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The Impact of Psilocybin on Patients Experiencing Psychiatric Symptoms: A Systematic Review of Randomized Clinical Trials

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ABSTRACT

Objective: This systematic review aims to evaluate the impact of psilocybin on patients experiencing psychiatric symptoms, with a focus on health-related quality of life (HRQoL) and safety. **Method of Research:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched the PubMed database and identified studies published from January 2011 to December 2021 pertaining to the impact of psilocybin on psychiatric symptoms. Two authors independently conducted a focused analysis and reached a final consensus on five studies meeting the specific selection criteria. Study bias was addressed using the Cochrane risk of bias tool. **Results:** The impact of psilocybin on psychiatric symptoms was examined in five randomized controlled trials (RCTs). Four studies administered 1 to 2 doses of psilocybin, with doses ranging from 14mg/70kg to 30mg/70kg, and one study administered a fixed dose of 25mg to all participants. Administration of psilocybin resulted in significant and sustained reduction in symptoms of anxiety and depression, enhanced sense of wellbeing, life satisfaction, and positive mood immediately after psilocybin administration and up to six months after conclusion of treatment. All studies included some form of psychotherapy, and none reported serious adverse effects. **Conclusion:** RCTs show the efficacy of psilocybin in the treatment of anxiety and depression symptoms, as well as improvement in HRQoL, and no serious side effects. However, additional research is necessary to characterize predictors of treatment response, patient screening requirements, effectiveness in broader clinical populations, and guidelines for psilocybin-assisted psychotherapy.

KEYWORDS: Psilocybin, psychedelics, psychiatric symptoms, anxiety, depression, health-related quality of life

Psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) is a 5-hydroxy-tryptamine (5-HT2A) receptor agonist that has shown promising efficacy in treating psychiatric symptoms, particularly in patients with cancer and emotional distress associated with life-limiting illness.[1] Psilocybin has not yet been approved by the United States (US) Food and Drug Administration (FDA) for any purpose and is not labeled for the uses discussed in this review, and its use is still investigational. The antidepressant effects of psilocybin are postulated to be mediated by the modulation of 5-HT2A receptors due to its high binding affinity to the 5-HT2A receptor, as well as second messenger signaling and gene-expression effects.[2] Furthermore, the effects of psilocybin on perceptual, affective, and cognitive functions, mediated by serotonergic, dopaminergic, and glutamatergic activity, may influence the capacity of an individual's response to psychotherapy.[3,4] The effects of psilocybin-assisted psychotherapy have been detected in the long-term, and in some trials, after just one single dose.[5,6]

Psilocybin, described by the US Drug Enforcement Agency (DEA) as "a hallucinogenic chemical obtained from certain types of fresh and dried mushrooms," has been classified as a Schedule I drug since 1971.[7] In November 2019, psilocybin was granted breakthrough therapy designation by the FDA for the treatment of major depressive disorder (MDD).[8] In November 2020, Oregon became the first state to legalize psilocybin for medical use when voters approved a measure authorizing the Oregon Health Authority (OHA) to create a program permitting licensed physicians to administer psilocybin-producing mushroom and fungi products to individuals 21 years of age or older.[9,10] As of December 2021, there were 71 psilocybin studies underway registered on ClinicalTrials.gov, and several states and cities were moving toward the decriminalization of psilocybin for both medical and recreational purposes.[11] This systematic review aims to examine the impact of psilocybin on patients experiencing psychiatric symptoms by addressing the following questions: 1) What is the impact of psilocybin on psychiatric symptoms? 2) What is the impact of psilocybin on health-related quality of life (HRQoL) in patients experiencing psychiatric symptoms? and 3) How safe is psilocybin for patients experiencing psychiatric symptoms?

METHODS

Search strategy. This systematic review was performed in accordance with the Preferred

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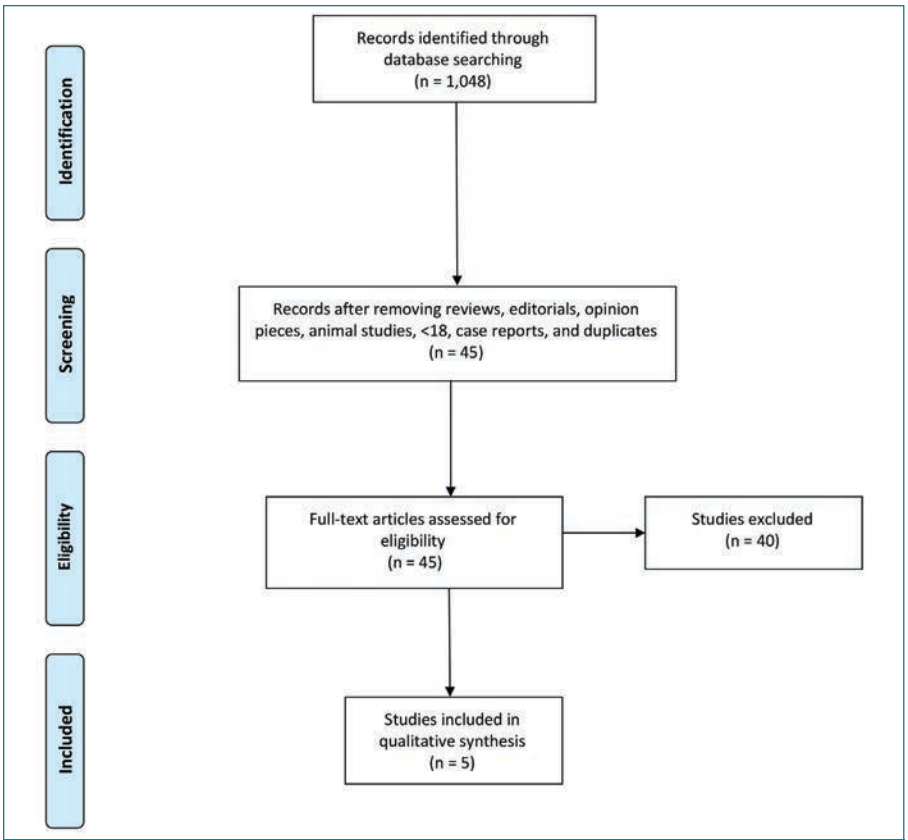

