Review
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Current Understanding on Psilocybin for Major Depressive Disorder: A Review Focusing on Clinical Trials

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Previous studies suggested effectiveness of psilocybin in the field of mental health. FDA designated psilocybin as a "breakthrough therapy" for the treatment of treatment-resistant depression (TRD) in 2018. This paper provided a review of psilocybin's potential role in treatment of depression by focusing on published clinical trials. Studies showed that psilocybin, an agonist on 5-HT_{2A} receptors, manifests antidepressant and anxiolytic effects by increasing glutamate transmission, reducing brain inflammation, decreasing default mode network activity. In terms of clinical trials, eleven studies (six open-label and five double blinded randomized clinical trials, DB-RCTs) trials exploring psilocybin's impact on depression were found. Among open-label studies, a pilot study on TRD patients demonstrated significant reductions in depressive symptoms after two psilocybin sessions. Psilocybin also improved cognitive bias associated with depression. Extension studies confirmed sustained improvements and high remission rates. Among five DB-RCTs, two showed that psilocybin led to significant reductions in anxiety and depression in cancer patients, and the improvements sustained for over 6 months. In MDD, psilocybin showed rapid reductions in depression, with higher remission rates compared to escitalopram in a DB-RCT. Another DB-RCT showed that psilocybin induced higher decrease in depression around 6 hours after their administrations than placebo. The last DB-RCT showed that in patients with TRD, a single dose of psilocybin 25 mg, but not psilocybin 10 mg, resulted in superior antidepressant effect than psilocybin 1 mg. Overall, psilocybin showed promise in treating depression and anxiety, with notable safety profiles. Further research should explore optimal dosages and long-term effects.

KEY WORDS: Psychedelics; Psilocybin; Depression; Treatment.

INTRODUCTION

Depression, a pervasive and debilitating mental health disorder, affects millions of individuals worldwide, contributing to substantial suffering and reduced quality of life [1]. Despite decades of research and therapeutic innovations, conventional treatments such as antidepressant medications and psychotherapy are not universally effective, leaving a significant proportion of individuals with treatment-resistant depression (TRD) [2,3]. This treatment gap, coupled with the pressing need for alternative approaches, has spurred interest in the therapeutic potential of psychedelic compounds, with psilocybin emerging as a prominent candidate [4].

Psilocybin, a naturally occurring psychedelic compound found in certain species of mushrooms, has captivated the attention of researchers and clinicians alike due to its ability to induce profound alterations in consciousness, cognition, and mood [5]. Historically, indigenous people have employed psilocybin-containing mushrooms in spiritual and healing practices [6]. Clinical research on psilocybin began in 1962 when Walter Pahnke and Timothy Leary initiated the "Marsh Chapel Experiment" or so called the "Good Friday Experiment." The results showed a statistically significant increase in halluci-

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nogenic experiences in the psilocybin group (n = 10) than in the niacin group (n = 20) [7]. Additionally, Leary and others also conducted research, known as the "Concord Prison Experiment," which suggested that it could reduce the recidivism rate among inmates [8].

While there were positive research results as mentioned above, the misuse use of psychedelics including lysergic acid diethylamide (LSD) and psilocybin increased drastically in the United States (US), which resulted in a growing negative perception and criticism in the media [9]. Thus, production, trade, or consumption of hallucinogenic drugs became prohibited in 1963 in the US [10]. Furthermore, in 1970, psilocybin and LSD were classified as Schedule I illegal substances, leading to stricter regulations on the use of hallucinogens. Schedule I substances are defined as drugs with a high potential for abuse and no recognized medical use [11].

Several recent studies suggested effectiveness of psilocybin in the field of mental health and pain treatment, and eventually, the city of Denver, Colorado, became the first in the US to decriminalize psilocybin [12]. Subsequently, the state of Oregon became the first in the US to allow the use of "magic mushrooms," or hallucinogenic mushrooms, for supervised mental health therapy starting from February 1, 2021 [13-15]. Furthermore, in 2018, the US Food and Drug Administration (FDA) designated psilocybin as a "breakthrough therapy" for the treatment of treatment-resistant depression, allowing it to receive priority in the FDA approval process based on future clinical trial results [16].

In this review, we will focus intensively on psilocybin, which has the most clinical data among various hallucinogens and has been designated as a "breakthrough therapy" by the FDA as mentioned above. As the field of psychedelic research continues to expand, it is crucial to assess the evidence, risks, and benefits associated with psilocybin in the context of depression treatment. Thus, the purpose of this paper is to provide a review of psilocybin's potential role in the treatment of depression by focusing on clinical trial data.

