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Review article

Classical psychedelics for the treatment of depression and anxiety: A systematic review

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ABSTRACT

Background: Depression and anxiety are prevalent psychiatric disorders that carry significant morbidity. Pharmacological and psychosocial interventions are used to manage these conditions, but their efficacy is limited. Recent interest into the use of psychedelic-assisted therapy using ayahuasca, psilocybin or lysergic acid diethylamide (LSD) may be a promising alternative for patients unresponsive to traditional treatments. This review aims to determine the efficacy and tolerability of psychedelics in the management of resistant depression.
Methods: Clinical trials investigating psychedelics in patients with depression and/or anxiety were searched via MEDLINE, EMBASE and PsychINFO. Efficacy was assessed by measuring symptom improvement from baseline, and tolerability was evaluated by noting the incidence and type of adverse effects reported. Risk of bias was assessed.
Results: Seven studies, with 130 patients, were analysed in this review. Three were conducted in patients with depression, two in patients with anxiety and two in patients with both. In a supportive setting, ayahuasca, psilocybin, and LSD consistently produced immediate and significant anti-depressant and anxiolytic effects that were endured for several months. Psychedelics were well-tolerated. The most common adverse effects were transient anxiety, short-lived headaches, nausea and mild increases in heart rate and blood pressure.
Limitations: At present, the number of studies on this subject is very limited; and the number of participating patients within these is also limited as the treatment under investigations is a relatively novel concept.
Conclusions: Though further evidence is required, psychedelics appear to be effective in significantly reducing symptoms of depression and anxiety and are well-tolerated.

1. Background

Depression and anxiety are two of the commonest psychiatric disorders worldwide (Ebmeier et al., 2006; Kessler et al., 2012). Depression is a multifaceted condition characterised by episodes of mood disturbances alongside other symptoms such as anhedonia, psychomotor complaints, feelings of guilt and suicidal tendencies, all of which can range in severity (Ebmeier et al., 2006). According to the World Health Organisation, depression affects over 350 million individuals and is the global leading cause of disability (Smith, 2014; Greenberg et al., 2015). The discovery of mainstream antidepressants has largely revolutionised the management of depression, yet up to 60% of patients remain inadequately treated (Penn and Tracy, 2012; Fava, 2003; Knoth et al., 2010). This is often due to the drugs' delayed therapeutic effect, side effects leading to non-compliance, or inherent non-responsiveness to them (Li et al., 2012; Pacher and Kecskemeti, 2004).

Similarly, anxiety disorders are a collective of aetiologically complex disorders characterised by intense psychosocial distress and other symptoms depending on the subtype (Thibaut, 2017). This review will focus on anxiety associated with life-threatening disease as only this subtype has been studied in terms of psychedelic-assisted therapy. This form of anxiety affects up to 40% of individuals diagnosed with a life-threatening disease like cancer (Mitchell et al., 2011). It manifests as apprehension regarding future danger or misfortune accompanied by feelings of dysphoria or somatic symptoms of tension, and often co-exists with depression (Die Trill, 2013). It is associated with decreased quality of life, reduced treatment adherence, prolonged hospitalisation, increased disability and hopelessness, which overall amounts to decreased survival rates (Brown et al., 2003; Ó et al., 2013; Jaiswal et al., 2014). Pharmacological and psychosocial interventions are commonly

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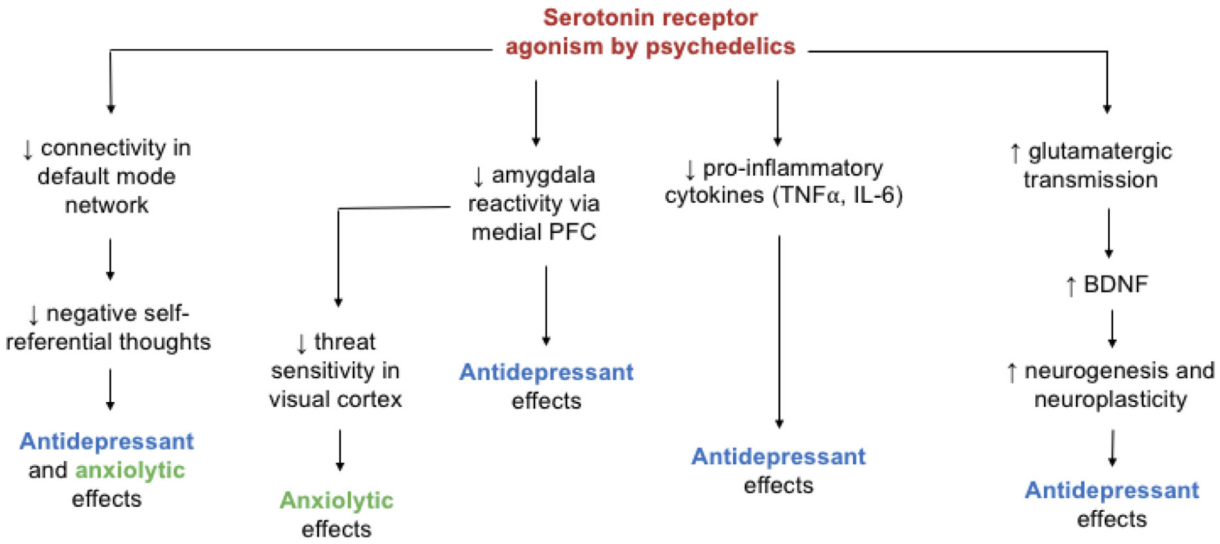

Fig. 1. Figure summarising the multiple neurobiological mechanisms mediating psychedelics' anti-depressant and anxiolytic effects, as a result of serotonin receptor agonism.

used to manage this type of anxiety, but their efficacy is mixed and limited such that they often fail to provide satisfactory emotional relief (Ostuzzi et al., 2015; Iovieno et al., 2011).

Recent interest into the use of psychedelic-assisted therapy may represent a promising alternative for patients with depression and anxiety that are ineffectively managed by conventional methods (Lemay and Wilson, 2008; Spiegel, 2015). The psychedelic treatment model consists of administering the orally-active drug to induce a mystical experience lasting 4–9 h depending on the psychedelic (Halberstadt, 2015; Nichols, 2016). This enables participants to work through and integrate difficult feelings and situations, leading to enduring anti-depressant and anxiolytic effects (Kurland, 1985). This is summarized in Fig. 1. The influence of context on the potential harms and benefits of this model has been heavily emphasised, such that accompanying psychotherapy, or at least a supportive environment, are key adjuncts (Hartogsohn, 2016; Kaelen et al., 2018).

Classical psychedelics like ayahuasca, psilocybin and lysergic acid diethylamide (LSD) are being studied as potential candidates. Psychedelics were first investigated as therapeutic agents in the 1960s, and although studies carried out then had several methodological shortcomings, they provided preliminary evidence that such compounds could be effective in treating conditions associated with psychological distress (Rucker et al., 2016). However, concerns over their safety in response to widespread non-medical use led to regulatory obstacles that halted research until recently, when conditions for safe administration were established (Johnson et al., 2008).