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12] A systematic literature search was conducted in PubMed, using the keyword "psilocybin," for articles pertaining to psychiatric symptoms published between January 2011 to December 2021, after setting exclusion and inclusion criteria. A manual search of reference lists for identified papers and previous reviews was also conducted.

Study selection criteria and methodology. The following inclusion criteria were used: articles published in English or with a published English translation; articles published in a peer reviewed journal (which all PubMed articles are); original studies in human adults (no reviews, no animal studies, no study subjects under 18 years of age); randomized controlled trials (RCTs); studies that used at least one assessment measure; and studies performed on patients experiencing psychiatric symptoms, as opposed to healthy subjects. Exclusion criteria included reviews, editorials, opinion pieces, and case reports. Two authors independently conducted a focused analysis and reached consensus on five studies meeting the specific selection criteria. An additional independent author examined the quality of each study by identifying its risk of bias using the Cochrane risk of bias tool, as well A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist, as detailed in the section below. The search method is displayed in a PRISMA flow diagram in Figure 1.[13–15]

Data extraction and yield. Key findings were derived from the full text and figures of the selected five studies. The study designs and findings were analyzed for quality and are detailed in Table 1.

Risk of bias and study quality. The quality of each study was assessed using the Cochrane risk of bias tool, which includes six criteria against which potential risk of bias is judged: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selectivity of outcome reporting, and other biases.[13,14] A summary of the risk of bias is presented in Table 2.

Quality of the current systematic review. For the quality of the present systematic review, the AMSTAR 2 checklist was utilized to ensure all components of a high-quality systematic review were addressed.[14,15] AMSTAR 2 consists of 16 items in total and is presented in Table 3.

RESULTS

Overview. The impact of psilocybin on psychiatric symptoms was examined in five randomized clinical trials: Grob et al (2011),[1] Ross et al (2016),[16] Griffiths et al. (2016),[5] Davis et al. (2021),[17] and Carhart-Harris et al. (2021).[18] The findings from the reviewed studies are summarized in Table 1.

All five RCTs were double-blind studies, except for one open-label study, and they included three crossover and two parallel-design studies. Three studies administered psilocybin to patients with cancer and an anxiety-related *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) diagnosis, whereas two studies focused on MDD. The sample sizes in the studies ranged from 12 to 59 patients. Four of the studies administered 1 to 2 doses of psilocybin, with doses ranging from 14mg/70kg to 30mg/70kg, whereas one study[18] administered a fixed dose of 25mg to all participants. All five studies included some form of psychotherapy/counseling within their treatment protocol. Three studies included participant meetings with study clinicians both before and after psilocybin sessions for the purposes of trust-building, information gathering, and therapy, and two studies provided supportive psychotherapy. The duration of treatment spanned from one day to 11 weeks. Follow-up measures were collected as soon as one day and up to 26 weeks after treatment. Additional long-term follow-ups after 3.2 and 4.5 years were conducted and published separately for one study. The measurement instruments employed by the reviewed studies for the assessment of psilocybin effects are detailed in Table 4.

What is the impact of psilocybin on patients experiencing psychiatric symptoms? The five RCTs demonstrated the efficacy of psilocybin in reducing anxiety and depressive symptoms.

Grob et al's (2011)[1] double-blind, crossover RCT (n=12) evaluated the impact of a single medium dose of psilocybin (14mg/70kg) on patients with advanced-stage cancer and an anxiety-related DSM-IV diagnosis using the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and Profile of Mood States (POMS) as primary outcome measures. The study demonstrated a significant reduction

TABLE 1. Study findings

STUDY	POPULATION	N	DOSE	TYPE OF STUDY	TREATMENT FREQUENCY/ DURATION	STUDY GROUP 1 (INTERVENTION)	STUDY GROUP 2 (COMPARATORS)
Grob et al (2011)[1]	Adults with advanced-stage cancer and a DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety	12	14mg/70kg	Randomized, double-blind, placebo-controlled, crossover clinical trial	1 dose of psilocybin	14mg/70kg psilocybin	205mg niacin (placebo)
Ross et al (2016)[16]	Patients with cancer and an anxiety-related DSM-IV diagnosis	29	21mg/70kg	Randomized, double-blind, placebo-controlled, crossover clinical trial	1 dose of psilocybin	21mg/70kg psilocybin	Placebo
Griffiths et al (2016)[5]	Adults with potentially terminal cancer diagnosis and a DSM-IV diagnosis with anxiety or mood symptoms	56 enrolled, 51 analyzed	20–30mg/70kg	Randomized, double-blind, placebo-controlled, crossover clinical trial	2 doses of psilocybin, but 1 intended to be an inactive placebo, separated by an average of 5 weeks	22mg/70kg psilocybin, reduced from 30mg/70kg after negative reactions from 2 of the 3 initial participants	1mg/70kg psilocybin (placebo), reduced from 3mg/70kg after data suggested that 3mg/70kg may not be inactive
Davis et al (2021)[17]	Adults with MDD currently not taking antidepressant medication and with scores of 17 or higher on the GRID-HAMD	27 enrolled, 24 analyzed	20–30mg/70kg	Randomized, open-label, waiting list-controlled clinical trial	2 doses of psilocybin, 20mg/70kg in the first session and 30mg/70kg in the second session; 8 week intervention period, psilocybin sessions spaced 1–2 weeks apart	20mg/70kg and 30mg/70kg psilocybin	Waiting list control group
Carhart-Harris et al (2021)[18]	Adults with long-term moderate-to-severe MDD	59	25mg	Randomized, double-blind, controlled clinical trial	2 doses of psilocybin, 3 weeks apart	25mg psilocybin and daily placebo	1mg psilocybin and daily 20mg escitalopram

DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; GRID-HAMD: GRID-Hamilton Rating Scale of Depression; MDD: major depressive disorder

in depressive symptoms at six months after administration, as measured by the BDI ($p<0.05$). According to STAI measures, trait anxiety was also significantly reduced from baseline when reassessed at one ($p<0.05$) and three months ($p=0.03$) after treatment. No significant effect was found for state anxiety, and no serious adverse events (AEs) were reported.[1]

Ross et al's (2016)[16] double-blind, crossover RCT (n=29) reported similar findings after a single high dose of psilocybin (21mg/70kg) was given to patients with cancer and an anxiety-related DSM-IV diagnosis, using the BDI, STAI, and Hospital Anxiety and Depression Scale (HADS) as primary outcomes. Seven weeks after psilocybin administration, scores were significantly reduced on measures of state anxiety ($d=1.18$; $p<0.01$), trait anxiety ($d=1.29$, $p<0.001$), and depression ($p<0.05$ for BDI and $p<0.01$ for HADS Depression, $d=0.82$ and 0.98, respectively), compared to the control group. These effects remained significant after 26 weeks for HADS total score ($p<0.05$) and reduction of state anxiety ($p<0.05$). Feelings of hopelessness and demoralization were significantly reduced in the study group, compared to controls, two weeks after a dose of psilocybin (both $p<0.01$). Furthermore, significant positive behavioral changes were seen in the psilocybin group two weeks after administration, compared to the placebo group ($p\leq0.001$). Feelings of death transcendence (defined as acceptance of and positive feelings toward the end of life) were significantly increased 26 weeks after psilocybin administration ($p<0.05$). Interestingly, after psilocybin administration, scores on mystical experience, as measured by the Mystical Experience Questionnaire (MEQ30), correlated significantly with reductions in BDI depression scores ($r=0.49$, $p=0.01$), state anxiety scores ($r=0.42$, $p=0.03$), and trait anxiety scores ($r=0.39$, $p=0.04$). AEs included increased blood pressure and heart rate, headache, nausea, transient anxiety, and "transient psychotic-like symptoms," none which were deemed serious.[16] Importantly, 15 out of the 16 participants who remained alive agreed to participate in a long-term follow-up study that was published separately.[6] The results showed statistically significant improvements in anxiety and depression primary measures from baseline after 3.2 years (mean $d=1.30$, range: 0.93–1.97) and 4.5 years (mean $d=1.41$, range: 0.86–1.89). Moreover, 60 to 80 percent of patients at the second (4.5 year) follow-up met criteria for clinically significant antidepressant or anxiolytic responses.[6]

Griffiths et al's (2016)[5] double-blind, crossover RCT (n=51) administered one high dose (20–30mg/70kg) of psilocybin and one very

