Review Article

The Therapeutic Potential of Psychedelic-assisted Therapies for Symptom Control in Patients Diagnosed With Serious Illness: A Systematic Review

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Abstract

Context. People affected by serious illness usually experience suffering in its various dimensions, not only in the physical but also in the psychosocial and spiritual aspects. The interest in psychedelic-assisted therapies as a potential new therapeutic modality has increased since evidence suggests a significant impact of their use on the outcomes of patients with serious illness.

Objectives. To systematically review the available evidence on the effects of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness.

Methods. The protocol of this systematic review has been prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. This review included randomized and non-randomized controlled trials published in peer-reviewed scientific journals. A comprehensive search for studies was carried out in the main scientific databases, including Web of Science, Scopus, Cochrane Library, PsycINFO, PubMed, CINAHL, and EMBASE. There were no limitations regarding the year or language of publication.

Results. The sample was composed of 20 studies. The results suggest positive effects of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness, with considerable safety of use. Most studies have been conducted with lysergic acid diethylamide, psilocybin, and *N,N*-dipropyltryptamine in cancer patients. The adverse effects reported were of physical and/or psychological nature and of mild to moderate intensity, transient, and self-resolutive.

Conclusion. The evaluated evidence suggests positive effects of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness, especially regarding symptoms of psychological and spiritual nature. J Pain Symptom Manage 2022;000:e1−e14.

Key Words

Palliative care, hospice care, hallucinogens, psychedelics, serious illness

Key Message

This study presents a synthesis of the scientific evidence on the therapeutic potential of psychedelic-assisted therapies for symptom control in patients with life-limiting conditions, advanced or terminal life-threatening illness. The results indicate the safety and positive effects of psychedelics for symptom control in patients with serious illness, especially regarding symptoms of psychological and spiritual nature.

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Background

> "Increasing pain, increasing anxiety, increasing morphine, increasing addiction, increasing demandingness, with the ultimate disintegration of personality and a loss of the opportunity to die with dignity."
> Aldous Huxley (1963)

People affected by serious illness often experience physical, psychological, and spiritual suffering, all of which negatively affect their quality of life and other healthcare outcomes.[1,2] However, alleviating clinically significant suffering in patients with serious illness remains a challenging issue.[3] In this context, a growing body of evidence has demonstrated that patients with serious illness can benefit from psychedelic-assisted therapies for the control of a variety of symptoms, of physical, psychosocial, and spiritual nature.[4–9]

Medicine and society are witnessing a resurgence of interest in the effects and applications of psychedelic-assisted therapies in a wide range of settings, including the treatment of serious illness.[10–16] During the 1960s and 1970s, several clinical studies assessed the therapeutic effects of lysergic acid diethylamide (LSD) and *N,N*-dipropyltryptamine (DPT) in combination with psychotherapy in patients with advanced-stage cancer.[4,17–20] More recently, new studies have been carried out, primarily employing psilocybin.[21–23] The main results demonstrate reductions in measures of anxiety and depression, reduced fear of death, and improvements in assessments of well-being, quality of life, and spirituality.[22,23]

Psychedelics (also known as "hallucinogens" – although they don't necessarily induce true hallucinations) are psychoactive compounds that alter perception, cognition, mood and may also facilitate/induce psycho-spiritual experiences depending on a variety of factors such as substance type, dosage, and personal and contextual characteristics. In general, psychedelic substances are considered to be physiologically safe and do not produce dependence or addiction.[24,25] Psychedelics can be divided into four pharmacological classes based on their mechanisms of action: 1) classic psychedelics, comprised of serotonin 2A receptor agonists such as LSD, 4-phosphoryloxy-*N,N*-dimethyltryptamine (psilocybin), and *N,N*-dimethyltryptamine (DMT); 2) empathogens or entactogens, which are mixed serotonin and dopamine reuptake inhibitors and releasers such as 3,4-methylenedioxymethamphetamine (MDMA); 3) dissociative anesthetic agents, which are *N*-methyl-D-aspartate receptors antagonists such as ketamine; and 4) atypical psychedelics such as tetrahydrocannabinol (THC, cannabinoid receptor CB1 agonist), salvinorin A and ibogaine (both kappa-opioid agonists).[25–27]

In a recently published agenda for psychedelic-assisted therapy research in patients with serious illness, the authors highlighted the need to clarify potential indications for this treatment modality in clinical practice.[10] In this sense, considering the need to deepen knowledge on indications of psychedelic-assisted therapies for people with serious illness, as well as their possible adverse effects in this population, the objective of this study was to systematically review the available evidence on the effects of psychedelic-assisted therapies for symptom control in patients with serious illness. In comparison to previously published revisions in the field,[4,5,28,29] this study presents a robust and comprehensive methodological design, covering aspects insufficiently explored so far, such as the inclusion of atypical – and not only classic – psychedelics (e.g., ketamine), the impact of psychedelic-assisted therapies on all dimensions of quality of life (i.e., physical, psychological, social, and spiritual pain),[30–32] besides performing a critical appraisal to evaluate the methodological quality of included studies.

Methods

The protocol for this review was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[33] and was registered in the international registry of systematic reviews PROSPERO (CRD42021238116). The reporting of this study was carried out according to the Preferred Reporting Items for Systematic Review (PRISMA-2020), when applicable.[34]

Development of the Guiding Question

The guiding question was developed based on the Population, Intervention, Comparator, Outcomes strategy (Table 1).[35]

Table 1
Development of the Guiding Question Based on the Population, Intervention, Comparator, Outcomes Strategy

PICO	Components
Guiding question	What is the available evidence in the literature on the effects of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness?
Population	Patients diagnosed with life-limiting conditions, advanced or terminal illness
Intervention	The use of psychedelic-assisted therapies in isolation or in association with other interventions (e.g., pharmacological, psychotherapeutic)
Comparator	Not applicable
Outcomes	The control of physical, psychological, social, and spiritual symptoms

Eligibility Criteria

Types of studies: this systematic review included publications reporting randomized controlled trials (clinical trials involving at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process - MeSH Unique ID: D016449) and nonrandomized controlled trials (clinical trials where participants are assigned to a treatment, procedure, or intervention by methods that are not random - MeSH Unique ID: D065228) published in peer-reviewed scientific journals. Observational studies, reviews, case reports, case series, case studies, commentaries, opinions, letters, or editorials were excluded. There were no limitations regarding the year or language of publication.

Types of participants: patients diagnosed with serious illness. There were no limitations regarding age, gender, and ethnic origin.

Types of interventions/exposure: interventions based on the use of psychedelic substances of any type and/or class, that is, classical (e.g., LSD, psilocybin, mescaline, DMT) or atypical (e.g., ketamine, MDMA, ibogaine, THC). Articles reporting the use of ketamine exclusively as a painkiller (i.e., no psychological outcomes assessed) and the use of pure cannabidiol (i.e., compound without psychedelic effects) were excluded.

