Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Psilocybin

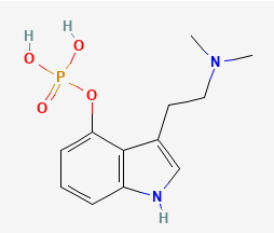
Evidence Summary

A single dose of psilocybin has shown lasting benefits for depression. In healthy people, psilocybin may acutely impair some cognitive functions. Long-term safety and efficacy of psilocybin are not established.

Neuroprotective Benefit: In depression, psilocybin exerts antidepressant effects and may improve some cognitive domains. In healthy people, psilocybin may acutely impair some cognitive functions. Long-term effects of psilocybin are not well established.

Aging and related health concerns: In advanced cancer patients, psilocybin-assisted therapy significantly reduced anxiety, pain, and depression. A case series reported remarkable pain relief in a few patients with chronic neuropathic pain.

Safety: Panic, psychosis, and other serious events can occur when taken in an unsupportive setting. Common adverse events include headache, nausea, increased blood pressure, hallucinations, anxiety, dizziness, and others. Long-term safety is not known.

Availability: not available; It is a Schedule I drug. It is being tested in clinical trials.	**Dose**: Most clinical studies used single oral doses ranging from 10 to 30 mg.	**Chemical formula:** $C_{12}H_{17}N_2O_4P$ **MW**: 284.25  Source: PubChem
Half-life: 3 hours	**BBB**: penetrant	
Clinical trials: The largest systematic review investigating the effects of psilocybin has included 20 studies involving a total of 2,959 participants.	**Observational studies**: Numerous case reports exist.	

What is it?

Psilocybin is a chemical compound present in over 180 species of hallucinogenic mushrooms (dried or fresh) found in Mexico, South America, and parts of the US (Drugs.com). Dried "magic mushrooms" contain about 0.2-0.4% psilocybin. Psilocybin can also be produced in the laboratory.

Psilocybin is quickly converted by the body to psilocin, which acts as an agonist for serotonin receptors, 5HT-2A, 5HT-2C, and 5HT-1A (Erkizia-Santamaria et al., 2022). Psychedelics acting on 5HT-2A and other serotonin receptors are drawing increasing interest as potential treatments for neurodegenerative diseases (Saeger et al., 2022; Kozlowska et al., 2022; vann Jones and O'Kelly, 2020; Zheng et al., 2024). This is stemming from studies showing that these compounds can exert persisting anxiolytic and antidepressant effects lasting up to 4.5 years after a single administration (Ross et al., 2016; Ross et al., 2021) and have shown potential for a wide range of brain disorders including depression, post-traumatic stress disorder, and substance use disorder. Psilocybin has received FDA Breakthrough Therapy designation for the treatment of drug-resistant depression (2018) and major depressive disorder (2019)(Scientific American).

Neuroprotective Benefit: In depression, psilocybin exerts antidepressant effects and may improve some cognitive domains. In healthy people, psilocybin may acutely impair some cognitive functions. Long-term effects of psilocybin are not well established.

Types of evidence:

- 11 systematic reviews or meta-analyses
- 12 placebo-controlled trials in healthy adults
- 1 open-label clinical study in healthy adults
- 1 open-label clinical trial in major depressive disorder
- Numerous review articles on the use of psychedelics for neurodegenerative disorders
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Overall, the effects of psilocybin on cognitive function have been mixed, with some studies showing a lack of change, some showing impairment, and a few showing potential benefits. Effects on cognition may depend on many factors, including the dose, expectation of the drug effect, mood, time course, and underlying health conditions (e.g., healthy vs depression/anxiety). Challenges in interpreting study results include limited sample sizes, heterogeneity in dosing and study protocols, and difficulties in double-blinding (including functional unblinding)(Meshkat et al., 2024; Yao et al., 2024). High dose psilocybin can impair cognitive function including attention due to increased awareness of sensory stimuli that are usually filtered out (vann Jones and O'Kelly, 2020). Recent studies are exploring low-dose or microdose psilocybin treatments that do not produce psychedelic or negative cognitive effects. There is rapid desensitization of 5HT-2A receptors by psilocybin, so single or infrequent dosing is likely better than daily dosing.

Healthy adults: Most studies evaluating cognitive effects of psilocybin in healthy adults have tested acute (single) doses with short-term follow-ups of up to several hours.

Global cognitive function in healthy people: Numerous systematic reviews have evaluated the effects of psilocybin administration on global cognitive function (Meshkat et al., 2024; Ramos and Vicente, 2024; Velit-Salazar et al., 2024). For example, a 2024 systematic review of 20 studies including a total of 2,959 participants (17 studies in healthy volunteers), reported that psilocybin treatment does not significantly affect global cognitive function based on 2 studies (Meshkat et al., 2024). In a phase 1 double-blind

randomized controlled trial of 89 healthy men and women, a single oral dose of psilocybin (10 or 25 mg) did not significantly alter global cognition measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) global composite score (Rucker et al., 2022). There was a trend of better performance for the 10 and 25 mg psilocybin treatment on day 29 compared to baseline, but no statistically significant difference was observed when compared with placebo. In another double-blind placebo-controlled clinical study of 20 healthy hallucinogen users, cognitive effects of psilocybin (10, 20, or 30 mg/70 kg, orally) and dextromethorphan (400 mg/70 kg) were compared with placebo (Barrett et al., 2018). Psilocybin administration did not result in global cognitive impairment, as measured by the MMSE, during peak drug effects (2 hours after psilocybin administration).

Learning and memory in healthy people: The effects of psilocybin on learning and memory have been mixed. In an acute dosing study of 20 healthy hallucinogen users, psilocybin administration (10, 20, and 30 mg/70 kg, orally) dose-dependently impaired episodic memory and associative learning and decreased the free recall of words (Barrett et al., 2018). In a study of 8 participants, a single dose of psilocybin (0.2 mg/kg, orally) increased indirect semantic priming (Spitzer et al., 1996). In a double-blind placebo-controlled trial of 22 healthy psychedelic-experienced adults, psilocybin administration (15 mg, orally) impaired immediate and delayed spatial memory recall (measured by the Spatial Memory Test) 225 minutes after dosing (Mallaroni et al., 2023). In a double-blind randomized controlled crossover study of 20 healthy people, psilocybin administration (0.26 mg/kg) did not improve or impair consolidation of spatial memory (measured by Groton Maze Learning task) or verbal memory (measured by Rey Auditory Verbal Learning test) (Nikolic et al., 2023). There was also no effect of psilocybin on sleep-related memory consolidation. In a post-acute setting, a single dose of psilocybin (25 mg) did not significantly alter episodic memory (measured by Paired Associates Learning-Total Errors Adjusted; PAL-TEA) 29 days after dosing compared to baseline or to placebo (Rucker et al., 2022).

