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REVIEW

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Psychedelics for treatment resistant depression: are they game changers?

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ABSTRACT

Introduction: A new era of treatment for adults with treatment-resistant depression (TRD), which involves psychedelic substances, is dawning. Emerging evidence indicates that psychedelics can exert antidepressant effects through multiple neurobiological and psychological mechanisms. However, it remains to be seen if these new treatments will revolutionize the treatment of TRD.

Areas covered: The present review focuses on the efficacy of serotoninergic psychedelics psilocybin, lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), ayahuasca, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) and mescaline (3,4,5-trimethoxyphenethylamine), as well as 3,4-methylenedioxymethamphetamine (MDMA), for TRD. A systematic search was conducted for psilocybin in TRD as emerging trials had not yet been subject to review. A narrative review summarized findings on other psychedelics.

Expert opinion: Psychedelic therapy has created a paradigm shift in the treatment of TRD, as it can maximize therapeutic benefits and minimize potential risks. Psilocybin holds promise as a potential game-changer in the treatment of TRD, with initial evidence suggesting a rapid antidepressant effect sustained for some responders for at least 3 months. Nevertheless, further adequately powered, double-blind, comparator-controlled trials are required to explore and clarify the mechanisms of action and long-term effects of psychedelics in TRD. Psychedelics also hold promise for other psychiatric conditions, such as bipolar depression and post-traumatic stress disorder.

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Psychedelics; psilocybin; major depressive disorder; treatment resistant depression; systematic review

1. Introduction

1.1. Major depressive disorder and treatment resistance

Major depressive disorder (MDD) is a psychiatric disorder characterized by a cluster of symptoms including low mood, anhedonia, hopelessness, feelings of guilt, lack of energy, poor concentration, suicidal ideation and changes in sleep and appetite. To meet the criteria of a major depressive episode, these symptoms need to persist for at least 2 weeks [1]. The 12-month prevalence of MDD is estimated to be around 5–6% [2,3]. MDD is associated with a considerable disease burden and is one of the leading causes of years lived with disability [4,5]. The total cost of depression in the United States was estimated to be more than $200 billion in 2010 [6].

There are various treatment options for MDD, including psychological therapies and pharmacological treatments. The National Institute for Clinical Excellence (NICE) guidelines recommend cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNIRs), as the first line of treatment for depression [7]. The remission rate following the first course of an SSRI (i.e. citalopram) is only 36.8%, whilst the remission rates are even lower in the second (30.6%), third (13.7%) and fourth course (13%) of treatment [8]. Although definitions may vary, treatment-resistant depression (TRD) is commonly defined as failure to respond to two or more adequate in dose and duration (at least 6 weeks) treatment courses for different classes of antidepressants [9]. TRD is associated with significant burden [10] and higher healthcare costs than non-TRD[11]. TRD also presents high suicide risk [12], with TRD patients reporting greater lifetime suicidal behavior and worse quality of life compared to those with non-TRD [13].

The treatment of TRD presents significant challenges. Current options for TRD include combinations of different antidepressants and augmentation strategies (e.g. addition of mood stabilizers, antipsychotics or thyroid hormone) [14,15]. These treatment options are associated with further side effects and complications. For example, in real-world settings, psychotropic drugs are associated with a higher severity of total and psychic side effects in TRD and non-responders when compared to responders [16].

A significant proportion of people with TRD continue to experience symptoms despite numerous courses of different treatments [17]. This highlights the need for novel treatment options in TRD, with the use of psychedelics being an emerging area of research in TRD. Recent meta-analyses have showed that psychedelics, and psilocybin in particular, produce rapid antidepressant effects in people with depression [18–20], although research in TRD is still limited.

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Article highlights

- Psychedelics may represent a new era of treatment in psychiatric disorders.
- Treatment-resistant depression (TRD) is prevalent and associated with a significant burden, highlighting a demand for novel treatments.
- Preliminary evidence suggests that psilocybin is effective and safe in TRD.
- Evidence on the efficacy of LSD, DMT, 5-MeO-DMT, ayahuasca, mescaline, and MDMA in TRD is limited.
- Psychological support is an important component of treatment with psychedelics which serves to maximize benefits and mitigate potential adverse reactions.
- Further research is needed to confirm efficacy and to understand the mechanisms and long-term effects of psychedelics in TRD.