Types of outcomes: in this review, the outcomes evaluated were those related to the control of distressing symptoms related to the physical, psychological, social, and spiritual dimensions. Conventionally, suffering has been classified into physical, psychological, social, and spiritual dimensions.[30–32]

Information Sources and Search Strategy

A preliminary search was carried out in the PubMed (US National Library of Medicine) database to determine the keywords and descriptors most commonly used to index studies related to the topics of interest in this review. The selected terms are presented in Table 2. These terms were combined with the Boolean operators AND and OR. The search strategy used (Table 2) was adapted to the specific needs of each database to be consulted for this review: Web of Science, Scopus, Cochrane Library, PsycINFO, PubMed, CINAHL, and EMBASE. The reference lists of all included articles were also checked for other studies that may contribute to the objective of this review. The search for the articles was conducted in May 2021 and was updated in September of the same year.

Table 2
Terms Used in the Search Strategy

#1	Lysergic Acid Diethylamide [Mesh, Title/Abstract]
#2	LSD [Title/Abstract]
#3	LSD-25 [Title/Abstract]
#4	Psilocybin [Mesh, Title/Abstract]
#5	Mescaline [Mesh, Title/Abstract]
#6	Peyote [Title/Abstract]
#7	Ayahuasca [Title/Abstract]
#8	N,N-Dimethyltryptamine [Mesh, Title/Abstract]
#9	Dimethyltryptamine [Title/Abstract]
#10	DMT [Title/Abstract]
#11	5-Methoxy-N,N-dimethyltryptamine [Title/Abstract]
#12	5-MeO-DMT [Title/Abstract]
#13	3,4-methylenedioxymethamphetamine [Mesh, Title/Abstract]
#14	MDMA [Title/Abstract]
#15	Ibogaine [Mesh, Title/Abstract]
#16	Ketamine [Mesh, Title/Abstract]
#17	Tetrahydrocannabinol [Title/Abstract]
#18	THC [Title/Abstract]
#19	Dronabinol [Mesh, Title/Abstract]
#20	Salvinorin [Title/Abstract]
#21	Hallucinogen* [Mesh, Title/Abstract]
#22	Psychedelic* [Title/Abstract]
#23	Classic psychedelics [Title/Abstract]
#24	Classic hallucinogens [Title/Abstract]
#25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26	Terminal [Mesh, Title/Abstract]
#27	Palliative Care [Mesh, Title/Abstract]
#28	Supportive Care [Title/Abstract]
#29	Hospice [Mesh, Title/Abstract]
#30	End of life [Title/Abstract]
#31	#26 OR #27 OR #28 OR #29 OR #30
#32	#25 AND #31

Study Records

Data Management. The results retrieved from the databases were exported to EndNote (EndNote Web, Clarivate, Philadelphia - https://www.myendnoteweb.com), and duplicate articles were removed. Subsequently, the articles were loaded into the Rayyan[36] software for carrying out the study selection step.

Selection Process. The selection of studies was performed by evaluating the titles, abstracts, and keywords according to the eligibility criteria. Relevant articles were read in their entirety, and those that failed to meet the predetermined criteria for this review were excluded. The study selection process was carried out independently by two reviewers (ACMG and LOM). In case of inconsistencies, these were discussed and agreed upon, and when necessary, a third reviewer was involved so that an agreement could be reached. The reviewers were not blinded regarding the publishing journal, authors, or institutions during any stage of the selection process.

Data Collection Process. The data extraction was carried out using an instrument developed and tested by the authors to extract the following: authorship, year of publication, design, objective, population, psychedelic substance studied, purpose of using the psychedelic-assisted therapies, presence of complementary intervention in association with psychedelics (pharmacological or not), adverse effects related to psychedelic-

assisted therapies, main results about symptom control, and conclusions.

The studies in the sample were divided equally among one of the authors of this study (ACMG) and three co-workers so that they could perform the data extraction independently, using the aforementioned data extraction template. This author and co-workers have reviewed and discussed this form before starting the data extraction. Furthermore, the author and co-workers have pilot tested the data extraction of a single selected study to ensure that there was a consistent interpretation of the data required for extraction. To minimize the inconsistency among reviewers, we have carried out training exercises using the data extraction form before further included study data were extracted for the review. One of the authors (LOM) revised the final version of the data extraction table in order to standardize the presentation of these data and to identify possible missing or incomplete information.

Data Synthesis and Analysis

We have described and synthesized the information collected based on the variables of interest for this review through a narrative synthesis approach.[37,38] Results were reported in a pragmatic and descriptive manner with textual data from the included studies. Also, when applicable, data were summarized using descriptive statistics (counting and percentages) and supplemented with a narrative description to provide an overview of the evidence base supporting the use of psychedelic-assisted therapies for symptom control in patients diagnosed with life-limiting conditions, advanced or terminal life-threatening illness.

Critical Appraisal of Studies

For the critical appraisal of studies, we have used the Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials and nonrandomized controlled trials (quasi-experimental studies).[39] The purpose of this assessment has been to evaluate the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis.[39] We assigned ratings of yes (Y), no (N), unclear (U), and not applicable (N/A) for each criterion on these checklists. This process was independently performed by two reviewers (ACMG and LOM). Discrepancies were resolved by a joint discussion with these authors to reach consensus.

Results

General Aspects

In total, the sample consisted of 65 articles. However, considering the high number of studies with cannabinoid substances (including dronabinol, THC, or a mixture of cannabidiol and THC) (n = 45), we have decided to present the results regarding cannabinoids in another future publication that will be specific for the presentation of these studies' results. We chose to keep cannabinoids in the study selection but drop them from this review's analysis to keep the original guiding questions, search strategy, and study records. Thus, the sample of the present review included non-cannabinoid psychedelics (all types) and was composed of 20 studies. The table with the data extracted from each study is available as Supplementary Material.

The selection process of the studies is presented in Fig. 1. The selected studies were published between 1964 and 2021, and among these, 11 (55%) were published between the 1960s and 1970s. From the 1970s to 2010, it is possible to observe the relative paucity of studies that focused on patients with life-threatening physical conditions.

A total of 640 adult patients were subjected to the use of psychedelic-assisted therapies in these studies. Regarding the characterization of the participants, in 50% (n = 10) of the included studies there is no information on the patients' sociodemographic characteristics.[40,18,19,21,41–46] In 25% (n = 5) of the studies, most participants were white men and women, with no information about education.[17,47–50] White men and women, with medium to high educational level, were the majority in 20% (n = 4) of the included studies.[22,23,51,52] In the study by Richards et al.,[20] the sample consisted of white and black men and women, with an average of 11 years of study (educational level).

