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# Exploring psychedelic therapies: A systematic review of the effectiveness of psilocybin in the treatment of depression

## Explorando las terapias psicodélicas: una revisión sistemática de la eficacia de la psilocibina en el tratamiento de la depresión

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**ABSTRACT**

**Introduction**: The main objective is to verify if the administration of psilocybin is effective for the treatment of depression. In addition, the aim is to verify whether psilocybin is more effective compared to escitalopram as well as to verify the existence of adverse effects due to the treatment. Currently, mental health faces global challenges; Proof of this is the 25% increase in depressive disorders during the first year of the pandemic, affecting one billion people. Major depressive disorder has increased by 50% in the last thirty years. Despite conventional treatments, attention is turning to innovative approaches such as psychedelic-assisted therapy, especially psilocybin, sparking global interest. **Method**: Pubmed and Sciencedirect were used as scientific data sources to carry out the review, following the PICO method. The process consisted of five phases, during which inclusion and exclusion criteria were applied, where a total of twenty-five articles were selected. **Results**: Psilocybin as assisted therapy is effective in the treatment of depression; reducing symptoms, changes in perspective and cognition as well as an improvement in mental health. **Discussion**: More research is required to determine long-term effectiveness as well as to establish treatment guidelines. Psilocybin stands out for its speed of action and safety profile, being effective for the treatment of depression. Likewise, the antidepressant escitalopram appears to show comparable efficacy to psilocybin.

**Keywords:**
psilocybin, depression, psychedelic treatment, efficacy, assisted therapy

**RESUMEN**

**Introducción**: El objetivo principal es comprobar si la administración de psilocibina es efectiva para el tratamiento de la depresión. Además, se pretende comprobar si la psilocibina es más eficaz en comparación con el escitalopram así como comprobar la existencia de efectos adversos

**Palabras clave:**

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| Psilocibina, depresión, tratamiento psicodélico, eficacia, terapia asistida | debido al tratamiento. Actualmente, la salud mental afronta desafíos globales; muestra de ello es el aumento de un 25% en trastornos depresivos durante el primer año de la pandemia, afectando a mil millones de personas. El trastorno depresivo mayor ha aumentado un 50% en los últimos treinta años. A pesar de los tratamientos convencionales, la atención se dirige hacia enfoques innovadores como la terapia asistida por psicodélicos, especialmente la psilocibina, suscitando un interés a nivel global. **Método**: Se empleó Pubmed y Sciencedirect como fuentes de datos científicas para llevar a cabo la revisión, siguiendo el método PICO. El proceso constó de cinco fases, durante las cuales se aplicaron criterios de inclusión y exclusión, donde se seleccionaron un total de veinticinco artículos. **Resultados**: La psilocibina como terapia asistida es efectiva en el tratamiento de la depresión; reduciendo la sintomatología, cambios en la perspectiva y cognición además de una mejoría en la salud mental. **Discusión:** Se requieren más investigaciones para determinar la eficacia a largo plazo así como para establecer pautas de tratamiento. Se destaca la psilocibina por su rapidez de acción y perfil de seguridad, siendo eficaz para el tratamiento de la depresión. Asimismo, el antidepresivo escitalopram parece mostrar una eficacia comparable con la psilocibina. |

# Introduction

Currently, mental health challenges continue to be one of the main problems at the global level and, despite the fact that international organizations are showing greater interest, actions seem to be insufficient and inadequate, without providing a satisfactory response to the needs of the population, so it continues to be a problem that affects countries and communities around the world (World Health Organization, 2022).

During the first year of the global pandemic, cases of the most common mental disorders in society, such as depression and anxiety, increased by 25%, reflecting the fact that approximately one billion people now have a diagnosis. The data show a truly significant increase from pre-pandemic figures (World Health Organization, 2022).

Continuing in the same vein, major depressive disorder (MDD) is considered one of the most common mental health problems; figures show a 50% increase in the last thirty years, which means that more than two hundred million people suffer from such a disorder (Liu et al., 2020). Precisely, the World Health Organization states that depression is one of the leading causes of physical and mental disability in global terms and a significant factor in the global burden of disease (World Health Organization, 2021).

Depression is considered a chronic illness that influences a person's thoughts, mood and even physical health, resulting in the same sadness, difficulty falling asleep, lack of vitality and even inability to experience pleasure in life (Cui, 2015).

The Diagnostic and Statistical Manual of Mental Disorders (DSM), fifth edition, defines depression as a mood disorder characterized primarily by a constant feeling of sadness and loss of interest. The DSM-5 classifies depressive disorders into five: Disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition (American Psychiatric Association [APA], 2013).

All depressive disorders have sadness and emptiness as a common factor coupled with both somatic and cognitive changes that alter the subject's ability to function (Ormel et al., 2019).

As a result of the stigma of the mental illness disorder by society, almost 60% of people suffering from depression do not seek professional help, thus getting in the way of the person's life (Chand & Arif, 2023).

Treatment for depression has been extensively studied in the literature, primarily research has focused on therapeutic interventions, pharmacological interventions or the combination of both (Greenberg et al., 2012) and evidence indicates that, although the vast majority of antidepressants work, individual response may vary by subject (Chand & Arif, 2023).

For the treatment of depression, Cognitive Behavioral Therapy (CBT) and Interpersonal Therapy (IPT) have proven to be really effective. While the most commonly used medications for the treatment of depression are: Selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin-dopamine activity modulators (SDAMs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Also, for people who do not respond to drug therapy, electroconvulsive therapy (ECT) is used, which has been shown to be a very effective treatment (Chand & Arif, 2023).

In addition, one of the major problems in the administration of conventional antidepressants is that a minimum of four weeks is required to demonstrate a response to treatment. For this reason, current trials use different therapeutic targets such as the glutamatergic system; as a result, it has been possible to demonstrate the advantages of esketamine, such as the rapidity of patient response

Similarly, the trials contemplate esketamine as a therapeutic option for those patients with higher severity who have not obtained a positive response after the administration of two antidepressants and who require a third therapeutic option

The U.S. National Institute on Drug Abuse classifies psychedelic drugs into two categories: Classical hallucinogens and dissociative drugs. Both can eventually cause the person to hallucinate (National Institute on Drug Abuse, 2019).