DATA SEARCH

We searched Cumulative Index to Nursing and Allied Health Literature, Embase, Medline, PsycINFO, PubMed, the and the Web of Science using the keywords "psychedelic," "psilocybin," "mushroom," and "depression," to identify relevant published articles. We focused on the clinical studies, so we excluded studies involving animal research and other basic studies. However, we referred to animal and basic studies to describe its potential mechanism of action in depression. Reference lists from identified articles, review papers, and meta-analysis were manually searched to find additional studies of interest. The language of all papers was restricted to English.

S.M.W. and W.S.C. initially reviewed the abstracts identified from the literature search independently to determine whether they met the scope of our review. Whether or not these papers met the selection criteria were re-evaluated by two other authors (S.W.K. and H.K.L.). When there were disagreements, following review by the three remaining authors (W.S.C., W.M.B., and C.U.P.) provided the final decision. This article is a narrative review focusing on the clinical trials investigating efficacy of psilocybin in the treatment of depression. Based on a consensus among the authors, all relevant studies meeting the scope of our paper were selected. As a narrative review paper, the study did not involve primary data collection or human subjects, thus an Institutional Review Board (IRB) approval was not required.

MECHANISM OF ACTION

Psilocybin, known as a psychoplastogen, is a compound capable of promoting rapid and sustained neuroplasticity [17]. It is rapidly metabolized in the body and acts as an agonist on various serotonin receptors, also known as 5-hydroxytryptamine (5-HT) receptors [18]. Among the serotonin receptors, it exhibits a high affinity for 5-HT_{2A} receptors, leading to its antidepressant and anxiolytic effects through serotonin receptor agonism [19]. Figure 1 illustrates summary of mechanism of action of psilocybin in the treatment of depression. First, it increases the release of neurotrophic factors, such as brain-derived neurotrophic factor, by enhancing glutamate transmission [20]. This ultimately promotes neuronal regeneration and neuroplasticity in the brain. 5-HT_{2A}-receptor activation in immune cells can decrease inflammatory cascade of the brain by reducing neuroinflammatory factors such as tumor necrosis factor-alpha and interleukin-6 [21,22]. It may also decrease the threat sensitivity in visual cortex, which is more closely linked with