Regarding the type of disease, 75% (n = 15) of the studies were conducted with cancer patients only;[17,20,22,23,52] of these, ten studies included patients with advanced cancer.[40,18,19,21,41–43,47,44,48] In the remaining articles (n = 5, 25%), the studies were conducted in patients with 1) AIDS;[51] 2) metastatic breast and gastric carcinoma, plasmocytoma, non-Hodgkin's lymphoma, celiac disease, Parkinson's disease, Bechterew's disease;[45] 3) cardiovascular, hepatic, neoplastic, pulmonary, renal, and other diseases;[49] 4) cancer, herpes zoster, severe burn, and foot or leg gangrene;[46] and 5) cancer or nondementing neurological illness.[50]

Regarding the psychedelic substances studied, 45% (n = 9) of the articles reported the use of LSD,[40,17,18,41–43,48,45,46] 25% (n = 5) used psilocybin,[21–23,52,51] 10% (n = 2) used DPT [19,20] and in one study (5%) ketamine was used.[49] MDMA was also used in only one study (5%).[50] In two studies (10%), two separate substances were used, namely LSD and DPT.[47,44] Regarding the total number of participants receiving each substance, 347 (54%) received LSD, 116 (18%) psilocybin, 81 (13%) LSD and DPT, 64 (10%) DPT, 18 (3%) MDMA,

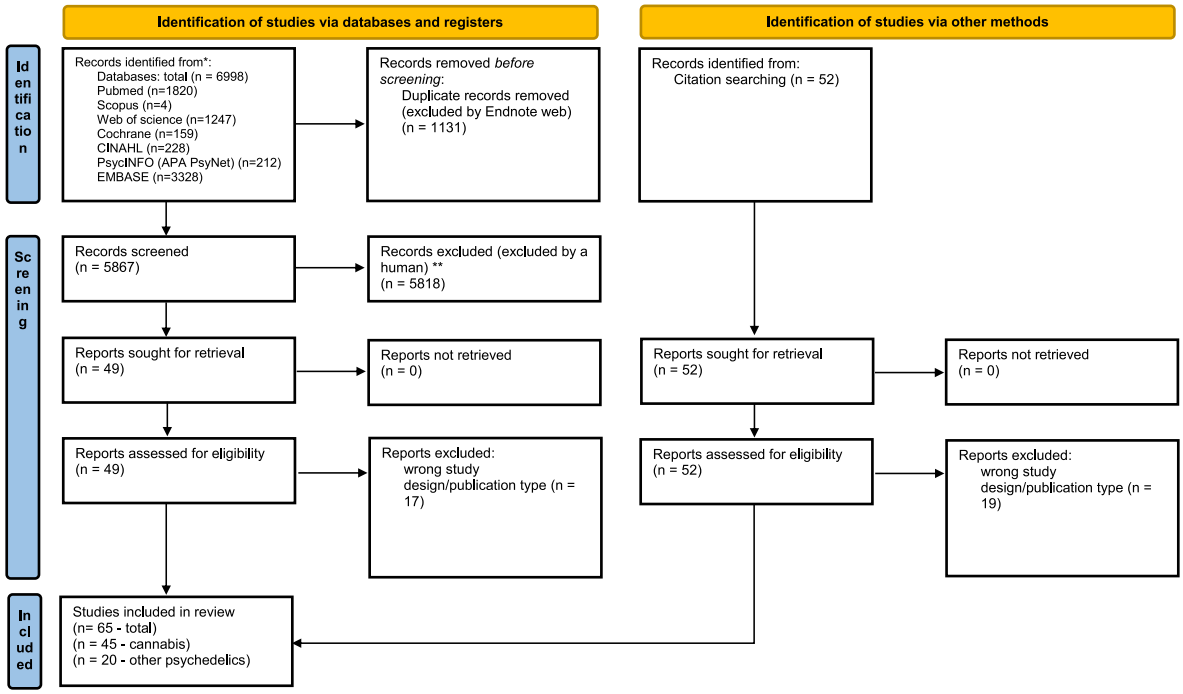

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

and 14 (2%) ketamine. No studies using ibogaine or salvinorin A have been found in this review.

The routes of administration used were oral (n = 8, 40%) for psilocybin,[21–23,52,51] ketamine,[49] LSD,[45] and MDMA[50]; intramuscular (n = 4, 20%) for LSD and DPT[17–20]; and subcutaneous for LSD (n = 1, 5%).[41] In two studies (10%), both oral and intramuscular routes were used.[47,48] In 5 (25%) studies, no information was provided regarding the administration route used.[40,42–44,46]

Complementary Interventions Associated With the Use of Psychedelics

Psychotherapy was the most used (n = 13, 65%).[40,17–20,52,43,47,44,48,51,45,50] The psychotherapy approaches varied across studies; in general, it consisted of three mutually interrelated phases and followed historical[17,18,44,48] and modern[23,24] recommendations for administering psychedelic drugs. *Preparatory psychotherapy* (1–2 hours nondrug sessions), aimed to review the purpose and intention of participation in the study, treatment goals, and structure of the treatment sessions; to establish rapport and trust between participants and therapists and/or monitors (usually one or two); to review the participants' life histories as well as the meaning and nature of the psychological and existential distress associated with illness; to review the nature and status of present relationships and concerns; to review the safety measures taken to minimize adverse psychological effects of the drug (psychedelic) and the specific plan to manage (psychotherapeutically and pharmacologically) the occurrence of any significant such effects.[23] *Drug (psychedelic) dosing sessions* (6–14 hours) were usually conducted in an aesthetic living-room-like environment and included participants' accommodation (lying on a couch/bed and wearing eyeshades, aiming to help participants focus their attention on the internal experience and to prevent distraction from external stimuli) and listening to preselected music (standardized to be the same for every participant and selected by the research team to temporally match the phenomenological effects of psychedelics over its course of action). Therapists and/or monitors were available during the entire session and provided psychological (nondirective) and medical support when appropriate; they encouraged participants to "trust, let go and be open" to the experience; and they could also employ relaxation technics and grounding exercises.[23,24] *Post-dosing integrative psychotherapy* (1–2 hours nondrug sessions), usually on the day following each dosing session and over the following weeks, where participants were encouraged to discuss the entirety of their subjective experience (debriefing) to further consolidate the memory of the experience, develop meaning, solidify any insights and actualize a potential new awareness into everyday life.

A relevant fact presented in the articles is the importance of the bond between patient and therapist and/

or monitor in psychedelic-assisted therapies, as well as the therapist's training in this specific psychotherapeutic intervention. Richards et al.[18] indicate that better results with therapy were observed when a steady therapeutic relationship was established between patient and therapist. In another study, one of the most important variables in considering the success of the psychedelic-assisted therapy was the quality of trust inherent in the therapeutic relationship.[20] Grof et al.[44] reported that the psychedelic session was only considered for completion when a positive therapeutic relationship was established between the patient and therapist. Similarly, in the study by Griffiths et al.,[22] the staff who would be present in the session with the patient were selected for having significant interpersonal relationship skills and experience with altered states of consciousness induced through practices such as meditation, yogic breathing, or relaxation techniques.

In one (5%) study, the analgesic action of LSD was compared to the analgesic action of two pain relief medications (meperidine and dihydromorphinone);[46] and in another study (5%), psilocybin was compared to niacin (vitamin B3), used as a positive control.[23] In 5 studies (25%), psychedelics were used in isolation, without complementary interventions (e.g., psychotherapy).[21,22,41,42,49]

Adverse Effects

In four studies (20%), patients presented no complications related to the intervention (psychedelic-assisted therapy), despite all participants being severely ill.[17,21,47,46] In the other studies (n = 11, 55%), when present, adverse effects related to the intervention, in general, were of mild to moderate intensity, transient, and self-resolutive, whether of physical origin (visual disturbances, nausea, and vomiting, changes in vital signs, headache, tremors, diarrhea, trouble sleeping, palpitations, difficulty in breathing, trouble sitting still, fatigue, dry mouth)[20,22,23,42,44,48,51,49,50] or psychological (fear, panic, hallucinations, frightening imagery, fearful fantasies, anxiety, psychological catharsis, anger, emotional distress, feeling abnormal, feeling cold, gait disturbance, illusion, thinking abnormally, post-traumatic stress flashbacks).[20,23,41,42,51,45,50] In Kast's study,[41] approximately 50% of the patients felt upset after 6 hours under the effect of LSD, with the need for interruption of the experience by using chlorpromazine. In another study, approximately 30% of the patients said they would be unwilling to repeat the LSD administration should it be offered again.[42] It is important to emphasize that in both these studies,[41,42] the drug was administered with no complementary intervention (e.g., psychotherapy). In the study by Grof et al.,[44] the overall ratings of adverse effects among 6.4% of the patients demonstrated a decrease in post-therapy evaluations. In five (25%) of the sample studies, no reports of absence or presence of adverse effects were provided.[40,17–19,52] Table 3 shows the adverse effects according to the substances studied.

