidence supports that 5-$HT_{2A}$ activity mediates most of psilocin's psychedelic properties, this substituted tryptamine also binds to many other receptors[135–137]. In fact, psilocin's binding affinity is even higher for some other serotonin receptors such as 5-$HT_{2C}$, 5-$HT_{1A}$, and 5-$HT_{2B}$[137]. It is currently difficult to determine the clinical significance of psilocin's interaction with these receptors. Although they do not seem to contribute to the hallucinogenic properties of psilocin, these other serotonin receptors could potentially play a role in mediating its therapeutic effect.[136,138–140]

Psilocin has a very low affinity for the serotonin transporter (SERT), and it does not interact directly with the norepinephrine transporter (NET) or the dopamine transporter (DAT).[137] Although it has the potential to bind with $D_1$ and $D_3$ receptors, it has no direct activity on the widespread $D_2$ receptors.[137] It does not interact with adrenergic, opioid, muscarinic, histamine, or cannabinoid receptors.[137] Even if psilocin does not directly interact with these receptors, dopamine, noradrenaline, and opioid neurons might be secondarily activated because of the initial disruption in serotonin signaling. The nature and significance of these potential interactions have yet to be understood.[135]

Interesting data has recently shown that psilocin directly interacts with brain-derived neurotrophic factor (BDNF) signaling,[141] which is crucially involved in neuronal plasticity, cognition, and mood regulation.[142–144] The BDNF/TrkB pathway involves the binding of BDNF to tropomyosin receptor kinase B (TrkB) on the surface of neurons. Psilocin acts as an allosteric modulator within the transmembrane domain and stabilizes TrkB dimers, thus enhancing the action of BDNF.[141,145] These results suggest that binding to TrkB could mediate the neuroplastic and antidepressant-like effects of psilocybin in rodents.[141]


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### Neuroendocrine effects

Oxytocin is a neuropeptide that plays an important role in prosociality.[146] Most serotoninergic psychedelics induce a 5-$HT_{2A}$-mediated increase in circulating oxytocin,[147–149] although psilocybin may not exhibit the same effect.[148] More importantly, psilocybin and other psychedelics uniquely have the potential to induce metaplastic restoration of oxytocin-mediated long-term depression in the nucleus accumbens and to reopen the critical period for social reward learning in mice.[150] These neuroendocrine mechanisms could lead to renewed social reward learning, which might explain some of the context-dependent therapeutic effects of psilocybin.

Psilocybin can cause negligible increases in prolactin, TSH, ACTH, and cortisol. These increases are dose-related, and levels return to normal within 5 hours.[128]

### Effects on cerebral metabolism and brain connectivity

Psilocybin can heighten cerebral glucose metabolism, with the most significant increases being measured in regions with high density of 5-$HT_{2A}$ receptors such as the frontal cortex, and anterior cingulate. Concurrently, relative cerebral blood flow is also increased in the frontal and temporal regions but decreased in the parietal region.[151]

Psilocybin has been shown to decrease the functional connectivity within the default mode network (DMN), a cerebral system engaged during resting states. During acute intoxication, psilocin plasma levels negatively correlate with DMN integrity.[152] One possible therapeutic mechanism is that psilocybin modulates DMN activity, which is often increased in MDD.[153] Although psilocybin leads to decreased within-DMN connectivity, it is also associated with increased connectivity between the DMN and higher-order cognitive networks such as the executive and salience networks.[154] Interestingly, in a small imaging study, psilocybin led to a persistent decrease in connectivity between the DMN and anterior hippocampus (lasting at least 3 weeks), even as whole-brain connectivity returned to baseline.[155]

### Potential drug interactions

The published literature on drug–drug interactions involving psilocybin is currently limited.[156,157] Therefore, much of the knowledge about potential interactions must be extrapolated from our understanding of psilocybin's pharmacology, case reports, and surveys of users in unregulated contexts. Data can also be found on drug–drug interactions involving other classic psychedelics that share similar pharmacodynamics (*e.g.* LSD, DMT, and mescaline). Clinicians can rely on shared decision-making with their patients to decide if and when a concomitant medication should be tapered before PT. To ensure safety and maximize the chances of therapeutic response, case-by-case decision-making should take into consideration the patient's preferences, our current knowledge of drug interactions, potential problems associated with drug tapering, and comorbid medical conditions.