Consequently, they are substances that produce effects primarily through an agonist (or partial agonist) action on the serotonin 5-hydroxytryptamine (5-HT) brain receptors (Nichols, 2016).

The U.S. Drug Enforcement Administration (DEA) classifies lysergic acid diethylamide (LSD), ayahuasca, psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), and MDMA (3,4-methylenedioxy-methamphetamine) as Schedule I substances, indicating a lack of information about safety or medical approval, as well as the possibility that it could be used inappropriately (Reiff et al., 2020).

Early clinical research with psychedelics employed LSD to address witnessed behavior in patients diagnosed with early childhood autism as well as in childhood schizophrenia (Simmons et al., 1972) (Simmons et al., 1966) (Hoch et al., 1952).

The 1970 U.S. government ban on scientific research on psychedelics significantly delayed medical progress on the therapeutic use of substances such as psilocybin (Lowe et al., 2021), although in recent years there has been an increase in research on the possibility of therapeutic benefit in the administration of psychedelic compounds (Reiff et al., 2020).

However, despite the cessation of all research, several clinical trials with psilocybin for the treatment of pain, anxiety and depression in patients with a diagnosis of cancer at an advanced stage of the disease were initiated in the 2000s (Lowe et al., 2021).

Such was the interest created worldwide that in 2019 John Hopkins University founded the Johns Hopkins Center for Psychedelic & Consciousness Research (Johns Hopkins Center for Psychedelic & Consciousness Research, 2019).

Psilocybin, or 4-phosphoryloxy-N,N-dimethyltryptamine, is the main psychoactive alkaloid present in certain types of mushrooms distributed throughout the world (Passie et al., 2002), in other words, psilocybin is the psychedelic compound isolated from hallucinogenic mushrooms, so the organism metabolizes it into psilocin (partial serotonin receptor antagonist) (Voineskos et al., 2020).

Recent studies began to assess the therapeutic potential of psilocybin in different psychological conditions such as end-of-life anxiety, obsessive-compulsive disorder, smoking dependence and depression (Carhart-Harris et al., 2016).

Despite advances in pharmacotherapy and psychotherapy, there is a need for more effective therapeutic options, especially for those subjects who do not respond adequately to conventional interventions. Also, in recent years, pilot studies and clinical trials have been developed that may suggest that psilocybin could have significant implications for the treatment of depression. It is for this reason that the aim of the present study is to test whether the administration of psilocybin is effective for the treatment of depression. In addition, we intend to test whether psilocybin is more effective compared to escitalopram as well as to test for adverse effects due to the treatment.

## Method

For the collection of information, the PICO method was used to gather those articles that investigated the efficacy of psilocybin in depression.

The search engines used in this systematic review were Pubmed and Sciencedirect, using the English terms "*psilocybin*", "*depression*" with the Boolean operator "*AND*".

In addition, the inclusion criteria for both databases were: Clinical studies, clinical trials, controlled clinical trials, and randomized controlled trials.

On the other hand, in order to carry out a proper screening, a reading of titles and abstracts of each article was performed, thus excluding studies that: They did not evaluate the efficacy of psilocybin in depression, were far from the main objective and single case studies. In addition, duplicate articles were also eliminated.

In the first phase, the key words in English were chosen for the search of the articles of the present systematic review ("*psilocybin*" and "*depression*").

The second phase consists of applying a search criterion to the information collected using the above-mentioned keywords in the two databases. The search yielded 529 results in Pubmed and 1,887 in Sciencedirect, for a total of 2,416 articles.

The third phase focuses on the application of the inclusion criteria, where 41 articles were obtained in Pubmed and 518 in Sciencedirect, that is, a total of 559 articles.

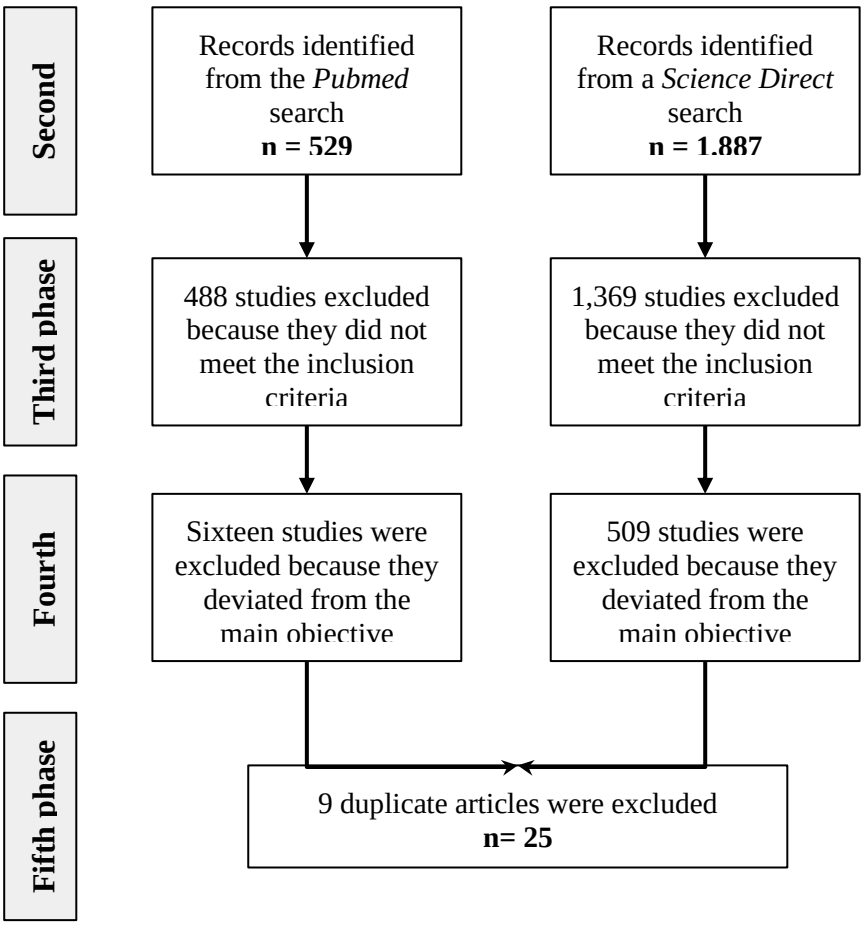
In the fourth phase, articles were excluded by reading the *abstract*, results and discussion. Therefore, articles that were far from the main objective of the present systematic review, as well as case studies, were discarded. After applying the aforementioned criteria and a complete reading of all the articles, 25 were selected from Pubmed and 9 from ScienceDirect, for a total of 34 articles.