Symptom Control

Regarding the control of physical symptoms, studies have indicated the potential of psychedelic-assisted therapies for decreased physical distress[41,47,44] related to pain reduction[40,17,18,41–43,47,46] and improved sleep.[41,42]

As for psychological symptoms, there is evidence demonstrating that psychedelic-assisted therapies can contribute to reduced emotional distress[20,47,44] with positive psychological effects[43] and decreased psychiatric symptoms.[19,20] Studies from the sample have reported reduced levels of anxiety,[21–23,43,47,45,49] depression,[40,23,43,47,49] fear and worry,[43] improved mood,[17,21,22,41,42] increased relaxation[17,43] and reduced cancer-related psychological and existential distress.[23,52]

Concerning spiritual and/or existential experience, studies have reported a considerable reduction in patients' fear of death following psychedelic-assisted therapies.[40,18,22,43,47] For instance, in Kast's study,[42] there are reports stating that patients claimed that death was near, that their situation was hopeless, but they felt it no longer mattered. The occurrence of metaphysical reactions such as oceanic feeling and happiness, acceptance, and surrender to the inevitable loss of control, increased their ability to appreciate the

Table 3
Drug-specific Adverse Effects

Psychedelic Substances	Adverse Effects
Classic psychedelics (LSD, psilocybin, DPT)	Frightening imagery, fearful fantasies, fear, panic, psychological distress, visual disturbances, hallucinations, psychosomatic problems (headaches, tremors, nausea, palpitations) and problems related to the patient's underlying disease, transient autonomic effects in some patients (often reported to have a meaningful subjective component); episodes of vomiting, headache, fatigue, insomnia, anxiety exacerbation, post-traumatic stress flashback, anger, anxiety, emotional distress, feeling abnormal, feeling cold, gait disturbance, illusion, thinking abnormal, nonclinically significant elevated systolic and diastolic blood pressure and heart rate, physical discomfort (any type), transient episodes of psychological discomfort (any type), a transient episode of paranoid ideation
Ketamine	Diarrhea, trouble sleeping, and trouble sitting still
MDMA	Jaw clenching, tight jaw, thirst, dry mouth, headache, perspiration (during experimental sessions); fatigue, need more sleep, anxiety, insomnia, jaw clenching, tight jaw, low mood

subtle and aesthetic nuances related to the experience.[41] The most dramatic effects occurred following the mystical psychedelic experience, with increased serenity, peace, and tranquility in the case of LSD use.[43] The mystical experience induced by psilocybin mediated the therapeutic effect of this substance on anxiety and depression.[23] Also, there is evidence of improvement in indicators related to life meaning and optimism,[22] decreased cancer-related demoralization[23,51] and hopelessness, reduced existential suffering, and improved spiritual well-being and behavior regarding death.[23]

As for social aspects, Kast[41] reports that LSD was able to render patients more responsive to their environment and families. Pahnke[43] states that following LSD-assisted psychotherapy, the patients' families and interpersonal relationships were improved, with more openness and honesty. Also, the change in patients' condition resulting from psychedelic therapy included an estimation of closeness and openness in interpersonal relationships with their families and other people.[17] Kurland et al.[47] point to the favorable effects of psychedelic therapy on the social isolation experienced by people with cancer.

Critical Appraisal of Studies

Tables 4 and 5 present the results regarding the risk of bias assessment of the studies included in this review.

Discussion

The results of the studies included in this review suggest positive effects of psychedelic-assisted therapies for symptom control in patients diagnosed with serious illness, especially regarding symptoms of psychological and spiritual nature. Most studies have been conducted with LSD, psilocybin, and DPT in patients with cancer and showed a good safety and tolerability profile overall.

More than half of the studies in the sample were published between the 1960s and 1970s, when several clinical studies using psychedelic substances (mostly LSD) in patients with advanced stages of cancer found significant improvements, such as the reduction of anxiety and depression-related symptoms associated with the anguish of death, for instance.[40,18,41,44,46] Around this same time, a combination of social, political, and medical factors altered the reputation of psychedelics in medicine, and research on them slowed down.[53] However, although the international ban on these substances halted further research,[54,55] new studies using more robust methods have reoccurred since the 2000s.[21–23,45,50,56] It is worth noting that the development of palliative care as a medical subspecialty coincides with this first era of psychedelic research, as the modern hospice movement is a product of the 1970s.[6]

The most researched psychedelic compounds in the studies included in this review were LSD and psilocybin. LSD was the first psychedelic substance synthesized and distributed on a large scale by the pharmaceutical company Sandoz to psychiatrists and researchers in different countries between the 1950s and 1960s.[55] At that time, studies with LSD for terminal cancer patients proved to be one of the most promising lines of research on the therapeutic potential of the substance in psychiatry.[4,57] With the halting of research on psychedelics from the 1970s on, few innovations at the intersection of psychedelic-assisted therapies and end-of-life care emerged until the 2010s, when new studies, primarily evaluating psilocybin and using more robust study designs, started to be conducted. Although psilocybin presents psychological effects similar to LSD, the duration of the psychedelic experience produced by psilocybin (4–6 hours) is considerably shorter than for LSD (6–12 hours), with a lower probability of triggering paranoia and panic reactions than LSD.[58–60] Isolated studies have been conducted with another tryptamine DPT, with positive results.[19,20] New studies employing different psychedelic agents, especially tryptamines (e.g., DMT, 5-MeO-DMT, ayahuasca), may hold promise for the therapeutic potential of psychedelics for patients diagnosed with serious illness.[61] No studies using ibogaine or salvinorin A have been found, so, research with these psychedelic agents might be needed.