Clinicians and researchers must also consider that even though some drug interactions can reduce the intensity of psilocybin's psychedelic effects, it is currently unknown if these interactions would hinder the efficacy of PT. While some data suggests that the intensity of the psychedelic experience predicts treatment response,[60,61,158,159] other studies have not replicated this finding.[49,56] Some data suggest that PT might be effective even if patients do not experience subjective psychotropic effects.[160] Exciting research is currently underway to understand PT's therapeutic mechanisms and to explore the possible consequences of drug–drug interactions during PT.[80,161–163]

#### Antipsychotics

5-$HT_{2A}$ antagonism is a major mechanism of action of second-generation antipsychotics (*e.g.* olanzapine, risperidone, aripiprazole, etc.), and some first-generation antipsychotics such as chlorpromazine also have significant antagonist effect on this receptor. When taken concomitantly with psilocybin, 5-$HT_{2A}$ antagonists will greatly reduce the intensity of the psychedelic experience.[29,156,157] Therefore, therapeutic response might be blunted if PT is performed with concomitant use of 5-$HT_{2A}$ antagonists.

#### Antidepressants

The subacute or chronic use of selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) leads to a down-regulation of serotonin receptors. This might explain why approximately half the people taking hallucinogenic mushrooms concomitantly with SSRI or SNRI report attenuated psychedelic effects.[164] Interestingly, results from an online survey suggest that prior exposure to SSRI or SNRI was associated with attenuated psychedelic experience up to three months after being stopped, which is far longer than the usual discontinuation period before dosing.[164]

In a small ($n$ = 19) open-label study on patients who did not taper their SSRI before PT,[54] patients experienced significant psychedelic effects, and no serious adverse event was observed (although two participants presented hypertension and had to receive clonidine). Three weeks after PT, depression had remitted in 42% of patients, which is similar to the effect size observed in other PT studies.[50] In another exploratory study in healthy controls, a short pretreatment with 20 mg escitalopram did not appear to attenuate the psychedelic effects of psilocybin, but it significantly reduced the occurrence of challenging experiences[165] and blunted the increase in blood pressure. These results further support that acute or chronic exposure to SERT inhibitors may have different effects when combined with psilocybin, and highlight the need for further studies.

Little is known about the interaction of psilocybin with bupropion or mirtazapine. Online surveys suggest that the acute subjective psilocybin experience is attenuated in approximately half of the cases combining it with mirtazapine, and in approximately a fifth of the cases combining it with bupropion. In the same survey, low rates of negative experiences are reported when combining these molecules with psilocybin.[164, 166] Trazodone is a 5-$HT_{2A}$ antagonist, and case reports have shown it can reduce the intensity of the experience with psilocybin, although this might not hinder therapeutic response in PT.[160,167]

Chronic use of MAO inhibitors causes a downregulation of serotonin receptors, which can suppress the effect of psychedelics.[106] On the contrary, short pretreatment with MAO inhibitors can reduce the metabolism of psilocin, thus potentiating its perceptual effects and marginally increasing blood pressure and mydriasis.[106,168] Some users have tried combining hallucinogenic mushrooms with herbal concoctions containing natural MAO inhibitors (e.g. *Banisteriopsis caapi*, *Peganum harmala*, etc.), which can potentiate the psychoactive effects of psilocybin.[106] These results suggest that psilocybin could safely be combined with MAO inhibitors, although such a mix could have unknown consequences on the efficacy of PT.


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We could find no information about the consequences of combining psilocybin with tricyclic antidepressants (TCA). Interestingly, combining LSD with TCA could lead to a heightened LSD experience with a faster onset.[169]

Because psilocybin competitively modulates the activity of 5-HT receptors without increasing levels of synaptic monoamines, the theoretical risk of triggering a serotonin syndrome is low. Empirical data from small clinical trials[54,165] and users in unregulated settings[164,170] seems to confirm the very low risk of worrisome serotonin toxicity.

### Psychostimulants and MDMA

Methylphenidate acts as an allosteric blocker of the dopamine transporter (DAT), while amphetamines are competitive substrates that interfere with DAT. Their common mechanism of action therefore involves an increase in synaptic dopamine. Since psilocybin has no clear affinity for DAT, NET, or $D_2$ receptors, no worrisome CNS interactions can be predicted with psychostimulants. Nevertheless, psilocybin can increase blood pressure and heart rate, and these cardiovascular effects could be inflated if psychostimulants are added. Caution should therefore be exerted for individuals with uncontrolled hypertension or other cardiovascular conditions.

