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ACUTE EFFECTS OF PSILOCYBIN IN NON-CLINICAL POPULATIONS: A SYSTEMATIC REVIEW OF CLINICAL TRIALS

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ABSTRACT

Objective: Psilocybin has been researched as a treatment for a variety of psychiatric disorders, with increasingly robust evidence for its efficacy in treating depressive disorders. As psilocybin gains legitimacy for clinical use, we foresee a climate in which there will be increased accessibility among the general population. The purpose of this paper is to review the literature concerning the acute effects of psilocybin in non-clinical populations to answer the following questions: (a) What is the impact of psilocybin in non-clinical populations in the acute phase? (b) What are the acute effects of different psilocybin doses in non-clinical populations? **Methods:** Following PRISMA guidelines, studies published from January 1990 to December 2023 pertaining to the acute effects of psilocybin in non-clinical populations were identified from the PubMed database, using the keywords: 'psilocybin' AND 'acute' OR 'immediate', AND 'effects' AND 'healthy' OR 'volunteer' OR 'non-clinical". Two authors independently conducted a focused analysis and reached a final consensus on 32 studies that met the specific selection criteria and passed the study quality checks. **Results:** Among the 32 studies of non-clinical populations, 30 were clinical trials, and 2 were pooled analyses. Doses ranged between very low (less than 5mg/70 kg), low (8-12 mg/70kg), medium (15-20mg/70kg), and high (22-30mg/70kg). Low doses of psilocybin were found to induce altered states of consciousness and mystical experiences, which intensified with higher doses. Studies showed that psilocybin is associated with dose-dependent cognitive impairments in domains such as attention, inhibition, and memory as well as adverse effects such as transient increases in systolic and diastolic blood pressure, heart rate, and dose-dependent anxiety, fear, paranoia, fatigue, headache, and difficulty with concentration. **Conclusion:** This review details a broad range of perceived benefits and risks associated with psilocybin use in healthy volunteers. Specifically, we identified highly variable, dose-dependent effects on consciousness, mysticism, affect, and cognition. Findings from our review indicate that the risks associated with psilocybin use are relatively low. However, most studies in our review were conducted among volunteers associated with mainstream demographics in industrialized communities. While psilocybin can be confirmed as safe for certain non-clinical populations, there is a need for further research among more diverse populations to generalize these conclusions.

KEYWORDS: Psilocybin, acute or immediate effects, healthy volunteers, non-clinical populations.

INTRODUCTION

Psilocybin is a hallucinogenic compound that occurs naturally in over 300 species of fungi. Archeological evidence across modern-day Mexico and Central America suggests that psilocybin has been consumed by humans for thousands of years. Modern-day indigenous groups in those same regions still use it in traditional ceremonies and healing rituals (Court 2022). However, psilocybin is currently classified as a Schedule I drug by the United States federal government under the Controlled Substances Act in 1971 (United States Drug Enforcement Agency).

Over the past several years, psilocybin's potential healing properties have garnered increasing attention from researchers, lawmakers, and the media alike. And not for lack of a good reason: a single, high dose of psilocybin has been shown to produce sustained,

clinically significant reductions in depression and anxiety (Grob 2011; Ross 2016; Griffiths 2016). Consequently, many reviews and meta-analyses have focused on the impact of psilocybin on individuals with psychiatric illnesses (i.e., Vargas 2020; Santos & Marques 2021; Yu 2022; Crowe 2023; Hodge 2023). Significantly less attention has been directed toward the effects of psilocybin on healthy volunteers. However, the need for a comprehensive understanding of how psilocybin impacts healthy volunteers is only increasing: despite its federal Schedule I status, psilocybin has been decriminalized and even legalized for recreational use in cities and states across the United States. As of August 1, 2022, 13 states were actively considering bills that would decriminalize psilocybin (Siegel 2022).

The limited body of research concerning the impact of psilocybin on healthy volunteers is promising, particularly regarding its potential to promote sustained increases in life satisfaction, appreciation, and gratitude, as well as positive mood, attitude, and behaviors (Griffiths 2006; Griffiths 2011; Griffiths 2018; Smigielski 2019a; Smigielski 2019b). As we move forward with establishing treatment protocols, however, it is crucial to better understand the *acute* impacts of psilocybin on this population. Once the immediate effects of psilocybin are comprehensively understood, clinicians will be better be able to consider and mitigate potential risks in both clinical and non-clinical populations. The present systematic review aims to synthesize and interpret the literature that focuses specifically on the acute impact of psilocybin on non-clinical populations.

METHODS

Search Strategy: Following the PRISMA guideline, studies published from January 1990 to December 2023 that pertain to acute effects of psilocybin in non-clinical populations were identified using the PubMed database, using the keywords: 'psilocybin' AND 'acute' OR 'immediate', AND 'effects' AND 'healthy' OR 'volunteer' OR 'non-clinical". Two authors independently conducted a focused analysis and reached a final consensus on 32 studies that met the specific selection criteria and passed the study quality checks.

Study Selection Criteria and Methodology: The following inclusion criteria were used: (a) articles published in English or had a published English translation; (b) articles published in a peer reviewed journal (with all articles in PubMed being published); (c) original studies in non-clinical populations; (d) original studies of any design that focused on describing acute effects of psilocybin; (e) studies that used at least one assessment measure. Exclusion criteria included editorials, opinion pieces, and case reports. Two authors independently conducted a focused analysis then together reached a consensus on 32 studies that met the specific selection criteria. The search method is displayed in a flow diagram in Figure 1.

Data Extraction and Yield

Key findings were derived from the full-text and table of the selected 32 studies. The study designs and findings were analyzed for quality and are detailed in the table provided.

RESULTS

I. Overview

The impact of psilocybin was evaluated using 32 studies of non-clinical populations. The findings from these studies are summarized in Table 1.

The 32 reviewed studies include 30 clinical trials (24 of which were cross-over studies), and two pooled analyses. One pooled analysis included eight double-blind cross-over RCTs, and the other included 23 placebo-controlled cross-over studies (with 16 double-blind RCTs and seven open-label clinical trials). The sample size of these studies ranged from 8–261. 1–14 doses of psilocybin were administered in each study, with dose amounts between 1.5 mg–30 mg/70 kg. Very low doses include those below 5 mg/70 kg, low doses were between 8–12 mg/70 kg, medium doses between 15–20 mg/70 kg, and high doses ranged from 22–30 mg/70 kg. The instruments used to assess these effects are described in Table 4.

II. Altered States of Consciousness

Even at low doses, psilocybin induced altered states of consciousness characterized by feelings of blissful transcendence, ego dissolution, and visual and auditory hallucinations. At higher doses, these effects intensified and were sometimes accompanied by intense anxiety.

5-Dimensional Altered States of Consciousness Rating Scale

The acute effects of psychedelic compounds are frequently measured using the 5-Dimensional Altered States of Consciousness Rating scale (5D-ASC). The 5-Dimensional Altered States of Consciousness Rating scale is a psychometrically improved version of the Abnormal Mental States Questionnaire (APZ) (Table 4). The 5D-ASC consists of five dimensions: (1) Oceanic Boundlessness (OB), Anxious Ego Dissolution (AED), Visionary Restructuralization (VR), Auditory Alterations (AA), and Vigilance Reduction (VIR). Note that the first three dimensions are very similar to the APZ. These three dimensions can also be further subdivided into 11 empirically derived scales. The oceanic boundlessness dimension includes experience of unity, spiritual experience, blissful state, and insightfulness subscales. Visionary restructuralization consists of complex imagery, elementary imagery, audio-visual synesthesia, and changed meaning of percepts subscales. Anxious ego dissolution includes disembodiment, impaired control of cognition, and anxiety subscales (Table 4). Some studies analyzed 5D-ASC dimension scores, others focused on subscales, and some analyzed both.

Low doses

Taken together, results from six studies indicate that a low dose (8–12 mg/70 kg) of psilocybin has the potential to impact all 5D-ASC subscales and dimensions, however, it is less likely to induce anxiety, spiritual experience, and auditory alterations. All four low-dose studies that assessed 5D-ASC subscales observed an effect of psilocybin on 9 out of 11 scales: experience of unity, blissful state, insightfulness, complex imagery, elementary imagery, audio-visual synesthesia, changed meaning of percepts, disembodiment, and impaired control of cognition (Mason 2021; Kraehenmann 2015; Bernasconi 2014; Schmidt 2012). Two of these studies also found that low-dose psilocybin increased spiritual awareness (Schmidt 2012; Mason 2021), and only one of these studies (n=60) found that low-dose psilocybin increases anxiety (Mason 2021). Two additional studies that analyzed 5D-ASC results by dimension rather than subscale found that low-dose psilocybin was consistently associated with oceanic boundlessness, visual restructuralization, and vigilance reduction, and had less reliable but occasional effects on auditory alterations and anxious ego dissolution (Vollenweider 2007; Pokorny 2016).

Medium doses

Results from eleven studies reveal that a medium dose (15–20 mg/70 kg) of psilocybin reliably increases all 5D-ASC subscales except anxiety, and all 5D-ASC dimensions except auditory alterations – although anxious ego dissolution did sometimes occur. Results from three crossover studies indicate that, compared to low doses, medium doses of psilocybin caused more visual hallucinations, feelings of bliss, disembodiment, and audiovisual synesthesia (Kometer 2015; Lewis 2017, Mallaroni 2023).

Results from five studies that analyzed 5D-ASC subscale results reveal that medium doses typically increase scores on all 5D-ASC subscales except anxiety (Kometer 2012; Pokorny 2017; Smigielski 2020; Holze 2022; Preller 2016). Only one of these studies (n=21) found that a medium dose increased the anxiety subscale of the 5D-ASC (Preller 2016). However, in this study, the mean score for anxiety was among the lowest of the 5D-ASC subscale scores. Interestingly, two studies (n=50; n=58) that performed combined analyses of low and medium doses found that low and medium doses of psilocybin increase scores on all 11 5D-ASC subscales, including anxiety (Kometer 2015; Lewis 2017). Thus, medium dose of psilocybin may increase anxiety under some circumstances, but not others.