In the fifth phase, articles appearing in both databases were eliminated. There were 9 duplicate articles, so the sample was reduced to 25.

Consequently, after the search conducted on November 21, 2023, 25 articles were selected for this systematic review. Figure 1 visually presents the graphic scheme of the process.

**Figure 1**

*Article selection search process.*




## Results

In relation to the results obtained in the present review, a total of 25 scientific articles were analyzed through which the efficacy of psilocybin as an assisted therapy for depressive disorder was investigated.

These 25 selected articles can be seen in the following table, as well as a summary of the details and main findings of these studies

**Table 1**

*Main results found in each article.*

| Authors | Sample | Type of assay and procedure | Instrument | Disorder | Results |
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| Agin-Liebes et al. 2020 | (*n=15*)<br><br>60% Women (*n=9*)<br>40% Men (*n=6*)<br><br>Average age 53 | Randomized controlled trial<br><br>1 dose | BDI | Mild depression (cancer) | Psilocybin + Therapy showed long-term improvement in cancer patients, addressing psychiatric and existential distress<br><br>Ef. Beneficial: Sustainability of existential psychiatric improvements<br><br>Ef. Secondary: No information provided |
| Anderson et al., 2020 | (*n=18*)<br><br>100% Men (*n=18*)<br><br>Average age 59.2 | Single-group open rehearsal<br><br>1 dose (0.3 - 0.36 mg) [oral]<br>+ Group therapy<br><br>7 weeks | CESD | Moderate depression (HIV/cancer) | Psilocybin in group therapy was safe and feasible. Safety and viability in the population of interest<br><br>Ef. Secondary: 0 serious adverse reactions, 2 unexpected and 7 expected, serious and self-limited. |
| Becker et al., 2022 | (*n=23*)<br><br>48% Women (*n=11*)<br>52% Men (*n=12*)<br><br>Average age 34 | Double-blind, placebo-controlled, crossover trial<br><br>Psilocybin after treatment with escitalopram or placebo<br><br>1 dose (25 mg) [oral]<br>+ Psychological support<br><br>7 weeks | 5D-ASC | Healthy volunteers | Acute effects of psilocybin persisted after pretreatment with escitalopram or placebo. Confirmation of acute effects of psilocybin.<br><br>Ef. Secondary: No information provided<br><br>Comparison: Psilocybin vs. Escitalopram |
| Carhart-Harris et al., 2016 | (*n=12*)<br><br>50% Women (*n=6*)<br>50% Men (*n=6*)<br><br>Average age 34 | Open feasibility trial<br><br>2 doses (10 - 25 mg) [oral]<br>+ Psychological support<br><br>7 weeks | QIDS | Moderate to severe unipolar major depression resistant to treatment. | Psilocybin + Psychological support effective in treatment-resistant depression. Significant improvements in depressive symptoms.<br><br>Ef. Secondary: Adverse reactions (transient anxiety 100%), transient confusion (9 patients), transient mild nausea (4 patients) and transient headache (4 patients). |

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| Carhart-Harris et al., 2017 | (*n=31*)<br><br>26% Women (*n=8*)<br>74% Men (*n=23*)<br><br>Average age 42.8 | Clinical trial<br><br>MRI scan before and after treatment with psilocybin and escitalopram<br><br>2 doses (10 - 25 mg) [oral]<br>+ Psychological support<br><br>7 weeks | QIDS-SR-16 | Treatment-resistant depression | Psilocybin compared favorably with escitalopram for the treatment of depression. Effectiveness similar to escitalopram, with a shorter duration of treatment.<br><br>Secondary Effects: No information is provided.<br><br>Comparison: Psilocybin vs. Escitalopram |
| Carhart-Harris et al., 2018 | (*n=20*)<br><br>30% Women (*n=6*)<br>70% Men (*n=14*)<br><br>Average age 44 | Clinical trial<br><br>2 doses (10 - 25 mg) [oral]<br>+ Psychological support<br><br>7 weeks | QIDS-SR-16<br><br>BDI | Treatment-resistant depression | Psilocybin + Psychological support effective in treatment-resistant depression. Significant improvements in depressive symptoms.<br><br>Ef. Secondary: No serious adverse effects |
| Carhart-Harris et al., 2021 | (*n=59*)<br><br>33.9% Women (*n=20*)<br>66.1% Men (*n=39*)<br><br>Average age 39.1 | Phase II double-blind, randomized, controlled trial<br>● Psilocybin (*n=30*)<br>● Escitalopram (*n=29*)<br>2 doses (25 - 1 mg) [oral]<br>+ Psychological support<br><br>9 weeks | BDI<br><br>HAM-D<br><br>MADRS<br><br>QIDS-SR-16 | Major depressive disorder | Psilocybin compared favorably with escitalopram for the treatment of depression. Effectiveness similar to escitalopram, with a shorter duration of treatment.<br><br>Secondary Effects: No information is provided.<br><br>Comparison: Psilocybin vs. Escitalopram |
| Carrillo et al., 2018 | (*n=35*)<br><br>34% Women (*n=12*)<br>66% Men (*n=23*)<br><br>Average age 40.5 | Open label design<br><br>Psilocybin (Dosage 10mg; Dosage 25mg)<br>● GExperimental(*n=17*)<br>● GControl (*n=18*)<br><br>2 doses (10 and 25 mg) [oral] + Psychological support | QIDS-16 | Treatment-resistant depression | Natural language processing algorithm predicted positive response to psilocybin in treatment-resistant depression.<br><br>Ef. Beneficial: Innovative use of algorithm to predict positive responses.<br><br>Ef. Secondary: No information is provided. |
| Davis et al., 2021 | (*n=24*)<br><br>67% Women (*n=16*)<br>33% Men (*n=8*)<br><br>Average age 39.8 | Randomized clinical trial<br><br>Psilocybin:<br>● Immediate treatment group | GRID-HAMD<br><br>QIDS-SR | Major depressive disorder | Trial on the effects of psilocybin-assisted therapy in MDD. Significant improvement of depressive symptoms.<br><br>Ef. Secondary: No |