1.1. Ayahuasca

Ayahuasca is a botanical hallucinogen traditionally used by aboriginal populations for ritual and medicinal purposes, which contains the psychedelic N-dimethyltryptamine (Riba et al., 2003; dos Santos et al., 2012; Riba et al., 2001; Frecska et al., 2016). Studies in healthy volunteers and animals have elucidated its anti-depressant and anxiolytic properties, such as improving mood and reducing panic-related signs (Riba et al., 2001; Hilber and Chapillon, 2005; Farzin and Mansouri, 2006; Fortunato et al., 2009; Fortunato et al., 2010a, b; Santos et al., 2007). Additionally, longitudinal observational studies in ritual users have suggested that ayahuasca is not detrimental to psychological well-being and is rather associated with reduced incidence of mental health problems (Guimarães dos Santos, 2013; Bouso et al., 2012; Barbosa et al., 2016; Barbosa et al., 2012).

Like ayahuasca, psilocybin is a naturally occurring plant alkaloid found in some mushroom species. It is a prodrug of psilocin (4-hydroxy-dimethyltryptamine) (Passie et al., 2002). In animals, administration has been linked to cognitive flexibility, cortical neural plasticity, and antidepressant responses (Harvey, 2003; Vaidya et al., 1997; B et al., 2014; H et al., 2013). These effects have also been observed in healthy volunteers, with psilocybin causing sustained improvements in well-being and optimism (Griffiths et al., 2008). This compound has a well-established physiological and psychological safety profile, and has been rated one of the least harmful and possibly 'most beneficial' drugs of potential misuse by experts (Carhart-Harris and Nutt, 2013; H et al., 2004).

In contrast, LSD is a semisynthetic psychedelic (Passie et al., 2008). Accounts from the mid-twentieth century describe cancer patients undergoing psycho-spiritual epiphanies following LSD administration, resulting in sustained improvements in mood and anxiety symptoms (Kast, 1967; Richards et al., 1977). Compared to psilocybin, LSD is thought to be more emotionally intense with higher risk of inducing paranoia. Although this can result in severe anxiety and panic attacks at high doses, administration in the medical setting with appropriate psychological support normally safeguards against this (Das et al., 2016).

Whilst there is sufficient evidence to suggest that ayahuasca, psilocybin and LSD are potent anti-depressant and anxiolytic agents, the mechanisms underlying their therapeutic effects are not fully understood. The putative pleiotropic actions of these compounds can be explored from both a neurobiological and a psycho-spiritual perspective.

Biochemically, classical psychedelics are 5-HT_{2A} receptor agonists (Pierce and Peroutka, 1989). The serotonergic system has long been implicated in the regulation of complex emotional behaviours (Cools et al., 2008). For example, post-mortem samples of depressed and suicidal patients have increased cortical 5-HT_{2A} receptor expression (Pandey et al., 2002; Shelton et al., 2009), and sustained treatment with antidepressants has been associated with a reduction in 5-HT_{2A} receptor density (Gómez-Gil et al., 2004). The neurotransmitter serotonin is involved in the feedback inhibition of the amygdala via the medial prefrontal cortex (Fisher et al., 2009). Amygdala hyperactivity has been linked to depressive symptoms and normalisation has been demonstrated with antidepressant treatment (Sladky et al., 2015). Psychedelics, as serotonergic agonists, enhance amygdala inhibition; the resulting reduction in amygdala reactivity correlates with increases in positive mood (Kraehenmann et al., 2016; Carhart-Harris et al., 2012).

Increased serotonergic signaling by psychedelics also attenuates amygdala activation in response to threat-related visual stimuli (Kraehenmann et al., 2015). This is because the processing of threat-related visual stimuli can be modulated via feedback connections from the amygdala to the visual cortex (Kraehenmann et al., 2016). Increased amygdala reactivity is associated with augmented attentional focus on negatively valenced environmental or social stimuli. This effectively blocks out the processing of positive information since the capacity of the visual cortex to process multiple stimuli is limited (Disner et al., 2011). Accordingly, hyper-connectivity between the amygdala and visual cortex has been linked to increased threat processing and anxiety (Frick et al., 2013). Therefore, decreasing threat sensitivity in the visual cortex with psychedelic administration can lead to top-down suppression of negative stimuli, thus acutely shifting emotional biases from negative to positive stimuli (Kraehenmann et al., 2016). This has important therapeutic implications for anxiety and depression, as persistence of negative cognitive biases is a central feature of these disorders (Disner et al., 2011; K et al., 2014).

In addition to modulating amygdala reactivity, ayahuasca and psilocybin decrease connectivity within the default mode network (DMN) (Carhart-Harris et al., 2012; Palhano-Fontes et al., 2015). DMN hyper-connectivity has been linked to depression and anxiety, and may contribute to the negative self-referential thoughts present in these conditions (Sheline et al., 2009; dos Santos et al., 2016; Berman et al., 2011; Greicius et al., 2007). Therefore, by decreasing DMN activity, psychedelics may exert beneficial effects.

Another possible mechanism of therapeutic action is modulation of glutamatergic neurotransmission induced by $5HT_{2A}$ receptor agonism (Moreno et al., 2011). Higher cortical glutamate concentration indirectly stimulates the expression of brain-derived neurotrophic factor (BDNF), which is associated with increased neurogenesis and neuroplasticity (Vollenweider and Kometer, 2010; Ross, 2012; Baumeister et al., 2014). As depression has been linked to deficient neurogenesis and neurotrophic activity (Duman, 2004), normalisation of BDNF levels can have therapeutic effects (Baumeister et al., 2014).

Psychedelics may also improve symptoms of depression by reducing inflammation (Baumeister et al., 2014; Nau et al., 2013). $5\text{-}HT_{2A}$ receptor activation in immune cells can modulate the immune system, resulting in lower circulating levels of pro-inflammatory cytokines like tumor necrosis factor-α and interleukin-6 (Nau et al., 2013; House et al., 1994). As high levels of these have been associated with depressive illness, normalisation could produce antidepressant effects (Réus et al., 2015). The above processes are summarised in Fig. 1.

In addition to their neurobiological mechanisms, psychedelics also elicit highly meaningful and spiritually significant experiences that are conducive to their therapeutic potential (Griffiths et al., 2008; Griffiths et al., 2011, 2006). In clinical trials, up to 87% of participants have attributed increased life satisfaction or wellbeing to this psycho-spiritual experience (Ross et al., 2016). Furthermore, the intensity of the mystical experience seems to be predictive of long-term therapeutic efficacy (Ross et al., 2016; Griffiths et al., 2016; Carhart-Harris et al., 2018; Grof et al., 1973; Roseman et al., 2017). This is because it creates a 'window of opportunity' in which changes in unhealthy thoughts, emotions and behaviours can take place in a psychotherapeutic context. Specifically, the heightened state of consciousness induced by these drugs interrupts the rigid and pathological pattern of negative and compulsive thoughts present in anxiety and depression (dos Santos et al., 2016). This contributes to mental flexibility and leads to enduring positive changes in attitudes, moods, perspective, values and behaviour (Griffiths et al., 2008, 2011, 2006). Some have termed this phenomenon an 'inverse posttraumatic stress disorder-like effect' in which a highly significant and positive experience causes lasting beneficial changes, as opposed to a single traumatic event causing chronic distress (dos Santos et al., 2016; MacLean et al., 2011; Young, 2013).

