Efficacy of Psilocybin Assisted Interventions for Psychological Disorders in Patients with Life Threatening Illness: A Systematic Review of Clinical Trials

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Abstract

This systematic review explores the potential of psilocybin-assisted interventions as a novel treatment for psychological disorders in patients with life-threatening illnesses. The high prevalence and complexity of psychological disorders, such as depression and anxiety, among this patient population presents unique treatment challenges. Traditional interventions often fall short in efficacy, necessitating the exploration of alternative treatments. Psilocybin, a naturally occurring plant alkaloid found in many species of mushrooms, has shown promise in preliminary research, indicating potential therapeutic benefits. This review, conducted following the PRISMA guidelines synthesizes the current evidence from clinical trials to address a PICOS framework question “What evidence have clinical trials provided on the efficacy of psilocybin-assisted interventions in addressing psychological disorders experienced by patients diagnosed with life-threatening conditions?” The review details the search strategy, inclusion and exclusion criteria, data extraction process, risk of bias assessment, and synthesis of results. The review provides an overview of the current state of research. Highlighting the potential of psilocybin as a novel intervention, whist also stressing the need for further research to validate findings and address existing gaps in the literature.

Introduction

Psychological Disorders in Patients with Life-Threatening Illness

Diagnosis of a life-threatening illness is understood to be a severe stressor, often leading to states of depression and anxiety (Sutherland, 1956; Leeds, 2020). Indeed, states of depression and anxiety are not only common amongst patients with life threatening illness (Leeds, 2020; Miovic et al., 2007), but are also predictors of whether patients will develop clinical symptoms of psychological distress (Breitbart, 2000; Leeds, 2020). Dependent on the criteria employed, up to 68% of patients diagnosed with a life-threatening illness reach thresholds for diagnosis of a psychological disorder (Kissane, 2004; Sellick & Crooks, 1999; Leeds, 2020). These psychological disorders are recognised as a consequence of both disease, and treatment (Grassi, 2015; Ignatius & De La Garza, 2019; Leeds, 2020). Amongst this patient group depressive and anxiety disorders are found at rates far exceeding those in the general population (Kolva et al., 2011; Walker et al., 2013; Leeds, 2020). Symptoms of these disorders have real life impacts, and can manifest in a variety of ways, ranging from feelings of depression and anxiety to increased pain sensitivity and a desire for a hastened death (Breitbart, 2000; Lemay & Wilson, 2008; Leeds, 2020). The impact of these disorders on the quality of life of patients during this period is associated with a number of adverse outcomes (Colleoni, 2000; Leeds, 2020; Kissane, 2000). Specifically, increased rates of suicide, heightened symptom burden, and reduced treatment adherence each independently contribute to decreased survival rates, diminished quality of life, and overall poorer treatment outcomes (Colleoni, 2000; Lehto et al., 2018).

Treatment of psychological disorders in patients with a life-threatening illness is unique in the risks and challenges it presents, with various factors adding complexity to the administration of commonly prescribed treatment strategies and impacting efficacy (Grassi et al., 2015; Landa-Ramirez et al., 2019; Leeds, 2020; Ostuzzi et al., 2015). For example,

treatments such as Cognitive behavioural Therapy (CBT) are require adaptation so they can be delivered over a reduced number of sessions (Greer et al., 2012; Landa-Ramirez et al., 2019; Leeds, 2020), and show a wide variation in efficacy (Antoni et al., 2001; Evans & Connis, 1995; Landa-Ramirez et al., 2019; Leeds, 2020). Selective Serotonin Reuptake Inhibitors (SSRI) take time to reduce symptoms, are prone to high relapse rates (Freedman, 2010; Leeds, 2020; Li et al., 2012), have potential to accelerate disease progression (Brandes et al., 1992; Leeds, 2020), and are shown to provide little to no benefit over placebo in meta-analyses (Iovieno et al., 2011; Leeds, 2020; Ostuzzi et al., 2015). Further, meta-analyses of preventative interventions have also been shown to provide no clinical effect (Sheard & Maguire, 1999). Taken together, this information demonstrates a lack of clear evidence to guide clinicians and provides insight as to why many patients do not receive effective treatment (Walker et al., 2013). Given these persistent problems, exploring alternatives to address the unique issues which arise in treatment of psychological disorders for patients with life-threatening illness is of significant importance (Wanat et al., 2017; Walker et al., 2013). Psilocybin assisted interventions are precisely one such novel alternative.

