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Research Article

Managing Treatment-Resistant Depression with Psilocybin

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Abstract

Background: Major Depressive Disorder (MDD) is responsible for most cases of social, physical and emotional disability. This disorder affects about 320 million people in the world and is one of the diseases of the 21st century.

Objective: To expose scientific data that suggests the use of Psilocybin as a form of therapy for treatment-resistant depression (TRD).

Method: Literature review through the search for scientific productions in the textual modality of articles, indexed in the Medical LiteratureAnalysis and Retrieval System Online, through the PUBMED search tool.

Results: It was observed that the use of psilocybin presents positive results for the treatment of MDD and TRD, where the rapid and sustained effect of this treatment against the symptoms of depression was demonstrated. Psilocybin has shown to be an innovative method with some advantages when compared to methods that use traditional antidepressants, suchas increased amygdala response and emotional stimuli allowing emotional reconnection of patients with TRD.

Conclusion: This treatment is presented as a promising alternative in cases where conventional treatment is not efficient. However, efforts are needed to produce new studies that confirm the efficacy and safety of using psilocybin as an effective treatment against TRD.

Keywords: *Depression; Psilocybin; Major Depressive Disorder; Treatment Resistant Depressive Disorder*

Introduction

Major Depressive Disorder (MDD) affects about 300 million people worldwide and, as a result, it is the leading cause of disability and increased risk of death in comparison with the rest of the population [1].

Several pharmacological therapies are used to treat depression, and yet they show limited effectiveness and can cause adverse reactions, which will eventually impact on patients´ ability to adhere to the treatment. In this context, pharmacotherapy may be ineffective in 50% of cases, and treatment resistance will affect roughly 30% of patients [2,3].

Managing treatment-resistant depression (TRD) is quite challenging: the incidence of remission tends to decline as antidepressant treatment trials progress, and patients who fail to produce significant clinical improvements after at least two trials are considered to have

TRD. TRD patients have higher levels of severity and duration of illness, disability, physical illness, incidence of hospitalization, suicide risk, and economic costs than patients with treatment-responsive depression [4,5].

Psilocybin is a prodrug for psilocin (4-OH-dimethyltryptamine) and a class of psychedelic substances, which initiates its action via agonist activity at the serotonin 2A receptor (5-HT2AR). This naturally occurring compound can be found in mushrooms of the genus *Psilocybe* and has great similarity with the endogenous neurotransmitter, serotonin (5-OH-tryptamine, 5-HT) [6]. 5-HT2AR signaling has been associated with better responses to conventional antidepressants, in addition to mediating the therapeutic effects of Selective Serotonin Reuptake Inhibitors (SSRIs), according to preclinical studies [7,8].

The discovery and commercial sales of psilocybin date back to the 1950s and 1960s; however, after this period, it was banned due to political issues, ultimately halting scientific research on this substance. Only in the past fifteen years have researchers resumed clinical studies [9,10].

Notably, psychedelic substances produce changes in mood and cognitive processes. Psilocybin, for example, has shown promising results for treatment of obsessive-compulsive disorder [11], alcohol and tobacco addiction, and anxiety related to terminal illness [12-16].

The action of antidepressants on structural neuroplasticity in the frontal cortex is paramount to their success, and these compounds with fast-acting antidepressant effects promote structural plasticity to reverse the synaptic deficits caused by chronic stress [17]. Antidepressants, such as ketamine, provide increased column density in the medial frontal cortex of rodents in a single dose, possibly involving calcium signaling in the dendritic compartment. In the case of psilocybin, it can modify the synaptic architecture by increasing the expression of genes involved in the synaptic plasticity in rats [17].

Purpose of the Study

The purpose of this article is to expose scientific data that suggest the use of psilocybin as a therapy for treatment-resistant depression.

Methods

Literature review through the search for scientific productions in the textual modality of articles, indexed in the Medical Literature Analysis and Retrieval System Online database, through the MEDLINE/PubMed search tool, carried out on 26 November 2022, using the following MeSH descriptors in the English language: Psilocybin; Depression; Depressive disorder; Depressive disorder, treatment resistant; Depressive disorder, major.

The preliminary result of the search showed 56 publications, according to the following search configuration: (depressive disorder, major [MeSH Terms]) OR (depressive disorder, treatment resistant [MeSH Terms]) AND (psilocybin [MeSH Terms]).

In the second stage, the following selection filters were applied as inclusion criteria: Article types - clinical trial, randomized controlled trial; publication dates - last 5 years; species - humans; text availability - full text; language - English, Portuguese. Ten abstracts were selected for thematic content and full-text analysis. Articles, the main subjects of which did not meet the objectives of this research, were excluded. Finally, 4 articles were eligible for this literature review.

The methodology for literature search and selection for this review is summarized in the flowchart in figure 1.