In terms of 5D-ASC dimensions, results from four crossover studies indicate that a medium dose of psilocybin is consistently associated with oceanic boundlessness, visionary restructuralization, and vigilance reduction, but only sometimes induces feelings of anxious ego dissolution. None of these studies found a significant effect for auditory alterations (Carter 2005; Vollenweider 2007; Holze 2022; Quednow 2012). This is unsurprising given the subjective and setting-dependent nature of psilocybin – these participants had very limited auditory input, so auditory alterations are less likely. Only two of these studies observed an effect on anxious ego dissolution, although they both consisted of very small sample sizes (Carter 2005, n=8; and Vollenweider 2007, n=16). Only one of the other two studies measured anxious dissolution, and did not find significant occurrence (Holze 2022).

High doses

Results from two studies that administered a high dose (22–30 mg/70 kg) of psilocybin to healthy participants reveal that high-dose psilocybin increases all 5D-ASC dimensions and subscales (Holze 2022; Griffiths 2018).

In highly experienced meditators, combining a high dose of psilocybin with meditation significantly increased scores on only three of five 5D-ASC dimensions – excluding anxious ego dissolution and auditory alterations – compared to meditation alone (Smigielski 2019a). Moreover, in this population, combining high-dose psilocybin and meditation increased scores on just 9 of 11 5D-ASC subscales – excluding anxiety and impaired control of cognition – compared to meditation alone (Smigielski 2019b).

Other Scales

The Abnormal Mental States Questionnaire (APZ)

The Abnormal Mental States Questionnaire (APZ) was one of the first scales intended to measure the effects of psychedelic drugs on states of consciousness. The APZ consists of three primary scales: Oceanic Boundlessness (OB), Dread of Ego Dissolution (DED), and Visionary Restructuralization (VR) (Dittrich, 1998) (Table 4). Four crossover studies measured the subjective effects of psilocybin on consciousness using the APZ. One study (n=18) found that scores on all subscales on the APZ were significantly increased after all doses of psilocybin, ranging from very low to high, with stronger effects seen for higher doses (Griffiths 2011). Hasler et al. (2004) (n=80) administered a similar range of doses and found significant correlations between psilocybin dose and scores on OB, AED, and VR (Hasler 2004). Other studies confirmed that medium and high doses of psilocybin increased scores on all APZ scales (Gouzoulis-Mayfrank 1999; Griffiths 2006).

Hallucinogen Rating Scale (HRS)

Another less common scale intended to measure the subjective effects of hallucinogenic drugs is the Hallucinogen Rating Scale (HRS), which contains six subscales: somatesthesia, affect, perception, cognition, volition, and intensity (Table 4). Results from three crossover studies indicate that all doses of psilocybin, ranging from very low to high, significantly increase scores on all subscales of the HRS (all $p<0.05$; Gouzoulis-Mayfrank 1999; Griffiths 2006; Griffiths 2011, Mallaroni, 2023).

Clinician Administered Dissociative States Scale (CADDS)

The Clinician Administered Dissociative States Scale (CADDS) is a structured clinical interview that assesses state dissociation rated by clinicians, which includes the subfactors of depersonalization, derealization, and amnesia. Results from a crossover study showed that subjective ratings of dissociation and their corresponding subfactors were significantly greater for psilocybin compared to placebo (Mallaroni, 2023).

Ego Dissolution Inventory (EDI)

The Ego Dissolution Inventory (EDI) is an 8-item self-report scale designed to measure ego-dissolution. Compared to the APZ or 5D-ASC which includes questions on depersonalization and derealization, the EDI was constructed as a direct measurement of ego-dissolution. Results from a cross-over study showed that psilocybin produced a significant increase in EDI compared with placebo (Mallaroni, 2023).

III. Mysticism and Mystical Experiences

Results from four studies indicate that even very low doses of psilocybin increase feelings of mysticism, however, medium, and high doses elicit more intense and transformative mystical experiences. Mystical experiences were assessed using the Mysticism scale (M-scale) and the States of Consciousness Questionnaire (SOCQ), which contains 30 items that comprise Mystical Experience Questionnaire (MEQ30). Both scales quantify feelings associated with mystical experience, such as unity with the world, ineffability, transcendence, ego dissolution, positive affect, noetic quality, and sacredness (Table 4).

Two crossover studies assessed psilocybin-induced mystical experiences in healthy adults that reported regular participation in religious or spiritual activities and no history of hallucinogen use. One of these studies (n=18) found that very low, low, medium, and high doses of psilocybin increased scores on all subscales of the SOCQ and M-scale; moreover, scores on all M-scale subscales were significantly higher after medium and high doses compared to low and very low doses. 72% of participants in their study had a complete mystical experience after a high dose of psilocybin, as defined by the MEQ30 (Griffiths 2011). The other crossover study on a similar population (n=30) found that high dose psilocybin increased scores on all subscales of the M-scale and the SOCQ. 61% of the participants in this study had a complete mystical experience (Griffiths 2006).

Another study (n=28) found that both medium and high doses of psilocybin increased scores on all subscales of the MEQ30 (Holze 2022). Half of the participants in this study, however, reported previous psychedelic compound use, and participant involvement in spiritual/religious activity was not measured or reported.

Notably, most of this work has been done with participants who report regular religious/spiritual participation or prior hallucinogen use, limiting the generalizability of these conclusions. However, a more recent study by Griffiths and colleagues (n=75) administered medium and high doses of psilocybin with accompanying spiritual support to adults who explicitly *did not* regularly participate in religious/spiritual activities and had not previously used psychedelics. In this population, medium and high doses of psilocybin increased scores on all subscales of the M-scale and the MEQ30. Moreover, participants who received a high dose of psilocybin accompanied by high spiritual support (compared to standard spiritual support) reported more intense mystical experiences, evidence by increased scores on introvertive mysticism (i.e., ego dissolution, transcendence, ineffability) and interpretation (i.e., positive affect, sacredness, noetic quality) (Griffiths 2018).

IV. Mood and Affect

Psilocybin had a broad range of impacts of mood states and affect – including increased positive mood, anxiety, dreaminess, introversion, peacefulness, arousal, emotional excitability, and altered emotional processing – with effects seen starting at low doses, but not very low doses. High doses induced intense happiness, psychological discomfort, and heightened anxiety.

Positive and Negative Mood

Findings from four crossover studies that used the Positive and Negative Affect Schedule (PANAS) reveal that low and medium doses of psilocybin increased positive mood but did not significantly impact negative mood (Kraehenmann 2015; Kometer 2012; Preller 2016; Pokorny 2017). However, one recent crossover study (n=34) found that a very low dose had no effect on positive or negative mood (Cavanna 2022). Interestingly, another recent crossover study (n=52) found that micro-dosing psilocybin over several weeks did not significantly impact symptoms of depression or anxiety for psychologically healthy volunteers within the 'normal' range of symptom severity (Marschall 2022).

Another crossover study utilized the profile of mood states (POMS) as a measure of mood changes. It found that psilocybin significantly increased levels across all negative mood subscales (total mood disturbance, tense, anger, fatigue, depression, and confusion) and increases in markers of positive affect (vigor, elation, and friendliness) compared with placebo (Mallaroni, 2023).

Anxiety

The evidence for psilocybin's effects on anxiety is mixed, although the likelihood of anxiety arising does appear to increase with dose. Three crossover studies measured the effect of psilocybin on state anxiety according to the State Trait Anxiety Inventory (STAI), and no effect was seen after a very low dose, a low dose, nor a medium dose (Cavanna 2022; Kraehenmann 2015;

Kometer 2012). However, one crossover study (n=28) found that a high dose of psilocybin, but not a medium dose, had a significant effect on anxiety as measured by the AMRS ($p < 0.05$) (Holze 2022).

Scales measuring altered states of consciousness such as the 5D-ASC and the APZ also measured anxiety. Briefly, results from these scales indicate that high doses typically heightened feelings of anxiety, while medium doses only had this effect in some studies. Anxiety was less common but occasionally observed after low doses. These results are reviewed in more detail in the Altered States of Consciousness section. Instances of more extreme fear, delusions, and paranoia after high doses are discussed in the Adverse Effects section.

Behavioral/Neural Measures

Four crossover studies assessed the affective impact of psilocybin through behavioral and neural responses, and their results indicate that low and medium doses (but not very low doses) of psilocybin influence emotional processing. Medium doses of psilocybin promoted a bias toward positive cues on an emotional go/no-go task, increased errors in negative facial emotion recognition, and reduced feelings of social exclusion (Kometer 2015; Preller 2016). One study (n=30) found that low doses alter neural responses to emotional faces (Bernasconi 2014). However, another study (n=52) found that micro-dosing psilocybin did not elicit a bias toward positive stimuli, suggesting that a micro-dose may not be enough to exert a strong effect on emotional processing (Marschall 2022).

Empathy

Three crossover studies assessed the impact of psilocybin on empathy. Taken together, their results reveal that medium doses of psilocybin may increase affective empathy, but very low doses do not have a significant impact. Pokorny and colleagues (n=32) found that a medium dose of psilocybin increased explicit and implicit emotional empathy. There was no effect of psilocybin on cognitive empathy or moral decision-making (Pokorny 2017). Another crossover study (n=34) found that a very low dose of psilocybin had no effect on cognitive or affective empathy (Cavanna 2022). A final study used the Interpersonal Reactivity Index (IRI) to measure changes in empathy, and found that a medium dose of psilocybin did not elicit significant changes to trait empathy relative to placebo (Mallaroni 2023).

Adjective Mood Rating Scale

Findings from three studies that used the Adjective-Mood Rating Scale (AMRS) (Table 4) indicate that medium and high doses of psilocybin acutely increase dreaminess, inactivation, introversion, and emotional excitation and can cause longer-lasting increases in inactivation (Hasler 2004; Holze 2022; Studerus 2011). Medium and high doses can also cause longer-lasting increases in dreaminess and inactivation, observed 24 hours after administration (Studerus 2011, Hasler 2004). A very low dose had no significant effect on any of the AMRS scales (Hasler 2004).

Monitor Rating Questionnaire

Two studies by Griffiths and colleagues used a Monitor Rating Questionnaire (MRQ) to evaluate participant mood and behaviors. In one crossover study (n=18), all doses of psilocybin, ranging from very low to high, increased monitor ratings of participant distance from reality, peacefulness, arousal, unresponsiveness, crying, and restlessness (Griffiths 2011). Another study (n=75) found that high doses accompanied by spiritual support increased monitor ratings of participant distance from reality, peacefulness, psychological discomfort, anxiety/fearfulness, and intense happiness (Griffiths 2018).