Psilocybin, and Psilocybin Assisted Interventions

Psilocybin is a naturally occurring plant alkaloid found globally in many species of mushroom (Stamets, 1996; Carhart-Harris et al., 2017; Leeds, 2020), and is classified as a classic hallucinogen (Johnson et al., 2008). Psilocybin is part of a group of serotonergic compounds commonly referred to as psychedelics, these compounds act as 5-HT_{2A} receptor agonists (Hasler et al., 2004), and are known to produce marked changes in consciousness (Carhart-Harris & Goodwin, 2017; Grof, 1973; Leeds, 2020). Psilocybin in its mushroom form has a long history of use within cultural and religious practices (Friedman,

2006; Leeds, 2020). However, research into the potential therapeutic use of psilocybin did not truly begin until 1960's and 70's (Kast, 1966; Leeds, 2020; Phifer, 1977). This "first wave" of research into the therapeutic potential of psychedelics was halted due to safety concerns raised by recreational use during the same time period (Carhart-Harris & Goodwin, 2017; Leeds, 2020). Research into the use of psilocybin for therapeutic benefit remained stagnant until recent decades, when a revival of interest was initiated after conditions for safe administration were established (Grob et al., 2011; Leeds, 2020; Ross et al., 2016; Studerus et al., 2010). Preliminary findings from this "second wave" of research have indicated towards a positive therapeutic benefit in multiple psychological disorders (Carhart-Harris & Goodwin, 2017). In particular, disorders related to end-of-life psychological distress, and treatment resistant depression (TRD) (Carhart-Harris et al., 2016; Roseman et al., 2018; Leeds, 2020; Mertens et al., 2020; Ross et al., 2016; Griffiths et al., 2016). A growing body of research supports psilocybin as potentially effective novel intervention (Grob et al., 2011; Ross et al., 2016; Grifriths et al., 2016; Belser et al., 2017). Safe psychological and physiological responses have been repeatedly recorded when appropriate screening practices have been applied (Grob et al., 2011; Ross et al., 2016; Studerus et al., 2010; Griffiths et al., 2016; Johnson et al., 2008). Participants suffering with life threatening illness have experienced therapeutic benefit through increased quality of life and spiritual wellbeing, and reduced feelings of demoralisation and hopelessness. Bearing in mind that there is limited research into combined pharmacological and psychotherapeutic interventions to address the unique issues faced by terminally ill people (Bogenschutz & Ross, 2018; Leeds, 2020), and that improvements in psychological wellbeing are crucial in improving outcomes in end-of-life treatment (Vehling et al., 2018; Carr & Steel, 2013; Leeds, 2020), research into novel interventions may prove particularly valuable in guiding future research. Previous systematic reviews and meta-analysis in this area exist (Vargas et al., 2020). However, changes in

psychedelic research are occurring rapidly in both methods used (Agrawal et al., 2023; Lewis et al., 2020; Shnayder et al., 2023) and their legality (Patchett-Marble et al., 2022). Therefore, comprehensive reviews that synthesize the current evidence are warranted and may to contribute to the existing body of knowledge. This review will provide a comprehensive synthesis of the current evidence, identify gaps in the literature, and provide recommendations for future research. The objective of this review will be to provide an up to date synthesis of information on a novel intervention to serious problem by addressing the PICOS framework derived question "What evidence have clinical trials provided on the efficacy of psilocybin-assisted interventions in addressing psychological disorders experienced by patients diagnosed with life-threatening conditions?". The pre-registration document for this review can be found here (Google drive link).

Method

The search and selection strategy for this review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Inclusion criteria

The inclusion and exclusion criteria were derived from the Participants, Intervention, Comparison, Outcome, and Study design (PICOS) framework in relation to the review question as follows: Studies must be clinical trials involving human participants who have been diagnosed with a life-threatening illness, in combination with meeting thresholds for diagnosis of a psychological disorder commonly associated with end-of-life psychological distress (depression, anxiety, demoralization). Studies must be interventional and the intervention under investigation must have incorporated psilocybin. Studies must have compared the effects of the psilocybin intervention to a control condition. Studies primary

outcome measures must have included the alleviation of psychological distress in the form of depression, anxiety, or demoralisation, and outcomes must have been assessed using validated measures. No specific limits were set for the time frame of when outcomes were measured.