Overall, psychedelics are able to provoke profound psycho-spiritual experiences as well as modulate neural circuits implicated in mood and affective disorders, to reduce their symptoms.

Therefore, administering these psychedelics as part of the treatment model could represent a new therapeutic approach for depression and anxiety, and potentially relieve patients that are unresponsive to traditional methods from suffering debilitating symptoms. Hence, the aims of this systematic review were twofold. Firstly, to determine the efficacy of classical psychedelics and consider their potential as treatment for depression and anxiety associated with life-threatening disease. Secondly, to assess their tolerability and adverse effects profile.

Until now, the use of psychedelics in clinical practice has been limited by concerns about the possible damage they may cause to the synaptic receptors in the short term, as well as implications for recovery in the long term. This cautious approach probably stems from a lack of understanding about their safety, therefore this review hopes to summarise all the evidence available and thus facilitate future decision-making regarding the use of classical psychedelics in medicine.

2. Methods

This systematic review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

2.1. Studies, participants and interventions

Only clinical trials (open-label, single-blind or double-blind) published in peer-reviewed journals were included. Manuscripts were limited to English with full publication access. Animal studies, experimental studies in healthy volunteers, posters, reviews, letters and case reports were excluded. Only studies in patients with an established diagnosis of anxiety and/or depression were included. Clinical trials investigating the effect of ayahuasca, psilocybin or LSD on anxiety and/or depression symptoms were included.

2.2. Outcome measures

Efficacy of the aforementioned psychedelics on anxiety and/or depression symptoms was measured as symptom improvement from baseline according to pre-defined validated scales. Also, tolerability of the compounds was considered by noting the incidence and type of adverse effects reported.

2.3. Search methods and extraction

The search was conducted in March 2018, utilising MEDLINE (Pubmed-Advanced Search), EMBASE and PsychINFO online databases. Additionally, manual search through reference lists of notable reviews was completed. The literature search was conducted separately by two authors (S.M. and M.A.).

The search terms used were: MeSH terms (depression, anxiety and psychedelics) and free text terms (psychedelic* OR psilocybin OR ayahuasca OR lysergic acid diethylamide AND depress* OR anxiety) in all databases. No date restrictions were applied. After duplicates were removed and screened via title and abstract, full-text articles were reviewed according to the eligibility criteria.

Details of author, publication date, sample size, study design, type of intervention and dosing protocol, characteristics of participants, response criteria and type of outcome measure were extracted.

Bias assessment

Each manuscript was investigated for bias, according to the Cochrane Risk of Bias tool (Higgins et al., 2011). The domains of bias were assessed and graded as below (Higgins and Green, 2018):

- Low risk: means to reduce bias are clearly defined and adequate.
- Unclear risk: means to reduce bias are unmentioned or its effects are unknown.

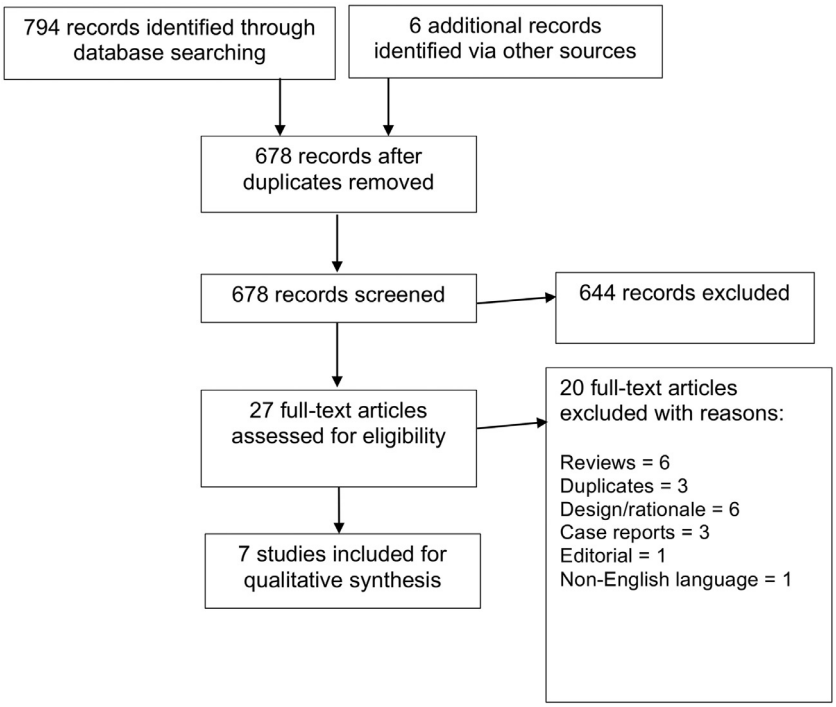

Fig. 2. PRISMA flowchart of article retrieval and exclusion with reasons.

- High risk: means to reduce bias are absent or inadequate.

Further details can be found in Supplementary Table 1. Then, results were tabulated and the overall bias risk was plotted.

2.4. Review of the mechanisms of therapeutic action

Considering the novelty of this research field, there were a low number of trials available and the level of heterogeneity among them hampered the ability to perform a meta-analysis. Therefore, psychedelics' possible mechanisms of therapeutic action were reviewed.

3. Results

3.1. Search results

The literature search yielded 794 database records (Fig. 2). 6 additional records were identified via manual searching. 116 duplicates were eliminated, and 678 titles were screened via abstract or title. Of these, 644 records were excluded and 27 full-text articles were assessed for eligibility. 20 articles were then further excluded, such that 7 studies were included in this review.

Studies were classified according to drug (ayahuasca, psilocybin or LSD) and disorder (depression and/or anxiety). Although study inclusion was based on a specific diagnosis, often both depression and anxiety symptoms were assessed in the trials as there is a high co-morbidity between them, especially in patients with a life-threatening disease (Thibaut, 2017). Of the included studies, one used ayahuasca (for major depressive disorder (MDD)), five used psilocybin (two for treatment-resistant depression (TRD), two for both anxiety and depression associated with life-threatening cancer, and one for anxiety associated with advanced-stage cancer), and one used LSD (for anxiety associated with life-threatening disease). Features of rating scales used to measure efficacy are summarised in Supplementary Table-2 (Jackson-Koku, 2016; Overall et al., 1962; Williams et al., 2008; Stern, 2014; Maier et al., 2019; Montgomery and Asberg, 1979; Morfeld et al., 2007; Hamilton, 1960; Rush et al., 2003; Nakonezny et al., 2010; Julian, 2011; Sereda and Dembitskyi, 2016; Kyriaki et al., 2001; Mcintyre et al., 2004). Details and main findings of the selected studies are summarised in Table-1, and Appendix A.

Despite the limited number of studies, the small sample sizes, the high degree of heterogeneity among studies, and the lack of control groups in the open-label trials, the results consistently showed that ayahuasca, psilocybin, and LSD had anti-depressant and anxiolytic effects.