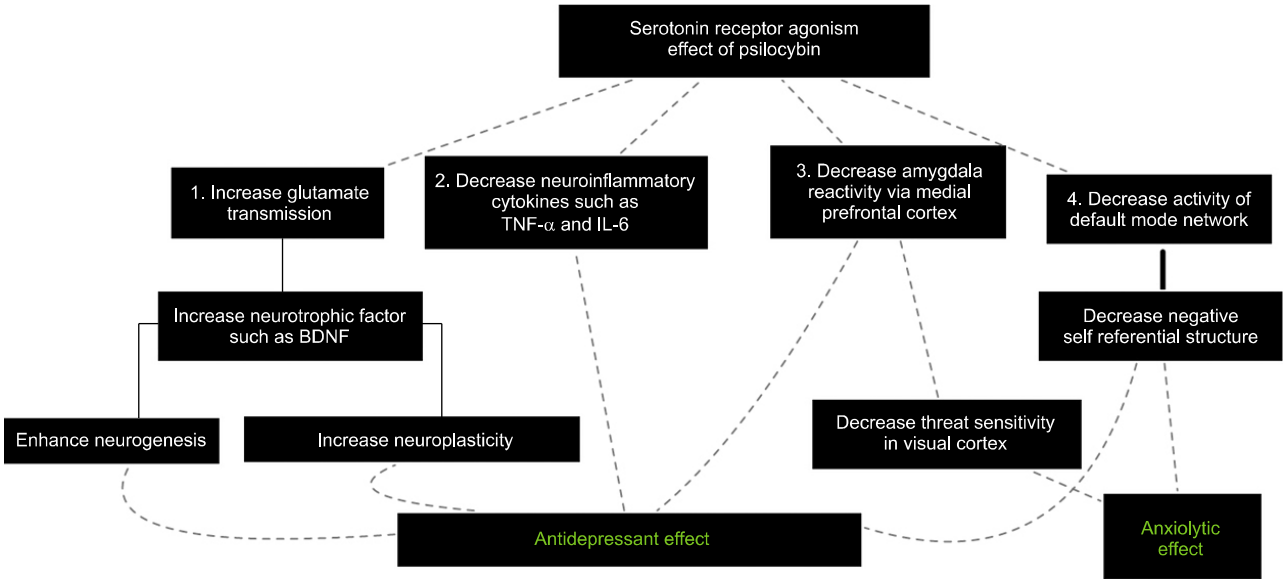

Fig. 1. Psilocybin exhibits antidepressant and anxiolytic effects through its agonistic action on serotonin receptors (5-HT_{2A}). Revised from the article of Muttoni *et al.* (J Affect Disord 2019;258:11-24) [19] with original copyright holder's permission.
BDNF, brain-derived neurotrophic factor; IL-6, interleukin-6; TNF-alpha, tumor necrosis factor alpha; 5-HT, 5-hydroxytryptamine.

decreasing anxiety symptoms rather than depressive symptoms per se [23]. Psilocybin reduces the hyperactivity of the default mode network, which is associated with negative intrusive thoughts and increased self-referential thinking, resulting in decreased depressive and anxiety symptoms [24].

Psilocybin's agonism actions at the 5-HT_{2A} receptors are also known to be associated with mystical experience, including visual hallucinations, that the patients experience after receiving psilocybin [25]. 5-HT_{2A}-receptor are highly expressed in the visual cortex, so receptor activity in visual cortical neurons may be sufficient to mediate hallucinatory effects [26]. In addition, 5-HT_{2A} agonism leads to increased dopamine levels in the ventral striatum resulting in hallucinogenic-like symptoms including depersonalization and euphoria [27]. Lastly, 5-HT_{2A} agonisn in the thalamus and medial prefrontal cortex may cause decrease thalamic functon, which might result in lowered consciousness, decreased arousal, and reduced sensory singal sensitivity [28].

RESULTS

The literature search resulted in 11 clinical trials that had investigated the effect of psilocybin in the treatment of depression. The selected studies were very heterogeneous in their design, settings, subjects, and outcome measures. Thus, we first subdivided them into the following groups: (1) open label clinical trials (Table 1) and (2) double-blinded (DB) randomized clinical trials (RCTs) (Table 2).

Open Label Clinical Trials

We identified 6 clinical trials investigating the effect of psilocybin in the treatment of depression (Table 1). Among the 6 open label trials 4 involved patients with TRD, and other 2 were conducted in patients with major depressive disorder (MDD).

Carhart-Harris and colleagues first reported the results of a pilot study evaluating the feasibility and efficacy of psilocybin in TRD patients in 2016 [29]. This open-label study included a total of 12 patients with moderate to severe MDD, as indicated by a 21-item Hamilton Depression Rating Scale (21-item HAM-D) score of 17 or higher, who had not shown significant improvement despite taking two different types of antidepressant treatments for at least 6 weeks. All patients received two oral doses of psilocybin with 7-day intervals, in conjunction with psychotherapy sessions. In the first session, patients took a low dose (10 mg) of psilocybin, and in the second session, patients took a high dose (25 mg) of psilocybin. The primary outcome measure was the patient-reported intensity of psilocybin's effects, which was rated 0 to 1. The results showed that the psilocybin's acute psychedelic effects be-

Table 1. Open label studies investigating psilocybin in the treatment of major depressive disorder

Author (yr)	Subjects	Design	Allocation	Sample size	Mean age	Length	Intervention	1° outcome measure	Results
Carhart-Harris *et al.* [29] (2016)	TRD	Single arm	Psilocybin only	12	42.7	12 wk	Two oral psilocybin capsule (10 mg and 25 mg, 7 days apart)	Subjective intensity of psilocybin's effects (0−1)	Low-dose session: 0.51 (SD 0.36) High-dose session: 0.75 (SD 0.27)
Carhart-Harris *et al.* [30] (2018)	TRD	Extension of Carhart-Harris (2016)	Psilocybin only	20	44.1	6 mo	Same as Carhart-Harris (2016)	QIDS-SR16	Improvement began 1 wk after psilocybin and maintained at 6 mo
Lyons and Carhart-Harris [31] (2018)	TRD	Extension of Carhart-Harris (2016)	Psilocybin CG	15 15	45.4 37.6	1 wk	Psilocybin = same as Carhart-Harris (2016) CG = healthy subjects	BDI and POFLE	Depression and negative cognitive bias improved after psilocybin
Roseman *et al.* [32] (2018)	TRD	Extension of Carhart-Harris (2016)	Psilocybin only	20	44.7	6 mo	Same as Carhart-Harris (2016)	ASC	Psilocybin-induced high mystical experience and low anxiety predicted positive long-term treatment outcome
Davis *et al.* [33] (2021)	MDD	Waiting list controlled RCT	Psilocybin Waiting	15 12	43.6 35.2	4 wk	Two psilocybin capsule sessions (20 mg/70 kg and 30 mg/70 kg)	GRID-HAMD	Significantly more improved in psilocybin group
Gukasyan *et al.* [34] (2022)	MDD	Extension of Davis (2021)	Psilocybin only	27	39.8	12 mo	Same as Davis (2021)	GRID-HAMD	GRID-HAMD improved over 12 mo