V. Cognition

Eleven studies measured the acute effects of psilocybin on various cognitive tasks, including nine crossover studies. Most studies reported that psilocybin did not cause global impairment at any dose, although local cognitive impairment was seen in domains including attention, inhibition, episodic memory, working memory, and creative thinking. These effects were stronger and more frequent after medium and high doses; however, low doses still caused some significant local cognitive impairment.

A crossover study by Barrett et al. (2018) (n=20) found that low, medium, and high doses of psilocybin did not cause global cognitive impairment, however, all doses caused some local impairment. Lower doses impacted episodic memory, while medium and high doses further impaired working memory, psychomotor coordination, and associative learning (Barrett 2018). Other studies found that a medium dose of psilocybin impaired controlled inhibition, but did not affect spatial working memory (Quednow 2012; Carter 2005). One crossover study (n=28) found that difficulty concentrating was among the most frequently reported adverse effects after medium and high doses of psilocybin (Holze 2022), and another pooled analysis revealed that participants still have trouble concentrating 24 hours after psilocybin administration (Studerus 2011). The frequency and severity of these effects increased as a function of dose.

Psilocybin has been shown to increase synaptic plasticity in tissues; thus, some researchers have hypothesized that it may be beneficial to memory formation (deVos 2011). One crossover study examining the effects of psilocybin on daytime or sleep-related declarative memory in 20 healthy volunteers, and used measures of spatial memory, verbal memory, and measured the influence of sleep on declarative memory processes. This study showed that there was no positive or negative effect on memory after the effects of psilocybin had subsided (Nikolič, 2023).

Attention

Low, medium, and high doses of psilocybin also impaired attentional capacities. Medium and high doses of psilocybin impaired sustained attention and attentional performance capacity (Vollenweider 2007; Hasler 2004). One of these studies (n=16) found that a low dose of psilocybin also impaired sustained attention and attentional performance, but the other study (n=80) found no effect for lower doses (Vollenweider 2007; Hasler 2004, respectively). Other crossover studies found that a medium dose of psilocybin reduces attentional tracking abilities (n=8) (Carter 2005), and a low dose of psilocybin increased reaction times on a visual vigilance task (n=39) (Schmidt 2012).

Creativity

Two studies evaluated the impact of psilocybin on creative thinking, and found that very low dose- and low-dose psilocybin did not increase creativity. One study (n=60) found that participants were less able to generate novel ideas and make novel associations while under the influence of a low dose psilocybin (Mason 2021). Another crossover study (n=60) found that a very low dose of psilocybin did not significantly impact any measure of creativity or cognitive flexibility (Cavanna 2022). From this limited evidence, it is difficult to conclude what the effects of psilocybin on creativity are, however, it seems that lower doses have no effect or a negative effect.

VI. Physiological Effects

Seven studies reported outcomes related to the physiological effects of psilocybin. These studies found that psilocybin causes transient increases in systolic blood pressure, diastolic blood pressure, and heart rate after low and high doses.

Blood pressure

There is significant evidence that psilocybin increases both systolic and diastolic blood pressure, even after a low dose. Six studies (n=253) reported significant increases in both systolic and diastolic blood pressure after a high dose of psilocybin (Griffiths 2018; Griffiths 2006; Holze 2022; Griffiths 2011; Hasler 2004; Mallaroni 2023). Two studies (n=54) also reported significant increases in systolic and diastolic blood pressure after a low dose of psilocybin (Griffiths 2011; Preller 2016). Gouzoulis-Mayfrank et al. (1999) (n=32) found no significant effect on diastolic blood pressure after a medium dose, but no other study observed a null effect of psilocybin on either systolic or diastolic blood pressure after any dose.

Heart rate

Although the results are mixed, it seems that psilocybin can increase heart rate at any dose, but this effect is more common after higher doses. Results from four studies (n=157) indicate that low, medium, and high doses of psilocybin can significantly increase heart rate (Preller 2016; Griffiths 2011; Griffiths 2018; Holze 2022). Two studies, however, found that psilocybin did not have a significant effect on heart rate. Gouzoulis Mayfrank et al. (1999) (n=32) found that a medium dose of psilocybin did not impact heart rate, while Hasler et al. (2004) (n=80) observed that psilocybin did not significantly affect heart rate at low, medium, or high doses.

VII. Adverse Effects

Seven studies assessed the acute adverse effects of psilocybin. In summary, adverse effects of psilocybin included anxiety, fear, paranoia, fatigue, headache, and difficulty concentrating. These effects were more frequently reported after higher doses. Sometimes, participants experienced more extreme fear and anxiety after higher doses, but these feelings did not impact their ability to have a mystical experience and did not persist beyond the experimental session. The day after receiving psilocybin, participants reported feeling fatigued and having trouble concentrating.

In one crossover study, the most frequently reported adverse effects after medium and high doses of psilocybin were fatigue, inability to concentrate, and headache (Holze 2022). In another crossover study, psilocybin significantly increased levels of negative mood subscales compared with placebo (total mood disturbance, tense, anger, fatigue, depression, and confusion) (Mallaroni 2023). Rucker et al. (2022) (n=89) also observed headaches as a common side effect, with 50% of participants reporting headache after a high dose of psilocybin and 30% after a low dose (compared with only 17% after placebo) (Rucker 2022). A pooled analysis by Studerus et al. (2011) revealed that these effects may be slightly longer lasting. They found that 24 hours after psilocybin administration, participants felt fatigued and had difficulty concentrating ($p < 0.01$ and $p < 0.05$, respectively). These effects increased with higher doses ($p < 0.01$ for fatigue, $p < 0.05$ for difficulty concentrating) (Studerus 2011). Other studies have also found that psilocybin reduces various attentional capacities and causes some other local cognitive impairment (see Cognition section).

Anxiety was also commonly reported. Higher doses were more likely to cause anxiety, but also occurred after medium and low doses. However, some studies found that low and medium doses of psilocybin had no effect on anxiety (see Mood and Affect section).

Sometimes, participants experienced more extreme levels of fear or anxiety. In one crossover study (n=30), some participants reported strong feelings of fear, anxiety, or paranoia after a high dose of psilocybin, however, these effects did not linger (Griffiths 2006). In another crossover study (n=18), 72.2% of the participants reported having feelings of extreme fear, fear of insanity, fear of being trapped, frightening delusions or paranoia after a high or medium dose of psilocybin, although mostly after a high dose. However, 71% of the participants who reported extreme fear, fear of insanity,

or fear of being trapped also had a complete mystical experience as assessed by the M-scale. Similarly, 50% of the participants who reported delusions and paranoia also reported a complete mystical experience. Importantly, the rates of complete mystical experience among participants who reported these feelings were not significantly different from the rest of the group. However, it should be noted that all participants in this study reported having some involvement in religious or spiritual activities (Griffiths 2011).

Table 1. Results

Authors	Sample size	Type of study	Treatment group	Control group	Measures	Results	Statistical significance
Gouzoulis-Mayfrank et al., (1999), Germany	32	Pseudo-randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 14 mg/70 kg psilocybin	2 mg/kg MDE, 0.2 mg/kg d-methamphetamine, placebo	HRS APZ STAI-State Vegetative Lability (B-L) PANSS BRMAS BRMES SBP DBP HR BT Hormone levels	Psilocybin increased scores on all scales measuring altered states of consciousness. Psilocybin also increased emotional intensity, emotional blunting, apathy, and energy, however, effects varied considerably across subjects. Some participants experienced transient adverse effects such as paranoia or feelings of lost control. Psilocybin did not affect state anxiety. Autonomic effects included increases in systolic blood pressure and body temperature, but no significant changes were seen in heart rate, hormone levels, or diastolic blood pressure.	Psilocybin significantly increased scores on all subscales of the APZ and HRS, and the B-L Vegetative lability score compared with placebo (all $p < 0.05$). Psilocybin also significantly increased scores on the PANSS positive symptom scale, PANSS negative symptom scale, PANSS general psychopathy scale, BRMAS Mania scale, and BRMES Melancholia scale compared with placebo (all $p < 0.05$). There was no significant effect on STAI state anxiety. Psilocybin significantly increased SBP and body temperature (both $p < 0.05$), but had no effect on DPB or heart rate.
Hasler et al., (2004), Switzerland	80	Randomized double-blind placebo-controlled cross-over clinical trial	4 doses: very low (3.15 mg/70 kg), low (8.05 mg/70 kg), medium (15.05 mg/70 kg), and high (22.05 mg/70 kg) of psilocybin. Each session was separated by at least two weeks	Placebo	5D-ASC AMRS FAIR SBP DBP HR BT Hormone levels	Scores on all three 5D-ASC dimensions increased as a function of psilocybin dose. Medium and high doses of psilocybin reduced sustained attention capacities, and increased inactivity, emotional excitability, and dreaminess. Psilocybin caused transient increases in systolic and diastolic blood pressure, and the highest dose increased plasma concentrations of thyroid-stimulating hormone (TSH), prolactin (PRL), adrenocorticotropic hormone (ACTH), and cortisol	There were significant correlations between psilocybin dose and scores on oceanic boundlessness ($r = 0.98$, $p < 0.003$), anxious ego dissolution ($r = 0.97$, $p < 0.005$), visual restructuralization ($r = 0.98$, $p < 0.004$), and the Global ABZ score ($r = 0.99$, $p < 0.002$). Following a high dose of psilocybin, AMRS general inactivation scores were increased after 95 and 275 minutes ($p < 0.001$ and $p < 0.01$, respectively), AMRS emotional excitability scores were increased after 95 minutes ($p < 0.001$), and AMRS dreaminess scores were increased after 95 minutes, 275 minutes, and 24 hours ($p < 0.001$, $p < 0.001$, $p < 0.01$, respectively) compared with placebo.