TABLE 1, CONT. Study findings

STUDY	PSYCHOTHERAPY	MEASURES	OUTCOMES	STATISTICAL SIGNIFICANCE
Grob et al (2011)[1]	Yes, sessions with study staff	Primary: BDI, POMS, STAI Secondary: 5D-ASC, Brief Psychiatric Rating Scale	Trait anxiety was significantly reduced 1 and 3 months after psilocybin treatment. Depression symptoms were also significantly reduced at 6 months. General improvements in mood were also observed after psilocybin treatment. No adverse effects were noted.	Six months after psilocybin treatment, scores on the BDI were significantly reduced from baseline ($p<0.05$). There was not a significant effect for STAI State Anxiety; however, there was a significant decrease in trait anxiety from baseline to 1 month after treatment ($p<0.001$) and 3 months after treatment ($p=0.03$).
Ross et al (2016)[16]	Yes	Primary: HADS Total, HADS Anxiety, HADS Depression, BDI, STAI Secondary: DEM, HAI, Death Anxiety Scale, DTS, WHOQOL-BREF, FACIT-SWB, MEQ30, MEQ retrospective scale, PEQ	Psilocybin reduced symptoms of depression and anxiety considerably, and these effects were sustained after 6.5 months. Mystical experiences were correlated with reductions in symptoms of depression and anxiety. Psilocybin improved ratings of positive behavior, spiritual wellbeing, quality of life/life satisfaction, and physical health. No serious adverse events were reported. Minor adverse events included blood pressure and heart rate elevation, headaches, nausea, transient anxiety, and transient psychotic-like symptoms.	7 weeks after 1 dose of psilocybin, scores were significantly reduced on HADS total ($p<0.001$), HADS Anxiety ($p< 0.01$), HADS Depression ($p<0.01$), BDI ($p<0.05$), STAI State ($p<0.01$), and STAI Trait ($p<0.001$), compared to the control group. These effects were sustained at the 6.5 month follow-up and were significant for STAI State ($p<0.05$) and HADS total ($p<0.05$). Scores on the MEQ30 after dose 1 significantly correlated with reductions in scores on HADS total (Spearman's $r=0.39$, $p=0.04$), HADS Anxiety (Spearman's $r=0.36$, $p=0.07$), HADS Depression (Spearman's $r=0.30$, $p=0.11$), BDI ($r=0.49$, $p=0.01$), STAI State ($r=0.42$, $p=0.03$), and STAI Trait ($r=0.39$, $p=0.04$) between baseline and 6 weeks after dose 1. Ratings of wellbeing/life satisfaction and positive behavioral changes were significantly increased 2 weeks after psilocybin treatment, compared to 2 weeks after placebo (both $p\leq0.001$) and were also significantly increased 33 weeks after psilocybin treatment, compared to 2 weeks after placebo (both $p\leq0.01$). Physical health was also significantly increased two weeks after psilocybin treatment, compared to placebo ($p\leq0.01$).
Griffiths et al (2016)[5]	Yes, session mentors	Primary: GRID-HAMD, HAM-A assessed with the SIGH-A Secondary: Monitor Rating Questionnaire, HRS, 5D-ASC, M-Scale (Experience-specific), SOCQ, BDI, HADS, STAI, POMS (Total Mood Disturbance Subscale), BSI, MQOL, LOT-R, DTS, PIL, LAP-R Coherence, community observer-rated changes participant behavior and attitudes, FACIT-SWB, Spiritual-Religious Outcome Scale, FMS, PEQ	A high dose of psilocybin reduced symptoms of depression, anxiety, and death anxiety, and these clinically significant changes were sustained 6 months later. 5 weeks and 6 months after a high dose of psilocybin, participants reported higher quality of life, optimism, increased wellbeing, and increased life satisfaction. Community observer ratings aligned with these results, with increases in ratings of participant positive mood and behavior. Measures of mystical experience taken after the first session were correlated with positive outcomes 5 weeks later, including increased life satisfaction and meaningfulness and reductions in clinical measures of depression and anxiety. No serious adverse events reported. Minor adverse events included blood pressure elevation, nausea, vomiting, physical discomfort, psychological discomfort, and transient anxiety.	Between baseline and the 6-month follow up, there were significant decreases for scores on HADS total (Cohen's $d=2.34$), HADS Anxiety (Cohen's $d=2.15$), STAI State Anxiety (Cohen's $d=1.25$), GRID-HAMD (Cohen's $d=2.98$), BDI (Cohen's $d=1.63$), HADS Depression (Cohen's $d=1.65$), HAM-A Anxiety (Cohen's $d= 3.40$), STAI Trait Anxiety (Cohen's $d=1.20$), POMS Total Mood Disturbance (Cohen's $d=1.26$), and BSI (Cohen's $d=1.17$), all $p<0.001$. Five weeks and 6 months after a high dose of psilocybin, participants reported significantly increased positive attitudes about life, positive attitudes about self, positive mood changes, positive social effects, positive behavior changes, and increased spirituality, compared to 5 weeks after the low dose of psilocybin (all $p<0.001$). Scores were also significantly increased 5 weeks and 6 months after a high dose of psilocybin, compared to 5 weeks after a low dose, for increased wellbeing/life satisfaction ($p<0.001$). Between baseline and 6-month follow up, there were significant increases for scores on PIL (Cohen's $d=0.85$), DTS (Cohen's $d=0.58$), MQOL Overall Quality of Life (Cohen's $d=1.14$), MQOL Meaningful Existence (Cohen's $d=1.12$), LAP-R Death Acceptance (Cohen's $d=0.84$), and LOT-R Optimism (Cohen's $d=0.66$), all $p<0.001$. Scores on community observer ratings were increased significantly from baseline after 6 months ($p<0.001$). MEQ30 scores assessed at the end of Session 1 were significantly correlated with increased ratings of meaningfulness ($r=0.77$, $p<0.0001$), spiritual significance ($r=0.75$, $p<0.0001$), HADS Depression ($r=-0.36$, $p<0.01$), and HAM-A ($r=-0.59$, $p<0.0001$).

BDI: Beck Depression Inventory; POMS: Profile of Mood States; STAI: State-Trait Anxiety Inventory; 5D-ASC: 5-Dimensional Altered States of Consciousness; HADS: Hospital Anxiety and Depression Scale; DEM: Demoralization Scale; HAI: Health Anxiety Inventory; DTS: Death Transcendence Scale; WHOLQOL-BREF: World Health Organization Quality of Life Scale Brief Version; FACIT-SWB: Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing; MEQ30: Mystical Experience Questionnaire; PEQ: Persisting Effects Questionnaire; GRID-HAMD: GRID Hamilton Rating Scale for Depression; HAM-A: Hamilton Anxiety Rating Scale; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale; HRS: Hallucinogen Rating Scale; M-Scale: Mysticism Scale; SOCQ: States of Consciousness Questionnaire; BSI: Brief Symptom Inventory; MQOL: McGill Quality of Life Questionnaire: LOT-R: Life Orientation Test-Revised; PIL: Purpose in Life Test; LAP-R: Life Attitude Profile-Revised; FMS: Faith Maturity Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Rated; MADRS: Montgomery–Åsberg Depression Rating Scale; BEAQ: Brief Experiential Avoidance Questionnaire; WSAS: Work and Social Adjustment Scale; SHAPS: Snaith Hamilton Anhedonia Pleasure Scale; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale; SIDAS: Suicidal Ideation Attributes Scale; PRSexDQ: Psychotropic-Related Sexual Dysfunction Questionnaire; LEIS: Laukes Emotional Intensity Scale; CI: confidence interval