One study exploring the effects of combining MDMA with psilocybin or LSD found that low-dose MDMA decreased the risk of challenging psychological experience, with no difference in subjective level of physical discomfort.[171] In the same study, scores for physical distress on the CEQ scale were slightly higher among people combining classical psychedelics with a medium-high dose of MDMA. In another study, combining MDMA with LSD had additive effects on blood pressure, heart rate, and pupil size, but it did not appear to alter the mind-altering consequences of LSD.[172]

### Anxiolytics

Buspirone has a high affinity for 5-$HT_{1A}$ and 5-$HT_{2A/C}$ receptors, thus it could potentially interact with psilocybin. Indeed, a small trial found that 20 mg buspirone attenuates psilocybin-induced visual perceptual changes.[173] Benzodiazepines are allosteric agonists of $GABA_A$ receptors. They have been safely used as rescue medications to alleviate panic reactions during PT.[82] No worrisome interaction can be predicted between anxiolytics and psilocybin, but these molecules could potentially interfere with the efficacy of PT.

### Mood stabilizers and anticonvulsants

Many first-person accounts suggest that combining lithium with classic psychedelics could induce seizures (47% of online accounts, $n = 62$).[174] Although the mechanism leading to these reactions remains putative, other authors identified that this risk was further increased in patients with a personal or family history of epilepsy.[175] Lamotrigine seems well tolerated and does not modulate the subjective effect of psychedelics, according to online first-person accounts.[174] No information could be found on the consequences of combining psilocybin with valproic acid, gabapentin, or pregabalin.

## Risks and potential adverse events

Good evidence has been collected on the innocuity of psilocybin and hallucinogenic mushrooms through pre-clinical studies,[109,176] recent RCTs,[177,178] and epidemiologic data from large community samples.[179–182] The risks associated with psilocybin or hallucinogenic mushrooms can be modulated by the set and setting, so the hazards can be very different in unregulated environments rather than in controlled therapeutic settings.

### *Direct toxicity*

Multiple preclinical studies have shown that psilocybin and its metabolites are not neurotoxic,[107,183,184] and animal studies demonstrate that enormous doses can be delivered without causing physiological toxicity. Indeed, studies with rodents have estimated its $LD_{50}$ to be around 280 mg/kg, which would only be reached if a 60 kg person ingested an astronomical 17 kg of fresh psilocybin mushrooms.[176,185,186] When compared to other controlled substances, psilocybin has systematically been classified among the least harmful.[181,182] To our knowledge, no deaths have convincingly been recorded because of its physiological toxicity in healthy human subjects.[185,187–189]

### *Psychological distress during acute intoxication*

The psychological effects of psychedelics can be highly variable from one episode of use to the other (even among experienced users), and the *Challenging Experience questionnaire* has been validated to record potential aversive reactions.[37] According to a meta-analysis of PT studies, anxiety occurred in approximately 12% of participants (with a relative risk of 3.81 compared to placebo), while paranoia or suspiciousness was recorded in only 3% (RR = 3.04).[178] Under the influence of psychedelics, some may experience feelings of isolation, grief, panic, or depression, and some fear losing their mind or recalling the impression of dying.[37] Although it is difficult to define the incidence of these reactions, a study suggests that 5% of individuals who have participated in experimental studies rated their experience as "very frightening" and 10% considered it "very unpleasant".[33] During PT, the occurrence of adverse psychological reactions may be limited by careful patient selection, psychological support, and a safe set and setting.[61,81–83,92]

The use of hallucinogenic mushrooms in uncontrolled environments carries additional risks, particularly if high quantities are combined with other drugs, or if they are taken in an unfavorable set and setting. Distressing "*bad trips*," sometimes accompanied by agitation or reckless behavior can also occur, and fatalities have unfortunately been recorded because of polysubstance use or gross disorganization. Cases of accidental falls or defenestration have been recorded,[190] and psilocybin intoxication can seriously impair the driving or handling of machinery. When poison centers are called, most cases are managed with supportive measures at home[191] and urgent medical care is rarely required. According to a large anonymous online survey, only 0.2% of past year magic mushroom users sought emergency medical treatment,[192] while the Drug Abuse Warning Network indicates that psilocybin-related emergency visits have an incidence of only 1.9 per 100 000 in the United States.[193] Even when consumed in the community, hallucinogens carry a very low risk of causing harm to their users or others around them.[181,182]