Working memory in healthy people: A 2024 systematic review reported that psilocybin treatment resulted in impaired working memory in 2 studies and had no effects on working memory in 2 other studies (Meshkat et al., 2024). In an acute dosing study of 20 healthy hallucinogen users, psilocybin administration (10, 20, and 30 mg/70 kg, orally) impaired working memory measured by increased response time for correct responses on the Letter N-Back Task (Barrett et al., 2018). Psilocybin treatment also dose-dependently decreased response bias during the 2-back condition which requires working memory. In a double-blind placebo-controlled study of 12 healthy human volunteers, psilocybin administration impaired working memory performance (measured by the Spatial Span test from CANTAB) 100 minutes after the high psilocybin dose (0.25 mg/kg) compared to placebo, but not after the medium dose of 0.115 mg/kg (Wittmann et al., 2007). In a post-acute setting, a single oral dose of

psilocybin (10 or 25 mg) showed a trend of better performance on a measure of working memory (SWM-BE) on day 29 compared to baseline, but no significant differences were observed when compared with placebo (Rucker et al., 2022).

Executive function in healthy people: In a double-blind placebo-controlled clinical study of 20 healthy hallucinogen users, psilocybin administration (10, 20, or 30 mg/70 kg, orally) led to an impairment in executive function measured by decreased accuracy (but not speed) on the digit symbol substitution test (DSST) 2 hours post-dosing (Barrett et al., 2018). Similarly, in a double-blind placebo-controlled trial of 22 healthy psychedelic-experienced adults, psilocybin administration (15 mg, orally) impaired executive function measured by decreased correct responses and attempts on the DSST 172 minutes after dosing (Mallaroni et al., 2023). However, mental planning, measured by the Tower of London, was not significantly affected by psilocybin administration 153 minutes after dosing. In a post-acute setting, psilocybin administration (25 mg) showed a trend for better performance in a measure of executive function and planning (SWM-S) on day 29 compared to baseline, but no difference was observed when compared with placebo (Rucker et al., 2022).

Attention in healthy people: A 2024 systematic review of 20 studies including a total of 2,959 participants (17 studies in healthy volunteers) reported that psilocybin treatment (most studies using a doses ranging from 115 to 315 µg/kg) resulted in diminished attention based on 7 studies (Meshkat et al., 2024). Psilocybin administration decreased performance in attention, measured by the Covert Orienting of Visuospatial Attention Task (COVAT) and multiple object tracking tests in 2 studies (Carter et al, 2005; Gouzoulis-Mayfrank et al., 2002) and measured by the Frankfurt Attention Inventory (FAIR) test in another study (Hasler et al., 2004). Pretreatment with ketanserin, a 5HT-2A antagonist, did not attenuate the effect of psilocybin on attentional performance, suggesting a primary involvement of the 5-HT1A receptor in the observed deficit (Carter et al, 2005). The authors speculate that this impaired attentional performance may reflect a reduced ability to suppress or ignore distracting stimuli rather than reduced attentional capacity. Attention measured by the trail-making test also decreased with psilocybin administration, along with an increase in the time needed to complete the task following a microdosing regimen (Cavanna et al., 2022; Duke and Keeler, 1968). Psilocybin administration also reduced power of EEG theta oscillations, reflecting reduced vigilance (Cavanna et al., 2022). In a post-acute setting, a single oral dose of psilocybin (10 or 25 mg) showed a trend of better performance on a measure of sustained attention (Rapid Visual Information Processing, sustained attention, RVP-A') on day 29 compared to baseline, but no significant differences were observed when compared with placebo (Rucker et al., 2022).

Cognitive flexibility and creative cognition in healthy people: The effects of psilocybin on cognitive flexibility and creative cognition depend on several factors (Meshkat et al., 2024). Psilocybin administration does not appear to affect cognitive flexibility or creative cognition in the acute setting, but increases objective and self-reported cognitive flexibility in the post-acute setting (Nayak et al., 2023). In a meta-analysis of 5 studies in healthy people, psychedelic administration (one or a few doses of psilocybin, LSD, or ayahuasca) did not significantly affect cognitive empathy (measured by the Multifaceted Empathy Test), but increased explicit emotional empathy compared to placebo or baseline measures (Olami et al., 2024).

Depression: Major depression is an established risk factor for subsequent dementia (Livingston et al., 2024). People treated for depression by medication, psychotherapy, or combination therapy were less likely to develop dementia than their untreated counterparts. In contrast to findings in healthy participants, people with depression may experience antidepressant effects along with improvements in a few cognitive domains following psilocybin therapy (Meshkat et al., 2024; Yao et al., 2024; Ramos and Vicente, 2024).

Different cognitive outcomes in people with depression versus healthy adults may, in part, be due to the concomitant psychotherapy sessions administered to these patients, or nocebo effects in the control group. Some of the effects may continue for days or weeks after the acute effects of psilocybin have subsided. Similar to the studies in healthy adults, there are challenges in interpreting studies in people with depression due to heterogeneity in dosing and study protocols, and difficulties in double-blinding due to the psychedelic effects of psilocybin, leading to functional unblinding (Meshkat et al., 2024; Yao et al., 2024). Only a few studies have directly compared the effects of psilocybin with standard antidepressant drugs in rigorously-designed trials (Scala et al., 2024). There are gaps in knowledge, including the optimal dose, treatment frequency, and the optimal psychological therapies that maximize therapeutic benefits of psilocybin.