1.2. Psychedelic substances

Psychedelics are a group of psychoactive substances that are associated with altered state of consciousness and perception [21]. There are two main categories of psychedelics; classic serotoninergic that primarily act on 5-HT_{2A} receptors, including psilocybin, N,N-dimethyltryptamine (DMT), ayahuasca, lysergic acid diethylamide (LSD), and atypical, such as 3,4-methylenedioxymethamphetamine (MDMA), that act on various receptors.

Psilocybin is the psychoactive alkaloid of some species of mushrooms, also known as 'magic mushrooms' and is considered a prodrug of psilocin [22]. Psilocybin exerts its effects through agonism of the serotonin 5-HT_{2A} receptors [23–25]. The 5-HT_{2A} receptors are necessary for the psychedelic experience, as the subjective effects of psilocybin seem to be blocked by 5-HT_{2A} antagonists [26]. Psilocybin also has affinity, albeit to a smaller extent, for several other serotonin receptors such as 5-HT_{1A} and 5-HT_{2C} [27,28]. Psilocybin has a short duration of action with the half-life of a 25 mg psilocybin estimated to be 108 min (range 66–132 min). The peak subjective effects occur 60–90 min after intake and last 4–6 h [29–31].

Ayahuasca has been historically used ceremonially, particularly in communities indigenous to the Amazon basin [32]. Ayahuasca is a psychoactive brew of two plants, Banisteriopsis caapi and Psychotria viridis, which contain β-carboline alkaloids (harmine, tetrahydroharmine, and harmaline) and DMT, respectively [33,34]. These β-carboline alkaloids are monoamine oxidase-A (MAO-A) inhibitors, whereas DMT is orally psychoactive only when it is ingested along with MAO inhibitors [34]. DMT is a classic serotoninergic psychedelic which is mainly an agonist of the 5-HT_{1A} and 5-HT_{2A} receptors [21,23].

5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a short-acting serotoninergic psychedelic which primarily acts as an agonist of the 5-HT_{1A} and 5-HT_{2A} receptors, but also has lower binding affinity for dopamine receptors and norepinephrine transporters [21,23,35].

LSD is primarily a 5-HT_{2A} receptor partial agonist and a 5-HT_{1A} receptor agonist but has also been shown to bind to 5-HT_{2C} receptors [36–38]. The use of LSD and psilocybin as recreational drugs became popular in the middle of the last century but were classed as a Schedule I drug in 1967, which prevented research in psychedelics [39].

Mescaline (3,4,5-trimethoxyphenethylamine) is a naturally occurring alkaloid, which has been used for millennia and is mainly found in the peyote cactus in Mexico [39,40]. Mescaline is an agonist of the 5HT_{2A} and 5-HT_{2C} receptors [41]. However, mescaline is a low potent psychedelic and a dose of about 300 mg is needed for a full-scale psychedelic experience [42].

3,4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy,' has been used for recreational purposes since the 1980s [43]. MDMA has high affinity for 5-HT receptors, and also binds to histamine, muscarinic and adrenergic receptors. It stimulates the release of monoamines, including serotonin, norepinephrine and dopamine [44,45]. In humans, 5-$HT2_{A/C}$ antagonist ketanserin significantly reduced the psychedelic effects (e.g. perceptual changes) of MDMA [46].

1.3. Antidepressant effects of psychedelics

Psychedelics are increasingly administered in human studies across various psychiatric disorders with promising findings [18,20,47]. A systematic review that included 19 studies found that 79.2% ($n = 335$) of patients with broadly defined unipolar mood disorder (i.e. MDD and dysthymia) showed improvement following psychedelic therapy with LSD or mescaline [48]. The doses of LSD (20–1500 µg) and mescaline (200–400 mg) as well as the therapeutic paradigms differed between studies. Psychedelics are thought to exert antidepressant effects in two ways: a) directly through serotoninergic agonism and b) indirectly through various mechanisms, including changes in other neurotransmission systems, neuroplasticity and modulation of inflammatory markers, cortisol, and brain activity. These mechanisms have also been implicated in the pathophysiology of depression [49–52].

1.3.1. Neurobiological mechanisms

1.3.1.1. Neurotransmission.. Classic serotoninergic psychedelics, such as psilocybin, LSD, mescaline and DMT (which is also included in ayahuasca) are thought to produce both direct and indirect antidepressant effects.

Agonism of the 5-HT_{1A} and 5HT_{2A} receptors may exert a direct antidepressant effect through the desensitization of these receptors, which is a hypothesized mechanism of SSRIs [36,53,54]. Nevertheless, the desensitization hypothesis in depression has received some criticism [55].