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| | | (*n=13*)<br>● Control group (*n=11*)<br><br>2 doses (20 - 30 mg) [oral]<br>+ Psychological support<br><br>8 weeks | | | information is provided. |
| Goodwin et al., 2022 | (*n=233*)<br><br>52% Women (*n=121*)<br>48% Men (*n=112*)<br><br>Average age 39.8 | Phase II double-blind trial<br><br>Psilocybin:<br>● G1 (*n=79*)<br>● G2 (*n=75*)<br>● G3 (*n=79*)<br><br>1 dose (25 - 10 - 1 mg) [oral]<br>+ Psychological support<br><br>3 weeks | MADRS | Treatment-resistant depression | Depression scores were significantly reduced<br><br>Ef. Secondary: Adverse events in 76.8% and serious adverse events in 3.4% |
| Goodwin et al., 2023 | (*n=19*)<br><br>68% Women (*n=13*)<br>32% Men (*n=6*)<br><br>Average age 42.2 | Phase II fixed-dose exploratory study<br><br>Psilocybin in synthetic form (COMP360) + SSRIs<br><br>1 dose (25 - 10 - 1 mg) [oral]<br>+ Psychological support<br><br>3 weeks | HAM-D-17<br><br>MADRS | Treatment-resistant major depressive disorder | Significant impact on severity of depression, anxiety, function and quality of life.<br><br>Ef. Secondary: No information is provided. |
| Griffiths et al., 2016 | (*n=51*)<br><br>49% Women (*n=25*)<br>51% Men (*n=26*)<br><br>Average age 56.3 | Randomized, double-blind, crossover trial<br><br>1 dose (1-3 mg/70kg) - (22-30 mg/70kg) [oral]<br><br>5 weeks | GRID-HAM-D-17<br><br>HAM-A | Cancer patients coping with anxiety disorders and depression | Substantial and sustained reductions in anxiety and depression.<br><br>Ef. Secondary: No adverse events occurred. |
| Gukasyan et al., 2022 | (*n=24*)<br><br>67% Women (*n=16*)<br>33% Men (*n=8*)<br><br>Average age 39.8 | Randomized controlled trial<br><br>● Psilocybin (immediate treatment) (*n=13*)<br>● Psilocybin (deferred treatment) | GRID-HAM-D-17 | Major depressive disorder | Confirmation of long-term efficacy and safety.<br><br>Ef. Secondary: There were no serious adverse events. |

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| | | (*n=11*)<br><br>2 doses (20 mg/70 kg) (30 mg/70kg)<br>+<br>Psychological support<br><br>8 weeks | | | |
| Kraehenmann et al., 2014 | (*n=25*)<br><br>36% Women (*n=9*)<br>64% Men (*n=16*)<br><br>Average age 24.2 | Randomized, double-blind, placebo-controlled, crossover design<br>● Psilocybin<br>● Placebo<br><br>1 dose (0.16 mg/kg) | PANAS<br><br>STAI | Healthy volunteers | Decreased amygdala reactivity correlated with improvements in positive mood.<br><br>Ef. Beneficial: Correlation + between decreased amygdala reactivity and improvements in mood.<br><br>Ef. Secondary: No information is provided. |
| Lewis et al., 2023 | (*n=12*)<br><br>67% Women (*n=8*)<br>33% Men (*n=4*)<br><br>Average age 48.2 | Open pilot study<br><br>Psilocybin-assisted group therapy<br><br>1 group session (25 mg)<br><br>2 weeks | HAM-D | Depression in cancer patients | Indications of efficacy in the improvement of psychological symptoms in oncology patients.<br><br>Ef. Secondary: No serious adverse events occurred. |
| Lyons and Carhart-Harris, 2018 | (*n=30*)<br><br>33.3% Women (*n=10*)<br>66.7% Men (*n=20*)<br><br>Average age 41.5 | Controlled and open trial<br>● Control group (*n=15*)<br>● Experimental group (*n=15*)<br><br>2 doses (10 - 25 mg)<br>+<br>Psychological support<br><br>7 weeks | BDI<br><br>POFLE | Major depressive disorder | Psilocybin improves realistic prediction of future events in treatment-resistant depression.<br><br>Ef. Beneficial: Improved accuracy in predicting future events.<br><br>Ef. Secondary: No information is provided. |
| Marschall et al., 2022 | (*n=96*)<br><br>52% Women (*n=50*)<br>48% Men (*n=46*)<br><br>Average age 35.2 | Intrasubject, double-blind, placebo-controlled crossover trial<br>Microdoses of psilocybin:<br>● S1 and S3 (*n=52*)<br>● S2 and S4 (*n=44*) | DASS-21<br><br>MAIA | Depression, Anxiety and Stress | Microdosing of psilocybin does not affect symptoms and emotional processing. Lack of significant effects on symptoms and emotional processing.<br><br>Ef. Secondary: No information is provided. |
| Mertens et al., 2020 | (*n=19*) | Open studio | QIDS- | Major depression | Changes in brain functional |