						(CORT). There was no effect on heart rate or body temperature.	After a medium dose of psilocybin, AMRS general inactivation scores were increased after 95 minutes and AMRS dreaminess scores were increased after 95 minutes (both $p < 0.001$). High and medium doses of psilocybin significantly decreased FAIR scores on performance value and continuity value compared with placebo (both $p < 0.001$). Compared with placebo, high dose psilocybin caused a significant increase in SBP at the 60 minute measurement only ($p < 0.001$) and a significant increase in DBP at the 90 minute measurement only ($p < 0.05$). After 105 minutes, high dose psilocybin caused significant increases in TSH, PRL, ACTH, and CORT ($p < 0.01$, $p < 0.001$, $p < 0.01$, $p < 0.05$, respectively)
Carter et al., (2005), Switzerland	8	Non-randomized double-blind placebo-controlled cross-over clinical trial	1 dose 15.05 mg/70 kg psilocybin	placebo, 50 mg ketanserin, and 15.05 mg/70 kg psilocybin + 50 mg ketanserin	5D-ASC AMRS FAIR SBP DBP HR BT Hormone levels	Psilocybin caused an increase in scores on all 5 dimensions of the 5D-ASC except auditory alterations. Psilocybin also reduced attentional tracking abilities, but did not impact spatial working memory. Pretreatment with ketanserin attenuated 5D-ASC scores, but did not influence psilocybin's effect on attentional tracking or spatial working memory.	Compared with placebo, psilocybin caused significant increases in all 5D-ASC dimensions (all $p < 0.001$, except $p < 0.05$ for reduced vigilance), excluding auditory alterations. Combining psilocybin with pretreatment ketanserin only revealed a significant effect for reduced vigilance compared with placebo ($p < 0.001$). 2 hours after drug administration, attentional tracking ability was significantly reduced after psilocybin and combined psilocybin with ketanserin compared with placebo (both $p < 0.05$). They were not significantly different from each other. Psilocybin did not significantly affect spatial working memory ability compared with placebo ($p = 0.46$). This effect was unchanged by pretreatment with ketanserin.
Griffiths et al., (2006), USA	30	Randomized double-blind	1 dose of 30 mg/70 kg psilocybin with	40 mg/70 kg methylphenidate	MRQ HRS	Scores on all hallucinogen-sensitive scales and subscales	Score on all subscales on the Hallucinogen Rating Scale, the APZ,

		controlled cross-over clinical trial	accompanying psychological support	hydrochloride with psychological support	APZ ARCI SOCQ M-scale SBP DBP	intended to measure altered states of consciousness were significantly higher after psilocybin compared with methylphenidate. Mystical experiences were common. Some participants experienced moderate or strong levels of fear, anxiety, and paranoia under the influence of psilocybin. These effects did not persist after the experimental session. Psilocybin also caused sustained increases in systolic and diastolic blood pressure for several hours after administration.	the Mysticism scale, the States of Consciousness questionnaire, and the LSD scale of the ACRI were significantly higher after psilocybin compared with methylphenidate (all p values <0.001). 61% of participants who received psilocybin had a "complete" mystical experience, compared with 11% of participants in the placebo condition. Compared with baseline taken before administration, SBP was significantly increased 30, 60, 90, 120, 240, and 300 minutes after psilocybin, and DBP was significantly increased 30, 60, 90, 120, and 180 minutes after psilocybin (all p <0.05).
Vollenweider et al., (2007), Switzerland	16	Randomized double-blind placebo-controlled cross-over clinical trial	3 doses: low (8.05 mg/70 kg psilocybin), medium (15.05 mg/70 kg psilocybin), and high: 22.05 mg/70 kg psilocybin. Each session was separated by four weeks	Placebo	5D-ASC FAIR Startle Response Measurement	Medium and high doses of psilocybin increased scores on 4 of 5 dimensions of the 5D-ASC (excluding auditory alterations), while the low dose only increased scores on 3 of 5 dimensions, excluding auditory alterations and anxious ego dissolution. Larger effects were seen at higher doses. Psilocybin also impaired attentional performance, however, it did not significantly affect startle reactivity.	Both the high and medium doses of psilocybin significantly increased scores on 4 of the 5 dimensions of the 5D-ASC, excluding auditory alterations (all p <0.001). The low dose of psilocybin significantly increased scores on visual restructuralization (p <0.01), oceanic boundlessness (p <0.001), and vigilance reduction (p <0.01) compared with placebo. No significant effects were observed for auditory alterations at any dose. 105 and 180 minutes after psilocybin administration, scores on the performance and continuity subscales of the FAIR were significantly decreased compared with placebo for all doses of psilocybin (both p <0.001 for performance, both p<0.05 for continuity).
Studerus et al., (2011), Switzerland	##	Pooled analysis of 8 randomized double-blind	1–4 doses of 3.15–22.05 mg/70 kg psilocybin. Each session was	Placebo	5D-ASC AMRS LC	All doses of psilocybin (except the very low dose) increased scores on all dimensions of the 5D-ASC,	Psilocybin significantly increased global 5D-ASC scores and scores on all five 5D-ASC dimensions (all p<0.001). Approximately 60–95 minutes after a

		placebo-controlled cross-over clinical trials	separated by at least two weeks			with increasingly larger effects as a function of dose. Acute effects of a medium dose included increased dreaminess, inactivity, introversion, feeling dazed, sensitivity, emotional excitability, and decreased concentration. Psilocybin also caused longer-lasting decreases in efficiency and activation, and increases in inactivity. Short term negative side effects were more frequent at higher doses, and included fatigue, lack of energy, difficulty concentrating, and exhaustion.	medium dose of psilocybin, scores on the dazed state, introversion, heightened mood, emotional excitation, sensitivity, and dreaminess subscales of the AMRS were all significantly increased, and concentration was decreased compared with placebo (all $p < 0.05$). At the 260–400 minute interval, scores on all of these scales, except for heightened mood and emotional excitation, remained significantly higher than placebo. During the 260-400 minute time interval and 24 hours later, scores on efficiency-activation were significantly decreased and scores on inactivation were significantly increased compared with placebo ($p < 0.05$). 24 hours after psilocybin ingestion, participants reported significant increases in fatigue ($p = 0.009$), exhaustion ($p = 0.009$), lack of energy ($p = 0.027$), and difficulty concentrating ($p = 0.046$). Item-level comparisons revealed dose effect relations for reports of fatigue ($p < 0.001$), headaches ($p < 0.001$), lack of energy ($p = .005$), and difficulty concentrating ($p = 0.015$).
Griffiths et al., (2011), USA	18	Randomized double-blind placebo-controlled cross-over clinical trial	4 doses: very low (5 mg/70 kg), low (10 mg/70 kg), medium (20 mg/70 kg), and high (30 mg/70 kg) of psilocybin. Each session was separated by at least four weeks and psychological support was provided	Placebo	HRS APZ M-scale ARCI SOCQ MRQ SBP DBP HR	Scores on all scales measuring altered states of consciousness and measures of mystical experience increased as a function of psilocybin dose, with significant effects observed for even the smallest dose. Monitors observed increased arousal, restlessness, unresponsiveness, anxiety, crying, and peacefulness. Adverse effects of higher doses included anxiety,	Scores on all subscales of the APZ and all subscales of the HRS were significantly increased compared with placebo for all active doses, increasing as a function of dose (all Fisher's LSD $p < 0.05$). Scores on all subscales of the SOCQ were significantly increased compared with placebo for all doses (all Fisher's LSD $p < 0.05$). Total M-scale scores and scores on all subscales measured after psilocybin administration were significantly higher than placebo for all doses (all Fisher's LSD $p < 0.05$). Scores on M-scale total

						extreme ratings of fear, fear of insanity, or fear of being trapped in some participants. Following the high dose of psilocybin, 39% of participants reported feelings of extreme fear or insanity, and 44% of participants reported frightening delusions or paranoia. 72% volunteers had a "complete" mystical experience in at least one of the higher dose sessions, including 71% of the participants who reported extreme fear or insanity, and 50% of those who reported delusions or paranoia. All doses of psilocybin increased systolic and diastolic blood pressure, and higher doses increased heart rate.	and all subscales were significantly higher for medium and high doses compared with the low and very low doses (Fisher's LSD p <0.05). On the MRQ, scores on stimulation/arousal, unresponsiveness to questions, distance from ordinary reality, anxiety/fearfulness, tearing/crying, restless/fidgety, and peace scales were significantly higher for all psilocybin doses compared with placebo (all Fisher's LSD p <0.05). Compared with placebo, all doses of psilocybin significantly increased SBP and DBP, and the medium and high doses significantly increased heart rate (all Fisher's LSD p <0.05).
Quednow et al., (2012), Switzerland	16	Randomized double blind placebo-controlled cross-over clinical trial	1 dose 18.2 mg/70 kg psilocybin	placebo, 40 mg ketanserin, and 18.2/70 kg psilocybin + 40 mg ketanserin	5D-ASC Stroop Task Startle Response Measurement	Psilocybin increased scores on all three 5D-ASC dimensions. Psilocybin also impaired controlled inhibition, but did not affect the startle reflex (i.e., prepulse inhibition). Combining psilocybin with ketanserin increased controlled inhibition, but weakened the startle reflex. Impairment of the startle reflex in this condition was associated with stronger alterations in states of consciousness.	Psilocybin significantly increased scores on all 5D-ASC dimensions (all p <0.0002) and increased error rates in the conflict condition of the Stroop task compared with placebo (p <0.0001). Compared with placebo, combining psilocybin and ketanserin significantly reduced error rates in the conflict condition of the Stroop task (p <0.0001) and reduced startle activity (p <0.015). Reduced startle reactivity was significantly correlated with higher scores on oceanic boundlessness (r =0.47, p <0.01) and visual restructuralization (r =0.40, p <0.05)
Studerus et al., (2012), Switzerland	##	Pooled analysis of 23 placebo-controlled	1–4 doses of 8.05–22.05 mg/70 kg psilocybin. Each	Placebo	5D-ASC OAV	Aside from drug dose, the personality trait absorption is among the most significant	Trait absorption predicted audio visual synesthesia (r~0.6, p <0.001), spiritual experience (r~0.4, p <0.01), experience