Psychosis is a medical emergency that can rarely result from psilocybin exposure. Many factors make it difficult to estimate its incidence. Clinical expertise is required to differentiate psilocybin's expected psychedelic effects from substance-induced psychosis, which should only be diagnosed when hallucinations or delusions last longer than the intoxication, and if they are sufficiently severe to require clinical attention.[194,195] In these rare cases, reality testing is impaired, and patients typically fail to recognize that their


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symptoms are substance-induced.[195] Fortunately, no case of psilocybin-induced psychosis has occurred in contemporary PT studies, although patients presenting risk factors for psychosis (e.g. personal or family history of psychotic disorder) were systematically excluded from these trials.[177,196,197] The risk of psychotic reactions might be higher in uncontrolled environments where no medical screening is offered before psilocybin exposure. Online surveys and large patient registries[198] suggest that the incidence of hallucinogen-induced psychosis is very low, even in uncontrolled settings. Most cases of hallucinogen-induced psychosis leading to hospitalization result from polyintoxication with multiple substances.[199] In a survey of investigators who had administered LSD or mescaline to 1200 non-patient research participants, a single case of a lasting psychosis was identified, and this unfortunate patient had a monozygotic twin suffering from schizophrenia.[200] The risk of prolonged psychotic reaction was slightly higher among patients undergoing psychotherapy with psychedelics, although the incidence according to this study was only 1.8 per 1000 patients.[200] Although somewhat reassuring, these statistics from old scientific literature must be regarded with caution.[200,201] Even if small, the risk of psilocybin-induced psychosis should not be viewed as trivial.

### Physical adverse events

Somatic complaints are not uncommon after the intake of psilocybin or psychedelic mushrooms. According to a meta-analysis of clinical trials, headaches occur in approximately a quarter of participants (RR of 1.99 compared to placebo), while nausea is experienced by about a fifth (RR around 8.85). Dizziness occurs in approximately 5% of PT subjects.[50,178] The occurrence of other somatic complaints seems negligible and varies between studies. Mild transitory residual symptoms are commonly reported on the day after psilocybin intake: fatigue (experienced by 40 to 60% of subjects), difficulty concentrating (7.5 to 17.5%), lack of appetite (7.5 to 17.5%), headaches (12.5 to 37.5%) or tired legs (0 to 12.5%) are frequent dose-related side effects.[33]

The cardiovascular effects of psilocybin are usually mild and asymptomatic. In PT trials, peak systolic blood pressure is on average 10–15 mmHg higher with psilocybin than with placebo, while peak diastolic blood pressure is on average 5–10 mmHg higher.[60,61] Some patients may nevertheless experience more pronounced increases in blood pressure.[54,60] Compared to placebo exposure, peak heart rate is on average increased by only 5 bpm.[60,61] The elevation in blood pressure and heart rate usually peaks around 120 minutes, which parallels maximal psilocin plasma concentration and subjective effects. It is unclear if these cardiovascular manifestations result from psilocin's direct physiological effects, or if they are an indirect consequence of its psychological effects. Psilocybin does not significantly increase QTc at doses around 25 mg, but dose-dependent QTc elongation can be expected at supra-therapeutic doses.[202] Some data suggests that chronic exposure to 5-$HT_{2B}$ agonists may be a risk factor for valvular heart disease, but such problems are judged to be unlikely with single-dose psilocybin treatments.[79,203]

### Persistent effects on mood, personality, perception, and cognition

Some individuals who have used psychedelics go on to suffer from persistent negative psychological outcomes. This uncommon phenomenon has been well described among people having experimented with psychedelics in uncontrolled settings, but we could not find any case of long-term adverse events in recent PT studies.[177,204] In a study conducted in the UK, a sample of individuals having suffered from psychedelic "*bad trips*" and persistent distress completed an online survey and were interviewed.[204] Almost all responders explained having suffered from anxiety or panic attacks. Some recalled flashbacks of their acute psychedelic experience or intrusive obsessive thoughts. Feelings of isolation, derealization, sleep disturbance, distractibility, or depressive symptoms were also described. Suicidal thoughts or behaviors were even reported by some responders. As mentioned previously, risk factors for prolonged negative psychological experiences may be minimized in a therapeutic setting with adequate support through preparation, dosing, and integration. Avoiding polysubstance use and ingestion of unusually high doses also mitigates the risk of suffering from persistent negative psychological outcomes.