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| | 31.5% Women (*n=6*)<br>68.5% Men (*n=13*)<br><br>Average age 44.7 | Amygdala response<br>1 day after overt psilocybin treatment<br><br>1 dose (25 mg) | SR16<br><br>fMRI design | resistant to treatment | connectivity after psilocybin in treatment-resistant depression.<br><br>Ef. Beneficial: Alterations in brain connectivity related to emotional processing.<br><br>Ef. Secondary: No information is provided. |
| Murphy et al., 2022 | 33.9% Women (*n=20*)<br>66.1% Men (*n=39*)<br><br>Average age 39.1 | Randomized double-blind clinical trial<br><br>2 doses (25 mg) [oral]<br>+<br>Psychological support<br><br>6 weeks | BDI<br><br>HAM-D<br><br>MADRS<br><br>QIDS-SR-16 | Major depressive disorder | Therapeutic alliance and rapport modulate responses to psilocybin-assisted therapy.<br><br>Ef. Beneficial: Importance of the quality of the therapeutic relationship on outcomes.<br><br>Ef. Secondary: No information is provided. |
| Roseman et al., 2018 | (*n=19*)<br><br>31.5% Women (*n=6*)<br>68.5% Men (*n=13*)<br><br>Average age 44.7 | Clinical trial<br><br>Psilocybin screening with RMF<br><br>2 doses (10 - 25 mg) [oral]<br>+ Psychological support<br><br>3 weeks | BDI<br><br>QIDS | Moderate to severe treatment-resistant depression | Increased amygdala responses to emotional faces after psilocybin for resistant depression.<br><br>Ef. Beneficial: Changes in amygdala response to emotional processing.<br><br>Ef. Secondary: No information is provided. |
| Ross et al., 2016 | (*n=29*)<br><br>62% Women (*n=18*)<br>38% Men (*n=11*)<br><br>Average age 56.28 | Randomized, blinded, controlled, crossover trial<br>● Psilocybin (*n=14*)<br>● Niacin + Psychotherapy (*n=15*)<br><br>1 dose (0,3 mg) [oral] + Psychological support<br><br>7 weeks | HADS<br><br>BDI<br><br>STAI | Clinically significant depression and anxiety in patients with life-threatening cancer | Rapid and sustained symptom reduction after psilocybin in cancer-related anxiety and depression.<br><br>Ef. Beneficial: Rapid and sustained therapeutic effects.<br><br>Ef. Secondary: There were no serious adverse events. |
| Stroud et al., 2017 | (*n=16*)<br><br>31% Women (*n=5*)<br>69% Men (*n=11*)<br><br>Average age 32 | Controlled trial<br>Emotional recognition<br>● Psilocybin<br>● Control<br><br>2 doses (10 mg - 25 mg) [oral] | QIDS-16 | Treatment-resistant depression | Psilocybin improves emotional facial recognition in treatment-resistant depression.<br><br>Ef. Secondary: No information is provided. |

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| | | + Psychological support<br><br>6 weeks | | | |
| von Rotz et al., 2023 | (*n=52*)<br><br>63.5% Women (*n=33*)<br>36.5% Men (*n=19*)<br><br>Average age 36.7 | Randomized, double-blind, placebo-controlled trial<br><br>● Psilocybin (*n=26*)<br>● Placebo (*n=26*)<br><br>1 dose (0.215 mg/kg) [oral]<br>+ Psychological support<br><br>2 weeks | MADRS<br><br>BDI | Major depressive disorder | Confirmation of the efficacy and safety of psilocybin compared to placebo.<br><br>Ef. Secondary: There were no serious adverse events. |
| Wall et al., 2023 | (*n=19*)<br><br>32% Women (*n=6*)<br>68% Men (*n=13*)<br><br>Average age 41.3 | Open design without control group or placebo<br><br>Psilocybin<br>● Low dose (10mg)<br>● High dose (25mg)<br><br>+ Music | QIDS-SR | Treatment-resistant depression | Increased low-frequency brain responses to music after psilocybin therapy for depression.<br><br>Changes in brain responses to music after psilocybin.<br><br>Ef. Secondary: No information is provided. |
| Zeifman et al., 2023 | (*n=59*)<br><br>34% Women (*n=20*)<br>66% Men (*n=39*)<br><br>Average age 41.2 | Double-blind randomized controlled trial<br><br>● Psilocybin<br>● Escitalopram<br><br>2 doses (25 mg) [oral]<br>+ Psychological support<br><br>6 weeks | MADRS<br><br>QIDS-SR-16 | Major depressive disorder | Exploration of experiential avoidance as a possible mechanism of change in psilocybin therapy.<br><br>Focus on the role of experiential avoidance in therapeutic outcomes.<br><br>Ef. Secondary: No information is provided.<br><br>Comparison: Psilocybin vs Escitalopram |

*Note.* GRID-HAM-D-17: GRID-Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; HADS: Hospital Anxiety and Depression Scale; BDI; Beck Depression Inventory; STAI: Spielberger State-Trait Anxiety Inventory; QIDS-SR-16: Quick Inventory of Depressive Symptomatology-Self-Report; DASS-21: Depression Anxiety and Stress Scale; MAIA: Multidimensional Assessment of Interoceptive Awareness Questionnaire; QIDS-SR: Quick Inventory of Depressive Symptoms; PANAS: Positive and Negative Affect Schedule; STAI: State-Trait Anxiety Inventory; MEQ30: Mystical Experience Questionnaire; CEQ: Challenging Experience Questionnaire; POFLE: Prediction Of Future Life Events task; CESD: Center for Epidemiological Studies Depression Scale-Revised; 5D-ASC: 5 Dimensions of Altered States of Consciousness Scale; fMRI: Functional Magnetic Resonance Imaging.

### *Participants*

Of the 25 articles selected, the sociodemographic characteristics were analyzed.

A total sample of 1,095 participants was obtained, of which 44.6% were women (n=488) and the remaining 55.4% were men (n=607). In turn, the mean age of the total set of studies reviewed was 41.7 years.

In general terms, it is possible to observe a variability in the percentage of gender in the different articles. However, in one of the articles (Anderson et al., 2020), the gender distribution is skewed towards a specific group, given that the total sample is male.

The mean age varies significantly in the different articles, ranging from 24 years to 59.2 years, so that, overall, there appears to be a diversity of ages in the studies.

In terms of sample size, significant differences were observed, ranging from 12 subjects to 233. On the other hand, research with a considerably larger sample size shows a more even gender distribution or even a larger sample of women.

### *Instruments*

The present systematic review shows that the most commonly used instruments to assess the variable of Major Depressive Disorder (MDD) have been: The BDI, the QIDS, the HAM-D and the MADRS.