Results

The syntheses of the articles selected in this review are presented in table 1.

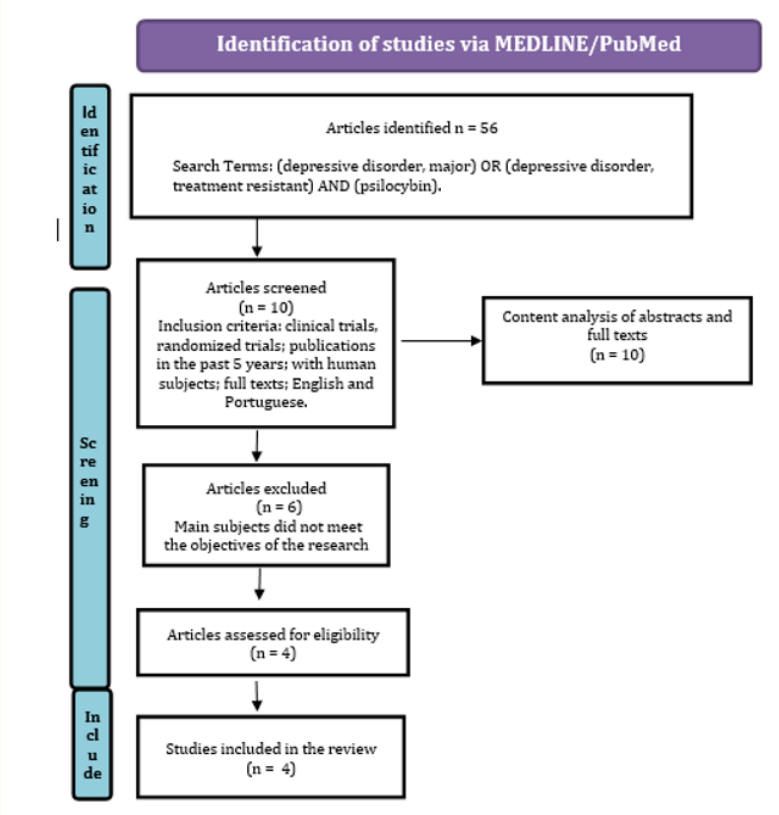

Figure 1: *Flowchart of literature search and selection for this review.*

Discussion

Numerous studies have reported the use of psilocybin to treat depression and TRD, providing important insights into this topic. The results support a general recognition of this substance as a possible innovative therapy, thus encouraging clinical studies aimed at using psilocybin as a new approach to treat depression [20].

Carhart-Harris., *et al.* (2017) [18] provided updated data from an open-label clinical trial investigating psilocybin with psychological support for TRD. Eighteen of the 20 patients met the criteria for severe or very severe depression at baseline (QIDS-SR16 score ≥ 16); two patients met the criteria for moderate depression (QIDS-SR16 scores ≥ 11, < 16). Data were analyzed for the 19 patients who completed all assessments. QIDS-SR scores were significantly lower with peak effect at 5 weeks; all showed some decrease in depression severity at 1 week and these were mostly sustained for 3 - 5 weeks. Anxiety levels reduced significantly 1 week (mean reduction = -23.8), 3 months (mean reduction = -12.2%), and 6 months post-treatment (mean reduction = -14.8). Anhedonia levels were significantly lower 1 week (mean reduction = -4.6) and 3 months post-treatment (mean reduction = -3.3). Hamilton Depression Rating Scale (HAMD) scores were significantly lower 1 week after treatment (mean reduction = -14.8) and global assessment of functioning (GAF) scores significantly increased 1 week after treatment (average increase = + 25.3). The treatment was generally well tolerated and without any serious adverse

Author/Year	Objective	Sample	Treatment	Result/Conclusions
Carhart-Harris., *et al*. (2017) [18]	To report safety and efficacy results for up to 6 months in an open-label trial of psilocybin for the treatment of resistant depression.	N = 20	Two oral doses of psilocybin (10 and 25 mg, 7 days apart and with psychological support.	Decrease in depression severity within 1 week and mostly sustained for 3-5 weeks; HAM-D scores were significantly reduced at 1 week after treatment and GAF scores significantly increased 1 week after treatment.
Roseman., *et al*. (2018) [19]	To investigate whether amygdala responses to emotional faces would be altered after psilocybin treatment.	N=20	Two doses of 5 mg with psychotherapy support before, during and after dosing sessions.	Rapid and sustained decrease in symptoms of depression; Psilocybin with psychological support was associated with increased amygdala responses to emotional stimuli.
Davis., *et al.* (2021) [20]	To investigate the effect of psilocybin therapy in patients with MDD.	N=27	First dose: 20 mg/70 kg; Second dose: 30mg/70 kg) Both doses with psychotherapy support (11 hours)	Rapid and significant decrease in depression after the psilocybin session at week 4.
Goodwin., *et al.* (2022) [21]	To identify an acceptable effective dose and evaluate the safety of a synthetic formulation of psilocybin, administered in conjunction with psychological support in patients with treatment-resistant MDD.	N=233	Single dose of synthetic formulation of psilocybin of 25 mg, 10 mg or 1 mg (control) and with psychotherapy support.	The MADRS total score was significantly better with a 25 mg dose than with a 1 mg dose over a period of 3 weeks.