3.2. Ayahuasca for major depressive disorder

An open-label trial assessed the anti-depressant potential of a single dose of ayahuasca (2.2 ml/kg) in 6 patients (2 males, 4 females) with MDD (Osório et al., 2015). Ayahuasca administration produced significant reductions of up to 82% in depressive scores between baseline and 1, 7 and 21 days after drug intake, according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS). Greatest score changes were observed for items relating to typical depressive symptoms such as depressed mood, feelings of guilt and suicidal ideation. Ayahuasca did not produce significant effects in the Young Mania Rating Scale (YMRS).

3.3. Psilocybin for treatment-resistant depression

An open-label feasibility study assessed the efficacy and safety of psilocybin in patients with TRD (defined as no improvement despite two adequate courses of antidepressants) (Carhart-Harris et al., 2016). 12 patients (6 males, 6 females) were administered two doses of psilocybin, an initial safety low dose (10 mg) and a subsequent treatment high dose (25 mg) 7 days apart. Psychological support was provided before, during and after each session.

Mean self-rated intensity of psilocybin experience was 0.51 and 0.75 for the low-dose and high-dose sessions, respectively ($p < 0.05$). Quick Inventory of Depressive Symptoms (QIDS) and Snaith-Hamilton Pleasure Scale (SHAPS) anhedonia scores significantly improved from baseline to 1 week and 3 months post-treatment, with maximum effect at 2 weeks. At 3-months follow-up, 58% of patients continued to meet

Table 1
Summary of clinical trials included in this systematic review assessing the anti-depressant and anxiolytic effects of ayahuasca, psilocybin, and LSD.
Abbreviations: BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; HADS, Hospital and Anxiety Depression Scale; HAMA-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Rating Scale for Depression; GRID-HAM-D, GRID Hamilton Rating Scale for Depression; LSD, lysergic acid diethylamide; MARDS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; QIDS, Quick Inventory of Depressive Symptomatology; SHAPS, Snaith-Hamilton Pleasure Scale; STAI, State Trait Anxiety Inventory (STAI-S is the state scale and STAI-T is the trait scale); TRD, treatment resistance depression.

Reference	N of patients /Diagnosis	Study design	Drug and dose	Main findings*
Osorio et al. *2015*	*n* = 6 Recurrent MDD	Open label	Ayahuasca 2.2 ml/kg	Reduction in HAM-D, MADRS, and BPRS scores between baseline and 1, 7 and 21 days after drug intake
Carhart-Harris et al. *2016*	*n* = 12 Moderate-severe unipolar TRD	Open label	Psilocybin 10 mg and 25mg	Reduction in QIDS, BDI, SHAPS scores relative to baseline at 1-week and 3-month follow-up
Carhart-Harris et al. *2018*	*n* = 12+8 Moderate-severe unipolar TRD	Open label	Psilocybin 10 mg and 25 mg	Reduction in QIDS, BDI, STAI-T scores relative to baseline at 1-week, 3- and 6-month follow-up
Griffiths et al. *2016*	*n* = 51 Anxiety and depression in patients with life threatening cancer	Double blind, randomised, cross-over trial (active control: 1 or 3 mg/70 kg psilocybin)	Psilocybin 22 or 30 mg/70kg	Reduction in GRID-HAM-D and HAM-A (& secondary STAI-S, STAI-T, BDI, HADS) at 5 weeks after each dosing session and at final 6-month follow-up
Ross et al. *2016*	*n* = 29 Anxiety and depression in patients with life threatening cancer	Double blind, randomised, cross-over trial (active control: 250 mg niacin)	Psilocybin 0.3 mg/kg	Reduction in HADS, BDI, STAI-S and STAI-T scores at day 1, week 2, 6, 7, 26 and 6.5-month follow-up
Grob et al. *2011*	*n* = 12 Anxiety associated with advanced-stage cancer	Double blind, randomised, cross-over trial (active control: niacin 250 mg)	Psilocybin 0.2 mg/kg	Reduction in STAI-T scores at 1 and 3-month follow-up, and in BDI scores at 6-month follow-up
Gasser et al. *2014*	*n* = 12 Anxiety associated with life threatening disease	Double blind, randomised, (active control: LSD 20μg)	LSD 2.9×10^{-3} mg/kg	Reduction in STAI-S anxiety scores at 2- and 12-month follow-up

* Further details of study findings are provided in Appendix A.

criteria for response (defined as ≥50% reduction in Beck Depression Inventory (BDI) score relative to baseline). Supplementary State Trait Anxiety Inventory (STAI) trait scale (STAI-T) scores also significantly improved with treatment.

A 6-month follow-up study (Carhart-Harris et al., 2018), in which a further 8 male participants were enrolled, found that the anti-depressant and anxiolytic effects of psilocybin were sustained and remained significant at 6 months post-treatment, according to QIDS, BDI and STAI-T.

3.4. Psilocybin for anxiety and depression associated with life-threatening cancer

Two double-blind, randomised, placebo-controlled cross-over trials assessed the effects of psilocybin on symptoms of depression and anxiety in patients with life-threatening cancer.

The first was in 51 cancer patients (26 males, 25 females) with a diagnosis of anxiety and mood disturbances (Griffiths et al., 2016). A low dose (1 or 3 mg/70 kg) or a high dose (22 or 30 mg/70 kg) of psilocybin was administered in a counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. Psilocybin produced significant anti-depressant and anxiolytic effects according to the Hamilton Anxiety Rating Scale (HAM-A) and GRID-HAM-D. 83% and 79% of patients continued to meet the criteria for response at 6 months according to HAM-A and GRID-HAM-D, respectively. These positive results were supported by significant improvements in a further 14 out of 15 outcome measures, such as BDI, STAI-state scale (STAI-S), STAI-T and the Profile of Mood States (POMS).

The second enrolled 29 patients (11 males, 18 females) with cancer and a diagnosis of adjustment disorder and/or generalised anxiety disorder (Ross et al., 2016). They were randomly assigned to receive treatment with single-dose psilocybin (0.3 mg/kg) or niacin (250 mg), both in conjunction with psychotherapy. Outcomes were assessed prior to crossover at 7 weeks, and up to 26 weeks after dosing session 2. Psilocybin demonstrated immediate and sustained reductions in anxiety and depression symptoms (measured by the Hospital Anxiety and Depression Scale (HADS), BDI, STAI-S and STAI-T) that remained significant until final follow-up. These effects were not mirrored in the niacin-first group prior to crossover. At the 6.5-month follow-up, anti-depressant (BDI) or anxiolytic response rates (HAD-A) were still as high as 60–80%.

3.5. Psilocybin for anxiety associated with life-threatening cancer

Another double-blind placebo-controlled cross-over trial assessed the effects of psilocybin in 12 subjects (1 male, 11 females) with advanced-stage cancer and a diagnosis of generalised anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety (Grob et al., 2011). They received oral psilocybin (0.2 mg/kg) or niacin (250 mg) on 2 separate dosing sessions, with subjects acting as their own control. STAI, BDI and POMS were administered regularly up to 6 months after the final session. All 12 participants completed the 3-month follow-up and 8 completed the 6-month follow-up (two subjects died and two became too ill to continue). Significant decreases were observed in STAI scores at 3-months follow-up, and in BDI scores at 6-months follow-up. No significant changes were observed in POMS scores.