Some evidence suggests that psilocybin may have long-lasting effects on some personality traits, personal values, and attitudes.[205] Although most subjects describe these changes as positive,[33] patients should be informed of these possible effects before consenting to PT. In one study, "mystical experience" during PT predicted a durable increase in the openness personality trait of healthy volunteers ($n = 52$), while other domains from the Big Five personality model were unchanged.[99] Also, in an analysis of long-term follow-up questionnaires from healthy volunteers having received psilocybin, about a third reported long-lasting change in aesthetic appreciation, in their relationship with the environment and nature, in the appreciation of their own body, or relationships.[33] The overwhelming majority of these responders regarded such changes as positive. In the same study, about a fifth of participants also reported a "positive change in values or world view".[33] Older studies on volunteers having tried psychedelics have also reported long-lasting subjective changes such as better self-understanding, increased tolerance to others, or enhanced appreciation of music, art, and nature.[206] A decrease in "materialistic or aggressive orientations" has also been described.[206] Results from these old studies must be regarded with caution and contemporary re-evaluation of these outcomes might be warranted. In studies where PT was offered for MDD, it is difficult to distinguish true personality changes from improvement in depressive symptoms.[207,208]

Some authors have suggested that psychedelics could rarely trigger enduring states of "spiritual emergency",[209] which has been defined as "a process of deep psychological change, often involving non-ordinary states of consciousness, intense emotions, visions, and unusual thoughts […] occurring when a spiritual experience is so overwhelming as to be temporarily non-assimilable".[210] A spiritual emergency is characterized by an abrupt surge of interest in spirituality or transcendental questions, and it can be experienced as overwhelming, chaotic, or destabilizing.[210] It has been suggested that patients may even report psychotic-like symptoms such as visual hallucinations and bizarre or unusual thoughts. Unlike most patients suffering from psychosis, those living a so-called spiritual emergency would typically have a partly preserved insight, their adaptative functioning is preserved, and they exhibit no prior history of prodrome or psychosis.[209–211] Although the literature on this phenomenon is very limited, "spiritual emergencies" should cautiously be viewed as rare adverse events that can result from psilocybin exposure.

Sustained perceptual aberrations have been reported after exposure to psychedelic substances. For example, some individuals can reexperience perceptual symptoms that were felt during intoxication such as geometric hallucinations, palinopsia, or flashes of


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color. Some experience these manifestations episodically, while others have reported them continuously for years without re-exposure to hallucinogens.[212,213] Although some find them pleasant, others experience these symptoms with vexation and discomfort. When causing significant distress or impairment, a diagnosis of hallucinogen persisting perception disorder (HPPD) can be made according to the DSM-5-TR or ICD-11 nomenclatures.[194,195] The prevalence of HPPD seems very low,[213] and no case could be found after exposure to psilocybin in recent trials.[177]

Studies have explored the long-term effects of psilocybin on cognition. Notably, a phase I study evaluated the cognitive performances of 89 healthy volunteers up to one month after receiving psilocybin 25 mg, 10 mg, or placebo.[214] This study found no significant change in cognitive capacities on any of the subscales used. According to a scoping review of the subject, assessments of long-term cognition or creativity after psilocybin exposure have mostly shown no change (72% of findings), while studies reporting improvements were more common than studies reporting negative outcomes (22% versus 6% of findings).[215] All these results suggest that psilocybin has no overall negative impact on cognition.

### Low abuse potential

Animal studies, controlled studies in humans, and epidemiologic data accumulated since the 1950s demonstrate that psilocybin and *Psilocybe* mushrooms carry a very low risk of abuse. Self-administration studies on animals have shown that psilocybin only has weak reinforcing effects or mixed reinforcing and aversive effects.[216] As stated earlier, humans taking psilocybin tend to experience an amalgam of pleasant and unpleasant effects, followed by a feeling of contentment. The sum of these subjective effects translates into a low abuse potential.[65,217,218]

Psilocybin does not cause physical dependence or withdrawal syndrome.[32,195,217,219,220] When compared to other substances of abuse, psychedelics show the smallest risk of transition from drug use to dependence.[221] The Treatment Episode Datasets (TEDS) show that hallucinogens are responsible for less than 0.1% of drug abuse treatment admissions in the United States.[222] No pattern of compulsive or problematic use was observed to date after subjects participated in contemporary psilocybin studies.[33,50]

### Reproductive toxicity

Very little is known about the risks of taking psilocybin or hallucinogenic mushrooms during pregnancy or breastfeeding.[223] No chromosome breakage or mutagenic activity was identified during the micronucleus test in mice at very high doses,[224] and a single study on mice showed no increase in birth defects after exposure to psilocin.[225] Considering the paucity of data on the reproductive toxicity of psilocybin, studies have reasonably excluded pregnant or breastfeeding women.