1°, primary; ASC, altered states of consciousness; BDI, Beck's depression inventory; CG, control group; DB, double blinded; GRID-HAMD, GRID Hamilton rating scale for depression; HAM-D 17, 17-item Hamilton depression rating scale; MADRS, Montgomery–Åsberg depression rating scale; MDD, major depressive disorder; POFLE, prediction of future life events task; QIDS-SR16, 16-item quick inventory of depressive symptoms; RCT, randomized clinical trial; TRD, treatment resistant depression; SD, standard deviation.

Table 2. Double blinded randomized controlled study investigating efficacy and safety of psilocybin in the treatment of major depressive disorder or depressive symptoms

Author (yr)	Subjects	Length	Allocation	Intervention	Sample size	Mean age	1° outcome measure	Results
Ross *et al.* [36] (2016)	Cancer	7 wk + 5 mo	Psilocybin 0.3 mg/kg first Niacin 250 mg first	Cross over study, all in oral formulation	14 15	52 60.3	HADS-A and HADS-D	Psilocybin superior to niacin
Griffiths *et al.* [35] (2016)	Cancer	5 wk + 5 mo	Psilocybin 22−30 mg first Psilocybin 1−3 mg first	Cross over study, all in oral, 5 weeks interval before crossover	25 26	56.5 56.1	GRID-HAMD, HAM-A	High dose superior to low dose
Carhart-Harris *et al.* [37] (2021)	MDD	6 wk	Psilocybin 25 mg Escitalopram	Psilocybin 25 mg × 2 + PBO vs. Psilocybin 1 mg × 2 + Escitalopram	30 29	43.3 39.1	QIDS-SR-16	None
von Rotz *et al.* [38] (2022)	MDD	14 d	Psilocybin 0.215 mg/kg PBO	1 dose of gelatin capsules + psychological support	26 26	37.6 35.9	MADRS and BDI	0.215 mg/kg > PBO for MADRS and BDI
Goodwin *et al.* [39] (2022)	TRD	12 wk	Psilocybin 25 mg Psilocybin 10 mg Psilocybin 1 mg (CG)	1 dose of synthetic formulation + psychological support	79 75 79	40.2 40.6 38.7	MADRS at wk 3	At wk 3, 25 mg > 1 mg. 10 mg vs. 1 mg no difference

1°, primary; BDI, Beck's depression inventory; CG, control group; DB, double blinded; HAM-D 17, 17-item Hamilton depression rating scale; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; MADRS, Montgomery–Åsberg depression rating scale; MDD, major depressive disorder; RCT, randomized clinical trial; TRD, treatment resistant depression; PBO, placebo.

came detectable 30−60 minutes after the first dosing, which peaked 2−3 hours after dosing, and subsided to negligible levels at least 6 hours after the dosing. Mean self-rated intensity was 0.51 (standard deviation [SD] 0.36) and 0.75 (SD 0.27) for the low-dose session and the high-dose session respectively. In addition, quick in-

ventory of depressive symptomatology (QIDS), and the average change in QIDS score was found to be significantly reduced at 1 week (−11.8, SD = 4.9; $p = 0.002$) and 3 months (−9.2, SD = 6.0; $p = 0.003$) after the treatment. Scores on other measures such as the beck depression inventory (BDI), state-trait anxiety inventory (STAI), Snaith-Hamilton pleasure scale, and Montgomery-Åsberg depression rating scale (MADRS) also significantly decreased at one week and three months. Patients who reached remission from depression with a BDI score < 9 points were observed in 8 patients (67%) 1 week after treatment and 5 patients (42%) at the 3-month. In terms of safety, psilocybin was well tolerated, and no serious adverse events (SAEs) occurred. The adverse reactions noted were transient anxiety during drug onset (all patients), transient confusion or thought disorder (nine patients), mild and transient nausea (four patients), and transient headache (four patients). Psychosis occurred in only one patient and was temporary, with no long-term psychotic symptoms observed.