3.6. LSD for anxiety associated with life-threatening disease

A double-blind, randomised, placebo-controlled study assessed the effects of LSD in 12 patients (8 males, 4 females) with anxiety associated with life-threatening diseases (cancer, chronic motor or inflammatory diseases)(108). All participants reported a STAI-S or STAI-T score greater than 40. The study included drug-free psychotherapy sessions and two LSD-assisted psychotherapy sessions. Volunteers

Table 2
Summary of adverse effects reported in each study and their respective incidence. A dashed line represents data not reported. *denotes statistical significance ($p < 0.05$)
Abbreviations: Aya, ayahuasca; BP, blood pressure; HR, heart rate; LSD, lysergic acid diethylamide; psi, psilocybin.

		Incidence of adverse effects							
Reference	**Drug**	Transient anxiety	Transient headache	Transient nausea	Vomiting	Transient paranoia	Illusions	Feeling cold	HR/BP
Osorio et al. *2015*	**Aya**	–	–	–	50%	–	–	–	↑
Carhart-Harris et al. *2016*	**Psi**	100%	33.3%	33.3%	0%	8.3%	–	–	–
Carhart-Harris et al. *2018*	**Psi**	75%	40%	25%	0%	15%	–	–	–
Griffiths et al. *2016*	**Psi**	26%	5.8%	15%	15%	2%	–	–	↑
Ross et al. *2016*	**Psi**	17%	28%	14%	–	7%	–	–	↑*
Grob et al. *2011*	**Psi**	–	–	–	–	–	–	–	↑*
Gasser et al. *2014*	**LSD**	22.7%	–	–	–	36.4%	72.7%	45.4%	↑

received either the experimental dose (200 μg) or the placebo-like dose (20 μg) of LSD during two dosing sessions 2–3 weeks apart, with an open-label crossover to 200 μg of LSD after the initial blinded treatment.

At 2-months follow-up, STAI-S was significantly reduced, with non-significant improvements in STAI-T. These trends were still evident after 12 months. Beneficial results were also observed in other outcome measures, including the 30-item European Cancer Quality of Life Questionnaire (EORTC-QLQ-30), the Symptom Checklist-90-Revised (SCL-90-R), and HADS.

3.7. Safety and tolerability

Overall, ayahuasca, psilocybin and LSD were relatively well-tolerated. Not all studies systematically assessed for adverse effects but the incidence of those reported are summarised below (Table 2). The commonest adverse effects were transient anxiety, headache and nausea. Nausea was sometimes accompanied by vomiting, especially with ayahuasca. LSD had the highest risk of paranoia and was the only psychedelic to cause illusions and feeling cold. All psychedelics caused mild increases in heart rate and blood pressure, which reached statistical significance in two of the studies with psilocybin ($p < 0.05$). All adverse effects resolved after acute drug effects subsided. There were no cases of hallucinogen persisting perception disorder or prolonged psychosis.

3.8. Bias assessment

The level of bias across the studies varied greatly, the highest being in the performance, selection and detection bias domains (Fig. 3a/b, Appendix B and Appendix C).

4. Discussion

Ayahuasca, psilocybin and LSD are classical psychedelics being studied as potentially therapeutic agents to reduce symptoms of depression and anxiety associated with life-threatening disease. Therefore, the present systematic review aimed to determine their efficacy, tolerability and mechanisms of action. The main findings were that psychedelics produced significant anti-depressant and anxiolytic effects with good tolerability response. These results, in addition to the putative mechanisms of action underlying their beneficial effects, will be further discussed below.

4.1. Therapeutic effects of classical psychedelics

In all studies, psychedelic administration caused statistically significant reductions in depression and anxiety symptoms. These findings corroborate the limited previous research conducted in animal studies and healthy volunteers, as well as anecdotal evidence describing improved mood and reduced feelings of apprehension following psychedelic administration (Riba et al., 2001; Hilber and Chapillon, 2005; Farzin and Mansouri, 2006; Fortunato et al., 2009; Fortunato et al., 2010a, b; Santos et al., 2007; Griffiths et al., 2008; Kast, 1967; Richards et al., 1977). These improvements were consistently observed across a variety of rating scales, and this is suggestive of a genuine therapeutic effect rather than a specific scale's tendency to show a positive effect. Moreover, the lack of equivalent symptom reduction in control patients indicates that the anti-depressant and anxiolytic effects can be attributed to psychedelic intervention. Participants also described the

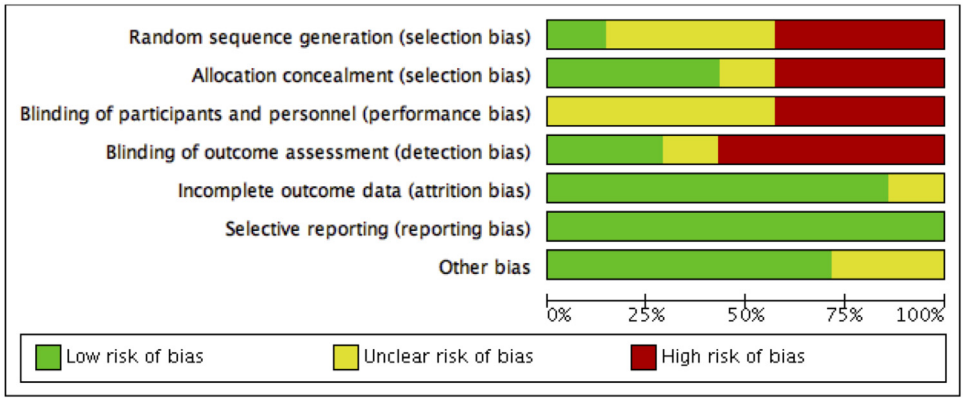

Fig. 3. a) Risk of bias in all included studies across the domains of selection, performance, detection, attrition, reporting and other bias. Presented as a percentage across the bias domains. 3b): Author's judgement on bias assessment per individual included study for each domain. Green (+) signifies low risk. Yellow (?) signifies unclear risk. Red (–) signifies high risk.
Abbreviations: BDNF, brain-derived neurotrophic factor; PFC, pre-frontal cortex; TNFα, tumour necrosis factor-α; IL-6, interleukin-6. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