In a 2024 meta-analysis of 6 randomized controlled trials including a total of 427 patients with major depressive disorder, psilocybin-assisted psychotherapy (with 1, 2, or 3 administrations of 16-25 mg dose of psilocybin) significantly improved depression ratings compared to the comparator interventions for at least up to 6 weeks post-intervention (Menon et al., 2024). Effect sizes of the psilocybin-assisted psychotherapy were at least medium. The control group received the same frequency and content of psychotherapeutic sessions as the intervention group except in the case of waitlist controls. Dosing sessions lasted 6-8 hours and were conducted in a living room-like area in the presence of one or more therapists, with music playlists and eye shields used for participants to focus inward. The response rate

and remission rate also favored the psilocybin-assisted psychotherapy compared to the comparator. Limitations of this meta-analysis include the small sizes of the included studies and the methodological heterogeneity, including control conditions and challenges in blinding.

In another 2024 meta-analysis of 6 randomized controlled trials including a total of 432 patients with major depressive disorder, administration of 1 or 2 psilocybin dosing sessions (with psychotherapy support) resulted in a large and clinically observable reduction in depressive symptomatology (measured by change score standardization; SMCC) compared to baseline and also when compared to placebo (with psychotherapy support)(Aghajanian et al., 2024). The Quick Inventory of Depressive Symptomatology Self-Report-16 (QIDS-SR-16) scores demonstrated a -8.73 point reduction in depression scale scores for <1 week post-psilocybin administration, -7.99 points for 14 to 30 days of post-dosing, and -7.38 point for scores evaluated beyond one month post-dosing, with moderate to large heterogeneity.

In a 2024 dose-response network meta-analysis of 3 randomized controlled trials including a total of 389 patients with major depressive disorder, psilocybin administration significantly reduced symptoms compared to placebo on days 8 and 15 (but not day 2)(Swieczkowski et al., 2024). Efficacy was measured by change in Montgomery–Asberg Depression Rating Scale (MADRS). On Day 8 and 15, pooled analysis showed a statistically better response to psilocybin compared to placebo (Day 8: mean difference [MD]=-7.42; 95% CI, -10.07 to -4.78; $p < 0.001$; Day 15: MD=-9.55; 95% CI, -12.44 to -6.65; $p<0.001$). The network meta-analysis found that a 25 mg dose was the most effective with a surface-under-the-cumulative-ranking (SUCRA) value of 92.25% compared to psilocybin doses of 0.215 mg/kg and 10 mg. Psilocybin at the 10 mg dose did not show significant effects on MADRS compared to placebo.

Because of the subjective effects of psychedelics, blinding can be compromised and affect the magnitude of placebo effects. To address these challenges and in an effort to compare the efficacy of psilocybin with a standard anti-depressant, a 2024 systematic review and Bayesian network meta-analysis assessed 15 trials of psychedelics (psilocybin, MDMA, LSD, or ayahuasca; total of 811 patients) and 5 trials of escitalopram (marketed as Lexapro; total of 1,968 patients) in people with depressive symptoms (Hsu et al., 2024). The meta-analysis found that placebo responses were significantly lower in psychedelic trials compared to escitalopram trials (mean difference, -3.9; 95% CI, -7.10 to -0.96). While most psychedelics showed greater improvement in depression (change in 17-item Hamilton Depression Rating Scale; HAMD-17) compared to placebo, only high-dose psilocybin (≥20 mg) showed a significant difference (mean difference greater than the minimal important difference of 3 points) compared to the placebo groups in escitalopram trials. When compared to the placebo response in escitalopram trials,

the effect size of high-dose psilocybin decreased from large (0.88) to small (0.31). The relative effect of high-dose psilocybin was larger than escitalopram at 10 mg and 20 mg, also exceeding the minimally important difference of 3 points on the HAMD-17.

In a 2024 meta-analysis of 59 clinical studies of psychedelics (psilocybin, ayahuasca, LSD, or MDMA) in people with mental disorders (e.g., depression, anxiety), psilocybin treatment (tested in 22 studies) showed the strongest therapeutic effect among the 4 psychedelics, followed by ayahuasca and LSD (Yao et al., 2024). Most studies used only a single or two doses of a treatment. In this meta-analysis, psilocybin treatment showed superior efficacy to citalopram (marketed as Celexa). Subgroup analyses found that in patients with anxiety or depression related to life-threatening diseases, psilocybin treatment showed stronger efficacy than LSD and MDMA regardless of study designs. However, for treatment-resistant depression or recurrent major depressive disorder, ayahuasca showed stronger efficacy than psilocybin. Psychedelics in general showed a faster onset of action of symptom relief compared to traditional antidepressants. With psilocybin, there was a small decrease of 9.3% in efficacy from 1 to 3 months after administration, but efficacy remained almost the same from 3 to 6 months.

In a long-term follow-up study of psilocybin-assisted psychotherapy in patients with life-threatening cancer, a single psilocybin treatment showed persistent reductions in demoralization (measured by Loss of Meaning) at 6.5 months, 3.2 years, and 4.5 years after therapy (Ross et al., 2021). Anxiolytic and anti-depressant effects also persisted at the 6.5 month follow-up (Ross et al., 2016). These lasting effects may be due to remodeling and persistent changes in functional brain networks.

In an open-label study of 24 patients with major depressive disorder, a single dose of moderately high (20 mg/70 kg body weight) or a high dose (30 mg/70 kg body weight) of psilocybin reduced symptoms of depression while increasing cognitive flexibility, an effect seen for at least 4 weeks post-treatment (Doss et al., 2021). However, cognitive tasks measuring response inhibition, selective attention, and abstract reasoning were not affected. One week after psilocybin administration, glutamate and N-acetylaspartate concentrations were decreased in the anterior cingulate cortex (ACC), and dynamics of functional connectivity (dFC) was increased between the ACC and the posterior cingulate cortex (PCC). But greater increases in dFC between the ACC and PCC were associated with less improvement in cognitive flexibility after psilocybin therapy. The authors speculate that subpopulations of patients, for example, those with lower baseline neural flexibility, may be more likely to benefit from psilocybin therapy. Because this study was an open-label study and not placebo-controlled, these results could be attributed to expectancy, practice, or exposure effects.