The *Beck Depression Inventory* (BDI) is a self-report that provides an objective measure to assess the severity of depressive symptomatology in adults and adolescents with a minimum age of thirteen years. The instrument is made up of twenty-one items, with a Likert-type format, with four alternatives each, where the evaluated subject has to mark those with which he/she feels more identified, taking into account the last two weeks. The items indicate symptomatology such as sadness, crying, loss of pleasure, feelings of failure and guilt and thoughts or desires of suicide among others (Sanz et al., 2005).

The estimated time for the application of the test is around ten minutes, showing a good reliability, with a Cronbach's α of .89 and the estimated time for the application of the test is around 10 minutes. As for the correction method, each item is evaluated from 0 to 3 points, adding the score of all the items, the total score ranges from 0 to 63. In cases in which the subject can mark two alternatives in the same item, the more severe one will be selected (Sanz et al., 2005).

Several studies support the reliability and validity of this inventory in subjects suffering from psychological or ambulatory disorders (Sanz et al., 2005). The original citation of the self-report is (Beck et al., 1996), while the Spanish validated version is (Sanz and Vázquez, 2011).

The *Quick Inventory of Depressive Symptomatology* (QIDS-SR16) is a structured self- and hetero-applied measure that assesses the severity of depression in adults, including all symptoms of the DSM-IV criteria for Major Depressive Disorder (Gili et al., 2014).

The estimated time for the application of the QIDS-SR is around seven minutes, including sixteen items in which the person evaluated has to select the statement that best describes how he/she has felt the last seven days (with a score ranging from 0 to 3 according to severity) (Gili et al., 2014).

Likewise, the QIDS-SR16 questionnaire shows good reliability and high internal consistency (α .871) (CIBERSAM, n.d.). Several versions of the QIDS, QIDS-16 and QIDS-SR instruments can be found in the articles selected for this systematic review.

Items include: Sleep disturbances, sad mood, changes in appetite and weight, concentration and/or decision making, opinion of self, suicidal ideation, interest, energy level and restlessness, where the total score of the instrument ranges from 0 to 27. The QIDS-SR shows good test-retest reliability and a Cronbach's α of .871 (Gili et al., 2014). The original citation of the QIDS-SR is (Rush et al., 2003), while the Spanish version is (Gili et al., 2014).

The *Hamilton Depression Rating Scale* (HAM-D) is a heteroapplied and structured scale that assesses the intensity and severity of depressive symptomatology in adults. The

instrument has seventeen items with an administration time ranging from twenty to thirty minutes (CIBERSAM, n.d.).

The instrument evaluates the intensity or severity of depression, where each item is measured with a scale of three (absent, doubtful or trivial and present) or five options (absent, doubtful or trivial, mild, moderate and severe) according to the intensity of the symptomatology of the person evaluated (CIBERSAM, n.d.).

The content of the questionnaire focuses mainly on the somatic and behavioral presence of depression, identifying different indices: Index of melancholy, anxiety and sleep disturbances. Each item is evaluated from zero to two points or from zero to four points depending on the item. The total score of the scale is obtained with the sum of the scores assigned to each item, offering a score range from 0 to 52 points (CIBERSAM, n.d.).

Finally, regarding the psychometric properties of the instrument, the two versions it has, it has a good internal consistency (Cronbach's α between .76 and .92) as well as showing good psychometric indices in terms of validity (CIBERSAM, n.d.). The original citation of the HAM-D is (Hamilton, 1960), while the Spanish version is (Ramos-Brieva and Cordero, 1986).

In the present review, the articles found have different versions of the HAM-D questionnaire, such as the GRID-HAM, the HAM-D-17 and the HAM-A.

The *Montgomery-Asberg Depression Rating Scale* (MADRS) is a heteroadministered interview scale designed to measure the intensity of depressive symptomatology in adult subjects in addition to the effects of antidepressant treatment. The estimated time for the application of the questionnaire is short, since it consists of ten items related to the ten depressive symptoms, where each item consists of seven levels of intensity and severity, scored from zero to six (Lobo et al., 2002).

Each item is evaluated by means of a Likert-type subscale with seven degrees of severity, being 0 the absence of symptom and 6 the maximum level of severity. The total score ranges from 0 to 60. The questionnaire shows good psychometric properties, with a Cronbach's α of .88, as well as discriminant, convergent, test-retest and inter-observer reliability and sensitivity to change (Lobo et al., 2002). The original MADRS citation is (Montgomery & Asberg, 1979), while the Spanish version is (Lobo et al., 2002).

The rest of the instruments used throughout the twenty-five articles in this study are as follows: The Center for Epidemiological Studies Depression Scale (CES-D), *Positive and Negative Affect Schedule* (PANAS), State-Trait Anxiety Questionnaire (STAI), *Prediction Of Future Life Events* (POFLE), *Depression Anxiety Stress Scale* (DASS-21) and *Multidimensional Assessment of Interoceptive Awareness Questionnaire* (MAIA).

## Procedure

Psychedelic-assisted therapy is a relatively new therapeutic model, so it does not have an established general procedure. No information is available in the literature on how to implement it, either in an individual or group format, nor on the number of sessions or their duration. Therefore, based on the articles reviewed in the present investigation, the various procedures used in the twenty-five clinical trials will be examined.

The doses of psilocybin used in the studies varied significantly among the clinical trials reviewed, indicating a range from 0.16 mg/kg (Kraehenmann et al., 2015) to 30 mg/70 kg (Griffiths et al., 2016).

Likewise, common doses of psilocybin are usually 25 mg and 10 mg, with some trial exploring wider ranges such as 20 mg and 30 mg (Davis et al., 2021) (Gukasyan et al., 2022).

It is noteworthy that there are only four studies that administer psilocybin doses taking into account the body weight of the subjects; two of them taking 70 kg as a reference (Gukasyan et al., 2022) (Griffiths et al., 2016), while the other two administered a psilocybin dose of 0.215 mg/kg (von Rotz et al.,. 2022) and 0.16 mg/kg (Kraehenmann et al., 2015).

Likewise, the study by Lewis et al., 2023 stood out for applying a single strategy by administering group doses of psilocybin, while the rest of the articles applied psilocybin-assisted therapy in an individual format.

Oral administration appears as the predominant method in the clinical trials analyzed. It was also observed that, in general terms, the frequency of dosing was fairly uniform, and although single oral doses were common in most studies, some chose to administer multiple doses throughout the treatment.