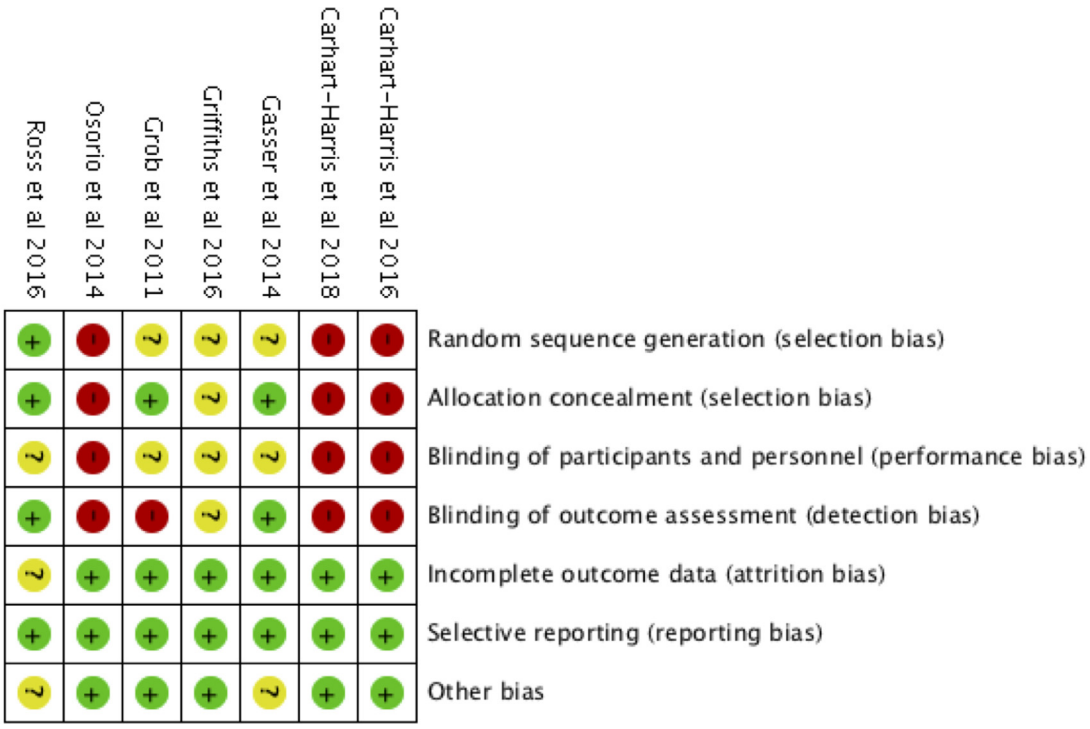

Fig. 3. (*continued*)

experience as spiritually meaningful, resulting in decreased disease-related demoralisation and hopelessness as well as improved quality of life (Ross et al., 2016; Griffiths et al., 2016; Grob et al., 2011; G et al., 2014).

Psychedelics' ability to provide acute symptom relief, within one day, is advantageous when compared to current antidepressants, which take several weeks to work. This is because antidepressants' delayed therapeutic effects can lead to non-compliance and contribute to increased morbidity (Machado-Vieira et al., 2010; Tylee and Walters, 2007). Moreover, since psychedelics' beneficial effects are maintained with impressive response rates for several months, this could imply that less frequent administration is required compared to typical pharmacotherapy for anxiety and depression. This, coupled to the fact that exposure to treatment is monitored, could help to overcome treatment-resistance stemming from non-compliance.

4.2. Safety and tolerability of psychedelic administration

Psychedelic treatment was generally well-tolerated. The commonest adverse effects included transient anxiety, headaches, nausea and vomiting. These were generally self-resolving except for three patients on LSD requiring benzodiazepines to counteract treatment-induced anxiety and/or emotional distress. One of these patients had received the placebo-like low-dose of LSD, suggesting that the need for tranquilising medication was also dependent on individual susceptibility in addition to dose-related drug factors. Vomiting was considered cathartic and thus an integral component of the therapeutic experience (Osório et al., 2015). Nevertheless, ways to manage it such as by pre-medicating with an anti-emetic can be explored. LSD-induced paranoia, illusions and feeling cold were predictable side effects and may be explained by its superior hallucinogenic strength compared to psilocybin and ayahuasca (Das et al., 2016; Schmid et al., 2015). All psychedelics also increased heart rate and blood pressure. The statistically significant elevations reported by Grob et al. and Ross et al. with psilocybin may have been confounded by niacin's ability to acutely lower blood pressure through vasodilation in the controls (Bays and Rader, 2009). Nevertheless, medical intervention was never required.

Previous research has shown these compounds to be relatively safe when used in medically-controlled environments (Guimarães dos Santos, 2013; Johnson et al., 2008; Nichols, 2004). They have no reported risk of dependence as daily administration causes serotonin (5-HT_{2A}) receptor downregulation, leading to rapid induction of tolerance (Nichols, 2004). In fact, they may even have anti-addictive properties (Bogenschutz et al., 2015; Johnson et al., 2014). Concerns over their impact on mental health have been challenged by large-scale population studies showing that psychedelic users have lower rates of psychological distress and suicidality compared to individuals who had never used psychedelics but an equivalent amount of other recreational drugs (Hendricks et al., 2015; Krebs and Johansen, 2013). Although the observational nature of these studies cannot establish causality, it suggests that psychedelics are not counter-productive over time.

5. Limitations

However, the findings of this research need to be considered in light of certain limitations. Only seven studies were included in this review, each with a small sample size (range 6–51 subjects), and a higher proportion of females, particularly Caucasian, among the cohort. These factors limit the generalisability of the results. Additionally, the significant level of bias present across the studies (Fig. 3a/b) affects the reliability of the conclusions. Three studies were open-label proof-of-concept studies, recruiting patients largely by self-referral who are possibly more inclined to endorse the positive effects of psychedelics. The fact that patients are aware of receiving the active drug could introduce expectancy bias, whereby they anticipate a beneficial effect. The double-blind randomised nature of the other four studies served to minimise this predisposition. However, even in these instances maintaining blinding proved challenging, as the drugs' psychoactive effects were florid, with patients experiencing a heightened state of consciousness with marked emotional accompaniments. Administering active placebos in the form of niacin or very low-dose psychedelic was an attempt to overcome this, as these would induce mild physiological and/or psychological effects but would be incapable of substantially facilitating the therapeutic process. When the psychedelic was

administered to both study groups, this also permitted study investigators to instruct patients in such a way as to reduce expectancy bias i.e. that everyone would receive the drug, albeit different doses. Nevertheless, it is likely that patients were usually unblinded by their experience on the active drug. Psychedelics are also known to promote suggestibility, which might have further enhanced positive outcomes (Carhart-Harris et al., 2015). The influence of these would be difficult to avoid in judging outcomes, especially since the scales used to measure efficacy are largely subjective. Therefore, at least inclusion of blinded clinician-raters is necessary in future studies. Additionally, more objective outcome parameters are possible and should be considered. For example, geolocation from mobile phones can be measured, as amount of time spent at home correlates with depression severity (Palmius et al., 2017). In cancer patients, treatment efficacy could also be reflected in patients' increased adherence to treatment or reduced need for narcotic pain-relief (Grof et al., 1973). Future trials could also address the role of expectancy and suggestibility by measuring and controlling for these variables. For example, patients could be asked about their pre-treatment expectations, and outcomes from self-referred patients could be compared with those from patients referred by clinicians. If expectancy and suggestibility are found to be influential, they could be treated as exploitable components of the treatment model rather than confounding variables (Carhart-Harris et al., 2016).

Limitations also exist in treating participants with grave somatic diseases in clinical trials. This is because improvements or deteriorations in their illness can impact psychological parameters independent of therapeutic intervention. Additionally, patients who become too ill to continue or pass away during the course of the experiment contribute to missing data. These factors can introduce bias in the results and affect the overall evidence base for psychedelics' therapeutic potential.