Postoperative cognitive decline: No clinical trials have tested the effects of psilocybin for the prevention or treatment of postoperative cognitive decline. The use of compounds including psilocybin to mitigate postoperative cognitive decline and psychological stress in patients undergoing surgery has been proposed in several patent applications (WO 2023/230303 A1 and WO 2023/230649 A1)(Kargbo, 2024). The application of this approach extends to different procedures and conditions, including heart surgery, major trauma, obstetrical interventions, and intensive care procedures.

Human research to suggest benefits to patients with dementia:

None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Psilocybin and other psychedelic compounds acting on 5HT-2A and other serotonin receptors are drawing increasing interest as potential treatments for neurodegenerative diseases (Saeger et al., 2022; Kozlowska et al., 2022; vann Jones and O'Kelly, 2020; Zheng et al., 2024; Haniff et al., 2024). Psilocybin activates the 5HT-2A receptor and produces hallucinogenic effects while also playing other roles such as promoting cortical neuron growth, activating neuronal survival mechanisms (e.g., modulating the TrkB receptor), increasing neuroplasticity and neurogenesis (e.g., via BDNF and mTOR pathways), and modulating the immune system (Saeger et al., 2022; Kozlowska et al., 2022; vann Jones and O'Kelly, 2020; Zheng et al., 2024; Meshkat et al., 2024; Yao et al., 2024).

Studies in humans: In Alzheimer's disease and related disorders, 5HT-2A receptor density is significantly reduced and this loss is correlated with cognitive decline (Franceschi et al., 2005; Lai et al., 2005).

Several clinical trials have evaluated the effects of psilocybin on plasma biomarkers, including the neurotrophic factor, BDNF (Calder et al., 2024; Constantino et al., 2025). In a systematic review of 9 clinical studies in healthy people, psilocybin administration resulted in a numeric increase in BDNF levels compared to baseline in 3 studies, but differences were not statistically significant compared to control (Constantino et al., 2025). In a double-blind randomized controlled crossover trial of 28 healthy participants, acute effects of psilocybin (15 and 30 mg), LSD (100 and 200 µg), and placebo were compared (Holze et al., 2022). Both psilocybin and LSD significantly increased plasma cortisol, prolactin, and oxytocin levels, but neither significantly elevated plasma BDNF levels. In a double-blind controlled crossover study of 32 healthy people, a single dose of psilocybin (20 mg) did not significantly alter plasma BDNF concentrations (Ley et al., 2023).

In a placebo-controlled study of 60 healthy people, a single dose of psilocybin (0.17 mg/kg) immediately reduced concentrations of the pro-inflammatory cytokine TNF-α (p=0.016), while other inflammatory markers (IL-1β, IL-6, and CRP) remained unchanged (Mason et al., 2023). After 7 days, TNF-α concentrations returned to baseline, while IL-6 and CRP concentrations were reduced in the psilocybin group. Participants with greater reduction in IL-6 and CRP 7 days post-psilocybin experienced greater persistence in positive mood and social effects. No psilocybin effects were observed with IL-1β or IL-8.

In a blinded placebo-controlled study of 15 healthy adults, oral administration of psilocybin (10 mg/70 kg body weight) induced widespread dysregulation of cortical activity, including significantly decreasing the amplitude of low frequency fluctuations as well as the variance of blood-oxygenation level-dependent (BOLD) signal in the left and right claustrum that highly expresses 5HT-2A receptors (Barrett et al., 2020). Psilocybin administration also significantly altered both left and right claustrum connectivity with brain networks that support sensory and cognitive processes [decreased functional connectivity of the right claustrum with auditory and default mode networks (DMN), increased right claustrum connectivity with the fronto-parietal task control network (FPTC), and decreased left claustrum connectivity with the FPTC].

In a double-blind placebo-controlled crossover trial of 20 healthy adults, a single oral dose of psilocybin (0.26 mg/kg, manufactured according to GMP standards from THC_Pharm GmbH, Frankfurt, Germany) induced robust psychedelic effects and psychotic symptoms while decreasing event-related potentials at the P300 amplitude, which reflects higher order cognitive processing, and decreasing N100 amplitude, which reflects sensory-related processing (Bravermanova et al., 2018). However, preattentive cognitive processing (mismatch negativity, or MMN amplitude) was not affected by psilocybin.

In a double-blind placebo-controlled study of 32 healthy adults, acute effects of psilocybin (0.2 mg/kg, 15 mg max), the entactogen 3,4-methylenedioxyethyl-amphetamine (MDE; 2 mg/kg), and the stimulant d-methamphetamine (0.2-0.4 mg/kg) (all obtained from the Pharmaceutical Institute of the University of Tubingen) were compared with placebo (Gouzoulis-Mayfrank et al., 1999). Psilocybin administration increased regional magnetic resonance glutamate levels of the right hemisphere frontotemporal cortical regions (particularly in the anterior cingulate) and decreased it in the thalamus. However, psilocybin administration led to significantly fewer words in an association task compared to placebo administration, which was accompanied by diminished activation of frontal regions. No significant differences across 4 treatment conditions were seen for global cerebral metabolism. Cognitive

activation-related increases in left frontocortical regions were dampened after administration of the three psychoactive drugs.

In an open-label study of 10 healthy adults, a single dose of 15 or 20 mg psilocybin produced a global increase in cerebral metabolic rate of glucose (CMRglu) with the greatest increases in the frontomedial and frontolateral cortex (by 24.3%), anterior cingulate (by 24.9%), and temporomedial cortex (by 25.3%)(Vollenweider et al., 1997). The CMRglu increases in the prefrontal cortex, anterior cingulate, temporomedial cortex, and putamen positively correlated with psychotic symptoms (hallucinatory ego disintegration).

Studies in laboratory models: In pig brain, a single dose of psilocybin (0.08 mg/kg, i.v.) increased hippocampal synaptic density by 4.42% (measured by SV2A, a synaptic protein), while lowering 5HT-2A receptor density by 15.21-50.19% in the hippocampus and prefrontal cortex (Raval et al., 2021). Seven days after psilocybin treatment, the increase in synaptic density was greater—by 9.24% in the hippocampus and by 6.10% in the prefrontal cortex. However, there were no longer any differences in 5HT-2A receptor density, suggesting that psilocybin effects on 5HT-2A density is acute and temporary, while changes in synaptic density are longer lasting.