TABLE 1, CONT. Study findings

STUDY	PSYCHOTHERAPY	MEASURES	OUTCOMES	STATISTICAL SIGNIFICANCE
Davis et al (2021)[17]	Yes, various staff	Primary: GRID-HAMD Secondary: QIDS-SR, BDI-II, Columbia-Suicide Severity Rating Scale, HAM-A, STAI	Psilocybin-assisted therapy sessions significantly reduced patient scores on the GRID-HAMD 1 and 4 weeks after sessions, compared to baseline and controls. Scores on the QIDS-SR were significantly reduced from baseline on the first day after the first psilocybin therapy session. Psilocybin-assisted therapy also reduced scores on the HAM-A after treatment. No serious adverse events were reported. Minor adverse events included blood pressure elevation, physical discomfort, emotional discomfort, and headache.	Patients in the psilocybin therapy group experienced significantly reduced GRID-HAMD scores after 1 (Cohen's d=2.2, 95% CI: 1.4–3.0, p<0.001) and 4 weeks (Cohen's d=2.6, 95% CI: 1.7–3.6, p<0.001), compared to the control group. Psilocybin-assisted therapy reduced individual scores on the GRID-HAMD significantly after 1 (Cohen's d=3.6, 95% CI: 2.2–5.0, p<0.001) and 4 weeks (Cohen's d=3.6, 95% CI: 2.2–4.9, p<0.001), compared to individual baseline scores. Four weeks after treatment, 71% of patients had ≥50% reduction in GRID-HAMD scores and 54% met criteria for remission of depression. Psilocybin-assisted therapy significantly reduced the mean score on the QIDS-SR from baseline to Day 1 after the first psilocybin session (Cohen's d=3.0, 95% CI: 1.9–4.0, p<0.001). Scores remained significantly reduced through Week 4 after the second session (Cohen's d=3.1, 95% CI: 1.9–4.2, p<0.001).
Carhart-Harris et al (2021)[18]	Yes, mental health professionals	Primary: QIDS-SR Secondary: BDI-1A, HAM-D, MADRS, Flourishing Scale, STAI, BEAQ, WSAS, SHAPS, WEMWBS, SIDAS, PRSexDQ, LEIS, Emotional Breakthrough Inventory Post-Treatment Changes Scale	Scores on the QIDS-SR were not significantly reduced after 6 weeks for participants who received psilocybin, compared to those who received escitalopram. Significance was not formally calculated for any other measures. However, the psilocybin group scored lower on the BDI, STAI, PRSexDQ, and BEAQ scales and higher on the LEIS and FS scales. No serious adverse events were reported. Minor adverse events included headache.	Scores on the QIDS-SR were not significantly different 6 weeks after psilocybin treatment, compared to escitalopram.

BDI: Beck Depression Inventory; POMS: Profile of Mood States; STAI: State-Trait Anxiety Inventory; 5D-ASC: 5-Dimensional Altered States of Consciousness; HADS: Hospital Anxiety and Depression Scale; DEM: Demoralization (DEM) scale; HAI: Health Anxiety Inventory; DTS: Death Transcendence Scale; WHOLQOL-BREF: World Health Organization Quality of Life Scale Brief Version; FACIT-SWB: Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing; MEQ30: Mystical Experience Questionnaire; PEQ: Persisting Effects Questionnaire; GRID-HAMD: GRID Hamilton Rating Scale for Depression; HAM-A: Hamilton Anxiety Rating Scale; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale; HRS: Hallucinogen Rating Scale; M-Scale: Mysticism Scale; SOCQ: States of Consciousness Questionnaire; BSI: Brief Symptom Inventory; MQOL: McGill Quality of Life Questionnaire: LOT-R: Life Orientation Test-Revised; PIL: Purpose in Life Test; LAP-R: Life Attitude Profile-Revised; FMS: Faith Maturity Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Rated; MADRS: Montgomery–Åsberg Depression Rating Scale; BEAQ: Brief Experiential Avoidance Questionnaire; WSAS: Work and Social Adjustment Scale; SHAPS: Snaith Hamilton Anhedonia Pleasure Scale; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale; SIDAS: Suicidal Ideation Attributes Scale; PRSexDQ: Psychotropic-Related Sexual Dysfunction Questionnaire; LEIS: Laukes Emotional Intensity Scale; CI: confidence interval

TABLE 2. Risk of bias for included studies assessed by Cochrane risk of bias tool

STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING
Grob et al (2011)[1]	L	?	H	H	L	L
Ross et al (2016)[16]	L	L	L	L	?	L
Griffiths et al (2016)[5]	L	L	L	L	L	L
Davis et al (2021)[17]	?	L	?	?	L	L
Carhart-Harris et al (2021)[18]	L	L	L	H	L	L

H: high risk of bias; L: low risk of bias; ?: unclear risk of bias

low dose (1–3mg/70kg) as placebo to patients with potentially terminal illness due to cancer and a DSM-IV diagnosis that included anxiety or mood symptoms, using the GRID-Hamilton Rating Scale for Depression (GRID-HAMD) and Hamilton Anxiety Rating Scale (HAM-A) as primary outcome measures. At the six-month follow-up, scores improved significantly from baseline on the GRID-HAMD (d=2.98) and HAM-A (d=3.40), in addition to BDI (d=1.63), HADS Depression (d=1.65), HADS Anxiety (d=2.15), state anxiety (d=1.25), and trait anxiety (d=1.20; all p<0.001). Importantly, high scores on mystical experience, as measured by the MEQ30, correlated significantly with reduced scores on six measures of depression and anxiety, including HADS Depression (r=-0.36, p<0.01) and HAM-A (r=-0.59, p<0.0001) five weeks later. At five weeks and six months, recipients of high-dose psilocybin reported significantly increased positive attitude, mood, social effects, and behavior, compared to subjects receiving the very low placebo dose of psilocybin (all p<0.001). At six months, there were significant increases in death transcendence and community observer ratings of positive mood and behavioral ratings (both p<0.001), compared to baseline. AEs included increased blood pressure, nausea, and vomiting, which were not deemed serious.[5]