		cross-over studies, some double-blind and most randomized	session was separated by at least two weeks			predictor variables for a pleasant and mystical experience. Other variables include being in an emotionally excitable and active state before drug intake, and having few psychological problems in the weeks before. High trait emotional excitability and being in a PET scanner predicted more negative outcomes.	of unity (r~0.5, p <0.001), oceanic boundlessness (r~0.4, p <0.001), and complex imagery (r~0.4, p <0.01). Emotional excitability predicted spiritual experience (r~0.5, p <0.001) and anxiety (r~0.6, p <0.001). High activity before drug intake predicted changed meaning of percepts (r~0.6, p <0.001), elementary imagery (r~0.5, p <0.001), complex imagery (r~0.4, p <0.01), and visual restructuralization (r~0.4, p <0.001). Being in a PET scanner predicted anxiety (r~0.6, p <0.001).
Schmidt et al., (2012), Switzerland	39	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 8.05 mg/70 kg psilocybin	Placebo, 10 mg S-ketamine followed by continuous infusions of 0.006 mg/kg per minute	5D-ASC (shortened) Distracting Visual Vigilance Test	Psilocybin induced an altered state of consciousness consisting of elementary and complex imagery, changed meanings of percepts, feelings of bliss, experiences of unity, and impaired control and cognition. Psilocybin slowed reaction times and reduced sensitivity in a visual vigilance task, but it did not disrupt prediction error processing or signaling.	Psilocybin increased global ASC scores (p <0.000001) and scores on all 11 5D-ASC subscales (all p <0.01) excluding anxiety. There was also no significant effect on auditory alterations. Psilocybin increased reaction times on a visual vigilance test compared with placebo (p <0.00001) and reduced sensitivity indices compared with placebo (p <0.000001).
Carhart-Harris et al., (2012), United Kingdom	10	Randomized open-label placebo-controlled cross-over clinical trial	1 dose of 2 mg psilocybin	Placebo	Ratings of personal memories	Psilocybin increased ratings of positive personal memories as more vivid, visual, emotional, and positive. Psilocybin increased activity in visual and other sensory areas of the brain during memory recollection. Participants did not report dramatic relivings of memories.	Psilocybin significantly increased ratings of how vivid (p <0.049) and visual (p <0.041) memories were compared with placebo. Ratings for positive and emotional were not independently significant, but when all four factors were combined, ratings for the combined measures were significantly higher for psilocybin than placebo (p =0.0003).
Kometer et al., (2012), Switzerland	17	Randomized double-blind placebo-	1 dose of 15.05 mg/70 kg psilocybin	Placebo, 50 mg ketanserin, and 15.05 mg/70 kg	5D-ASC PANAS STAI–State	Psilocybin increased scores on all 5D-ASC subscales (excluding anxiety),	Compared with placebo, psilocybin significantly increased global 5D-ASC scores (p <0.000001) and scores on 10

		controlled cross-over clinical trial		psilocybin + 50 mg ketanserin	Facial emotional recognition task Emotional go/nogo task	increased positive mood, and reduced recognition of negative facial expressions. When combined with ketanserin, these effects were reduced. Psilocybin had no significant effect on negative mood or state anxiety. Psilocybin also increased goal-directed behavior toward positive cues on the emotional go/nogo task.	of the 11 subscales of the 5D-ASC, excluding anxiety (all $p < 0.01$). Compared with placebo, psilocybin significantly increased positive affect scores ($p < 0.00001$) and increased error rates for negative facial emotional recognition ($p < 0.05$). None of these effects were significant when psilocybin was pretreated with ketanserin. On the emotional go/nogo task, error rates were higher for negative stimuli than for positive stimuli after psilocybin ($p<0.05$), but not after placebo. There was a significant increase in error rates significant decreases in reaction times to go-stimuli were observed after consecutive positive stimuli compared to non-consecutive positive stimuli, and reaction times were significantly increased after consecutive negative stimuli compared with non-consecutive negative stimuli for psilocybin administration, but not placebo ($p < 0.001$, $p < 0.01$, respectively).
Kometer et al., (2013), Switzerland	15	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 15.05 mg/70 kg psilocybin	placebo, 50 mg ketanserin, and 15.05 mg/70 kg psilocybin + 50 mg ketanserin	5D-ASC Visual stimuli categorization task	Psilocybin increased global 5D-ASC scores when it was not preceded by ketanserin. Psilocybin did not impair performance in a visual stimuli categorization task.	Psilocybin with placebo pretreatment increased general 5D-ASC scores ($p < 0.0000001$) but psilocybin with ketanserin pretreatment did not ($p=1$).
Bernasconi et al., (2014), Switzerland	30	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 11.9 mg/70 kg psilocybin	Placebo	5D-ASC	Psilocybin increased global 5D-ASC scores and scores on 9 of 11 subscales of the 5D-ASC, excluding anxiety and spiritual experience. Elementary and complex imagery had the highest mean scores on all subscales. Psilocybin also modulated emotional face processing, causing an initial reduction in	Psilocybin significantly increased global 5D-ASC scores and scores on 9 of the 11 5D-ASC subscales (excluding spiritual experience and anxiety) compared with placebo (all $p < 0.001$). Psilocybin caused significant initial reductions in response to neutral and fearful faces in the left STG, bilateral cingulate cortex, left parahippocampal gyrus, and right insula/parahippocampal gyrus ($p < 0.01$). In a slightly later time

						limbic activity in response to fearful and neutral faces, and a delayed reduction in limbic activity in response to happy faces.	period, a significant reduction in response to happy faces was seen in the right prefrontal cortex, right occipito-temporal cortex, and left STG ($p < 0.01$).
Kraehenmann et al., (2015), Switzerland	25	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 11.2 mg/70 kg psilocybin	Placebo	5D-ASC PANAS STAI–State	Psilocybin increased scores on 9 of 11 5D-ASC subscales, excluding spiritual experience and anxiety. Psilocybin also increased positive affect, and this increase in positive affect was associated with reduced reactivity in the right amygdala. There was no effect of psilocybin on negative affect or state anxiety.	Psilocybin significantly increased scores on 9 of 11 5D-ASC subscales (all $p < 0.001$, except $p < 0.05$ for impaired control and cognition) excluding spiritual experience and anxiety. Psilocybin significantly increased positive affect compared with placebo ($p < 0.001$). Increase in positive affect was significantly correlated with decreased activity in the right amygdala ($r = -0.46$, $p < 0.05$).
Kometer et al., (2015), Switzerland	50	Randomized double-blind placebo-controlled cross-over clinical trial (data collapsed across 3 studies)	1 dose: low (11.9 mg/70 kg) or medium (15.05 mg/70 kg) of psilocybin	Placebo	5D-ASC	Psilocybin increased scores on all 11 subscales of the 5D-ASC. Compared to the low dose, the medium dose increased basic visual imagery and feelings of bliss, but all other subscales were not significantly affected by dose.	Psilocybin significantly increased scores on all 11 subscales of the 5D-ASC compared with placebo (all $p < 0.05$). Scores on elementary hallucinations and blissful state subscales were significantly higher after the medium dose compared with the low dose ($p < 0.05$, $p < 0.01$, respectively).
Pokorny et al., (2016), Switzerland	36	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose 11.9 mg/70 kg psilocybin	Placebo	5D-ASC	Psilocybin increased scores on all 5D-ASC dimensions in one experimental group. In the other experimental group, psilocybin increased scores on all dimensions except auditory alterations.	In one experimental condition, psilocybin significantly increased scores on all 4 of 5 dimensions of 5D-ASC (all $p < 0.05$), excluding auditory alterations, compared with placebo. In the other condition, psilocybin increased scores on all dimensions of the 5D-ASC compared with placebo ($p < 0.01$).
Preller et al., (2016), Switzerland	21	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 15.05 mg/70 kg psilocybin	Placebo	5D-ASC PANAS Post-social exclusion task questionnaire SBP DBP	Psilocybin increased ratings on all 11 5D-ASC subscales and increased positive affect. Subscales within the visual restructuralization dimension had the highest mean scores	Psilocybin increased ratings on all 11 5D-ASC subscales compared with placebo (all $p < 0.001$, except anxiety and spiritual experience, both $p < 0.05$). Psilocybin also significantly increased positive affect from baseline ($p < 0.05$).

					HR	of all subscales, while anxiety and spiritual experience had the lowest. Other effects included decreased feelings of social exclusion, with corresponding decreases in neural responses to social exclusion. Psilocybin also caused slight increase in systolic blood pressure, diastolic blood pressure, and heart rate.	Participants who received psilocybin reported significantly reduced feelings of social exclusion compared with those who received placebo ($p < 0.01$). Psilocybin also caused significant increases in SBP ($p < 0.001$), DBP ($p = 0.01$), and heart rate ($p = 0.04$).
Pokorny et al., (2017), Switzerland	32	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 15.05 mg/70 kg psilocybin	Placebo	5D-ASC PANAS MET Moral Dilemma Task	Psilocybin significantly increased scores on 10 of 11 subscales (excluding anxiety) of the 5D-ASC. Psilocybin also increased positive affect, explicit emotional empathy, and implicit emotional empathy. Increases in implicit emotional empathy were associated with changed meanings of percepts. There was no significant effect of psilocybin on negative affect, cognitive empathy, or moral decision-making.	Psilocybin increased scores on all 11 subscales of the 5D-ASC excluding anxiety compared with placebo (all $p < 0.001$, except spiritual experience $p < 0.05$). Compared with baseline, psilocybin significantly increased positive affect ratings ($p < 0.05$), but placebo did not ($p > 0.02$). Compared with placebo, psilocybin significantly increased mean ratings of explicit and implicit emotional empathy (both $p < 0.01$). Higher scores on the changed meanings of percept subscale significantly predicted increased scores of implicit emotional empathy ($beta = .52$, $t(31) = 3.35$, $p < 0.01$).
Lewis et. al, (2017), Switzerland	58	Randomized double-blind placebo-controlled cross-over clinical trial	1 dose of 11.2 mg/70 kg (low) or 15.05 mg/70 kg (medium) psilocybin	Placebo	5D-ASC Cerebral blood flow	Psilocybin increased scores on all 11 subscales of the 5D-ASC. Compared with the low dose, the medium dose of psilocybin caused more disembodiment, audiovisual synesthesia, and elementary and complex imagery. Psilocybin also caused distinct changes in global and cerebral blood flow.	Scores on all 11 5D-ASC subscales were increased significantly after psilocybin compared with placebo (all $p \leq 0.001$). Significantly larger effect sizes were seen for the medium dose on scales of disembodiment ($p = 0.017$), elementary imagery ($p = 0.016$), complex imagery ($p = 0.026$), and audiovisual synesthesia ($p = 0.005$) compared with the low dose.
Griffiths et al., (2018),	75	Randomized	2 doses of	1 mg/70 kg	5D-ASC	Psilocybin increased scores	Ratings on all dimensions of the 5D-