Several commonly used measures for depression, anxiety, and demoralisation were identified as meeting the criteria, these were:

- Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960)
- The GRID-Hamilton Depression Rating Scale (GRID-HAMD)
- Beck Depression Inventory (BDI) (Beck et al., 1961)
- Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)
- Quick Inventory of Depressive Symptomatology (Rush et al., 2003)
- Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)
- State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983)
- Beck Anxiety Inventory (BAI) (Beck et al., 1988)
- Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959)
- Demoralization Scale (DS-I) (Kissane et al., 2004),
- Demoralization Scale (DS-II) (Robinson et al 2016)

Additional inclusion/exclusion criteria

As research, and the legality of the availability of such interventions is rapidly evolving (Patchett-Marble et al., 2022), and in order to potentially include the maximum number of relevant studies, while aiding rapid dissemination of data, it was decided to include research letters and pre-print articles where adequate reporting of detail were present and all other inclusion criteria were met.

Search strategy

For the present review, a comprehensive search of all document types held on two electronic databases (Scopus, and Web of science) was conducted on June 16th 2023. In order to gather as much relevant material as possible these databases were searched using Boolean terms on titles, abstracts, and keywords/indexing. The terms employed for the search strategy of both databases were as follows; (psilocybin OR "psilocybin assisted psychotherap*") AND (terminal* OR "end of life" OR cancer OR "life threatening" OR palliative) AND (depress* OR MDD OR anxiety OR distress* OR demorali?ation* OR existential) AND NOT (cannabis OR lsd OR "lysergic acid diethylamide" OR ketamine OR mdma OR methylenedioxymethamphetamine OR peyote OR dmt OR dimethyltryptamine OR ayahuasca). Following guidance from PRISMA statement (2020), and guidance from the Cochrane collaboration (https://training.cochrane.org/handbook/current), all documents returned by the search were pre-screened for relevance via their titles and abstracts. Following this, the full text of documents considered relevant were analysed in depth. The entire search, screening, and selection process for this review was conducted independently by a single author.