TABLE 3. AMSTAR 2 checklist

ITEM	DETAILS	YES/NO
1	Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, control group, and outcome)?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review, and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was justified, did the review authors use appropriate methods for statistical combination of results?	N/A
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

AMSTAR 2: A Measurement Tool to Assess Systematic Reviews 2; N/A: not applicable

Davis et al's (2021)[17] open-label, parallel-design RCT (n=24) examined the impact of psilocybin-assisted therapy on patients with MDD, compared to a waitlist control group, using the GRID-HAMD as the primary outcome measure. During the eight-week intervention period, the study administered two high doses of psilocybin, 20mg/70kg in the first session and 30mg/70kg in the second session, spaced 1 to 2 weeks apart. Patients in the psilocybin therapy group experienced significantly reduced GRID-HAMD scores after one (d=2.2) and four weeks (d=2.6), compared to the control group (all p<0.001). Four weeks after treatment, 71 percent of patients had a 50-percent or greater reduction in GRID-HAMD scores, and 54 percent met criteria for remission of depression. Psilocybin-assisted therapy significantly reduced the mean score on the Quick Inventory of Depression Symptomology-Self-Rated (QIDS-SR) from baseline to Day 1 after the first psilocybin session (d=3.0) and remained significantly reduced through Week 4 after the second session (d=3.1; all p<0.001). AEs included headache, but otherwise no serious adverse effects were noted.[17]

Carhart-Harris et al's (2021)[18] double-blind, parallel-design RCT (n=59) examined the noninferiority of psilocybin, compared to the standard antidepressant escitalopram, in patients with long-standing (15–22 years) moderate-to-severe MDD. Patients were randomized to receive either two high doses of psilocybin (25mg) three weeks apart or daily escitalopram plus two very low doses (placebo) of psilocybin three weeks apart. After six weeks, the primary outcome measure of improved depression scores on the QIDS-SR from baseline were not significantly different between the two groups (p=0.17). This trial established the noninferiority of psilocybin at six weeks to conventional, daily selective serotonin reuptake inhibitor (SSRI) treatment for long-standing major depression. Remarkably, 70 percent of patients in the high-dose psilocybin group versus 48 percent of patients in the very low psilocybin plus escitalopram group achieved response (reduction in QIDS-SR of >50%), and 57 percent versus 28 percent, respectively, achieved remission. No serious AEs were observed.[18]

What is the impact of psilocybin on HRQoL in patients experiencing psychiatric symptoms? The two RTCs that included HRQoL measures showed significant improvement in HRQoL in patients experiencing psychiatric symptoms.

Ross et al (2016)[16] studied 29 patients with cancer and an anxiety-related DSM-IV diagnosis and found a significant increase in ratings of wellbeing/life satisfaction two weeks after one high-dose psilocybin session (p≤0.001). There were similar findings regarding ratings of physical health (p≤0.01). These differences remained significant when comparing ratings up to 33 weeks after psilocybin administration with ratings two weeks after placebo administration (both p≤0.01).[16]

Griffiths et al (2016)[5] studied 51 patients with terminal cancer and a DSM-IV diagnosis of a mood or anxiety disorder and showed that one high dose of psilocybin, compared to one very low dose (placebo), led to a significant increase in ratings on overall quality of life (d=1.14), meaningful existence (d=1.12), and optimism (d=0.66; all p<0.001) at five weeks, which remained higher in the study group at six months, compared to baseline. The study also reported higher ratings of wellbeing/life satisfaction among those who received a high dose of psilocybin, compared to placebo, at five weeks and six months (both p<0.001).[5]

How safe is psilocybin in patients experiencing psychiatric symptoms? Regarding safety, none of the five studies reported occurrence of serious AEs. Two of the RCTs evaluating psilocybin in patients with cancer, Ross et al (2016)[16] and Griffiths et al

TABLE 4. Instruments used by the reviewed studies for measurement of psilocybin's effects