Among the four studies involving TRD, three were extension research of the Carhart-Harris (2016) study. The first study was a 6-month extension study of the Carhart-Harris (2016) research [30]. The number of patients treated was increased from 12 to 20. The change of self-rated QIDS-SR16 from 1 week to 6 months post-treatment was used as the primary outcome measure. The results showed that the marked reductions in depressive symptoms were observed for the first 5 weeks post-treatment (Cohen's d = 2.2 at week 1 and 2.3 at week 5, both $p < 0.001$). Quality of the acute psychedelic experience after the psilocybin predicted reductions in depressive symptoms at week 5. The positive effect remained positive at 3 and 6 months (Cohen's d = 1.5 and 1.4, respectively, both $p < 0.001$).

The second extension study involved an open-label pilot research investigating the effects of psilocybin on measures of depressive symptoms and cognitive biases in TRD patients [31]. The study included 15 patients with TRD from the Carhart-Harris (2016) study [29]. In addition, the study enrolled 15 additional healthy non-treated control subjects (control group). The result showed that patients with TRD (n = 15) had higher baseline pessimism (prediction of future life events task) than the control group [$t(14) = -3.260$, $p = 0.006$]. Moreover, the pessimism severity showed association with the depressive symptoms measured using BDI ($rs = -0.55$, $p = 0.017$). This cognitive bias [$t(14) = -2.714$, $p = 0.017$] and depressive symptoms improved significantly one week after the psilocybin treatment [$t(14) = 7.900$, $p < 0.001$]. In addition, patient's ability to predict the occurrence of future life events became significantly more accurate after the psilocybin treatment [$t(14) = 1.857$, $p = 0.042$] while no such improvement was observed in the control group.

The last extension study showed that the acute psychedelic experience after psilocybin administration predicted therapeutic efficacy of psilocybin for TRD [32]. The altered states of consciousness (ASC) questionnaire was used to assess the quality of experiences in the second psilocybin session, which was dose of 25 mg. Among the ASC questionnaire, oceanic boundlessness (OBN) and dread of ego dissolution (DED) were used to measure mystical-type and challenging experiences and anxiety, respectively. The results showed the psilocybin-induced high OBN (mystical-type experience), and low DED (anxiety) predicted positive long-term (6 months) clinical outcomes of psilocybin for TRD.

In terms of two studies in patients MDD, the first study was a randomized, waiting list-controlled clinical trial [33]. The study included a total of 27 patients with MDD, aged 21−75 years, not currently using antidepressant medications, and without histories of psychotic disorder, serious suicide attempt, or hospitalization. Among them 15 patients were randomized to immediate treatment condition group while 12 patients were allocated to delayed treatment condition group (waiting list control condition). The immediate treatment group received two psilocybin sessions (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) administered in opaque gelatin capsules with approximately 100 ml of water with total of 11 hours of supportive psychotherapy at week 3 and week 4. The delayed treatment group received psilocybin after week 11, so the delayed treatment group were used as a control group. Among the randomized participants, 24 of 27 (89%) completed the intervention and thus were included in the analysis (n = 13 for immediate treatment group and n = 11 for delayed treatment group). The mean (SD) GRID Hamilton rating scale for depression (GRID-HAMD) scores, which was the primary outcome measure, at weeks 1 and 4 (8.0 [7.1] and 8.5 [5.7]) in the immediate treatment group were statistically significantly lower than the scores at the comparable time points of weeks 5 and 8 (23.8 [5.4] and 23.5 [6.0]) in the delayed treatment group. In addition,

the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR), which was the secondary outcome measure, showed a rapid decrease from baseline to day 1 after the first psilocybin session, (16.7 [3.5] vs. 6.3 [4.4]; Cohen's d = 2.6; $p < 0.001$), which remained statistically significant the week 4 follow-up (6.0 [5.7]; Cohen's d = 2.3; $p < 0.001$). In terms of safety, there were no SAEs in this trial. Mild to moderate transient headache was reported during 14 of 48 sessions (29%). Other noted side effects included physical discomfort (n = 1), mild controllable muscle motion (n = 1), visual distortion (n = 3), tenseness/soreness (n = 2), chest tightness (n = 1), vivid dreams (n = 1), and altered body sensation (n = 1). In addition, a transient increase in blood pressure that occurred during 1 session, but no medical intervention was needed.