USA		double-blind placebo-controlled clinical trial	psilocybin: medium (20 mg/70 kg) and high (30 mg/70 kg), accompanied either by standard support for spiritual practice or high support for spiritual practice. Sessions were separated by approximately four weeks	psilocybin (placebo) with standard support for spiritual practice	M-scale MRQ HRS SOCQ SBP DBP HR	on all dimensions of the 5D-ASC and all subscales of the HRS. Mysticism was increased after both active doses of psilocybin, particularly when they were accompanied by high support for spiritual practice. Monitors reported a broad range of participant moods and behaviors, including feelings of distance from ordinary reality, intense happiness, peace, anxiety, psychological discomfort, physical distress, and nausea. High doses of psilocybin also caused increases in systolic blood pressure, diastolic blood pressure, and heart rate.	ASC and all subscales of the M-scale, MEQ30, and HRS were significantly higher for both high dose conditions compared to the low dose placebo condition (all $p < 0.01$). The high-dose high support group had significantly higher ratings on the interpretation, introvertive, and total subscales of the M-scale compared with the high dose standard support condition (all $p < 0.05$). MRQ ratings of phyical distress, psychological discomfort, peace/harmony, joy, nausea, distance from ordinary reality, and anxiety/fearfulness were significantly higher in both active dose conditions compared with placebo (all $p < 0.05$). Compared with placebo, SBP, DBP, and heart rate were significantly higher in both high dose conditions (all $p < 0.01$).
Barrett et al., (2018), USA	20	Randomized double-blind placebo-controlled cross-over clinical trial	3 doses: low (10 mg/70 kg), medium (20 mg/70 kg), and high (30 mg/70 kg) of psilocybin. Each session was separated by an average of 10 days	Placebo and high-dose DXM (400 mg/50 kg)	Select tasks from the CNB (MMSE, PLOT, Mpraxis, Letter N-back) DSST Word encoding, recognition, and recall task	Psilocybin did not cause global cognitive impairment. Local cognitive impairment was seen after psilocybin administration in domains including psychomotor coordination, visual perception, associative learning, episodic memory, and working memory. Higher doses caused more significant local cognitive impairment than low doses.	MMSE scores were not significantly correlated with drug condition. Medium and high doses of psilocybin both significantly increased response times on a motor praxis task compared with placebo (both $p < 0.01$). The high dose of psilocybin significantly increased reaction times for incorrect trials on the PLOT compared with the medium dose ($p < 0.001$), the low dose ($p < 0.05$), and placebo ($p < 0.05$). Compared with placebo, there were significant decreases in scores on a word recall task after low dose psilocybin ($p < 0.05$), medium dose psilocybin ($p < 0.001$), and high dose psilocybin ($p < 0.0001$). Compared with placebo, psilocybin also exerted a significant dose-dependent decrease on discriminability in the letter N-back task ($p < 0.05$ for the medium

							dose). Medium and high doses of psilocybin impaired associative learning on the DSST and decreased the number of trials attempted (all p <0.0001)
Smigielski et al., (2019a), Switzerland	38	Randomized double-blind placebo-controlled clinical trial	1 dose of 22.05 mg/70 kg psilocybin on the 4th day of a 5-day meditation retreat	Placebo on the 4th day of a 5-day meditation retreat	5D-ASC	Psilocybin-assisted meditation increased 5D-ASC dimension scores on oceanic boundlessness, visual restructuralization, and vigilance reduction, but had no significant effect on anxious ego dissolution or auditory alterations	Compared with placebo, psilocybin significantly increased scores 5D-ASC dimensions oceanic self-boundlessness (p <0.0001), visionary restructuralization (p <0.0001), and vigilance reduction (p <0.05).
Smigielski et al., (2019b), Switzerland	39	Randomized double-blind placebo-controlled clinical trial	1 dose of 22.05 mg/70 kg psilocybin on the 4th day of a 5-day meditation retreat	Placebo on the 4th day of a 5-day meditation retreat	5D-ASC M-scale TMS FMI short-form MEDEQ	Psilocybin-assisted meditation increased scores on 9 of 11 5D-ASC subscales, specifically those related to oceanic boundlessness and visual restructuralization, but did not increase scores on anxiety or impaired control and cognition (subscales associated with anxious ego dissolution). Psilocybin increased meditation depth, which was positively associated with feelings of oceanic boundlessness and positive interpretations of mystical experience. Psilocybin-assisted meditation induced strong mystical experiences. There was no effect of psilocybin on state mindfulness. However, trait mindfulness immediately after the retreat was higher for the psilocybin group than the placebo group. Trait optimism and openness	Psilocybin significantly increased scores on 9 of 11 5D-ASC subscales (all p <0.01), excluding anxiety and impaired control and cognition, compared with placebo. Compared with placebo, psilocybin also increased scores on all 3 dimensions of the M-scale (p <0.01) and all subdimensions of the M-scale (p <0.001). The psilocybin group also had higher MEDEQ scores on the day of drug administration and higher FMI scores 2 days later than the placebo group (p <0.05, p <0.001, respectively). Reappraisal of emotions decreased anxious ego dissolution (p <0.0001, η2 =0.21), and non-judgmental acceptance of thoughts and emotions increased introvertive mysticism (p <0.05 η2 =0.14) and interpretation of mystical experience (p < 0.05 η2 = 0.16). Meditation depth significantly predicted variance in oceanic boundlessness (p <0.0001, η2 =0.38) and interpretation of mystical experience (p <0.05 η2 =0.13). Optimistic attitudes about life predicted a significant amount of variance in oceanic boundlessness and visual restructuralization (η2 =0.23–25, both p

						were associated with stronger subjective effects and increased mysticism. Mindfulness-related emotional regulation skills were associated with decreased anxiety and increased mysticism.	<0.01), as well as all 3 dimensions of the M-scale (η2 =0.16–0.27, all p <0.01). Openness also predicted a significant amount of variance in oceanic boundlessness (η2 =0.18) and all 3 dimensions of the M-scale (η2 =0.12–0.18, all p <0.05).
Smigielski et al., (2020), Switzerland	17	Randomized, double-blind, placebo-controlled crossover clinical trial	1 dose of 16.1 mg/70 kg psilocybin	Placebo	5D-ASC Auditory self-recognition	Psilocybin increased scores on 9 of 11 5D-ASC subscales, excluding anxiety and spiritual experience. Psilocybin also impaired participants' ability to recognize their own voice.	There was a significant difference between placebo and psilocybin for 9 of the 11 subscales of the 5D-ASC (all p < 0.001, except insightfulness was p < 0.05), excluding anxiety and spiritual experience
Mason et al., (2021), the Netherlands	60	Randomized double-blind placebo-controlled clinical trial	1 dose of 11.9 mg/70 kg psilocybin	Placebo	5D-ASC PCT AUT	Psilocybin increased scores on all 11 subscales of the 5D-ASC. While under the influence of psilocybin, participants were worse at generating novel ideas and making associations.	Psilocybin was associated with increased scores on all 11 5D-ASC subscales (p <= 0.001). Compared with placebo, psilocybin decreased scores on the fluency scales of both of the AUT and PCT, and the convergence scale of the PCT (all p < 0.01), and decreased scores on the originality scale of the PCT (p = 0.02).
Marschall et al., (2022), The Netherlands	52	Randomized double-blind placebo-controlled cross-over clinical trial	14 doses of 1.5 mg psilocybin, self-administered every 3 days for 3 weeks	Placebo	DASS-21 Emotional go/no-go task MAIA	Compared with placebo, microdosing psilocybin did not significantly improve symptoms of depression or anxiety, nor did it improve interoceptive body awareness or emotional processing.	Scores on the DASS-21 and the MAIA were not significantly different between psilocybin and placebo. Performance on an emotional go/no-go task also did not differ significantly between psilocybin and placebo.
Rucker et al., (2022), United Kingdom	89	Randomized, double-blind, placebo-controlled clinical trial	1 dose of 10 mg (low) or 25 mg (high) psilocybin. Psychological support was provided from a trained therapist	Placebo	Monitoring of TEAEs	The most commonly reported Treatment-Emergent Adverse Events (TEAEs) after low and high doses of psilocybin were visual hallucinations, illusions, mood alterations, headache, and fatigue. TEAEs were more frequent after a high dose than a low dose	After a high dose of psilocybin (n =30), 70% of participants reported visual hallucinations, 60% reported illusions, 50% reported mood alterations, and 50% reported headache. After a low dose of psilocybin (n =30), 60% of participants reported visual hallucinations, 63% reported illusions, 43% reported mood alterations, and 30% reported headache. After receiving

							placebo (n =29), 7% of participants reported visual hallucinations, 14% reported illusions, 21% reported mood alterations, and 17% reported headache.
Holze et al., (2022), Switzerland	28	Randomized double-blind placebo-controlled cross-over clinical trial	2 doses: 1 medium (15 mg) and 1 high (30 mg). Sessions were separated by at least 10 days.	placebo 100-200 micrograms LSD	5D-ASC VAS AMRS SOCQ SBP DBP HR BT Hormone levels	A high dose of psilocybin increased scores on all 5D-ASC dimensions and subscales, while a medium dose increased scores on almost all dimensions and subscales, exclcuding anxious ego dissolution, auditory alterations, disembodiment, and anxiety. Both doses increased excitation, introversion, inactivity, dreaminess, and mystical experience. The most frequently reported adverse effects were fatigue, headache, and inability to concentrate. The high dose, but not the medium dose, increased anxiety on the AMRS. Both doses increased systolic and diastolic blood pressure, body temperature, and cortisol (CORT) plasma levels. The high dose also increased heart rate, as well as plasma levels of prolactin (PRL) and oxytocin.	A high dose of psilocybin increased scores on all dimensions and subscales of the 5D-ASC compared with placebo (all $p < 0.001$, except $p < 0.05$ for anxiety). Compared with placebo, a medium dose of psilocybin increased scores almost all dimensions and subscales of the 5D-ASC ($p < 0.05$), except for anxious ego dissolution, auditory alterations, disembodiment, and anxiety. Both doses significantly increased VAS scores on content, talkativeness, openness, decreased concentration, perception of time, speed of thinking, and desire to be alone from baseline compared with placebo (all $p < 0.001$). Both doses also increased scores on the emotional excitation, introversion, inactivity, and dreaminess subscales on the AMRS (all $p < 0.01$), as well as scores on all subscales of the MEQ30 and MEQ43 compared with placebo (all $p < 0.001$). The high dose of psilocybin, but not the medium dose, had a significant effect on anxiety compared to placebo ($p < 0.05$). Compared with placebo, both doses of psilocybin significantly increased SBP, DBP, and CORT plasma levels (all $p < 0.001$), while the high dose also significantly increased heart rate ($p < 0.01$) and PRL and oxytocin plasma levels ($p < 0.001$, $p < 0.01$, respectively).
Cavanna et al., (2022), Argentina	34	Randomized double-blind placebo-controlled	1 dose of 5 mg psilocybin	Placebo	VAS TAS TECA Well-being (STAI,	Self-reported subjective effects were only more significant for participants who correctly guessed their	Participants who correctly guessed their experimental condition had significantly higher VAS scores on both psilocybin dose days compared with days they