In mouse model of fear conditioning and extinction, a single dose of psilocybin (2.5 mg/kg, i.p.) facilitated rapid fear extinction while preventing the decrease in new hippocampal cells and hippocampal dendritic complexity (including spine density) in the dentate gyrus (Du et al., 2023).

In rats, an acute low dose pretreatment with psilocybin (0.05-0.1 mg/kg, s.c.) improved attentional accuracy and a measure of impulsive action exclusively in low performers, but no overall effects were seen when data from all rats were combined (Higgins et al., 2021).

In rats, a single administration of psilocybin (0.5-20 mg/kg) increased the expression of c-Fos, an immediate early gene implicated in neuroplasticity, in the prefrontal cortex, but not the hippocampus (Jefsen et al., 2021).

In rats, a single dose of psilocin (1 or 4 mg/kg; s.c.; synthesized at Pharmaceutical Faculty of Charles University in Prague) significantly impaired the acquisition of the Carousel maze (Rambousek et al., 2014). In the Morris water maze, the 4 mg/kg dose of psilocin disrupted reinforced retrieval, but the lower dose had no significant effect. When psilocin was injected during the post-training period,

memory consolidation in the water maze was unaffected, suggesting that psilocin does not interfere with memory consolidation.

In mice, a single dose of psilocybin (1 mg/kg, i.p.; Usona Institute) led to a ~10% increase in dendritic spine size and density, driven by an increase in spine formation rate, in the medial frontal cortex (Shao et al., 2021). This neuronal structural remodeling occurred within 24 hours and 34-37% of the spines that were formed remained persistent 1 month later. These changes were accompanied by reduced stress-related behavioral deficit and increased excitatory neurotransmission.

In a different study in mice, a 1 mg/kg dose (i.p.) of psilocybin significantly decreased the number of newborn neurons in the hippocampus, while lower doses (0.1 or 0.5 mg/kg, i.p.) showed a trend toward an increase in hippocampal neurogenesis compared to vehicle treatment (Catlow et al., 2013).

In microglia culture, treatment with psilocin upregulated the neuroprotective TREM2 receptor important for phagocytosis and synaptic refinement, while reducing proinflammatory markers (TLR4, p65, CD80 proteins)(Kozlowska et al., 2021). There is also evidence that psilocybin has anti-inflammatory effects in peripheral tissues (Kozlowska et al., 2022).

APOE4 interactions: Unknown.

Aging and related health concerns: In advanced cancer patients, psilocybin-assisted therapy significantly reduced anxiety, pain, and depression. A case series reported remarkable pain relief in a few patients with chronic neuropathic pain.

Types of evidence:

- 3 systematic reviews or meta-analyses (2 in cancer patients, 1 in chronic pain)
- 1 double-blind randomized controlled trial on sleep measures
- 1 clinical study in cancer patients
- 1 controlled study on blood and imaging biomarkers
- 1 case series of chronic pain
- Numerous review articles

Cancer: REDUCED DEPRESSION, EFFECTS MAY BE SUSTAINED FOR MONTHS/YEARS

In a 2024 network meta-analysis of 9 randomized controlled trials of psychedelics (psilocybin, ketamine, MDMA, or LSD) including a total of 606 terminally ill patients (mostly cancer), psilocybin was the most effective compound for depression and its superiority was statistically significant compared to placebo and midazolam (marketed as Versed)(Marchi et al., 2024). LSD was the most effective compound for anxiety, but head-to-head comparisons did not reach statistical significance. Limitations of this network meta-analysis include the small number of studies, methodological issues related to blinding, and the lack of direct comparisons between psychedelic compounds.

In a 2024 meta-analysis of 7 studies (5 randomized controlled trials) including a total of 132 advanced cancer patients, psilocybin-assisted therapy (1 or 2 dosing sessions) significantly improved quality of life, pain control, and anxiety (Bader et al., 2024). Statistically significant reductions with psilocybin were seen with symptoms of anxiety at 4-4.5 months and at 6-6.5 months. Patients reported sustained improvements in psychological well-being with psilocybin therapy.

In a long-term follow-up of 15 patients with life-threatening cancer who received psilocybin-assisted psychotherapy, significant reductions in anxiety, depression, hopelessness, demoralization, and death anxiety in 60-80% of the participants, 4.5 years after the therapy (Agin-Liebes et al., 2020).

Sleep: MIXED; MAY SUPPRESS SLOW WAVE ACTIVITY

In a double-blind randomized controlled crossover clinical trial of 20 healthy adults, a single dose of psilocybin (0.26 mg/kg; range of 15-22 mg) prolonged REM sleep latency and caused a trend toward a decrease in overall REM sleep duration (Dudysova et al., 2020). No significant differences in sleep latency, total sleep time, sleep efficiency, NREM sleep, or number of sleep cycles were observed between psilocybin and placebo conditions. Psilocybin did not affect EEG power spectra in NREM or REM sleep, but it did suppress slow wave activity (measured by absolute delta power) during slow wave sleep in the first sleep cycle.

Neuropathic pain: INCONCLUSIVE; PAIN RELIEF

In a case series of 3 patients with chronic neuropathic pain, low-dose psilocybin-containing mushroom self-administration (varying preparations) achieved robust pain relief with decreased reliance on analgesic medications (Lyes et al., 2022). The exact contents of the dried mushrooms and doses of

psilocybin cannot be determined but can roughly be estimated at 1.25 mg-10 mg across the 3 subjects (the dried *Psilocybe cubensis* mushrooms contain roughly 0.5-1.0% psilocybin by mass). Analgesic effects for all 3 patients occurred at doses without a psychedelic effect with minimal cognitive or somatic adverse events.