Gukasyan *et al.* [34] conducted a 12-month extension study of the previous randomized waiting-list controlled study [33]. All 24 participants attended all follow-up visits through the 12-month timepoint. Depression symptom improvements based on GRID-HAMD scores were observed at 1-, 3-, 6-, and 12-month follow-up (Cohen's d = 2.3, 2.0, 2.6, and 2.4, respectively). In addition, treatment response and remission were 75% and 58%, respectively, at 12 months. No SAEs related to psilocybin were reported. Interestingly, mystical experience after sessions predicted increased well-being at 12 months, but it did not predict improvement in depression.

Double Blinded Randomized Controlled Studies

We identified five DB-RCTs investigating the effect of psilocybin in the treatment of depression (Table 2). Among the five DB-RCTs identified, two studies investigated effects of psilocybin in decreasing depression and anxiety in patients with life-threatening cancer [35,36]. The first DB-RCT was conducted by Ross and colleagues [36]. In this DB-crossover study, a total of 29 cancer patients with anxiety and depression symptoms were enrolled to investigate the efficacy of a single high dose of psilocybin (0.3 mg/kg) in conjunction with psychotherapy, compared to a control group receiving niacin 250 mg. Participants were randomly assigned to two oral dosing session sequences: psilocybin 0.3 mg/kg first then niacin 250 mg second (psilocybin group; n = 14), or niacin 250 mg first then psilocybin 0.3 mg/kg second (niacin group; n = 15). The two dosing were administered around 7 weeks apart. The severity of anxiety and depression measured using hospital anxiety and depression scale (HADS-A for anxiety and HADS-D for depression), BDI, STAI with self-report measure of state (STAI-S) and trait (STAI-T) before cross over or at week 7 were defined as the primary outcome measure. The results revealed that the psilocybin group showed significantly greater reductions in HADS-A and HADS-D. In addition, STAI-state, STAI-trait, and BDI were also more improved in the psilocybin group than in the niacin group. Furthermore, clinically significant reductions in depressive and anxiety symptoms were observed in approximately 60−80% of participants, and these improvements were sustained for more than 6.5 months. There was also an enhancement in the quality of life, and a reduction in the fear of death among the participants. In terms of safety, there were no SAEs. There were no cases of prolonged psychosis or hallucinogen persisting perceptual disorder, and no participants required psychiatric hospitalization. In terms of AEs attributable to psilocybin, the most common AEs were non-clinically significant elevations in blood pressure and heartrate (76%), headaches or migraines (28%), and nausea (14%). The most common psychiatric AEs included transient anxiety (17%) and transient psychotic-like symptoms (7%).

The effects of psilocybin in cancer patients with symptoms of depression and/or anxiety were also shown in a study conducted by Griffiths *et al.* [35] This randomized, DB, cross-over trial investigated the effects of a very low dose (1 or 3 mg/70 kg) and a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. The very low dose could be considered as placebo. The clinician-rated measures of depression (GRID-HAMD) and anxiety (HAM-A) were analyzed as primary efficacy measures. The result showed that percentage of participants with clinically significant response rate assessed using GRID-HAMD was statistically higher in high-dose first group (92%) than in low dose first group (32%) at 5 weeks after the first session ($p < 0.001$). The remission of depression was also higher for the high-dose first group than in the low dose first group (60% vs. 16%, $p < 0.01$). Likewise, response rate and remission using HAM-A were also higher for the high-dose first group than in the low dose first group (response: 76% vs. 24%, $p < 0.001$; remission: 52% vs. 12%, $p < 0.01$) at 5 weeks after the first session. Five weeks after the crossover, or 5 weeks after low dose first group received high dose and high dose group re-

ceived low dose, the remission and response rate of depression and anxiety in the low dose first became comparable to the high dose first group. At 6-month follow-up, the remission and response rate of both groups were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Moreover, mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes. In terms of safety, no SAEs attributed to psilocybin administration occurred. A few adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Systolic and/or diastolic blood pressure showed temporary, moderate increases after the administration of psilocybin. Nausea or vomiting was experienced by 15% of participants in the high-dose session, while none reported such symptoms in the low-dose session. Instances of psychological distress were more frequent in the high-dose sessions compared to the low-dose sessions, with anxiety occurring in 26% of high-dose participants and 15% in the low-dose group. Additionally, one participant encountered a short-lived episode of paranoid ideation, which accounted for 2% of high-dose sessions.