Table 1*: Synthesis of the selected articles.*

events. The most common adverse effects were: transient anxiety during a few minutes (n = 15) and headaches for 1 - 2 days (n = 8). Transient nausea and transient paranoia were less frequently reported during the experiment with a short duration in all cases.

Also in this context, functional magnetic resonance imaging demonstrated the effect of psilocybin on cerebral blood flow (CBF), blood oxygen level dependent (BOLD) and resting state functional connectivity (RSFC) before and after treatment with this compound for TRD, making substantial contributions to elucidating cerebral effects after treatment with psilocybin [18].

Previously published studies have supported the safety and efficacy of psilocybin for depression and anxiety symptoms [14,15,22]. They have demonstrated the feasibility of treating patients with major depressive disorder with psilocybin alongside psychotherapy. Two double-blind randomized clinical trials of psilocybin for symptoms of depression and anxiety evaluated a total sample of 80 patients with life-threatening cancer and showed consistent results of safety and efficacy [14,15]. The physiological mechanism proposed by Carhart-Harris., *et al*. (2016) specified that psychedelic-induced 5-HT2AR signaling rapidly caused an acute state of plasticity that can lead to

cognitive biases. Further studies should aim to characterize and measure the various psychological components contained in the current models of psychedelic therapy [14,15,22].

Basic safety principles of psychedelic-assisted psychotherapy must be observed and systematic verification of treatment approaches is necessary for its implementation. Experiments intended to evaluate the contribution of psychological variables resulting from the psychedelic experience using psilocybin should be carefully conducted given the vulnerability of individuals under the influence of psychedelics. Thus, high standards of care, including psychological support, are of utmost importance [18].

Roseman., *et al.* (2018) [19] investigated whether amygdala responses to emotional faces would be changed after the treatment with psilocybin and whether this would be related to a decrease in depression severity. First, the authors noted that the amygdala is a complex subcortical structure, sensitive to emotional stimuli; next, they highlighted its previously-described role in the pathophysiology of depression, similarly to some antidepressants and psychedelics. In another study, a decrease in the amygdala response to emotional stimuli with selective serotonin reuptake inhibitors (SSRI) was also observed [7]. In Roseman., *et al.´*s study (2018) [19], twenty patients diagnosed with moderate-to-severe TRD were selected, who were submitted to two separate dosing sessions with psilocybin. They received psychological support before, during and after both sessions and 19 functional magnetic resonance imaging (fMRI) exams were performed one week before the first session, on the first and second days after the exam. Patients were shown images of neutral, fearful and happy human faces and the fMRI analysis focused on the amygdala. The results of the images showed responses to neutral, fearful and happy expressions in the right amygdala after psilocybin treatment, and an increase in the right amygdala was noted for fearful and happy expressions when compared to neutral ones. Increased amygdala responses to emotional faces were observed one day after the treatment with psilocybin for TRD. Responses to fearful versus neutral faces revealed clinical improvements of depression one week after the treatment [19].

The results in Roseman., *et al.´*s study (2018) [19] differ from previously reported findings of decreased amygdala responses after treatment with conventional antidepressants, particularly with SSRIs. According to Harmer., *et al.* (2017) [8], the decrease in amygdala responsiveness to negative emotional stimuli with SSRIs is essential for its therapeutic action, but the results of the present study suggest that this model is not a predictor of therapeutic outcomes of psilocybin for TRD [18].

Long-term SSRI antidepressants have a more general effect on emotional processing, moderating not only responsiveness to negative emotional stimuli but overall emotional stimuli. These effects are concentrated in the amygdala, a structure that is sensitive to emotional variations according to the stimuli received [19].

SSRI antidepressants promote inhibition of amygdala responses to emotional stimuli and this mechanism is associated with the activation of postsynaptic serotonin 1A receptors (5-HT1ARs), which have an inhibitory action on the firing of pyramidal cells [23].

The results of this study show an increase in the amygdala response to psilocybin treatment, which results in the recovery of emotional connection in patients with TRD, and presents neurobiological data that support psilocybin therapy as an alternative to SSRI antidepressants to relieve depression symptoms [18].