On the other hand, most studies incorporate psychological support as an integrated component of the interventions and, generally conducted in an individual format, the Anderson et al., 2020 trial was notable for specifying that the therapy administered in conjunction with psilocybin dosing was group-based.

The duration of treatment in the application of psilocybin-assisted therapy varied significantly among all studies; ranging from two to nine weeks. However, although the average duration settles around six weeks, studies such as Goodwin et al., 2023 and Goodwin et al., 2022 in which treatment lasted three weeks could be observed. Likewise, the studies by Lewis et al., 2023 and von Rotz et al., 2022 where the treatment lasted two weeks were also noteworthy.

Overall, the analysis of the psilocybin-assisted therapy procedure indicates a diversity in the implementation of interventions for the treatment of depression. Variability in dosing or the use of different doses among other data in the studies highlight the difficulty of the field.

## Results

### *Efficacy of Psilocybin*

After reviewing all twenty-five articles, it can be seen that psilocybin, as an assisted therapy, is effective for the treatment of depression.

In general terms, a reduction in depressive symptomatology has been observed, as well as a change in perspective, cognition and the way in which subjects process their emotions.

The results consistently indicate that psilocybin, as an assisted therapy, in combination with psychological support has efficacy for the treatment of depression, especially in situations of patients resistant to conventional treatment.

In several of the studies such as those by Carhart-Harris et al., 2016 and Goodwin et al., 2022 and 2023, it is shown that psilocybin when administered with psychological support may be more effective in the treatment of treatment-resistant depression in single doses. In addition, Carhart-Harris et al., 2018, provides evidence of long-term benefits; likewise, Davis et al., 2021 also demonstrated the effectiveness of psilocybin-assisted therapy for the treatment of major depressive disorder by 71%.

Following the same line, psilocybin microdosing does not noticeably affect both symptomatology and emotional processing, which poses a rather favorable safety profile (Marschall et al., 2022).

On the other hand, the use of innovative tools such as natural language processing algorithms shows really positive predictions in the face of psilocybin response, where it has been proven that the machine learning algorithm manages to predict with an accuracy of over 85% which patients with treatment-resistant depression would respond effectively to treatment (Carrillo et al., 2018).

Similarly, in studies such as Stroud et al., 2018, psilocybin with psychological support was observed to improve emotional face recognition in patients with a diagnosis of treatment-resistant depression.

Some of the articles such as Kraehenmann et al., 2014 and Mertens et al., 2020 have concluded, through neurological scans, how decreased amygdala reactivity and changes in brain connectivity correlate significantly in positive mood.

Furthermore, Lyons and Carhart-Harris, 2018 and Roseman et al., 2018 showed that psilocybin exhibits changes in amygdala response as well as a much more realistic prediction of future situations in treatment-resistant depression.

Trials on the use of psilocybin for the treatment of depression show very promising results in terms of response rates and efficacy. In statistical terms, throughout the trials, significant rates of improvement in depressive symptomatology can be observed, exceeding 50% efficacy.

Trials such as Ross et al., 2016 and Gukasyan et al., 2022 show consistent results with 83% and 75% effectiveness respectively, thus supporting the ability of psilocybin to generate significant responses.

Also noteworthy are studies such as that of Agin-Liebes et al., 2020, which shows remarkable results such as a 70% response rate at four and a half years.

Of note, some of the studies look at psilocybin-assisted therapy in depressed patients coping with cancer. In studies such as Agin-Liebes et al., 2020, Anderson et al., 2020, Lewis et al., 2023, Ross et al., 2016, it can be seen that psilocybin combined with psychotherapy is effective in patients with a diagnosis of cancer, presenting depressive symptomatology, addressing psychiatric and experiential distress, as well as perceived improvements in attitudes about life, mood, relationships and spirituality to experience among others.

Also noteworthy is the study by Wall et al., 2023, which highlights an increase in low-frequency brain responses to music after psilocybin-assisted therapy, suggesting a possible positive effect on the musical experience.

In turn, Zeifman et al., 2023 examine experiential avoidance as a potential transformative mechanism in psilocybin therapy, offering insight into the efficacy of the therapeutic approach.

Also, several of the subjects reported spiritual or mystical experiences during the sessions, which were related to improvements in mental health.

Similarly, the study by Murphy et al., 2022 demonstrates that the quality of the therapeutic relationship as well as *rapport* are key factors for treatment effectiveness.

### *Comparison with Escitalopram*

Comparative studies with escitalopram (12% of studies), a commonly used antidepressant, such as Carhart-Harris et al., 2017 and Carhart-Harris et al., 2021, suggest that psilocybin appears to show similar effectiveness, albeit with a shorter treatment duration. Escitalopram prior to psilocybin reduced negative affect and anxiety but did not affect positive affect.

The study by Carhart-Harris et al., 2021 showed that psilocybin has a higher response rate (70%) than the escitalopram group (48%).

In statistical terms, throughout the trials, significant rates of improvement in depressive symptomatology can be observed, as in the study by Carhart-Harris et al., 2021, which highlights an improvement in the psilocybin group, where a 70% response rate is obtained, surpassing the escitalopram group, which obtained 46%.

It is worth mentioning the study by Becker et al., 2022, which highlights the importance of the acute effects of psilocybin after pretreatment with escitalopram or placebo in healthy subjects as well as the relevance of investigating about the combination of psilocybin with other psychiatric treatments.

### *Adverse Effects*

Although the information provided is quite limited in several of the studies, in general terms, psilocybin appears to be of acceptable safety.

It could be observed that, at four and a half years, 70% of the patients in the study met the criteria for antidepressant responses (Agin-Liebes et al., 2020) as well as demonstrated the feasibility, relative safety and potential efficacy of psilocybin-assisted group therapy for demoralization (Anderson et al., 2020).

Studies such as Gukasyan et al., 2022 and von Rotz et al., 2022 provide 12-month follow-up that corroborate the long-term efficacy and safety of psilocybin administration for the treatment of depression.

However, although mild and transient adverse events occurred, such as anxiety, confusion, nausea or headache; no serious adverse events were noted in most studies, supporting the concept that psilocybin is safe if administered in an appropriate manner.