In terms of methodology, accepting only English citations with full publication access may have introduced a minor degree of publication bias (Pilkington et al., 2005). Moreover, the subjective nature of the Cochrane Risk of Bias tool may have caused inaccuracies in the bias assessment results. Considering that inter-assessor agreement can be inconsistent (Armijo-Olivo et al., 2014, 2012; Savović et al., 2014), inclusion of multiple reviewers would strengthen its validity as any discrepancies would be discussed.

5.1. Direction of future research

Before widespread use of psychedelics can be contemplated, there are several challenges that future research needs to address. Firstly, the aforementioned promising results need to be replicated in larger-scale trials with more participants. Ideally, these studies would also be longer in duration to determine long-term safety and efficacy. Although observational studies have provided some evidence that long-term psychedelic use is not harmful (Guimarães dos Santos, 2013; Bouso et al., 2012; Barbosa et al., 2016, 2012; Hendricks et al., 2015; Krebs and Johansen, 2013), the inherent limitations of these studies call for more robust long-term clinical trials to be carried out. It must be recognised that despite clinical interest in psychedelics resuming, regulatory obstacles still exist, therefore performing such research is not straightforward (Nutt et al., 2013). Nevertheless, future questions to be answered include whether repeated administration for long-term treatment is possible and how frequently it should be done.

Alongside these, optimum dosing must be determined, and target population identified. For example, Griffiths et al. reduced the psilocybin dose once the trial had commenced because there were concerns over the high dose causing too psychologically challenging experiences, and the low dose producing psychoactive effects, thus not serving as an appropriate placebo-like control (Griffiths et al., 2016). Protocol amendments like this are less than ideal, therefore defining correct dosing is key. Regarding target population, it is necessary to identify whether this treatment should only be considered for individuals with depression and anxiety that are non-responsive to other treatment methods, or whether it could be prophylactic for patients with severe symptoms. This is relevant as long-term antidepressant use can obstruct the potential therapeutic action of psychedelics (Bonson et al., 1996). As it is unclear whether a wash-out period would be enough to negate this effect, it seems worthwhile to avoid delaying psychedelic treatment too long. Additionally, treating cancer-related psychological distress with psychedelics is desirable, however in reality it is limited by a variety of exclusion criteria. Patients may also be reluctant to participate in such an intervention as high doses have sometimes been associated with transient episodes of psychological distress or anxiety (Griffiths et al., 2011, 2006, 2016).

It would also be necessary to determine an early proximal end-point to prove initial impact of treatment. As previously mentioned, several studies have shown that the intensity of the subjective mystical experience was correlated with long-term clinical outcomes (Ross et al., 2016; Griffiths et al., 2016; Carhart-Harris et al., 2018; Grof et al., 1973; Roseman et al., 2017; Pahnke, 1969; Carhart-Harris et al., 2017). Hence, this could serve as a useful early predictor of treatment response, but first it needs to be further explored and better defined.

Finally, cost-effectiveness must be established. The fact that psychological support or at least a supportive environment are required every time could be a major limitation (Johnson et al., 2008). In light of this, future research needs to determine the relative therapeutic contribution of psychotherapy as part of the treatment model. The results presented herein indicate that psychedelics caused comparable antidepressant and anxiolytic effects when administered with and without formal psychological intervention. Although the high degree of heterogeneity among studies limits this interpretation, it suggests that providing a supportive environment may be enough. Understanding whether this is the case is important, as minimising therapy requirement is desirable to reduce costs, however such therapy minimisation should not compromise treatment efficacy or jeopardise patient safety. Overall, the direct medical costs need to be balanced against the social and economic costs of illness (C-H et al., 2017).

6. Conclusions

The present review looked at classical psychedelics for the treatment of depression and anxiety associated with life-threatening disease. It found that, in a supportive setting, ayahuasca, psilocybin, and LSD consistently produced significant and sustained anti-depressant and anxiolytic effects. Psychedelic treatment was generally well-tolerated with no persisting adverse effects. Regarding their mechanisms of action, they mediate their main therapeutic effects biochemically via serotonin receptor agonism, and psychologically by generating meaningful psycho-spiritual experiences that contribute to mental flexibility.

Given the limited success rates of current treatments for anxiety and mood disorders, and considering the high morbidity associated with these conditions, there is potential for psychedelics to provide symptom relief in patients inadequately managed by conventional methods. The novelty of this research means that before psychedelics' wider-use can be contemplated, the results presented herein need to be replicated in larger studies with a longer follow-up to determine lasting efficacy and safety. Moreover, the role of psychotherapy as an adjunct to psychedelic treatment should be better explored. Ultimately, this would help to improve the care of patients suffering from depression and anxiety.

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CRediT authorship contribution statement

Silvia Muttoni: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Maddalena**

Ardissino: Investigation, Writing - review & editing. **Christopher John:** Conceptualization, Methodology, Resources, Supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.07.076.

Appendix A

Study results

Gasser et al.

Reduction in STAI-S anxiety scores at 2- and 12-month follow-up

STAI-S

- 2 months = mean score reduction from 53.1 (SD 4.7) to 41.5 (SD 3.2) ($p = 0.021$)
- At 12 months = mean score was 36.1 (p = NS)

Osorio

Reduction in HAM-D, MADRS, and BPRS scores between baseline and 1, 7 and 21 days after drug intake

HAM-D

- Average baseline score was 17.56 +/- 7.73
- Day 1: 62% reduction ($p = 0.01$)
- By day 7: had reached 72% reduction ($p = 0.01$)
- By day 14 (reduction in symptoms by 45% from baseline – not statistically significant $p = 0.11$)
- Day 21 further significant decrease in depressive symptoms $p = 0.01$

MADRS

- Average baseline score 23.5 +/- 11.14
- Day 1: $p = 0.003$
- Day 7: 82% reduction below baseline $p = 0.009$
- Day 14 significant increase in symptoms $p = 0.001$
- Day 21: significant decrease occurred $p = 0.002$

BPRS

- At 140 mins after administration, symptoms were significantly reduced (72% below baseline, $p = 0.02$) and remained so until day 7. After began to increase but still remained significantly lower than baseline values

Grob et al.