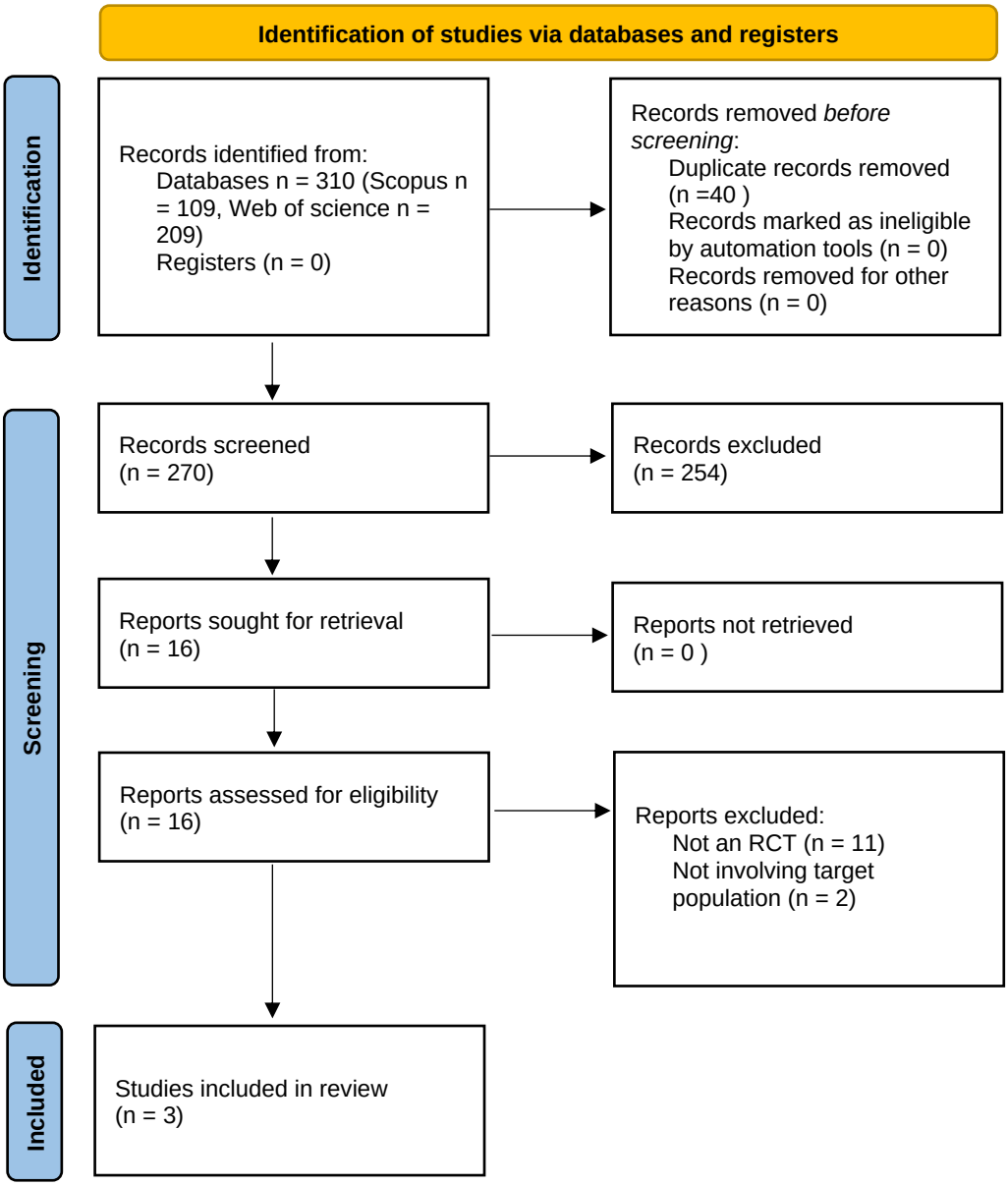
Study selection

The initial database search yielded 310 articles, with 109 sourced from Scopus, and 201 from Web of Science. Duplicates were removed (40), leaving 270 unique articles. Titles and abstracts were screened for relevance, this process excluded 254 articles and identified 16 articles for full-text review. After a detailed examination, 13 of these articles were excluded, either due to not being a randomized controlled trial with a true control condition (11), or not

involving the target population (2). Consequently, 3 studies met all the criteria and were included in the systematic review.

Figure 1.

Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) flow-chart of database search, study selection and articles included



Data Extraction Process

A data extraction form tailored from the standard template provided by the Cochrane Collaboration (Found here: Google drive link), was used to systematically collect essential information from each study that was included in the current review. The data collected included the author and year of publication, the design of the study, the characteristics and diagnosis of the participants, the specifics of the intervention, the primary outcome measures, and the main findings of each study.

Data Items

Data extracted from each study included the author and year of publication. The design of the study was noted to understand the methodological framework. Participant characteristics and diagnoses were extracted to understand the population the study was conducted on. Details of the intervention were gathered to understand the type of psilocybin assisted intervention applied in the study. Primary outcome measures, and time points of collection, were noted to understand the specific metrics used to gauge the effects of the intervention. Lastly, the main findings of each study were extracted to summarise the results and conclusions drawn from the study. The results of this data extraction were displayed in a table (Table 1).

Risk of Bias Assessment

Risk of bias for each included study was assessed using the Revised Cochrane risk-of-bias tool for randomized crossover trials (Link: RoB 2 for crossover trials). This tool evaluates the risk of bias across six domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported

result, and period and carryover effects. Each domain was rated as 'low', 'some concerns', or 'high' risk of bias based on a series of signalling questions. As this review has only one author, this classification was independently assigned by the author. The results of the risk of bias assessment were presented in a risk of bias summary, and a risk of bias table (Table 2).

Summary Measures

The primary outcome measures of interest for this review employed in the included studies were changes in scores for depression and anxiety at baseline, crossover point, and at follow-up assessments. These scores were measured using:

- The GRID-Hamilton Depression Rating Scale (GRID-HAMD), an improved version of the Hamilton Depression Rating Scale (Hamilton, 1960), a widely used clinician-administered rating scale to measure of symptom severity in depressive disorders.
- The Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), a widely used and validated clinician-rated measure of severity of anxiety symptoms (Matza et al., 2010).
- The State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), a self-report questionnaire which is divided into 2 subscales. STAI-State (STAI-S) which detect levels of current symptoms of anxiety, and the STAI-Trait (STAI-T) which detects general tendency to be anxious.
- The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), a self-report questionnaire commonly used to assess the severity of symptoms of anxiety and depression in primary care patients. The HADS provides results from subscales for anxiety (HADS-A), and depression (HADS-D), as well as total scores (HAD-T).