Furthermore, as striking data, the safety and feasibility of psilocybin in different populations, including HIV patients (4% of the studies) and healthy volunteers (8% of the studies), has also been highlighted. In addition, the speed and sustainability of the therapeutic effects, especially in oncology patients, should be highlighted.

Studies such as Lewis et al., 2023 additional benefits can be observed in psilocybin-enhanced group therapy in cancer patients compared to conventional therapy.

## Discussion and Conclusions

### Efficacy of Psilocybin

After analyzing the results obtained, it is evident that psilocybin as an assisted therapy is effective for the treatment of depressive symptomatology.

Nevertheless, it can be observed that psychological support could be decisive in the treatment with psilocybin, since the experience with psychedelics could be intense and a professional accompaniment in the process is beneficial for the subject. Likewise, psychological support can help in the process of integrating the experiences into daily life, thus increasing the long-term benefits.

On the other hand, analysis of studies suggests that the combination of psilocybin as an assisted therapy accompanied by psychological support is effective in treating depression. However, not enough specific information is provided about the comparison of the efficacy of psilocybin with and without psychological support.

Likewise, and although according to the analysis made of the different scientific studies that analyze the efficacy of psilocybin for the treatment of depression show positive results, where there seems to be an improvement in patients, a fairly recent study by Marshall et al., 2022, investigated whether microdoses of psilocybin could alter interoceptive awareness, as well as the reduction of anxious and depressive symptomatology. The results revealed that microdosing did not affect emotion processing or symptoms of anxiety and depression compared to placebo, results that cast doubt on the main hypothesis of the present study.

Therefore, the results of the review suggest significant clinical implications, where psilocybin could be considered as an adjunct or alternative for the treatment of depressive disorder. However, further research is required to determine its long-term efficacy and to establish treatment guidelines.

### Comparison with Escitalopram

The analysis of the studies included in the present systematic review provides promising evidence about the efficacy of psilocybin for the treatment of depression, where an improvement of depressive symptomatology can be observed in patients treated with psilocybin, compared to escitalopram.

Likewise, the duration of the therapeutic effects of psilocybin is longer, so it could be used to reduce the frequency of doses as well as to improve adherence to treatment.

The study by Becker et al., 2022 provides an interesting perspective regarding the comparison of psilocybin and escitalopram, suggesting the use of psilocybin as an alternative to conventional antidepressants.

Thus, the study by Carhart-Harris et al., 2021 reinforces the idea put forward by the previous author, highlighting the need for research with the aim of interpreting more precisely the differences in the efficacy of both interventions.

The results of the clinical trials indicate that psilocybin may be equally or more effective than escitalopram for the reduction of depressive symptomatology, since response and remission rates could be observed between the psilocybin and escitalopram groups; therefore, psilocybin could be a therapeutic option for those patients suffering from treatment-resistant depression.

## Adverse Effects

Regarding the adverse effects of psilocybin administration, while participants have been able to experience marked improvement in terms of depressive symptomatology, anxiety and quality of life (Goodwin et al., 2022), others may face more intense adverse effects.

Results such as Gukasyan et al., 2022 show a 12-month perspective, highlighting the need to take into account the duration and frequency of exposure to reduce potential risks.

Several of the studies have critical long-term safety issues, and while psilocybin has demonstrated therapeutic efficacy, the potential risks of its continued use need to be known.

Also, the inherent subjectivity of the adverse effects of psychedelics such as psilocybin suggests uncertainties as to how they are assessed and interpreted. This is why it is essential to take into account the cost of evaluating negative aspects as well as to consider subjective experiences that may vary according to the individual context, the environment as well as expectations.

## Limitations

One of the main limitations found in the present review was the absence of detailed information about the psychological therapy applied. Although most studies include psychological support as part of psilocybin-assisted treatment, the absence of specific details about the nature or manner of employing the therapy has affected the full understanding of the intervention.

In addition, it is important to note that a minority proportion of the clinical trials focused on oncology patients and healthy volunteers, which limits the generalizability of the results to a wider range of patients with depression as well as potentially introducing bias and limiting the practical applicability of the findings in the therapeutic context of depression.

Likewise, the limitations related to smaller studies should be taken into account in order to evaluate the conclusions in relation to the number of subjects included in each study, as well as to highlight the importance of collecting the results for future research in the generalization of results.

However, it should be noted that the exploration of psilocybin-assisted therapy is relatively recent, so more research is needed to comprehensively understand the mechanisms and to enhance its clinical application.

## Future research

Recent research on psilocybin as a therapeutic option for the treatment of depression has generated a promising outlook in psychology. However, questions and future areas for research have also emerged.

Mainly, the development of controlled clinical trials with long-term follow-up would be one of the first needs to be contemplated in order to be able to evaluate in a much deeper way the effectiveness and safety of psilocybin and provide long-term results. In addition, research focused on understanding the underlying neurobiological and psychological mechanisms of action of the consequences of psilocybin is critical to further understanding the impact of the substance on depression.

Likewise, we believe that future research should implement trials that develop direct comparisons between psilocybin treatment and conventional treatments for depression, providing a more accurate picture of its efficacy.

Finally, research into both the economic feasibility and accessibility of psilocybin therapy compared to conventional therapies is imperative to evaluate its implementation.

## Conclusions

Regarding the main objective of the present study, the compilation of the results of scientific articles, support psilocybin as a therapeutic option for the treatment of depression, highlighting especially its efficacy, rapidity of action and safety profile, in addition to emphasizing the great importance surrounding contextual factors as well as the exploration of neurobiological mechanisms.

Regarding the second objective of the present study, research contrasting psilocybin with the antidepressant escitalopram indicates that both show comparable efficacy, although psilocybin stands out for its shorter treatment duration. In addition, modifications in the response of the amygdala are observed, as well as an improved ability to anticipate future situations in patients with treatment-resistant depression.

Regarding the third objective of the present study, in general terms, psilocybin seems to have an acceptable safety, being thus supported by studies providing long-term follow-up. Although mild and transient adverse events such as anxiety, confusion, nausea or headache were reported, no serious adverse events were reported in most studies. Proper administration appears to be the key to ensuring safety.

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