		cross-over clinical trial			PANAS, PSS, BIEPS, MWQ) Creativity (CFS, CPS, FSS, RAT, AUT, WK) Cognition (BR, BM, TMT, AB, Go/No-go, Stroop Test)	condition compared with placebo. There was no significant effect of microdosing psilocybin on measures of creativity, well-being, empathy, or cognitive flexibility. Microdosing slightly impaired performance on cognitive tasks related to attention and coordination.	received placebo (both $p < 0.05$). There was no significant difference between psilocybin and placebo on measures relating to well-being, creativity, empathy, and cognitive flexibility, including STAI, PSS, PANAS, TAS, BIEPS, MWQ, FSS, CPS, RAT, AUT, TECA, CFS, and WK. Compared with placebo, psilocybin decreased visibility in the Attentional Blink Task and increased reaction time in the Stroop task ($p < 0.05$), but both differences are only significant before correction for multiple comparisons.
Nikolic et al., (2023), Czech Republic	20	Randomized double blind placebo-controlled cross-over clinical trial	1 dose 18.2 mg/70 kg psilocybin	Placebo	GMLT, RAVLT, PALT	Psilocybin did not improve memory consolidation or negatively affect memory consolidation	No significant difference in the psilocybin group for the maze learning task, verbal learning retention/recognition, or memory consolidation
Mallaroni et al., (2023), Netherlands	22	Randomized double blind placebo-controlled cross-over clinical trial	1 dose of 15 mg psilocybin	1 dose 20mg 2C-B	VAS, 5D-ASC, EDI, IRI Mood (POMS Dissociation (CADSS) Psychedelic effects (BVAS) Drug liking (SDRQ)	Psilocybin caused an increase in scores across measures of drug intensity, mood and time perception, emotional lability, drug liking, dissociation, perception, consciousness, 5D-ASC, cognitive impairments, and cardiovascular effects	Psilocybin generated significant increases in most VAS scores of subjective drug intensity, mood, time perceptions, happiness, creativity, emotional lability, dissociation, alterations in consciousness, all dimensions of 5D-ASC, EDI, HRS, impairments in cognitive function, and effects on vital signs.

Table 2: Instruments used by the reviewed studies for measurement of psilocybin's acute effects.

Name	Abbreviation	Domains Measured
Hallucinogen Rating Scale (Griffiths et al., 2011, Mallaroni et al., 2023)	HRS	Measures acute subjective effects of hallucinogenic drugs. The scale includes six subscales: somatesthesia, affect, perception, cognition, volition, and intensity.
Abnormal Mental States Questionnaire (Dittrich, 1998)	APZ	Measures altered states of consciousness and contains three primary scales: Oceanic Boundlessness, associated with feelings of unity with the world and transcendence of space and time, Dread of Ego Dissolution, which includes feelings of dysphoria and anxiety associated with ego loss, and Visionary Restructuralization, which involves visual hallucinations and audiovisual synesthesia.
State-Trait Anxiety Inventory (Gouzoulis-Mayfrank et al., 1999)	STAI	Measures both state and trait anxiety. Consists of two subscales: STAI-State measures transient anxiety, and STAI-Trait measures dispositional anxiety.
Bech-Rafaelsen Mania Scale (Gouzoulis-Mayfrank et al., 1999)	BRMAS	Measures severity of a manic state.
Bech-Rafaelsen Melancholia Scale (Gouzoulis-Mayfrank et al., 1999)	BRMES	Measures severity of a melancholic (depressed) state.
Positive and Negative Syndrome Scale (Gouzoulis-Mayfrank et al., 1999)	PANSS	Assesses symptom severity in schizophrenia.
5-Dimensional Altered States of Consciousness rating scale (Dittrich, 1998; Studerus et al., 2011)	5D-ASC	The scale includes five main dimensions: oceanic boundlessness, visionary restructuralization, anxious ego dissolution, reduced vigilance, and auditory alterations. Only the first three dimensions are used to calculate global scores, and these three dimensions can be further divided into 11 subscales. The oceanic boundlessness dimension includes experience of unity, spiritual experience, blissful state, and insightfulness subscales. Visionary restructuralization consists of complex imagery, elementary imagery, audio-visual synesthesia, and changed meaning of percepts subscales. Anxious ego dissolution includes disembodiment, impaired control of cognition, and anxiety subscales. The 5D-ASC is a revised version of the OAV and contains all OAV items.
Adjective Mood Rating Scale (Hasler et al., 2004)	AMRS	This scale is designed to measure mood states, and consists of 15 subscales: efficiency-activation, concentration, inactivation, tiredness, drowsiness, extroversion, introversion, self-confidence, heightened mood, emotional excitation, sensitivity, aggression-anger, apprehension-anxiety, depressiveness, dreaminess. These subscales can be reorganized into seven affective domains: performance-related activity, general inactivation, extroversion-introversion, general well being, emotional excitability, anxiety-depressiveness, and dreaminess.
Frankfurt Attention Inventory (Hasler et al., 2004)	FAIR	This task assesses concentration behavior and includes four subscales: marker value (understanding of instructions), performance value (performance on task), quality value (proportion of attentively made decisions during task), continuity value (continuity of concentration during task).
Monitor Rating Questionnaire (Griffiths et al., 2006; Griffiths et	MRQ	Monitor ratings of participant mood and behavior along 11–20 dimensions (depending on the version).

al., 2011; Griffiths et al., 2018)		Examples of dimensions include overall drug effect, distance from ordinary reality, anxiety, joy, systematized ideas of reference, crying, and nausea/vomiting.
Addiction Resource Center Inventory (Griffiths et al., 2006)	ARCI	Differentiates between the subjective effects of different psychoactive drugs and measures severity of effects.
States of Consciousness Questionnaire (Griffiths et al., 2006)	SOCQ	This scale is intended to assess mystical experience and contains 7 subscales: internal unity, external unity, transcendence of time and space, ineffability and paradoxicality, sense of sacredness, noetic quality, and deeply felt positive mood. 43 items on this scale compose the MEQ, and the MEQ30 is a shortened 30-item version.
Mysticism Scale (Hood et al., 2001)	M-Scale	Assesses mystical experience and consists of 3 subscales: introvertive, extrovertive, and interpretation. Introvertive mysticism is characterized by ego dissolution, transcendence of time and space, and ineffability of the experience. Extrovertive mysticism includes a sense of unity with the world and feelings of inner subjectivity (i.e., perceiving everything in the world as conscious). Finally, interpretation consists of positive affect, sacredness, and noetic quality of the experience (i.e., they gained some knowledge beyond what could be deduced from sensory perception or logic).
List of Complaints (Studerus et al., 2011)	LC	Measures general discomfort, incorporating both psychological and somatic symptoms.
Altered States of Consciousness Rating Scale (Studerus et al., 2012)	OAV	Measures alterations in consciousness using 3 dimensions of the 5D-ASC: oceanic boundlessness, dread of ego dissolution, and visionary restructuralization. The OAV is a revised and improved version of the APZ.
Positive and Negative Affect Schedule (Kometer et al., 2012)	PANAS	Measures positive and negative affect
Multifaceted Empathy Test (Pokorny et al., 2017)	MET	Assesses cognitive empathy (ability to read other's emotions), explicit emotional empathy, and implicit emotional empathy.
Mini-Mental Status Examination (Barrett et al., 2018)	MMSE	Measures global cognitive function.
Penn Line Orientation Task (Barrett et al., 2018)	PLOT	Measures visual-spatial orientation.
Digit Symbol Substitution Task (Barrett et al., 2018)	DSST	Measures executive function, cognitive flexibility, and associative learning.
Toronto Mindfulness Scale (Smigielski et al., 2019b)	TMS	Assesses state mindfulness.
Freiburg Mindfulness Inventory (Smigielski et al., 2019b)	FMI	Assesses trait mindfulness.
Meditation Depth Questionnaire (Smigielski et al., 2019b)	MEDEQ	Measures depth of meditation, focusing on five main aspects: hindrances, relaxation, concentration, transpersonal qualities, and non-dual qualities.
Picture Concept Task (Mason et al., 2021)	PCT	Measures both convergent thinking (correctness) and divergent thinking (novel idea generation).
Alternative Uses Task (Mason et al., 2021)	AUT	Measures divergent thinking.
Depression Anxiety Stress Scale (Marschall et al., 2022)	DASS-21	Measures mood and anxiety symptoms.
Multidimensional Assessment of	MAIA	Measures interoceptive awareness.