Davis., *et al.* (2021) [20] investigated the effects of psilocybin therapy in patients with MDD. Twenty-seven participants were assessed with the GRID-Hamilton Depression Rating Scale (GRID-HAMD): after the psilocybin session, clinically significant response was found in 16 participants (67%) at week 1 and in 17 participants (71%) at week 4; remission was observed in 14 participants (58%) at week 1 and 13 participants (54%) at week 4. QIDS-SR showed a marked decrease in depression scores after the psilocybin session, which was maintained through week 4 after the second session. No serious adverse events were reported in the study. In the first session, there was a transient increase in diastolic blood pressure that exceeded protocol criteria (> 100 mm Hg), with no need for medical intervention. Blood pressure level remained within pre-established safety parameters and naturally returned to baseline during the session. Emotional (fear

and sadness) and physical experiences (tremble, mild-to-moderate transient headache) were some non-serious adverse effects reported by the participants after completing at least one-half of the psilocybin sessions [20].

Psilocybin therapy shows rapid and long-lasting antidepressant effects among patients with MDD. Although psilocybin and ketamine have similar rapid antidepressant effects, different therapeutic effects can be pointed out: ketamine effects usually last for a few days to 2 weeks, and the antidepressant effects of psilocybin show significant response for at least 4 weeks. Furthermore, psilocybin showed low addiction potential and minimal adverse event characteristics, suggesting therapeutic benefits with more protective factors than ketamine. In patients with MDD, psilocybin as an antidepressant treatment strategy proved to be effective in cancer patients with psychological distress and in patients with TRD. A great body of evidence supports the use of psilocybin as an adjunct treatment of several psychiatric conditions, such as depression and tobacco and alcohol abuse, indicating a transdiagnostic mechanism [20].

Davis., *et al*. (2021) [20] reported that psilocybin administered in the context of 11-hour supportive psychotherapy produced rapid and enduring antidepressant effects. The antidepressant effects showed a 2.5-fold increase in comparison with psychotherapy treatments and a 4-fold increase in relation to the psychopharmacological depression treatment. These results are in line with the literature, which maintains that a combination of pharmacotherapy and psychotherapy was more effective in treating MDD than either intervention alone.

They further highlighted that the adverse effects of psilocybin were mild-to-moderate headache and negative emotions, experienced only during the sessions. These may be more acceptable effects than those caused by most antidepressants, namely suicidal thoughts, decreased libido and weight gain. Finally, another advantage was the effectiveness of psilocybin therapy after a single or a few administrations, instead of daily administration [20].

Goodwin., *et al.* (2022) [21] sought to identify an acceptable effective dose and evaluate the safety of a synthetic formulation of psilocybin, administered along with psychological support in patients with treatment-resistant MDD. Three groups were formed: 79 participants in the 25 mg group, 75 the 10 mg group, and 79 in the 1 mg group. The mean total score for Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline ranged between 32 or 33 in each group. Mean changes in score from baseline to week 3 were -12.0 for 25 mg, -7.9 for 10 mg, and -5.4 for 1 mg. The difference between the 25-mg group and the 1-mg group was -6.6, and between the 10-mg and the 1-mg group was -2.5. Adverse events were observed in 179 of 233 participants (77%), namely headache, nausea and dizziness. Suicidal behaviors or intentional self-injury were reported in all groups. According to the results, psilocybin monotherapy has proved to be feasible for up to 12 weeks in patients with a treatment-resistant episode of major depression. MADRS total score in week 3 was significantly better with a 25 mg dose than with a 1 mg dose, with no significant difference between the 10 mg dose and the 1 mg dose. Some participants reported headache, nausea, dizziness, and fatigue, as well as suicidal ideation or self-injurious behavior, and the number of participants was proportionally greater in the 25 mg and 10 mg groups than in the 1 mg group. Some participants increased suicidality, therefore clinical surveillance is required in future psilocybin trials to treat depression. The incidences of response and remission at 3 weeks were in line with primary endpoint results; however, the analyses of ordered endpoints followed a pre-specified fixed sequence procedure after the significance test and no final conclusions could be drawn from these results [21].

Ultimately, a drawback of this study was a dearth of research on this topic, especially clinical studies [24].

Conclusion

Some studies show results with the use of psilocybin in reducing the symptoms of treatment-resistant depressive disorder.

Psilocybin appears to increase responsiveness to facial expressions due to increased amygdala stimulation compared to more commonly prescribed antidepressants. Concomitantly, patients described feelings of emotional reconnection and greater willingness to accept all emotions after treatment.

This treatment presents itself as a promising alternative in cases where conventional treatment is not efficient.

However, efforts are needed to produce new studies that confirm the efficacy and safety of using psilocybin as an effective treatment against TRD.

It is important to highlight that the use of agents such as psilocybin still lacks more consistent evidence that justifies its systematic use in patients with TRD.

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