- The Beck Depression Inventory (BDI) (Beck et al., 1961). The BDI is a widely used and validated a 21-item self-report questionnaire that measures attitudes and symptoms of depression.

The key findings from each of these measures were reported in a narrative format, highlighting the most significant results from each individual study.

Synthesis of Results

In synthesizing the results of this review, a narrative approach was adopted. A qualitative synthesis was conducted, with each study individually analysed for its objectives, population studied, nature of the psilocybin intervention, outcome measures, timeline, and key findings. Emphasis was placed on outcome measures that pertained to depression, anxiety, or demoralisation as these are commonly experienced disorders in patients with life-threatening conditions. The results from each study were compared to identify any themes or differences, and to evaluate whether findings supported or contradicted each other. The findings from each study, and the overall themes in the results were identified and summarized to see if they contribute to addressing the research question. The findings were then interpreted in the context of the existing literature and theory. Finally, the implications of the findings for future research were evaluated and discussed.

Results

Study Selection

As described previously and displayed in Figure 1, the initial database search yielded 310 articles. After the removal of duplicates (40), and exclusion of non-relevant records via title and abstract screening (254), 16 articles were found to be potentially relevant for full-text review. After a detailed examination, 13 of these articles were subsequently excluded for

not meeting the eligibility criteria. One case study did meet eligibility as an RCT (Patchett-Marble et al., 2022), three studies did not employ a control condition (Agrawal et al., 2023; Lewis et al., 2020; Shnayder et al., 2023), two were follow up studies and therefore did not present a true control condition (Agin-Liebes et al., 2020; Swift et al., 2017), two were studies of qualitative interviews, again without control condition (Belser et al., 2017; Lewis et al., 2022), three were secondary analyses of data (Benville et al., 2021; Malone et al. 2018; Ross et al., 2021), two were studies with participants who had survived serious illness and so did not target the intended population for the research question of this review (Anderson et al., 2019; Anderson et al., 2020). This process left three studies which met all of the inclusion and exclusion criteria (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), which were included for synthesis in the current review.

Study Characteristics

The key characteristics of the included studies are displayed in table 1. The three studies included for review were published between 2011 and 2016. All three studies employed a randomized controlled double-blind with crossover design, with one acting as a pilot study. Sample sizes ranged from 12 to 51 participants. All studies were conducted with patients who had been diagnosed with life-threatening or advanced stage cancer and who were experiencing symptoms of anxiety and/or depressive disorders. Synthesized psilocybin was administered via oral capsules in doses ranging between 02mg/kg and 0.4mg/kg. Interventions varied between psilocybin as a standalone, psilocybin with psychological support, and psilocybin with psychotherapy. Results of interventions were generally assessed one day after administration, and in the following weeks and months, with long term follow up at six months.

Table 1

Characteristics of Contributing Studies

Author / Year	Study Design	Diagnoses / Conditions	N	Intervention / Control	Primary Outcome Measures	Main Findings
Grob et al 2011	Randomized controlled double-blind with crossover / feasibility pilot	anxiety, depression, advanced stage cancer	12	Psilocybin (0.2 mg/kg) Control = niacin (250 mg)	BDI for depression STAI-T and STAI-S for anxiety	Reductions in BDI score at 6-month follow-up. Reductions in STAI-T score at 1 and 3 months follow up. Summary Psilocybin intervention resulted in significant and sustained improvements in anxiety at 1- and 3-month time points, and in depression at 6-month time point.
Ross et al 2016	Randomized controlled double-blind with crossover	Depression and anxiety, life-threatening cancer	29	Psilocybin (0.3 mg/kg) + psychotherapy Control = niacin (250 mg)	HADS-A for anxiety; HADS-D for depression; HAD-T (overall total) STAI-T and STAI-S for anxiety BDI for depression	Reductions in STAI-T, STAI-S, HADS-A, HADS-D, HAD-T and BDI at all time points from 1 day post psilocybin intervention up until 7-week crossover point. HAD-A - 58% anxiolytic response vs 14% for the control group. BDI - 83% anti-depressant response vs 14% for control group BDI - 85% vs 15% remission in depression for control group Reduction in anxiety and depression at all time points up to 26 weeks post dose 2. Summary