Interoceptive Awareness Scale (Marschall et al., 2022)		
Treatment-Emergent Adverse Events (Rucker et al., 2022)	TEAEs	Measures adverse psychological and physical effects following drug administration.
Visual Analogue Scale (Holze et al., 2022; Cavanna et al., 2022, Malllaroni et al., 2023)	VAS	Assesses subjective effects beyond those covered in other scales. Content of the VAS varied between studies.
Tellegen Absorption Scale (Cavanna et al., 2022)	TAS	Measures an individual's tendency to become in absorbed in a task.
Cognitive-Affective Empathy Test (Cavanna et al., 2022)	TECA	Measures cognitive and affective empathy.
Psychological Well-being Scale (Cavanna et al., 2022)	BIEPS	Measure subjective well-being on dimensions including acceptance, perceived control, social relationships, and autonomy.
Mind Wandering Scale (Cavanna et al., 2022)	MWQ	Measures mind-wandering trait levels
Cognitive Flexibility Scale (Cavanna et al., 2022)	CFS	Measures three factors of cognitive flexibility.
Creative Personality Scale (Cavanna et al., 2022)	CPS	Assesses creative personality traits and creative behavior.
Flow State Scale (Cavanna et al., 2022)	FSS	Measure flow state along nine dimensions.
Remote Associates Test (Cavanna et al., 2022)	RAT	Measures creative convergent thinking.
Wallach-Kogan Test (Cavanna et al., 2022)	WK	Assesses creativity and divergent thinking (novel idea generation).
Binocular rivalry (Cavanna et al., 2022)	BR	Measures visual perception.
Backwards masking (Cavanna et al., 2022)	BM	Measures conscious visual perception.
Trial Making Test (Cavanna et al., 2022)	TMT	Measures attention, cognitive flexibility, and coordination.
Groton Maze learning task (Nikolič et al., 2023)	GMLT	Measures spatial memory
Rey auditory verbal learning test (Nikolič et al., 2023)	RAVLT	Test of verbal memory
Paired associative learning test (Nikolič et al., 2023)	PALT	Influence of sleep on declarative memory processes
Profile of Mood States (Malllaroni et al., 2023)	POMS	Measures changes in mood
Clinician Administered Dissociative States Scale (Malllaroni et al., 2023)	CADDS	Measures levels of dissociative symptomatology
Sensitivity to Drug Reinforcement Questionnaire (Malllaroni et al., 2023)	SDRQ	Measures general levels of drug liking and wanting
Ego dissolution inventory (Malllaroni et al., 2023)	EDI	Measures levels os subjective ego dissolution
Interpersonal reactivity Index (Malllaroni et al., 2023)	IRI	Measures end of session changes in trait empathy
Motor Control Tast (Malllaroni et al., 2023)	MCT	Measures sensorimotor coordination
Psychomotor vigilance Task	PVT	Measures sustained attention
Digit symbol substitution test (Malllaroni et al., 2023)	DSST	Measures overall cognitive impairment
Tower of London (Malllaroni et al., 2023)	TOL	Measures executive functioning
Spatial Memory Test	SMT	Measures immediate and delayed spatial memory

(Malllaroni et al., 2023)		
Matching familiar figures test (Malllaroni et al., 2023)	MFFT	Measures reflection impulsivity
Multifaceted Empathy test (Malllaroni et al., 2023)	MET	Measures cognitive and emotional empathy

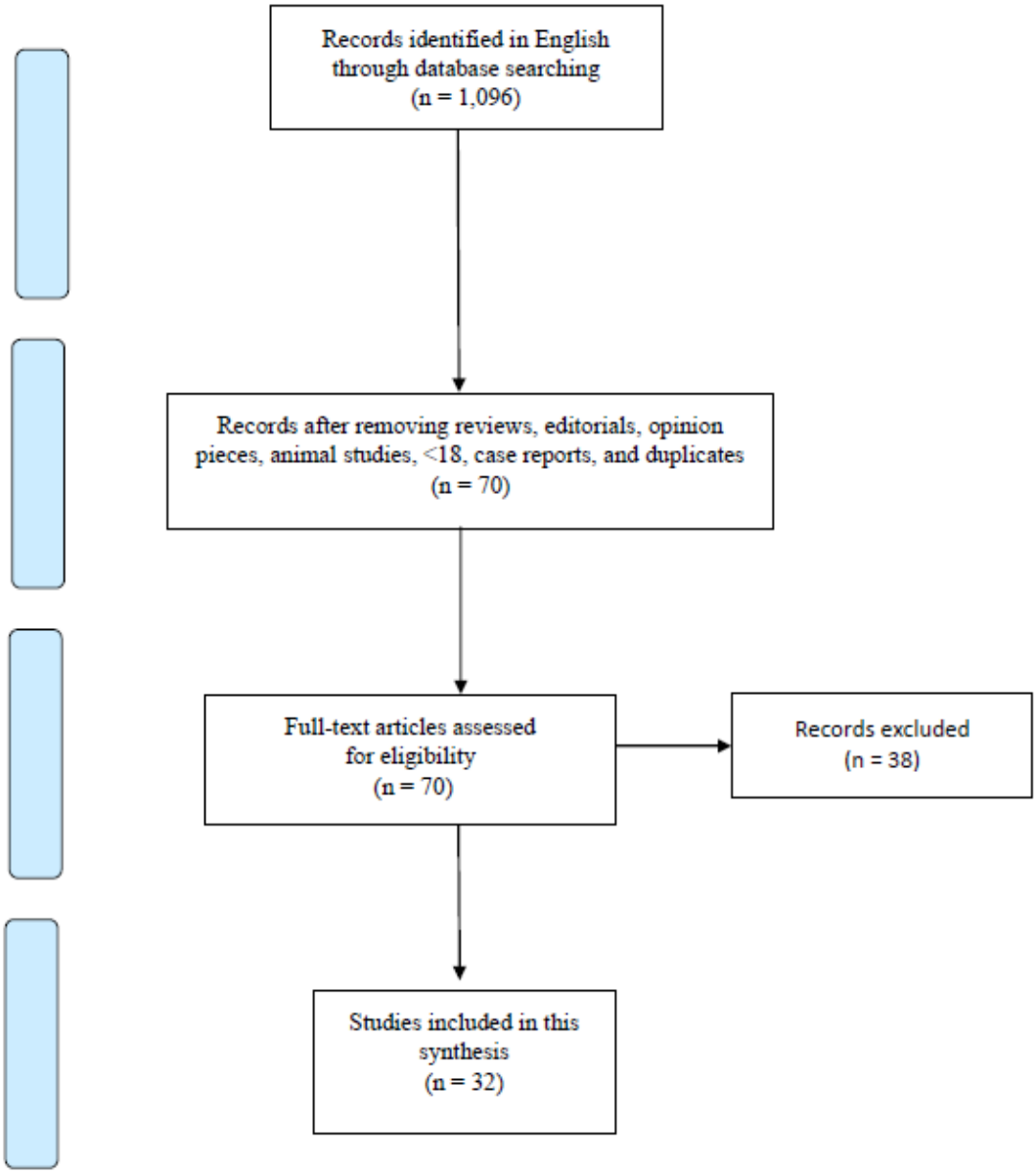

Figure 1: PRISMA Flow Diagram.

DISCUSSION

Findings from the 32 reviewed studies indicate that psilocybin causes a broad range of acute, dose-dependent psychological and physiological effects. After psilocybin administration, volunteers reported altered states of consciousness characterized by feelings of blissful transcendence, ego dissolution, hallucinations, anxiety, intense emotional arousal, and mystical experiences. Affective impacts include enhanced mood and alter emotional processing. While most studies revealed that psilocybin did not cause global cognitive impairment, focal cognitive impairment was observed in domains including attention, memory, and visual perception. Psilocybin also caused transient increases in systolic blood pressure, diastolic blood pressure, and heart rate. Common adverse effects included anxiety, fear, paranoia, fatigue, and headache. These effects did not typically persist beyond the experimental session, and were more frequently reported after higher doses.

The results of the present study regarding the acute effects of psilocybin on healthy participants are consistent with findings on the acute effects of psilocybin administered to patients with psychiatric

disorders (Griffiths 2016; Davis 2021). Our findings suggest that psilocybin is relatively safe for healthy volunteers, however, its effects are somewhat unpredictable and vary significantly across individuals. There were several factors associated with more positive experiences, such as a receiving high level of spiritual support or guidance during the session. Individual temperament also predicted positive responses to psilocybin: a pooled analysis by Studerus et al. found that the personality trait 'absorption' was among the most significant predictors of a positive and transformative experience (Studerus 2012). The notion that 'set' (mindset) and 'setting' influence the quality of a psychedelic experience has become widely accepted and established in the years since the Harvard psychologist and psychedelic advocate Timothy Leary initially popularized the theory in the 1960s (Hartogsohn, 2017). Future work should focus on identifying the suitable conditions and candidates (i.e., 'sets' and 'settings') for psilocybin treatment, as uncertainty concerning how different individuals might respond to psilocybin remains to be a prominent issue.

Limitations

A significant limitation of this review concerns the characteristics of the volunteers in the reviewed studies. Most of these studies worked with self-selected groups of participants who had, by virtue of volunteering for the study, already expressed interest in achieving the potential benefits of psilocybin. For example, Griffiths et al. (2018) recruited participants through flyers that called for "volunteers interested in developing their spiritual lives" through a study that involved psilocybin. In addition to being more open to the experience, these participants likely held more concrete, positive expectations about their post-treatment mental state. Moreover, most of these studies were done with highly educated, white, urban populations, and many were uncompensated, limiting their financial accessibility. Some studies included a mix of participants with and without prior psychedelic use. All these factors raise questions about how generalizable the conclusions of these studies are.

Another limitation of this work is the variability among the different experimental paradigms and settings. While this does allow for more conclusions about some effects of psilocybin, it also encumbers our ability to confidently advocate for a given treatment protocol based on this work. As previously mentioned, future research should seek to inform the development of an evidence-based, personalized treatment protocols as these "bad trip," with its own fear, anxiety and mood disturbance may be of utility in processing trauma in the long run. So, if these feelings are carefully held and explored in a therapeutic environment, there is more room to tailor the experience to the optimal benefit of the individual.

CONCLUSIONS

This review details a broad range of perceived benefits and risks that psilocybin may have in healthy volunteers. It has been shown that certain aspects of the acute psychedelic experience are associated with better long-term treatment outcomes in patients with treatment-resistant depression (Roseman 2018) and in highly experienced meditators (Smigielski 2019b). If psilocybin becomes more widely available to the general population, it is important to develop an exhaustive list of acute risks, and potential strategies to mitigate them. We found that low, medium, and high doses of psilocybin had highly variable, and sometimes profound, dose-dependent effects on conscious experience, perception, affect, and cognition, in healthy volunteers. Studies showed that psilocybin is associated with dose-dependent cognitive impairments in domains such as attention, inhibition, and memory as well as adverse effects such as transient increases in systolic and diastolic blood pressure, heart rate, and dose-dependent anxiety, fear, paranoia, fatigue, headache, and difficulty concentration. This review indicates that risks associated with psilocybin use are relatively low, however most research among healthy volunteers was limited to mainstream demographics in industrialized communities. The present review indicates that more work in more diverse populations must be done to better characterize its effects and risks in the general population, and to explore how to optimize positive effects and mitigate negative effects in the development of future treatment protocols.

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