Regarding safety, the studies included in this review did not report serious adverse effects. When present, these were mild to moderate in intensity, transient, and self-resolutive, of physical and/or psychological nature. In a systematic review of studies investigating the use of psychedelics in the treatment of existential distress in people affected by serious illness, researchers concluded that given the reasonable safety profile of serotoninergic psychedelics in a controlled clinical setting, psychedelic-assisted therapy may be a promising treatment option in this context – especially for patients in whom other approaches have been ineffective.[4] While our study confirms this therapeutic potential and extends it to physical symptoms (e.g., cancer pain) and other forms of psychiatric/psychological distress (e.g., anxiety, depression, and adjustment disorders), it also highlights the importance of the conditions in which the treatment is delivered to ensure safety. Thus, psychedelic-assisted therapies must include careful consideration related to appropriate screening, preparation, dosing, and integration sessions according to evidence-based protocols.[11] In the case of psychiatric disorders, although scholars support the continued investigation of psychedelic compounds for the treatment of such conditions, they still do not support the use of any of these substances for clinical patient care outside of the research setting,

Table 4
Joanna Briggs Institute Critical Appraisal for Nonrandomized Controlled Trials

Study	C1	C2	C3	C4	C5	C6	C7	C8	C9
Kast; Collins, 1964	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Kast, 1966	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Kast, 1967	Y	Y	N/A	N	Y	N/A	Y	U	Y
Pahnke, 1969	Y	Y	N/A	N	N	N/A	U	N	N
Pahnke et al., 1969	Y	Y	N/A	N	Y	N/A	Y	U	Y
Pahnke et al., 1970	Y	Y	N/A	N	Y	N/A	Y	U	Y
Kurland et al., 1972	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Richards et al., 1972	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Grof et al., 1973	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Richards et al., 1977	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Richards et al., 1979	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Kurland, 1985	Y	Y	N/A	N	N	N/A	U	N/A	N/A
Irwin et al., 2013	Y	Y	N/A	N	Y	N/A	Y	Y	Y
Anderson et al., 2020	Y	Y	N/A	N	Y	N/A	Y	Y	Y

Y = yes; N = no; U = unclear; N/A = not applicable.
C1: Is it clear in the study what is the 'cause' and what is the "effect" (i.e., there is no confusion concerning which variable comes first)? C2: Were the participants included in any similar comparisons? C3: Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? C4: Was there a control group? C5: Were there multiple measurements of the outcome both pre and post the intervention/exposure? C6: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? C7: Were the outcomes of participants included in any comparisons measured in the same way? C8: Were outcomes measured in a reliable way? C9: Were appropriate statistical analyses used?

considering the need for more studies with robust design on the topic.[62] For instance, some psychiatric conditions such as schizophrenia and other psychosis present more risks.[62–64] Also, it is vital to conduct future studies on the therapeutic potential of psychedelic-assisted therapy in standardized clinical trials, as well as on the potential therapeutic and adverse effects of psychedelics.[62]

The interpersonal bond established between patient and therapist was considered a vital factor for positive results of psychedelic-assisted therapy among the included studies. Richards et al.[18] state that the quality of the human encounter, the sensitive psychotherapeutic orientation, and the therapist's optimism are equally important factors in psychedelic-assisted therapies. The skills needed to sit with a patient as a psychedelic therapist include skills long associated with the humanistic and biopsychosocial approach common in professions such as nursing, for example.[65] Such skills include permanent empathic presence, increased trust, spiritual intelligence, knowledge of the physical and psychological effects of psychedelics, the therapist's self-awareness, ethical integrity, and proficiency in complementary approaches.[66]

Therapists need to be properly trained to work in the field of psychedelic-assisted therapy. Pahnke et al.[40] state that they definitely do not recommend the therapeutic use of psychedelics by personnel lacking specialized training. They further state that psychedelic-assisted therapy sessions should be conducted under the supervision of personnel already familiar with the reactions enabled by these substances.[40] The rapid growth of psychedelic research after several decades of stagnation requires education and certification programs.[10] Thus, it is necessary to think of regulatory changes that are more favorable to psychedelic research and the growing need for healthcare providers trained in both psychedelic-assisted therapies and in caring for patients with serious illness.[10] In this regard, institutional and social organizations could assist this process through the development of educational and certification programs, policy review around

Table 5
Joanna Briggs Institute Critical Appraisal for Randomized Controlled Trials

Study	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13
Grob et al., 2011	U	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	U
Gasser et al., 2014	U	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
Griffiths et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
Ross et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
Wolfson et al., 2020	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ross et al., 2021	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y

Y = yes; N = no; U = unclear; N/A = not applicable.
C1: Was true randomization used for assigning participants to treatment groups? C2: Was allocation to treatment groups concealed? C3: Were treatment groups similar at the baseline? C4: Were participants blind to treatment assignment? C5: Were those delivering treatment blind to treatment assignment? C6: Were outcomes assessors blind to treatment assignment? C7: Were treatment groups treated identically other than the intervention of interest? C8: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? C9: Were participants analyzed in the groups to which they were randomized? C10: Were outcomes measured in the same way for treatment groups? C11: Were outcomes measured in a reliable way? C12: Was appropriate statistical analysis used? C13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

regulation, funding, and building diverse, equitable, and inclusive research programs in the field of psychedelic therapies.[10]

Concerning the type of disease, most studies have been conducted in cancer patients. In recent years, several researchers, in a more rigorous and scientifically disciplined way than their predecessors, have been engaged in exploring the role of psychedelic-assisted therapies in the treatment of depression, anxiety, and psycho-existential suffering in cancer patients,[22,23,52] including those in advanced stages.[21] Especially regarding existential suffering, although some approaches are promising and are associated with improvement in patients' sense of meaning and purpose, as in the case of dignity therapy,[67,68] there is still much to be advanced in the study of interventions aimed at addressing the psycho-existential suffering experienced by cancer patients. Thus, psychedelics, which possess unique physiological and psychological properties, including altering consciousness and inducing what can be described as mystical experiences, have drawn the interest of researchers as possibilities in addressing these conditions.[3] Mystical experiences induced by psychedelics, also referred to as "psychedelic peak experience," were described by Pahnke[43] according to nine categories that share similar characteristics with non-drug-related mystical experiences: 1) a sense of unity; 2) the transcendence of time and space; 3) a deeply felt positive mood; 4) a sense of sacredness; 5) the noetic quality; 6) paradoxicality; 7) alleged ineffability; 8) transiency; and 9) persisting positive changes in different domains, including attitudes and behavior towards the self, others, life and the experience itself (for review, see Majić et al.[57]).

The studies in this review point to promising effects on symptom control, especially those of psychological and spiritual nature. For Richards et al.[20], the psychedelic substances do not provide an "experience," but an opportunity for the resolution of internal conflicts and subsequent self-actualization. The psychedelic mystical experience appears to have the potential to enable new ways of thinking and feeling.[43] The studies by Griffiths et al.[22] and Ross et al.[23] indicate a significant association between mystical experiences and therapeutic outcomes concerning the reduction of depression and anxiety in cancer patients. The association between spiritual experiences and the capacity for psychological well-being may point to a model for therapeutic modalities that have not been considered for the treatment of depression and anxiety, for instance, interventions that awaken the inner human capacity for meaning and transcendence.[43] A growing basis of evidence supports the importance of integrating the spiritual aspects of psychedelic experiences into the traditional therapeutic process.[69] In a randomized clinical trial being conducted to exploit the therapeutic potential of psilocybin-assisted psychotherapy for alcohol dependence, many participants reported experiences that have assumed a variety of forms, including spiritual perceptions, beatific visions, and communion with the divine.[69] It seems that the mystical experience provided by psychedelic substances, by opening patients to generally unexplored areas of human consciousness, can provide a sense of security that transcends even death[43]. For Pahnke et al.,[70] once the patient is able to release all the psychic energy that was bound up with the fear of death and concerns over the future, the patient seems to be able to live more meaningfully in the present. Kurland[48] reports that under the impact of LSD, patients can stand outside the higher defensive mental structures and see them for what they are, methods of deflecting and reporting reality. Having seen through them, it becomes difficult to take refuge behind them. This opens up to conscious perception a clearer, more realistic view of the world.[48] Suppose psychedelic-assisted therapy continues to demonstrate promising results in clinical trials. In that case, there is a strong possibility that these medicines will become an integral part of psychotherapy, which will require the integration of direct spiritual experiences and spiritual care in the therapeutic process.[69]