Reduction in STAI-T scores at 1 and 3-month follow-up, and in BDI scores at 6-month follow-up

- **STAI-T** sustained decrease was observed for the entire 6 month follow up, reaching statistical significance at 1 month ($p = 0.001$) and 3 months ($p = 0.03$) after the second treatment session
- **BDI:** reduction by almost 30% from the first session to 1 month after the second treatment session ($p = 0.05$). This difference was sustained and became significant at the 6 month follow up ($p = 0.03$)

Carhart Harris et al. 2016

Reduction in QIDS, BDI, SHAPS scores relative to baseline at 1-week and 3-month follow-up

QIDS

Baseline 19.2 (SD 2.0)

At 1 week score was 7.4 (SD 4.9) $p = 0.002$

At 3 months score was 10 (SD 6) $p = 0.003$

BDI

- Baseline 33.7 (SD 7.1)
- At 1 week 8.7 (SD 8.4) $p = 0.002$
- At 3 months 15.2 (SD 11.0) $p = 0.002$)

SHAPS

- Baseline 7.5 (SD 3.7)
- 1 week 1.4 (SD 2.7) $p = 0.002$

- 3 months 2.8 (SD3.7) $p = 0.002$

Carhart Harris et al. 2018

Reduction in QIDS, BDI, STAI-T scores relative to baseline at 1-week, 3- and 6-month follow-up

QIDS

- Relative to baseline, reduced at all 6 post treatment time points $p < 0.001$, max effect at 5 weeks (- 9.2, CI −11.8 to −6.6, $p < 0.001$)

BDI

- Significantly reduced at 1 week, mean reduction −22.7 (95% CI −17.6 to −27.8 $p < 0.001$) and at 3 months (mean reduction −15.3, CI −8.7 to −21.9, $p < 0.001$) and at 6 months (mean reduction −14.9, CI −8.7 to −21.1, $p < 0.001$)

STAI-T

- Significant reduction at 1 week (mean reduction −23.8, CI −16.5 to −31.1, $p < 0.001$), at 3 months (mean reduction −12.2, CI −6.1 to −18.3, $p < 0.001$) and at 6 months post treatment (mean reduction −14.8, CI −8.1 to −21.6, $p < 0.001$)

Griffiths et al.

Reduction in GRID-HAM-D and HAM-A (& secondary STAI-S, STAI-T, BDI, HADS) at 5 weeks after each dosing session and at final 6-month follow-up

This was a crossover trial

GRID-HAM

- 5 weeks after session 1: clinical response in 92% high dose group ($p < 0.001$), and symptom remission in 60% ($p < 0.01$)
- At 5 weeks after session 2 and at 6 months, clinical response and symptoms reduction apparent in high dose group but not statistically significant

HAM-A

- 76% achieved clinical response ($p < 0.001$) and 52% achieved symptom remission ($p < 0.01$)
- The only statistically significant ones were reduction in STAI-S anxiety at 5 weeks post session 2 ($p < 0.05$), HADS at 5 weeks post session 2 ($p < 0.05$).

Ross et al.

Reduction in HADS, BDI, STAI-S and STAI-T scores at day 1, week 2, 6, 7, 26 and 6.5-month follow-up

- Psilocybin first group deomnstrated significant reduction (within group) in anxiety and depression scores at every time point (HADS and BDI scores)
- 7 weeks post Dose 1, 83% of psilocybin group met criteria for antidepressant response (on BDI) versus 14% niacin group.
- 7 weeks post Dose 1, 58% of psilocybin group met criteria for anxiolytic response (on HAD A) versus 14% niacin group.
- At 6.5 month follow-up, after crossover, total anxiolytic and anti-depressant rates were 60–80%.

Appendix B

Risk of bias tables

Osorio et al. 2014 (Berman et al., 2011)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	High	Not randomised
Allocation concealment (selection bias)	High	Open label design
Blinding of participants and personnel (performance bias)	High	Not blinded
Blinding of outcome assessment (detection bias)	High	Not blinded
Incomplete outcome data (attrition bias)	Low	100% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Low	No evidence of other bias

Carhart-Harris et al. 2016 (Greicius et al., 2007)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	High	Not randomised
Allocation concealment (selection bias)	High	Open label design
Blinding of participants and personnel (performance bias)	High	Not blinded
Blinding of outcome assessment (detection bias)	High	Not blinded
Incomplete outcome data (attrition bias)	Low	100% completion rate, no missing outcome data

Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Low	No evidence of other bias

Carhart-Harris et al. 2018 (Moreno et al., 2011)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	High	Not randomised
Allocation concealment (selection bias)	High	Open label design
Blinding of participants and personnel (performance bias)	High	Not blinded
Blinding of outcome assessment (detection bias)	High	Not blinded
Incomplete outcome data (attrition bias)	Low	95% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Low	No evidence of other bias

Grob et al. 2011 (Baumeister et al., 2014)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomsied, insufficient information on process
Allocation concealment (selection bias)	Low	Third party distribution (pharmacist)
Blinding of participants and personnel (performance bias)	Unclear	Double blinded but possible that blinding integrity was compromised by drug's psychoactive effects
Blinding of outcome assessment (detection bias)	High	Raters were not blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low	100% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Low	No evidence of other bias

Griffiths et al. 2016 (Vollenweider and Kometer, 2010)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomised, insufficient information on process
Allocation concealment (selection bias)	Unclear	Not stated
Blinding of participants and personnel (performance bias)	Unclear	Double blinded, unclear whether blinding integrity was maintained
Blinding of outcome assessment (detection bias)	Unclear	Not stated whether raters/statisticians were blinded to treatment
Incomplete outcome data (attrition bias)	Low	90% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints were reported
Other bias	Low	No evidence of other bias

Ross et al. 2016 (Ross, 2012)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	Low	Blocked randomisation
Allocation concealment (selection bias)	Low	Third party distribution (pharmacist)
Blinding of participants and personnel (performance bias)	Unclear	Double blinded but possible that blinding integrity was compromised by drug's psychoactive effects
Blinding of outcome assessment (detection bias)	Low	Raters were blinded
Incomplete outcome data (attrition bias)	Unclear	79% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Unclear	Randomisation did not stratify for any demographic or clinical characteristics

Gasser et al. 2014 (Duman, 2004)

Bias	Judgement of risk	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomised, insufficient information on process
Allocation concealment (selection bias)	Low	Sequentially numbered containers
Blinding of participants and personnel (performance bias)	Unclear	Double blinded but possible that blinding integrity was compromised by drug's psychoactive effects
Blinding of outcome assessment (detection bias)	Low	Independent raters were blinded
Incomplete outcome data (attrition bias)	Low	82% completion rate, no missing outcome data
Selective reporting (reporting bias)	Low	All pre-specified endpoints reported
Other bias	Unclear	Uneven concurrent use of benzodiazepines during study between participants

Appendix C

Risk of bias assessment

Regarding random sequence generation, one trial clearly described this process (low risk). Three were referred to as “randomised” but lacked

specific description (unclear risk). The other three trials were not randomised (high risk).

Allocation concealment was present in three studies (using sequentially numbered containers or via third-party distribution). Two trials lacked specific description (unclear risk). Three studies were open-label (high risk).

In terms of blinding of participants and personnel, the open-label studies were classed as high risk. The remaining four studies were double-blinded but the drugs' psychoactive effects may have compromised blinding integrity (unclear risk).

Blinding of outcomes was present in two studies, which had blinded raters. Four studies had unblinded raters (high risk) and one study did not specify (unclear risk).

Bias resulting from incomplete outcome data was generally low risk as completion rates ranged from 79–100%, with 5 trials reporting ≥95% completion.

Additionally, all trials reported primary and secondary endpoints along with adverse effect data, thus at low risk of selective reporting.

Two trials were considered to have other sources of unclear bias. One did not stratify for demographic or clinical characteristics during randomisation(73), and the other had uneven use of benzodiazepines among participants during the study(75).

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