The first DB-RCT in MDD per se was conducted by Carhart-Harris *et al.* [37], and it compared psilocybin with escitalopram, a selective serotonin-reuptake inhibitor, over a 6-week period. In this phase 2 trial targeting patients with moderate to severe MDD, HAM-D $>$ 17, 30 patients received psilocybin and 29 patients received escitalopram. Patients were administered either two doses of 25 mg of psilocybin (psilocybin group) at three-week intervals or two doses of 1 mg of psilocybin plus oral escitalopram for 6 weeks (escitalopram group). Patients in both groups received brief supportive psychotherapy. After 6 weeks of treatment, the QIDS depression scores in the psilocybin group (-8.0 ± 1.0) and the escitalopram group (-6.0 ± 1.0) did not show a statistically significant difference when compared to baseline scores. However, based on QIDS criteria, the percentage of patients who achieved remission at 6 weeks was statistically higher in the psilocybin group (57%) compared to the escitalopram group (28%). Other secondary measures of depression (changes from baseline to week 6 in the scores on the BDI-1A, HAM-D-17, and MADRS) and the between-group differences in the scores on other scales mostly favored psilocybin over escitalopram. Both the psilocybin group and the escitalopram group did not experience SAEs, and the proportion of patients reporting side effects was similar in both groups, with 26 patients (87%) in the psilocybin group and 24 patients (83%) in the escitalopram group. The incidence of anxiety and nausea was higher in the escitalopram group, and side effects in the psilocybin group generally occurred within 24 hours of administration, with the most common side effect being a headache.

A study showed that a single dose of psilocybin, in combination with psychotherapy, has a rapid and sustained effect in MDD [38]. In this DB-RCT, 52 patients with MDD were randomized to a single dose of psilocybin (0.215 mg/kg) or placebo in conjunction with psychological support. Mean change of MADRS and BDI scores from baseline to 14 days after the psilocybin administration were defined as the primary outcome measure. The study showed that the psilocybin group (n = 26) had higher decrease in symptom severity of MADRS and BDI around 6 hours after their administrations. Moreover, this statistical difference in MADRS and BDI continued until 14 days after the administrations. The study showed that the psilocybin condition had an absolute decrease of 13 point for MADRS (Cohens' d = 0.97; $p = 0.0011$) and 13.2 points for BDI (Cohens' d = 0.67; $p = 0.019$) 14 days after the intervention when compared to the placebo. The response rates 14 days after administration were also higher in psilocybin group than in placebo group for both MADRS (psilocybin: 15/26 vs. placebo: 4/26; $p = 0.0034$) and BDI (psilocybin: 14/26 vs. placebo: 3/26; $p = 0.0025$). Same trend of results was note for the remission rates assessed by MADRS (psilocybin: 14/26 vs. placebo: 3/26; $p = 0.0023$) and BDI (psilocybin: 12/26 vs. placebo: 3/26; $p = 0.013$). In terms of safety, heart rate was not different between two groups throughout the 7 hours of assessment $p > 0.05$. However, the mean systolic and diastolic blood pressure (BP) were highest 60 minutes post-intake (+14.5 mmHg; t(41.6) = -2.96; $p = 0.0051$ for systolic BP and +12.5 mmHg; t(40.1) = -5.09; $p = 0.0003$ for diastolic BP) in the psilocybin condition. More importantly, rescue medication was not needed during the trial. The study also showed no symptomatic hypertension, extreme anxiety, and psychotic/delusional symptoms. These results suggest that a single, moderate dose of psilocybin significantly reduces depressive symptoms compared to a placebo condition for at least 2 weeks with

no SAEs.

Goodwin *et al.* [39] conducted a phase 2 DB-RCT and assigned adults TRD to receive a single dose of psilocybin at a dose of 25 mg (25-mg group; n = 79), 10 mg (10-mg group; n = 75), or 1 mg (control; n = 79), along with psychological support. The study showed that the mean changes from baseline to week 3 in the MADRS, which was used as the primary outcome measure, were −12.0 for 25 mg, −7.9 for 10 mg, and −5.4 for 1-mg. The statistical analysis showed that the 25-mg group was superior to 1-mg group (−6.6; $p < 0.001$). However, there were no statistical difference between 10-mg group and 1-mg group (−2.5; $p = 0.18$). In addition, the 25-mg group showed significantly higher rate of response (odds ratio [OR] = 2.9) and remission (OR = 4.8) at week 3, but not sustained response at week 12, than the 1-mg group. In terms of safety analysis, 66 participants (84%) in the 25-mg group, 56 (75%) in the 10-mg group, and 57 (72%) in the 1-mg group reported AEs. The most frequent AEs reported in the 25-mg group with onset on the day of psilocybin administration (day 1) were headache (in 24% of the participants), nausea (in 22%), and dizziness and fatigue (in 6% each). On day 1, 4% of the 25-mg group, 8% of the 10-mg group, and 1% the 1-mg group had AEs that were rated as severe. Among them, only 1 patient in the 25-mg group needed adjunctive medication (lorazepam for acute anxiety). In contrast, no SAE was reported for 1-on day 1. Likewise, SAEs were significantly higher in both 25-mg group and 10-mg group for day 2 to week 3. The 25-mg group showed suicidal ideation (n = 2) and non-suicidal self-injurious behavior (n = 2). In the 10-mg group, two participants had suicidal ideation (in two participants), one participant had intentional self-injury, and one participant were hospitalized due to for severe depression. Once again, no SAEs were reported from day 2 up to week 3 in the 1-mg group.