According to the results of Kurland's[48] study, it is suggested that the sooner patients have access to psychedelic-assisted therapies, the more rewarding the therapy will be. The response, however, seems to vary to a considerable extent from person to person, depending on the subject's willingness to be open to the psychedelic-induced subjective effects.[48] This apparent contradiction − that the patient is simultaneously hyperalert and perceiving at a vastly accelerated rate and in new and extraordinary ways, while also experiencing dreamlike mental images (one of the unique effects of hallucinogens) − can broaden and improve the patient's relationship with oneself.[48] However, the individual response to psychedelics' subjective effects is also related to the pharmacokinetic profile of each substance. Evidence shows considerable variability in bioavailability, in particular for psilocybin. A study found that the peak psilocin (the active metabolite of psilocybin) concentration was more gradually attained in some subjects than in others, suggesting metabolism rates can vary between individuals.[71]

Some studies indicated the potential of psychedelic-assisted therapies for pain relief.[17,18,41–43,47,46] However, Pahnke et al.[40] state that, in the case of LSD, for example, although greater pain tolerance was achieved, the effect of the psychedelic did not seem to be long-lasting or predictable enough to justify the large expenditure of time and energy involved in carrying out the intervention if pain relief is the primary goal. However, in patients with chronic and/or

refractory pain, psychosocial and existential distress often intertwine with pain perception and intensify it.[72–75] Studies of psychedelic-assisted therapies suggest a potential benefit in these patients.[76,77] Whelan and Johnson[77] argue that psychedelics may alleviate pain indirectly through the action that a psychedelic experience has on an individual's metacognitive interpretation of their pain.

Regarding social aspects, it seems that following the use of psychedelic-assisted therapies, the patients' interpersonal relationships became closer, more frank, honest, and open.[40,17,41,47] The literature indicates that psychedelics, such as LSD, can induce feelings of closeness with other people and increase emotional empathy and sociability.[78]

Psychotherapy was the most commonly used complementary intervention in association with psychedelics. Initially, LSD was used as an adjunct to psychotherapy for the treatment of alcohol use disorder, depression, and anxiety.[79] However, in the 1970s, when the misuse of LSD in popular culture led to its prohibition, the use of the substance for such treatments was discontinued.[65] It wasn't until 1994 that researchers started to re-examine the potential use of psychedelics in psychiatry.[80,81] Currently, studies have followed a similar model: the administration of a psychoactive substance, such as psilocybin, paired with psychotherapy sessions conducted before the psychedelic session (to prepare participants) and after the session (to assist them in integrating their psychedelic experience).[65] Some studies have employed specific psychotherapy approaches. For example, Ross et al.[23] report using supportive psychotherapy, cognitive-behavioral therapy, existentially oriented therapy, and psychodynamic/psychoanalytic therapy. In contrast, other studies used approaches not specifically defined as psychotherapy. Griffiths et al.[22] report using "psychologically supportive conditions, comprising meetings with session monitors before and after sessions; meetings after sessions generally focused on novel thoughts and feelings that arose during psilocybin sessions." Similarly, Grob et al.[21] do not define a specific psychotherapy approach; however, authors report meetings between the research staff and participants before and after psilocybin sessions, essentially functioning as preparatory and integrative sessions.

In our analysis, we found that most studies lack detailed information about the psychotherapeutic approaches employed in psychedelic-assisted therapy, as well as detailed and standardized information regarding the nonpharmacological factors "set" (individual characteristics such as expectations, intentions, mood state, personality, and life history) and "setting" (context-related elements such as aesthetic, musical, cultural, and interpersonal relationships).[82–84] It should be considered that the concept of set and setting and its implications in the context of psychedelic-assisted therapy is a relatively new topic and under ongoing discussion and development.[84,85] Reporting guidelines and checklists are intended to assist researchers in formulating and reporting high-quality studies and providing comprehensive research information.[86] In this sense, the development of specific reporting guidelines and checklists to be applied in trials of psychedelic-assisted therapies can be valuable for the production and advancement of knowledge in this field. We also highlight the importance of considering the development of a core outcome set (COS) for specific outcomes related to psychedelic-assisted therapies in the context of life-threatening illness. The definition of appropriate designs and outcomes is essential for planning and developing rigorous clinical trials which allow comparison of results across studies and minimize bias.[87,88] Furthermore, given the popularity and importance of systematic reviews and meta-analysis for evidence-based practice, there is a greater need to assess the risk of bias and the quality of studies and access clear, standardized information in research reports.[86] Thus, developing a COS and guidelines and/or checklists for reporting results of psychedelic-assisted therapy trials may benefit the research in this field.

The data from these studies included in this review should be analyzed with caution, considering their methodological issues. It is worth encouraging the development of research on the therapeutic potential of psychedelic-assisted therapies. Most notably, we emphasize the importance of conducting larger, randomized clinical trials with rigorous methodologies that evaluate the efficacy and safety of psychedelic-assisted therapies for different homogeneous indications and populations, in patients whose psycho-existential needs have been addressed according to the best standard of care.[7,62]

Strengths and Limitations

The development of the review protocol according to PRISMA-P and the reporting of this article according to PRISMA-2020 provides greater methodological reliability to the study. The use of the internationally recognized and reliable Joanna Briggs Institute checklists for critical appraisal of the studies in the sample can also be considered a methodological strength of this review. Additionally, independent reviewers in the stages of selection and critical appraisal of the studies also contribute to improved result reliability.

This study may present some limitations. Most studies were conducted on cancer patients; therefore, the results may not be transferable to patients with different diagnoses. Most of the studies were carried out in white and educated people, a fact that suggests that inherent racial and ethnic bias that exists in medical research also affects psychedelic research. This

limitation, which can compromise extrapolating results of such studies to the wider population of seriously ill patients, needs to be addressed in future psychedelic research.[89–91] Gray literature sources were not searched; however, this decision was made in order to avoid including nonstandardized content and publications that have not been peer-reviewed. However, no accepted gold standard method exists to this date, and there are few specific guidelines for conducting rigorous gray literature searches.[92,93] Another possible limitation is related to the search strategy adopted, considering that we identified articles that were not retrieved by searching the databases. However, through the manual search, mainly by consulting the reference list of selected articles, it was possible to retrieve important papers that were part of this review sample.

Conclusion

This study presents a literature synthesis of the therapeutic use of psychedelic-assisted therapies for symptom control in patients with serious illness. The results suggest positive effects regarding the use of psychedelic-assisted therapies in the control of physical, social, and particularly psychological and spiritual symptoms.

The adverse effects reported were of physical and/or psychological nature, and of mild to moderate intensity, transient, and self-resolutive. However, it is essential to conduct future studies to further the knowledge on this subject, especially randomized studies with rigorous methodologies to evaluate the efficacy and safety of psychedelic-assisted therapies as therapeutic possibilities in the care provided to patients with serious illness. We also suggest developing a core outcome set on the primary outcomes to be evaluated in psychedelic-assisted therapy trials in the context of serious illness and developing guidelines and/or checklists for reporting the results of these studies.