- The first patient is a 37-year-old man with a history of quadriplegia due to a vehicle accident that resulted in a cervical spinal cord injury and lower extremity neuropathic pain. He was prescribed tramadol and diazepam, but they were ineffective and produced cognitive side effect. His first exposure was a 5 g dose of dried ground psilocybin-containing mushroom powder that produced a psychedelic experience, accompanied by near total relief from his lower extremity neuropathic pain that lasted for 8-10 hours. Subsequently, he tried lower doses in the 250 mg range and the analgesic effects persisted with a similar magnitude of relief, but for a shorter duration of 6-8 hours. In addition to pain relief, he experienced stimulating muscle spasms that were soothing and therapeutic to the paralyzed muscles. He then lowered the dose further to 50 mg daily with no muscle spasms and 90-95% pain relief lasting 6-8 hours. He has continued to use this dose daily for 6 months and he has stopped using tramadol, valium, and cannabis, as the analgesic effects from psilocybin exceeded the marginal benefit from these other medications. The patient denied rebound pain or withdrawal symptoms, but the pain returns to baseline on days when he does not self-administer psilocybin.
- The second patient is a 69-year-old female with a history of complex regional pain syndrome secondary to lower extremity trauma, the injuries of which were non-operative. The debilitating pain has made it impossible for her to perform activities of daily living without assistance, and she has tried numerous interventions including physical therapy, acupuncture, yoga, biofeedback, desensitization therapy, nerve blocks, steroid injections, and stem cell injections without success. She has tried NSAIDs and opioid agonists (oxycodone, fentanyl patches and buprenorphine patches), gabapentinoids, and antidepressants (duloxetine and amitriptyline), with limited efficacy and untoward side effects. Her first experience with psilocybin was with 2 g of ground, dried psilocybin-containing mushroom powder and within an hour, her pain level reduced to zero, though this was accompanied by significant psychotropic effects including altered mood, changes in visual/auditory perception as well in thought patterns and cognition that continued for 6 hours. The analgesia lasted 18-20 hours. She experimented with microdosing to reduce side effects, and she typically uses a 500 mg/day dose for 7-10 days (producing 80% pain relief for 3-4 hours, gradually returning to baseline after 12 hours) followed by a rest period of 2-3 days to prevent gastrointestinal side effects. She denies rebound pain or withdrawal effects when she skips doses, and she has been microdosing for over a year and has not noticed any tolerance or loss of efficacy.

- The third patient is a 40-year-old female with a history of radiculopathy secondary to degenerative disc disease, with pain that decreased over time such that it interferes with activities of daily living. The pain was unresponsive to medications, physical therapy, and epidural steroid injections. She began experimenting with psilocybin-containing mushrooms to reduce opioid use, starting at 1000 mg of dried ground mushroom incorporated into a chocolate bar. Within one hour, her bilateral radicular pain and focal low back pain was completely resolved. She experiences a sensation of improved flexibility and relaxation in areas that are usually stiff and painful. After a single dose coupled with exercise, analgesic effects persist for two weeks. Pain slowly returns to baseline over the subsequent 2-4-week period; thus, she spaces out psilocybin administration by 6-8 weeks. She has found the longevity of analgesic effects are far more sustained when used as an adjunct to physical therapy exercises. She has experienced an overall improvement in baseline pain with each psilocybin session. Musculoskeletal pain has gone from a pain score of 9 (out of 10) to a 7. Neuropathic pain relief has been profound, with a complete resolution after the third session, and has not recurred. The patient denies noticeable somatic, cognitive, or behavioral side effects, and her mood has been unaffected. She has not noticed tolerance to pain relieving effects, rebound pain, or withdrawal effects.

Findings from this study may not be generalizable to other chronic neuropathic pain patients, as these patients sought psilocybin on their own and experienced positive effects (Lyes et al., 2022). As this was not a placebo-controlled study, the role of placebo effect cannot be determined. Also, no objective measures of function or efficacy were used. Randomized, double-blind, placebo-controlled trials are needed, with formal pain assessment and psychiatric evaluation to minimize the impact of confounding factors.

Chronic pain: POTENTIAL PAIN RELIEF

In a systematic review of 28 clinical trials and observational studies in people with chronic pain (mostly in chronic headaches), 2 to 3 dosings of psilocybin (e.g., 0.143 mg/kg) showed some level of improvement in pain symptoms, but not all studies achieved statistical significance (Jevotovsky et al., 2024). Statistically significant benefits were reported in 8 studies, accounting for 38.1% of the studies. Ten studies found clinically important improvements, defined as at least a 30% reduction in pain intensity, measured by the Visual Analog Scale (VAS). In general, the quality of evidence was low, including methodological issues and risks of bias.

In a double-blind placebo-controlled crossover study in adults with migraine, a single psilocybin administration (0.143 mg/kg, orally) led to a significant reduction in migraine frequency from baseline (-1.65 days/week; 95% CI, -2.53 to -0.77) compared to placebo (-0.15 days/week; 95% CI, -1.13 to 0.83)(Schindler et al., 2021).

Survey-based studies suggest that psilocybin treatment controls cluster headaches long-term with efficacy rates of 56-75% (reviewed in Strand et al., 2025). However, a double-blind randomized placebo-controlled trial of 16 patients with cluster headache reported that psilocybin treatment (0.143 mg/kg, orally, in a pulse of 3 doses, 5 days apart) did not significantly reduce cluster headache frequency (Schindler et al., 2022).

Safety: Panic, psychosis, and other serious events can occur when taken in an unsupportive setting. Common adverse events include headache, nausea, increased blood pressure, hallucinations, anxiety, dizziness, and others. Long-term safety is not known.

Types of evidence:

- 6 systematic reviews or meta-analyses
- 5 double-blind controlled clinical trials
- Numerous review articles

General safety:
Psilocybin use can cause visual and auditory hallucinations, an inability to discern fantasy from reality, and at high doses, may also cause panic reactions and psychosis (Drugs.com; WebMD.com). Other common effects of psilocybin (and other hallucinogens) include intensified feelings/sensations, changes in sense of time, confusion, headache, nausea, dry mouth, increased blood pressure, increased breathing rate, increased body temperature, loss of appetite, sleep problems, spiritual experiences, uncoordinated movements, lowered inhibition, excessive sweating, and paranoia.