DISCUSSION

The purpose of this review was to provide a narrative of published articles that investigated the effect of psilocybin, which has been designated as a "breakthrough therapy" by the FDA, in the treatment of depression. Psilocybin, through its agonist action on serotonin receptors, increases glutamate transmission, leading to enhanced brain cell regeneration and plasticity, reduced brain inflammation, decreased activity in the medial prefrontal cortex and the default mode network, and manifests antidepressant and anxiolytic effects [19].

We identified 11 clinical trials that had investigated the effect of psilocybin in the treatment of depression. Among them six were open label and five were DB studies. One open label study showed that psilocybin, in conjunction with psychotherapy, can effectively reduce depression symptoms in patients with TRD [29]. An extension study showed TRD patients who received psilocybin showed cognitive bias, or pessimism, improved significantly one week after the psilocybin treatment. Moreover, patient's ability to predict the occurrence of future life events became significantly more accurate after the psilocybin treatment while no such improvement was observed in the healthy control. Two extension studies demonstrated longer term safety and efficacy of psilocybin in TRD. A 6-month extension study of the Carhart-Harris (2016) research showed that the depression reduction remained positive at 3 and 6 months [30]. Another 6-month extension study showed that the acute psychedelic experience after psilocybin administration predictsed therapeutic efficacy of psilocybin for TRD [32]. The study showed the psilocybin-induced high mystical-type experience and low anxiety predicted positive long-term (6 months) clinical outcomes of psilocybin for TRD. Two other studies, one 4-week trial and 12-month extension trial, showed that the psilocybin was generally safe and effective in the treatment of MDD.

We identified five DB-RCTs investigating the effect of psilocybin in the treatment of depression. Two studies showed that psilocybin with psychological support were effective in reducing depressive and anxiety symptoms in patients with life-threatening cancer [35,36]. In terms of safety, no SAEs attributed to psilocybin administration occurred. Systolic and/or diastolic blood pressure showed temporary, moderate increases after the administration of psilocybin. Two DB-RCTs were conducted in MDD while one study involved patients with TRD. In one study, after 6 weeks of treatment, depression scores in the psilocybin group and the escitalopram group did not show statistical difference [37]. However, the percentage of patients who achieved remission at 6 weeks was statistically higher in the psilocybin group (57%) compared to the escitalopram group (28%). Another study showed that the psilocybin induced higher decrease than the placebo in both ob-

jective and subjective symptom of depression around 6 hours after their administrations [38]. Moreover, this statistical difference in MADRS and BDI continued until 14 days after the administrations. One DB-RCT showed that a single dose of psilocybin 25 mg resulted in superior antidepressant effect than psilocybin 1 mg [39]. However, such superior efficacy over psilocybin 1mg was not observed for psilocybin 10 mg.

In summary, when used as an adjunctive therapy in psychiatric treatment, psilocybin shows a high potential for antidepressant effects, and these effects can persist over an extended period. Furthermore, there is research indicating its effectiveness in improving depression, anxiety, and quality of life in terminally ill cancer patients when used appropriately. Therefore, when used correctly, psilocybin is expected to have high clinical utility. Finally, as there have been cases of misuse in the past in the United States, appropriate regulation, and a high level of responsibility from expert groups are deemed necessary.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Sheng-Min Wang, Won-Myong Bahk. Data acquisition: Won-Seok Choi, Sunghwan Kim, Hyun Kook Lim, Young Sup Woo. Data analysis: Sheng-Min Wang, Chi-Un Pae, Young Sup Woo, Won-Myong Bahk. Writing—original draft: Sheng-Min Wang. Writing—review & editing: Sheng-Min Wang, Chi-Un Pae, Won-Myong Bahk. All authors reviewed and approved for publication.

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