						Single moderate dose psilocybin in combination with psychotherapy resulted in immediate, substantial, and sustained improvements in depression and anxiety compared to control at crossover point, and at 26 week follow up.
Griffiths et al 2016	Randomized controlled double-blind with crossover	Depression and anxiety, life-threatening cancer	51	Psilocybin (22 or 30mg/70kg (0.3mg/kg - 0.4mg/kg) + psychological support Control = psilocybin (1 or 3 mg/70kg)	GRID-HAMD-17 for depression HAM-A for anxiety	GRID-HAMD-17 Greater clinical response for the High-Dose-1st (Low-Dose-2nd) group - 92% vs 32% at the 5-week crossover point. Clinically significant response sustained at 79% for High-Dose-1st (Low-Dose-2nd) group after 6 months. GRID-HAMD-17 Greater remission rate for High-Dose-1st (Low-Dose-2nd) group - 60% vs 16% at the 5-week crossover point and sustained at 71% after 6 months. HAM-A Greater clinical response in High-Dose-1st (Low-Dose-2nd) group - 76% vs 24% at the 5-week crossover point. Clinically significant response sustained at 83% for High-Dose-1st (Low-Dose-2nd) group after 6 months. HAM-A higher remission in High-Dose-1st (Low-Dose-2nd) group - 52% vs 12% at the 5-week crossover point, sustained at 63% after 6 months. Summary Single dose psilocybin resulted in significant long-lasting improvements in both depression and anxiety when compared at crossover and 6-month point.

Risk of Bias

The findings from the risk of bias assessment are displayed in Table 2. Overall, all of the studies fulfilled the majority of the six domains of bias defined by the Cochrane collaboration tool for crossover trials. All three studies were double-blind trials with randomized participant allocation. However, details of the randomization process employed were not specified, and so the uncertainty in this domain must be considered to present some concerns. All three studies reported that all participants received their intended interventions without deviation. Across all three studies missing data is not explicitly mentioned. Nevertheless, all participants were appropriately accounted for at the conclusion of each trial. Across all three studies primary outcomes were assessed using validated scales, mitigating risk of bias arising from the measurement of outcomes. Further, all studies reported results for all pre-specified measures of outcomes. All three studies employed a cross-over design and so potential for carryover effects is of concern. However, none of the included studies provide enough information to assess the risk of bias in this domain and so it must be considered to present some concerns. Overall, the reporting of all three studies is generally sound, with only some concerns in domains where further detail is required to make a full assessment of risk.

Table 2
Risk of Bias Assessment

Study	Bias from Randomization	Deviations from Interventions	Missing Outcome Data	Measurement of Outcome	Selection of Reported Result	Crossover period and carryover effects	Overall Risk of Bias
Grob et al., 2011	Some concerns	Low	Low	Low	Low	Some concerns	Some concerns
Ross et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns	Some concerns
Griffiths et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns	Some concerns

Synthesis of Included Studies

In temporal terms the first of the three included studies to investigate the efficacy of employing psilocybin as an intervention was conducted by Grob et al. (2011). Using a randomized controlled double-blind crossover design Grob et al. (2011) were able to take a small sample of participants who were suffering with advanced stage cancer and implement a protocol which allowed all participants to take part in a low dose psilocybin intervention. This study did not provide additional therapy or psychological support to participants during the psilocybin dose session and was the only study of the three in which psilocybin alone was assessed against placebo for its effect on outcomes measures. Grob et al. (2011) reported outcomes for depression and anxiety over a 6-month period using the BDI, and STAI respectively. The second of the three studies to be considered here, conducted by Ross et al. (2016), also employed a randomized controlled double-blind crossover design to explore the potential of psilocybin as an intervention for a sample of participants (29) with diagnosis of advanced-stage cancer and symptoms of anxiety and/or depression. This study administered a single dose of psilocybin (0.3 mg/kg) to each participant during one of two sessions, with the other session involving a placebo. In addition to psilocybin, a form of supportive