After consumption of psilocybin, episodes characterized by intense negative motions, often referred to as "bad trips", can occur and lead to rare instances of self-harm or harm to others. These experiences occur more frequently when dosing occurs in a poorly controlled environment and can be prevented or managed by following safety guidelines (reviewed in Johnson and Griffiths, 2008; Bonnieux et al., 2023; Strand et al., 2025). Safeguards in clinical research of psilocybin and other hallucinogens include excluding people with personal or family history of psychotic disorders or other severe psychiatric

disorders, establishing trust and rapport between session providers and study participants before the session, and providing a safe session environment and support from at least two well-trained providers during the study session to guide the participants and mitigate adverse psychological and psychiatric reactions.

There is a risk of developing hallucinogen-persisting perception disorder (HPPD), which includes two subtypes (reviewed in Scala et al., 2024). HPPD I, also known as "benign flashback", has a short-term, reversible, and benign course. In contrast, HPPD II usually occurs as recurrent, long-term, distressing, and pervasive perceptive disturbances.

Because psilocybin affects the serotonin system, there is a possibility of serotonin toxicity which can be potentially life-threatening, though psilocybin shows a lower risk of toxicity compared to other psychedelics (Scala et al., 2024). Serotonin-related symptoms may include nausea, anxiety, hypertension, tachycardia, visual deficits, motor incoordination, and tremors. Symptoms of severe serotonin toxicity include myoclonus (sudden spasms), rigidity, severe hyperthermia, and impaired mental status.

Despite being a Schedule I controlled substance, the risk of abuse with psilocybin appears to be low, and withdrawal symptoms and physical dependence do not appear to be a major concern (WebMD.com; Scala et al., 2024). At this time, there is a lack of a specific antagonist to psilocybin that can counteract adverse experiences.

Serious adverse events after abuse of psychoactive fungi have been reported in several case studies, including takotsubo cardiomyopathy (Nef et al., 2009) and severe rhabdomyolysis (Bickel et al., 2005; Suleiman et al., 2022).

While rare, suicidality, prolonged paranoia, and persistent visual perceptual effects should be monitored (Yerubandi et al., 2024).

Safety in healthy people:
In a phase 1 double-blind randomized controlled trial of 89 healthy men and women, a single oral dose of psilocybin (10 or 25 mg) was well-tolerated compared to placebo, with no detrimental short- or long-term effect on cognitive functioning or emotional processing, and no clinically significant findings in vital signs (Rucker et al., 2022). A total of 511 treatment-emergent adverse events (TEAEs) were reported, with a median duration of one day; 67% of all TEAEs started and resolved on the day of administration.

Of these, 208, 188 and 77 were deemed by the investigator to be potentially related to study treatment in the 25 mg psilocybin, 10 mg psilocybin, and placebo arms, respectively. There were no serious TEAEs. Four participants reported anxiety on the day of study drug administration (2 people with 25 mg psilocybin, 1 person with 10 mg psilocybin, and 1 person with placebo). There were 57 adverse events related to "altered mood", which included negative mood, introspection, reflection, and sense of oneness. There were 86 reports of hallucination, 56 reports of illusion, 15 reports of euphoric mood, and 11 reports of altered time perception. There was one participant in the 10 mg psilocybin arm who reported suicidal thoughts, which started and resolved on day 19, was mild in severity and was deemed by the investigator to be possibly related to study drug. But there was also one participant in the placebo arm who reported two TEAEs of suicidal ideation (one started on day 4 and lasted for 5 days; one started on day 18 and lasted for 17 days) and two TEAEs of suicidal thoughts (one started and resolved on day 79; one started and resolved on day 91). All four events were moderate in severity and considered possibly related to study drug.

In a double-blind randomized controlled crossover trial of 28 healthy participants where acute effects of psilocybin (15 and 30 mg), LSD (100 and 200 µg), and placebo were compared, both psilocybin and LSD significantly increased diastolic and systolic blood pressure, body temperature, and pupil size compared with placebo (Holze et al., 2022). Psilocybin at a dose of 30 mg, but not 15 mg, moderately increased heart rate compared with placebo. Psilocybin at a dose of 30 mg significantly impaired normal light-induced pupil constriction compared with placebo. Other adverse effects included headaches (4 subjects after psilocybin), nosebleed (1 subject after psilocybin), low mood (2 subjects after psilocybin), nausea (2 subjects after psilocybin), nightmares (1 subject after psilocybin), restlessness (1 subject after psilocybin), insomnia (1 subject after psilocybin), and flashback episodes (4 episodes after psilocybin). No severe adverse events were observed.

In a double-blind placebo-controlled crossover trial of 20 healthy adults, a single oral dose of psilocybin (0.26 mg/kg, manufactured according to GMP standards from THC_Pharm GmbH, Frankfurt, Germany) led to a significant increase in systolic and diastolic blood pressure by about 10-20 mmHg and heart rate by about 10 beats per minute during peak intoxication (Bravermanova et al., 2018). No psychotic symptoms or other psychopathology were observed in any of the subjects.

In a double-blind controlled crossover study of 32 healthy people, a single dose of psilocybin (20 mg) moderately increased systolic and diastolic blood pressure, body temperature, and pupil size compared to placebo (Ley et al., 2023). Adverse events included severe headaches, muscle twitches, and depressive symptomatology that lasted for several days to weeks, each occurring in 1 participant after

psilocybin dosing. All of these adverse events resolved spontaneously. There were no serious adverse events.

In a double-blind placebo-controlled trial of 22 healthy psychedelic-experienced adults, a single dose of psilocybin (15 mg, orally) showed significant pressor effects, with systolic hypertension (> 140 mmHg) observed in 8 participants receiving psilocybin (and 2 participants receiving placebo)(Mallaroni et al., 2023). There were no effects on heart rate.

Because the studies to date have been limited to small short-term studies, more studies with a larger sample size and longer follow-up are needed to understand the full spectrum of adverse events associated with psilocybin.

Safety in people with depression:
Psilocybin treatment is generally well tolerated in people with depression or anxiety, with the most common adverse events including nausea, headache, and minimal reductions in cardiovascular parameters (e.g., basal heart rate, blood pressure)(Scala et al., 2024).