SCALE	DOMAINS MEASURED
Beck Depression Inventory (BDI)[1]	Measures severity of depressive symptoms.
Profile of Mood States (POMS)[1]	Assesses an individual's mood states in the past week.
State-Trait Anxiety Inventory (STAI)[1]	Measures both transient (state) and long-standing (trait) anxiety.
5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)[1]	The scale includes 5 main dimensions: oceanic boundlessness, visionary restructuralization, anxious ego dissolution, reduced vigilance, and auditory alterations. Three of these dimensions are further divided into 11 subscales. The oceanic boundlessness dimension includes experience of unity, spiritual experience, blissful state, and insightfulness subscales. Visionary restructuralization consists of complex imagery, elementary imagery, audio-visual synesthesia, and changed meaning of percepts subscales. Anxious ego dissolution includes disembodiment, impaired control of cognition, and anxiety subscales.
Brief Psychiatric Rating Scale[1]	Measures symptoms such as hostility, suspiciousness, hallucination, and grandiosity.
Hospital Depression and Anxiety Scale (HADS)[16]	Assesses symptoms of depression and anxiety in medical patients, specifically designed to minimize the impact of physical ailments on the total score.
Demoralization Scale (DEM)[16]	Assesses degree of cancer-related demoralization by measuring factors such as despair, helplessness, and existential distress.
Hopelessness Assessment and Illness Scale (HAI)[16]	Measures degree of hopelessness in advanced-stage cancer.
Death Anxiety Scale[1]	Assesses death anxiety.
Death Transcendence Scale (DTS)[1]	Assesses the ways in which individuals experience death transcendence, with factors such as mysticism, religion, nature, creativity, and biosocial factors.
World Health Organization Quality of Life Scale-Brief (WHOQOL-BREF)[16]	Measures quality of life in 4 domains: physical, psychological, social, and environmental.
Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing (FACIT-SWB)[16]	Measures spiritual well-being and consists of 2 subscales: peace/meaning and faith.
Mystical Experience Questionnaire (MEQ30)[16]	Assesses mystical experience.
Persisting Effects Questionnaire (PEQ)[5]	Designed to assess changes in participant moods, behaviors, and attitudes about life and self.
Monitor Rating Questionnaire[5]	Monitors ratings of participant mood and behavior.
Hallucinogen Rating Scale (HRS)[5]	Includes 6 subscales: somatesthesia, affect, perception, cognition, volition, and intensity.
Mysticism Scale (M-Scale)[5]	Assesses mystical experience and consists of 3 subscales: interpretation, introvertive, and extrovertive.
States of Consciousness Questionnaire (SOCQ)[5]	Intended to assess mystical experience and contains 7 subscales: internal unity, external unity, transcendence of time and space, ineffability and paradoxicality, sense of sacredness, noetic quality, and deeply felt positive mood. Forty-three items on this scale compose the MEQ (the MEQ30 is a shortened 30-item version).
GRID-Hamilton Depression Rating Scale (GRID-HAMD)[5]	Measures severity of depressive symptoms.
Hamilton Anxiety Rating Scale (HAM-A)[5]	Measures severity of anxiety symptoms.
Brief Symptom Inventory (BSI)[5]	Measures psychiatric symptoms.
McGill Quality of Life Questionnaire (MQOL)[5]	Measures overall quality of life and meaningful existence in potentially terminal illness.
Life Orientation Test-Revised (LOT-R)[5]	Measures optimism about health outcomes.
Purpose in Life Test (PIL)[5]	Assesses meaningfulness in life.
Life Attitude Profile-Revised (LAP-R)[5]	Assesses attitudes about many different aspects of life, including coherence and death acceptance.
Spiritual Religious Outcome Scale[5]	Measures spiritual/religious changes during illness.
Faith Maturity Scale (FMS)[5]	Assesses the degree to which an individual embodies the teachings of mainstream Protestant faith.
Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR)[17]	Measures severity of depression.
Columbia-Suicide Severity Rating Scale[17]	Measures severity of suicidal ideation.
Montgomery–Åsberg Depression Rating Scale (MADRS)[18]	Measures severity of depression.
Flourishing Scale (FS)[18]	Measures self-perception of success.
Brief Experiential Avoidance Questionnaire (BEAQ)[18]	Measures experiential avoidance, which is when an individual tries to avoid internal experiences, such as certain thoughts, memories, or feelings.
Work and Social Adjustment Scale (WSAS)[18]	Assesses social and occupational functioning.
Snaith Hamilton Anhedonia Pleasure Scale (SHAPS)[18]	Assesses severity of anhedonia, a common symptom of depression.
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)[18]	Assesses mental wellbeing.
Suicidal Ideation Attributes Scale (SIDAS)[18]	Assesses severity of suicidal ideation.

TABLE 4, CONT. Instruments used by the reviewed studies for measurement of psilocybin's effects

SCALE	DOMAINS MEASURED
Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ)[18]	Assesses sexual dysfunction in response to psychotropic medication.
Laukes Emotional Intensity Scale (LEIS)[18]	Measures emotional blunting.
Emotional Breakthrough Inventory (EBI)[18]	Assesses the occurrence of an emotional breakthrough.

(2016),[5] noted minor AEs, including nonclinically significant increases in heart rate and blood pressure, as well as gastrointestinal complaints, such as nausea and vomiting. Headache was reported in the studies by Ross et al (2016)[16] and Davis et al (2021).[17]

DISCUSSION

Findings from RCTs indicate that psilocybin, when used in conjunction with therapy, may alleviate symptoms of depression and anxiety as early as 2 to 4 weeks from administration, with long-term sustainment of positive mood. RCTs showed improvement in HRQoL, and none of the reported side effects were deemed to be serious. While most studies were small, the most rigorous study to date suggests that psilocybin has comparable efficacy to escitalopram in reducing depression at six weeks from administration.[18] In patients with terminal cancer, HRQoL improved after psilocybin therapy, with long-term results in the order of several years.[6] The findings from this systematic review indicate that psilocybin is generally well tolerated and produces a host of immediate and sustained beneficial effects for patients with cancer suffering from symptoms of depression and anxiety. Additionally, the striking response (70% vs. 48%) and remission (57% vs. 28%) secondary outcome measures of high-dose psilocybin versus escitalopram in the Carhart-Harris et al (2021)[18] study merit replication and subgroup analyses in order to identify who would benefit most from psilocybin treatment.