psychotherapy was provided to participants during sessions. Similar to the Grob et al. (2011), this study tracked outcomes for depression and anxiety over a 6-month period using various measures, including HADS, BDI, and STAI. The last of the three studies analysed Griffiths et al. (2016), also employed a randomized controlled double-blind crossover design to investigate the potential of psilocybin as an intervention. This study recruited a larger sample of participants (51) with a potentially life-threatening cancer diagnosis and symptoms of depression and/or anxiety. The study administered two separate doses of psilocybin to each participant over two sessions: one high dose (22 or 30 mg/70 kg) and one very low dose (1 or 3 mg/70 kg). In addition to psilocybin, a form of non-directive psychological support was provided to participants during the dose sessions. As with the Study by Grob et al (2011) Griffiths et al. (2016) tracked outcomes for depression and anxiety over a 6-month period using several measures, including the GRID-HAMD, HAM-A, BDI, and STAI. All three of the studies described above, collectively demonstrated a significant and substantial impact of psilocybin in alleviating depression in patients with life threatening illness. In the pilot study by Grob et al. (2011), a low dose of psilocybin resulted in significant improvements in depression, with effects sustained for at least three months. Further, Ross et al. (2016) found that a single dose of psilocybin in conjunction with psychotherapy, resulted in immediate, substantial, and enduring reductions in symptoms of depression. Similarly, Griffiths et al. (2016), found that a high dose of psilocybin resulted in substantial and sustained decreases in depression, with 92% antidepressant response rates at 5 weeks post treatment. Moreover, effects of the interventions in both Ross et al. (2016) and Griffiths et al. (2016), were still evident for at least six months, indicating the long-term efficacy of the intervention. Effects of the psilocybin intervention on anxiety were also consistently positive across the three studies. In the pilot study by Grob et al. (2011), psilocybin intervention resulted in significant improvements in anxiety that were sustained for at least three months. Griffiths et al. (2016)

found substantial and sustained decreases in anxiety following a single dose of psilocybin, with a 76% anxiolytic response rates at 5 weeks post treatment. Moreover, effects endured for at least six months. Likewise, Ross et al. (2016) found that psilocybin produced rapid, substantial, and sustained improvements in anxiety, with effects enduring at 26-week follow-up. Collectively, the results of these three studies suggest that psilocybin, when administered in a supportive setting, has potential to provide substantial and sustained alleviation of anxiety and depression experienced by patients with life-threatening illness.

Discussion

This review found promising results for the efficacy of psilocybin as a novel approach to addressing depression and anxiety in patients with life threatening illness. Unfortunately, despite much more research taking place today than at any other time, recent clinical trials have rarely employed methods as robust as double-blind RCT's and so this review was only able to include a total of 3 studies, comprising a overall participant number of 92. Future reviews may benefit from placing further consideration into selecting eligibility criteria in order to capture more of the available research. Nevertheless, the results provided in this review demonstrate that psilocybin assisted interventions appear to be effective at alleviating depression and anxiety symptoms across a range of validated scales. This review is not able to provide any direct insight into the mechanisms which underlie the effects witnessed in the included studies. Whilst some research has implied a psychological mechanism of action (Grof et al., 1973; Grof & Halifax, 1977), theoretical conceptualisations in this area are yet to be fully established. Greater understanding of any underpinning mechanisms could enhance knowledge of psychological disorders in general and provide guidance for the development of future psychotherapeutic interventions. Nevertheless, the results of the studies within this review provide cause for optimism. The capability of single dose psilocybin interventions to

produce lasting improvements in difficult to treat disorders where treatment options currently fall short, is a novel discovery that should invite further research.

Research represented in the current review although positive is limited by the number of studies included and aspects of methodology which limit interpretation and generalisability. For example, this review not only encompasses a very limited number of studies, but the number and demographic of the participants within these studies were small and non-representative. Something which must be considered when evaluating the generalisability of findings. For this reason, findings should be re-evaluated as studies with more representative samples are published. Furthermore, all of the included studies used a cross-over design, which allowed for all participants to experience a psilocybin intervention, but prevented double blind assessment of efficacy after the cross over point (Leeds, 2020). Additionally, because of the nature of the psilocybin experience it is somewhat apparent to participants if they are receiving psilocybin or placebo, which allows for the possibility of expectancy effects (Leeds, 2020).

In conclusion, psychological disorders affecting patients with life threatening illness can have grave consequences. Novel treatments are needed as current treatment options are largely ineffective. The Psilocybin assisted interventions included in this review appear to provide important therapeutic benefits for highly complex and difficult to treat conditions. In order to truly understand the efficacy of psilocybin in this context will require not only further research, but research with carefully chosen and targeted methodologies that establish reliable protocols and robust scientific results.

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