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The authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jpainsymman.2022.01.024.

References

1. Bandeali S, des Ordons AR, Sinnarajah A. Comparing the physical, psychological, social, and spiritual needs of patients with non-cancer and cancer diagnoses in a tertiary palliative care setting. Palliat Support Care 2020 Oct;18:513–518.

2. Chochinov HM, Johnston W, McClement SE, et al. Dignity and distress towards the end of life across four noncancer populations. PLoS One 2016;11:e0147607.

3. Blinderman CD. Psycho-existential distress in cancer patients: a return to "entheogens. J Psychopharmacol 2016;30:1205–1206.

4. Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majić T. Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry 2018;81:1–10.

5. Ross S. Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. Int Rev Psychiatry 2018;30:317–330. https://doi.org/10.1080/09540261.2018.1482261.

6. Dyck E. Psychedelics and dying care: a historical look at the relationship between psychedelics and palliative care. J Psychoactive Drugs 2019;51:102–107.

7. Beaussant Y, Sanders J, Sager Z, et al. Defining the roles and research priorities for psychedelic-assisted therapies in patients with serious illness: expert clinicians' and investigators' perspectives. J Palliat Med 2020;23:1323–1334.

8. Bossis AP. Utility of psychedelics in the treatment of psychospiritual and existential distress in palliative care: a promising therapeutic paradigm. In: Grob CS, Grigsby J, eds. Handbook of medical hallucinogens, New York: The Guilford Press; 2021:441–473.

9. Garcia ACM, LO Maia. The therapeutic potential of psychedelic substances in Hospice and Palliative Care. Prog Palliat Care 2022;30:1–3.

10. Beaussant Y, Tulsky J, Guérin B, Schwarz-Plaschg C, Sanders JJ. Radcliffe institute for advanced study working group on psychedelic research in serious illness. Mapping an agenda for psychedelic-assisted therapy research in patients with serious illness. J Palliat Med 2021;24:1657–1666. https://doi.org/10.1089/jpm.2020.0764.

11. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the controlled substances. Act. Neuropharmacology 2018;142:143–166.

12. Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology 2018;142:200–218. https://doi.org/10.1016/j.neuropharm.2017.12.040.

13. Chi T, Gold JA. A review of emerging therapeutic potential of psychedelic drugs in the treatment of psychiatric illnesses. J Neurol Sci 2020;411:116715. https://doi.org/10.1016/j.jns.2020.116715.

14. Inserra A, De Gregorio D, Gobbi G. Psychedelics in psychiatry: neuroplastic, immunomodulatory, and neurotransmitter mechanisms. Pharmacol Rev 2021;73:202–277. https://doi.org/10.1124/pharmrev.120.000056.

15. Marks M, Cohen IG. Psychedelic therapy: a roadmap for wider acceptance and utilization. Nat Med 2021;27:1669–1671. https://doi.org/10.1038/s41591-021-01530-3.

16. Nutt D, Carhart-Harris R. The current status of psychedelics in psychiatry. JAMA Psychiatry 2021;78:121–122. https://doi.org/10.1001/jamapsychiatry.2020.2171.

17. Pahnke WN, Kurland AA, Unger S, et al. Psychedelic therapy (Utilizing LSD) with cancer patients. J Psychedelic Drugs 1970;3:63–75.

18. Richards WA, Grof S, Goodman LE, et al. LSD-assisted psychotherapy and the human encounter with death. JTP 1972;4:121–150.

19. Richards WA, Rhead JC, Dileo FB, Yensen R, Kurland AA. The peak experience variable in DPT-assisted psychotherapy with cancer patients. J Psychedelic Drugs 1977;9:1–10.

20. Richards WA, Rhead JC, Grof S, et al. DPT as an adjunct in brief psychotherapy with cancer patients. Omega: J Death Dying 1979;10:9–26.

21. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011;68:71–78.

22. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 2016;30:1181–1197.

23. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016;30:1165–1180.

24. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008;22:603–620. https://doi.org/10.1177/0269881108093587.

25. Nichols D. Psychedelics. Pharmacol Rev. 2016;68:264–355.

26. Garcia-Romeu A, Kersgaard B, Addy PH. Clinical applications of hallucinogens: a review. Exp Clin Psychopharmacol 2016;24:229–268.

27. Carlini EA, LO Maia. Plant and fungal hallucinogens as toxic and therapeutic agents. In: Gopalakrishnakone P, Carlini C, Ligabue-Braun R, eds. Plant toxins. Toxinology, Dordrecht: Springer; 2015:1–44.

28. Templer DI, Arikawa H, Gariety PC. Psychotropic drugs in terminally Ill patients: a review of the clinical and research literature. OMEGA - J Death and Dying 2004;49:249–274. https://doi.org/10.2190/9V5J-FG82-QRRN-UF87.

29. Varley J. Psychedelic-assisted therapy for anxiety and depression in the face of death: a critical review with an anthropological lens. J Psychedelic Stud 2019;3:14–18.

30. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129–136.

31. Saunders C, Baines M. Living with dying: The management of terminal disease. UK: Oxford; 1983.

32. Sulmasy DP. A biopsychosocial-spiritual model for the care of patients at the end of life. Gerontologist 2002;42:24–33.

33. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

35. Aslam S, Emmanuel P. Formulating a researchable question: a critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS 2010;31:47–50.

36. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan — a web and mobile app for systematic reviews. Syst Rev 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.

37. Ryan R. Cochrane consumers and communication review group. Cochrane consumers and communication review group: data synthesis and analysis. 2013. Available from: https://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/Analysis.pdf. Accessed July 27, 2021

38. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme. 2006. https://doi.org/10.13140/2.1.1018.4643.

39. Joanna Briggs Institute - JBI. Critical appraisal tools. Available from: https://jbi.global/critical-appraisal-tools. Accessed September 13, 2021

40. Pahnke WN, Kurland AA, Goodman LE, et al. LSD-assisted psychotherapy with terminal cancer patients. Curr Psychiatr Ther 1969;9:144–152.

41. Kast E. LSD and the dying patient. Chic Med Sch Q 1966Summer;26:80−87.

42. Kast E. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. Psychiatr Q 1967;41:646–657.

43. Pahnke W. The psychedelic mystical experience in the human encounter with death. Harv Theol Rev. 1969;62:1–21. https://doi.org/10.1017/S0017816000027577.

44. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. Int Pharmacopsychiat. 1973;8:129–144.

45. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 2014;202:513–520.

46. Kast EC, Collins VJ. Study of lysergic acid diethylamide as an analgesic agent. Anesth Analg 1964;43:285–291.

47. Kurland AA, Grof S, Pahnke WN, et al. Psychedelic drug assisted psychotherapy in patients with terminal cancer. J Thanatol 1972;2:644–691.

48. Kurland AA. LSD in the supportive care of the terminally ill cancer patient. J Psychoactive Drugs 1985;17:279–290.

49. Irwin SA, Iglewicz A, Nelesen RA, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med 2013;16:958–965.

50. Wolfson PE, Andries J, Feduccia AA, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. Sci Rep 2020;20442. https://doi.org/10.1038/s41598-020-75706-1.