Our findings, while focused on RCTs (the gold standard for effectiveness research) are consistent with evidence from systematic reviews that have reviewed a variety of study designs of psilocybin use in depression and anxiety.[19–23] However, the lack of information on how to predict who would be at risk for AEs continues to be a concern in clinical and research applications. Additional limitations include a small quantity of RCTs, relatively small sample sizes, demographic homogeneity, challenges related to adequate blinding, heterogeneous target outcome measures, and the context-dependent nature of the efficacy of psilocybin.[24]

Current research indicates that psilocybin is particularly valuable within a psychotherapeutic context, where individuals can develop new perspectives brought about by the actual cognitive and emotional changes precipitated by psilocybin, as seen in Davis et al (2021)[17]

While preliminary studies are promising, a standardized protocol for psilocybin administration for patients with cancer would require expanded research on safety and efficacy as a means for establishing formal treatment guidelines to suit individual patient needs. Findings from patients in existing studies might not generalize well to clinical populations, especially when considering compromised cardiovascular, renal, and/or hepatic function associated with cancer progression and use of chemotherapy, where pharmacokinetics may be less predictable. Many cancer survivors report a fear of recurrence or describe living in a constant state of "waiting for the other shoe to drop." Qualitative reports suggest that patients receiving psilocybin-assisted therapy have been able to unburden themselves of such feelings.[19] However, additional rigorous clinical trials are needed to establish a cost-benefit analysis for this subset of patients in the context of a psilocybin safety profile. There is also a need to investigate ways of avoiding or minimizing AEs associated with psilocybin, such as headache, nausea, vomiting, and blood pressure elevation, particularly in patients with active medical issues, such as cancer. A promising study showed that a 14-day administration of escitalopram prior to administration of psilocybin reduced these side effects.[25]

A systematic review of psilocybin dosing by Li et al[26] concluded that the most effective treatment for depression is achieved at doses of 30mg/70kg. The administration of 20mg/70kg or above of psilocybin may require additional monitoring and psychological support before, during, and after treatment.[27] A 2021 press release[2] about an RCT by COMPASS (n=233) that is yet to be published in a peer-reviewed journal showed that twice the number of patients with treatment-resistant depression (TRD) in the 25mg group achieved response and remission at Weeks 3 and 12, compared to the 1mg group. Twelve patients overall (0.43%) reported suicidal behavior, intentional self-injury, and suicidal ideation.[2] While these phenomena occur in TRD, they were reported more frequently in the 25mg group than in the 1mg group. It is difficult to interpret this information without a published peer-reviewed report that includes methodology and more specifics, especially because no suicidal ideation or behaviors were detected in the five studies we reviewed. Furthermore, findings from Ross et al (2021)[29] and Hendricks et al (2015)[30] suggest that psilocybin may decrease suicidal ideation. Nonetheless, such concerns must be taken into consideration when constructing frameworks for widespread psilocybin treatment and should be explored in further studies evaluating psilocybin regarding dose, duration, concurrent therapy, and predictors of self-harm ideations and behaviors.

It should also be noted that current research efforts are investigating the impact of psychedelic-assisted therapy on a broader scope of psychiatric disorders. Santos et al[31] reviewed studies showing the efficacy of psilocybin in the management of obsessive compulsive disorder (OCD) and depression, as well as tobacco and alcohol use. Gard et al[32] reviewed case studies showing a positive, albeit weak, response of bipolar depression to psilocybin. According to a preliminary study by Woolley et al[33] (n=18) at ClinicalTrials.gov, participants with human immunodeficiency virus (HIV) and psychiatric symptoms showed improvement at the conclusion of a seven-week treatment with psilocybin and group therapy, as well as at three months posttreatment.

Despite legalization attempts, psilocybin remains at Schedule I status at the US federal level. A 2018 review by investigators at Johns Hopkins University, using the eight factors used by the Controlled Substances Act to schedule controlled substances, concluded that it would be appropriate to schedule psilocybin for Schedule IV (which also includes benzodiazepines and hypnotics).[34,35] Therefore,

the issue of potential abuse must be the subject of prospective clinical studies in order to put this issue to rest.[36]

Limitations and strengths. The primary limitation of this review lies in the context-dependent nature of psilocybin's efficacy. The set (an individual's expectations and current psychological state) and setting (the environment in which the experience occurs) are thought to be key predictors in psychedelic experience outcomes.[23] Thus, findings from these studies may be influenced by an additional independent variable: the quality of the set and setting. While many of the reviewed studies recognized the importance of these factors in promoting positive outcomes and incorporated them into their study design, studies varied significantly in their methods, with no established standard protocol.

The variability of psilocybin dosages from 14mg to 30mg per 70kg and broad range of follow-up times can be viewed as a strength because they provide an opportunity for comparison between different psilocybin treatment methods. Furthermore, this lays the framework for future work to delineate the relationship between these factors and efficacy of treatment. It is also necessary to evaluate the safety, tolerability, and efficacy of psilocybin on patients who are at risk for psychotic disorders. Other study-specific limitations include the fact that many patients in the studies by Grob et al[1] (66% of participants) and Griffiths et al[5] (45% of participants) had prior experience with hallucinogenic substances, and the study by Grob et al had a relatively small sample size of 12, which included 11 (87.5%) female subjects. The study by Griffiths et al[5] lacked educational diversity, with 98 percent of subjects having a bachelor's degree at minimum. The study by Davis et al[17] lacked a standard psychotherapy approach and involved a group of counselors with various educational backgrounds on psychotherapy. Finally, it should be noted that the psychedelic nature of psilocybin makes a placebo-controlled study unlikely to be truly blinded.

CONCLUSION

This systematic review of RCTs shows the efficacy of psilocybin in the treatment of anxiety and depression symptoms, as well as improvement in HRQoL, and no serious AEs. Future research should address predictors of treatment response, patient screening requirements, effectiveness in broader clinical populations, and guidelines for psilocybin-assisted psychotherapy.

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