In a 2024 meta-analysis of 6 double-blind randomized controlled trials including a total of 528 people with depression or anxiety, psilocybin administration led to significantly higher incidences of headache (RR=1.99; 95% CI, 1.06 to 3.74), nausea (RR=8.85; 95% CI, 5.68 to 13.79), anxiety (RR=2.27; 95% CI, 1.11 to 4.64), dizziness (RR=5.81; 95% CI, 1.02 to 33.03), and elevated blood pressure (RR=2.29; 95% CI, 1.15 to 4.53)(Yerubandi et al., 2024). These adverse events resolved within 48 hours. Adverse events that occurred commonly included elevated heart rate, visual perceptual effects, physical discomfort, fatigue, and mood alteration. In this meta-analysis, psilocybin administration was not associated with risk of paranoia and transient thought disorder.

In a 2024 dose-response network meta-analysis of 3 randomized controlled trials including a total of 389 patients with major depressive disorder, psilocybin administration was associated with a significantly higher risk of any adverse event compared to control (RR=1.43)(Swieczkowski et al., 2024). The risk of nausea was significantly higher with psilocybin administration (RR=8.35; $p<0.001$).

In a 2024 meta-analysis of 6 randomized controlled trials including a total of 427 patients with major depressive disorder, psilocybin-assisted psychotherapy (with 1, 2, or 3 administrations of 16-25 mg dose of psilocybin) had a small but significantly increased risk of any adverse event (RR=1.20; 95% CI, 1.01 to 1.42; based on 4 randomized controlled trials with 373 patients)(Menon et al., 2024). Psilocybin-assisted

psychotherapy also resulted in a significantly higher risk of experiencing headache (RR=1.78; 95% CI, 1.10 to 2.86) and dizziness (RR=6.52; 95% CI, 1.19 to 35.87).

In a 2024 meta-analysis of 59 clinical studies of psychedelics (psilocybin, ayahuasca, LSD, or MDMA) in people with mental disorders (e.g., depression, anxiety), psilocybin treatment (tested in 22 studies) led to no serious adverse events (Yao et al., 2024). Adverse events occurred in 70-90% of patients, with headache being the most common.

Safety in people with other conditions:
In a 2024 network meta-analysis of 9 randomized controlled trials of psychedelics (psilocybin, ketamine, MDMA, or LSD) including a total of 606 terminally ill patients (mostly cancer), psilocybin administration was overall safe and well tolerated (Marchi et al., 2024). Of the evaluated studies, there was one case where therapy was stopped due to anxiety accompanied by transient paranoid thoughts during psilocybin treatment. No other severe adverse events were reported. Mild adverse events were transient and self-resolving by the end of treatment. Adverse events with psilocybin included nausea, vomiting, psychological discomfort, and anxiety. The meta-analysis found no significant differences between psilocybin and placebo on the rates of treatment discontinuation or occurrence of any adverse events.

In a 2024 meta-analysis of 30 studies testing various psychedelic compounds (psilocybin, LSD, ayahuasca) in people with various conditions (depression, life-threatening disease, alcohol use disorder, migraine, or healthy), only 9 serious adverse events were reported for over 1000 administrations of psychedelic substances (Romeo et al., 2024). There were no suicide attempts during the acute phase and 3 participants engaged in self-harm during the post-acute phase. There was an increased risk for elevated heart rate and systolic/diastolic blood pressure for all substances and doses tested, as well as an increased risk of nausea during the acute phase. Other common side effects included headache, anxiety, decreased concentration, and decreased appetite.

Drug interactions:
Psilocybin may increase serotonin levels, and therefore, taking psilocybin with other medications that increase serotonin might increase serotonin too much, causing serious side effects including heart problems, seizures, and vomiting (WebMD.com). Taking psilocybin with stimulants (e.g., amphetamines, cocaine) may cause serious problems including increased heart rate and high blood pressure.

Sources and dosing:

Psilocybin is a Schedule I controlled substance and is not available. However, in several US states, psilocybin is accessible to people who need them clinically (e.g., Oregon, Washington DC)(Drugs.com). In May 2019, Denver, CO was the first US city to decriminalize psilocybin (reviewed in Zheng et al., 2024). Oregon was the first US state to legalize supervised medical application of psilocybin for the treatment of mental disorders. In 2020, legal possession and personal use of psilocybin mushrooms were permitted in Canada.

Dosage has not been established for any condition. In clinical trials, single oral doses ranging from 10 to 30 mg have often been used. Because there is rapid desensitization of 5HT-2A receptors by psilocybin, a single or infrequent dosing is likely better than daily dosing (vann Jones and O'Kelly, 2020).

Psilocybin can also be taken in very low, non-hallucinogenic microdoses, ranging from 100 mg to 500 mg of dried mushrooms taken orally, or 5-10% of the typical dose (reviewed in Bonnieux et al., 2023). While some anecdotal reports suggest benefits of psilocybin microdose in cognition and creativity, findings in this area of research are mixed.

Research underway:

Based on ClinicalTrials.gov, there are 123 ongoing clinical studies that are testing psilocybin (ClinicalTrials.gov). Most trials are in people with major depressive disorder, anxiety, alcohol use disorder, anorexia nervosa, obsessive-compulsive disorder, bipolar disorder, pain, fibromyalgia, seizures, and other conditions.

There is one ongoing open-label pilot study testing psilocybin for depression in people with mild cognitive impairment or early Alzheimer's disease (NCT04123314). The first dose is 15 mg/70 kg. For the second session participants will either remain at the initial dose or increase to 25 mg/70 kg at the discretion of the study team. The estimated study completion is in September 2025.

A randomized controlled trial is testing the effects of 2 macrodoses of psilocybin (25 mg, separated by one week) on synaptic vesicular density, measured by PET 18F-SynVesT-1 in people with amnestic mild cognitive impairment and in healthy participants (NCT06041152). Secondary endpoints include global cognition, memory, and executive function. This study is estimated to be completed in July 2026.

Search terms:

Pubmed, Google: psilocybin

- + Alzheimer
  + meta-analysis
  + clinical trial
  + cognitive
  + pain
  + neuropathy
  + safety
  + toxicity

Websites visited for psilocybin:

- Clinicaltrials.gov
- NIH RePORTER
- Examine.com
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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