51. Anderson BT, Danforth A, Daroff R, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. EClinical Medicine 2020: 27.

52. Ross S, Agin-Liebes G, Lo S, et al. Acute and sustained reductions in loss of meaning and suicidal ideation following psilocybin-assisted psychotherapy for psychiatric and existential distress in life-threatening cancer. ACS

Pharmacol Transl Sci 2021;18:553–562. https://doi.org/10.1021/acsptsci.1c00020.

53. Dyck E. Just say know: criminalising LSD and the politics of psychedelic expertise. In: Montigny EA, ed. The real dope": Historical and legal perspectives on the regulation of drugs in Canada, Toronto: University of Toronto Press; 2011:169–196.

54. Nutt D, King L, Nichols D. Effects of schedule I drug laws on neuroscience research and treatment innovation. Nat Rev Neurosci 2013;14:577–585.

55. Das S, Barnwal P, Ramasamy A, Sen S, Mondal S. Lysergic acid diethylamide: a drug of 'use'? Ther Adv Psychopharmacol 2016;6:214–228.

56. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J Psychopharmacol 2015;29:57–68.

57. Majić T, Schmidt TT, Gallinat J. Peak experiences and the afterglow phenomenon: when and how do therapeutic effects of hallucinogens depend on psychedelic experiences? J Psychopharmacol 2015;29:241–253.

58. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. Addict Biol 2002;7:357–364.

59. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther 2008Winter;14:295−314.

60. Passie T. A history of the use of psilocybin in psychotherapy. In: Metzner R, ed. Teonanacatl: Sacred mushroom of vision, El Verano, CA: Four Trees; 2004:109–134.

61. Maia LO, Daldegan-Bueno D, Tófoli LF. The ritual use of ayahuasca during treatment of severe physical illnesses: a qualitative study. J Psychoactive Drugs 2021;53:272–282. https://doi.org/10.1080/02791072.2020.1854399.

62. Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and psychedelic-assisted psychotherapy. Am J Psychiatry 2020;177:391–410.

63. Rinkel M, DeSHON HJ, Hyde RW, Solomon HC. Experimental schizophrenia-like symptoms. Am J Psychiatry 1952;108:572–578.

64. De Gregorio D, Comai S, Posa L, Gobbi G. d-Lysergic acid diethylamide (LSD) as a model of psychosis: mechanism of action and pharmacology. Int J Mol Sci 2016;17:E1953.

65. Penn A, Dorsen CG, Hope Rosa WE. Psychedelic-assisted therapy: emerging treatments in mental health disorders. Am J Nurs 2021;121:34–40.

66. Phelps J. Developing guidelines and competencies for the training of psychedelic therapists. J Humanist Psychol 2017;57:450–487.

67. Chochinov HM, Kristjanson LJ, Breitbart W, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients. Lancet Oncol 2011;12:753–762.

68. Faller H, Schuler M, Richard M, Heckl U, Weis J, Küffner R. Effects of psycho-oncology interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. J Clin Oncol 2013;31:782–793.

69. Podrebarac SK, O'Donnell KC, Mennenga SE, et al. Spiritual experiences in psychedelic-assisted psychotherapy: case reports of communion with the divine, the departed, and saints in research using psilocybin for the treatment of alcohol dependence. Spirituality Clin Pract 2021;8:177–187. https://doi.org/10.1037/scp0000242.

70. Pahnke WN, Kurland AA, Unger S, Savage C, Grof S. The experimental use of psychedelic (LSD) psychotherapy. Int Z Klin Pharmakol Ther Toxikol 1971;4:446–454.

71. Brown RT, Nicholas CR, Cozzi NV, et al. Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. Clin Pharmacokinet 2017;56:1543–1554. https://doi.org/10.1007/s40262-017-0540-6.

72. McCowat M, Fleming L, Vibholm J, Dixon D. The psychological predictors of acute and chronic pain in women following breast cancer surgery: a systematic review. Clin J Pain 2019;35:261–271.

73. Ong C-K, Forbes D. Embracing cicely saunders's concept of total pain. BMJ 2005;331:576–577.

74. Strang P. Existential consequences of unrelieved cancer pain. Palliat Med 1997;11:299–305.

75. Malhotra C, Harding R, Teo I, et al. Financial difficulties are associated with greater total pain and suffering among patients with advanced cancer: results from the COMPASS study. Support Care Cancer 2020;28:3781–3789.

76. Castellanos JP, Woolley C, Bruno KA, Zeidan F, Halberstadt A, Furnish T. Chronic pain and psychedelics: a review and proposed mechanism of action. Reg Anesth Pain Med 2020;45:486–494. https://doi.org/10.1136/rapm-2020-101273.

77. Whelan A, Johnson MI. Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role? Pain Management 2018;8:217–229.

78. Dolder PC, Schmid Y, Müller F, Borgwardt S, Liechti ME. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. Neuropsychopharmacology 2016;41:2638–2646.

79. Sessa B. The psychedelic renaissance: Reassessing the role of psychedelic drugs in 21st century psychiatry and society. London: Muswell Hill Press; 2012.

80. Strassman RJ, Qualls CR, Uhlenhuth EH, Kellner R. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 1994;51:98–108. https://doi.org/10.1001/archpsyc.1994.03950020022002.

81. Strassman RJ, Qualls CR, Uhlenhuth EH, Kellner R. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 1994;51:98–108. https://doi.org/10.1001/archpsyc.1994.03950020022002.

82. Leary T, Foreword Alpert R. Joyous cosmol. Advent. Chem. Consciousn. 1962: 1–3.

83. Zinberg NE. Drug, set, and setting: the basis for controlled intoxicant use. New Haven: Yale University Press; 1984.

84. Hartogsohn I. Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. J. Psychopharmacol 2016;30:1259–1267. https://doi.org/10.1177/0269881116677852.

85. Haijen ECHM, Kaelen M, Roseman L, et al. Predicting responses to psychedelics: a prospective study. Front. Pharmacol. 2018;9:897. https://doi.org/10.3389/fphar.2018.00897.

86. Brand J, Hardy R, Monroe E. Research pearls: checklists and flowcharts to improve research uality.

Arthroscopy 2020;36:2030–2038. https://doi.org/10.1016/j.arthro.2020.02.046.

87. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012;13:132. https://doi.org/10.1186/1745-6215-13-132.

88. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Rev Clin Pharmacol 2021;14:1133–1152. https://doi.org/10.1080/17512433.2021.1933434.

89. George JR, Michaels TI, Sevelius J, Williams MT. The Psychedelic renaissance and the limitations of a white-dominant medical framework: a call for indigenous and ethnic minority inclusion. J Psychedelic Stud 2020;4:4–15.

90. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. BMC Psychiatry 2018;18:245.

91. Williams MT, Reed S, Aggarwal R. Culturally informed research design issues in a study for MDMA-assisted psychotherapy for posttraumatic stress disorder. J Psychedelic Stud 2020;4:40–50.

92. Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in metaanalyses. Nurs Res 2003;52:256–261.

93. Bellefontaine SP, Lee CM. Between black and white: examining grey literature in meta-analyses of psychological research. J Child Fam Stud 2014;23:1378–1388.