### Epistemic harm and risks associated with psychotherapeutic interventions

Psychedelic substances induce a state of vulnerability and increased suggestibility. Therefore, psychotherapeutic interpretations are at increased risk of being misleading and psychologically harmful. Furthermore, boundary violations in the therapeutic setting are possible, and cases of sexual misconduct have been reported in clinical trials with MDMA. These risks surrounding PT must be seriously considered and mitigated.

## Other psychedelic substances with therapeutic potential

Other psychedelic drugs with a similar mechanism of action exhibit promising potential for the treatment of mental disorders. MDMA, ayahuasca, and DMT are discussed in other chapters, even though they share some similarities with psilocybin. Ibogaine will not be discussed here, since it has a unique mechanism of action.

### Lysergic acid diethylamide (LSD)

The Swiss chemist Albert Hofmann first synthesized LSD in 1938 and serendipitously discovered its psychoactive properties in 1943.[19] LSD is well known for potently inducing altered states of consciousness, and it was extensively used recreationally in counterculture movements during the 1960s and 1970s. During these decades, abundant scientific research was also conducted to explore its pharmacologic properties and its potential therapeutic use.

LSD is an ergoline derivative that binds with high affinity and activates $5HT_{2A}$ receptors. It also has significant agonist activity on dopamine $D_2$ receptors, which can produce an activating effect.[32,137,226] The mind-altering effect of LSD is phenomenologically similar to that of psilocybin, although LSD has a longer duration of action lasting approximately 8–10 hours.[148]

LSD therapy has also regained attention in the last two decades. Many small clinical trials have been conducted with LSD to alleviate anxiety and depression in patients suffering from life-threatening medical conditions.[117,227,228] These small trials suggest that LSD therapy has the potential to rapidly and sustainably reduce anxiety and depressive symptoms in some patients. Recently, the FDA has given breakthrough therapy status to lysergide d-tartrate, an LSD salt that showed encouraging results in a phase 2B trial for generalized anxiety disorder,[229] although these results are currently unpublished. Low doses of the same molecule are currently being tested for ADHD in adults.[230] Through a review of clinical trial registries, a recent Swiss study was found for patients with MDD,[231] although its results are yet unpublished. Interestingly, many studies were conducted in the 1960s and 1970s to evaluate the efficacy of LSD for alcohol use disorder, although these studies produced mixed results and presented scientific limitations.[232–235]

### Mescaline

Mescaline is another psychedelic substance with similarities to psilocybin and LSD. This molecule is naturally present in several species of cacti, most notably the North American peyote (*Lophophora williamsii*).[236,237] It has a long and rich history of being used as an entheogen by indigenous communities in America.[236,237] After the Second World War, many psychonauts and intellectuals were introduced to the effects of mescaline, among whom Aldous Huxley famously recalled his experience in the 1954 essay *The Doors of Perception.* Mescaline is a phenethylamine with a chemical structure closely related to MDMA. Significant cross-tolerance can be observed between mescaline, psilocybin, and LSD, which initially hinted at their common mechanism of action. Indeed, mescaline also primarily acts as a $5HT_{2A}$ receptor agonist, although with a much lower affinity than other psychedelics. This molecule also binds to $5\text{-}HT_{1A}$ and central $\alpha_{2A}$ adrenergic receptors.[238]

Mescaline produces similar mind-altering effects as LSD and psilocybin, but it has a slower onset of action, and its effects typically last between 10 to 12 hours.[148] Mescaline often causes nausea, which could hinder its therapeutic use.[239] Although mescaline has also benefited from renewed popularity and interest in


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the scientific community, no recently published clinical trials could be found for the treatment of mental disorders. Our search of clinical trial databases only resulted in finding one Phase I study announced for the treatment of alcohol-use disorder.[239]

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