Serotoninergic psychedelics can also exert antidepressant effects indirectly through changes in other neurotransmission systems. For instance, psilocybin and LSD are thought to produce antidepressant effects through changes in glutamate and dopamine levels in the prefrontal cortex [36,56–58]. It should be noted that hallucinogenic 5-HT_{2A} receptor agonists may present a unique ability to modulate 5-HT_{2A} receptor signaling pathways (G protein-coupled receptors), compared to non-hallucinogenic agents [24,59,60]. MDMA, similarly to antidepressant agents, increases the levels of serotonin, dopamine and norepinephrine [44,45], which can produce antidepressant effects.

1.3.1.2. Neuroplasticity.. Serotoninergic psychedelics, such as psilocybin, LSD and DMT can induce changes in pyramidal neurons in the prefrontal cortex, including glutamate release and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation. This can enhance brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signaling, and thus promote synaptogenesis [61–63]. BDNF promotes neurogenesis [64] and is thought to play a role in the pathophysiology of depression and suicidality [50,65]. Neuroplasticity induced by psychedelics may also be mediated by intracellular 5-HT_{2A} receptors [66].

Compared to placebo, ayahuasca also increased BDNF levels in people with TRD and healthy controls [67], which was correlated with reduction in MADRS scores ($rho = -0.55$, $p < .05$). It has also been suggested that serotoninergic psychedelics may possess a unique ability to promote plasticity compared to other serotoninergic agents [66].

1.3.1.3. Cortisol levels and inflammation.. Dysregulation in the serotonin system is associated with alterations to cortisol levels. It is hypothesized that, because psychedelics such as psilocybin can result in a spike in cortisol levels, the spike may activate the executive control network, resulting in increased control over emotional processing and negative thoughts [68]. This may potentially result in a mild antidepressant effect. Galvao et al. [69] report that although at baseline participants with TRD presented blunted awakening salivary cortisol response, 48 h following ayahuasca their cortisol response was comparable to the control group. However, cortisol levels were not associated with severity of depressive symptoms [69]. Similar increases in cortisol levels have also been observed in healthy adults following the administration of other psychedelics, such as psilocybin [70], LSD [71], MDMA [72], 5-MeO-DMT [73], as well as fluoxetine and citalopram [74,75]. Nevertheless, cortisol levels are not always associated with response to antidepressants, and further research is therefore necessary [76,77].

Although research is still limited, psychedelics seem to possess anti-inflammatory properties, which may be attributed to agonism of the $5HT_{2A}$ receptors [78]. Ayahuasca was found to reduce C-reactive protein (CRP) levels following administration in people with TRD and healthy controls [79]. Interestingly, these changes in CRP were correlated with reduction in MADRS scores ($rho = 0.57$, $p < .05$).

1.3.1.4. Modulation of brain activity.. In people with TRD, psilocybin decreased cerebral blood flow (CBF) in temporal cortex regions, including the amygdala. Decreased amygdala CBF correlated with reduction in depressive symptoms ($r = 0.59$, $p = 0.01$) [80]. This is in line with existing research which indicates increased activity in the amygdala in depression [81]. Psilocybin was associated with increased ventromedial prefrontal cortex resting-state functional connectivity (RSFC) with the bilateral inferior-lateral parietal cortex, which predicted treatment response at 5 weeks [80]. In people with recurrent depression, ayahuasca was associated with increased blood perfusion in brain regions implicated in mood regulation, such as the left nucleus accumbens, right insula, and left subgenual area [82].

1.3.2. Psychological mechanisms of psychedelics

Historically, the psychological state associated with the psychedelic experience was believed to 'model psychosis' and was therefore approached with both interest and suspicion [83]. Newly emerging research has supported the hypothesis that the immediate and enduring psychological effects of psychedelics are associated with improvements in depressive symptomology [84].

It is believed that components of the psychological state induced by psychedelics allow psychotherapeutic patients to engage in new thinking patterns, facilitating the therapeutic process and outcomes [85]. Other potential mechanisms include emotional breakthroughs [86], enhanced emotional empathy [87,88], ego dissolution [89] and increased feelings of trust [87]. These may further differentially facilitate the therapeutic process, as well as directly targeting symptoms of TRD.

Another psychological outcome of interest for TRD is strongly held negative biases. For example, psychedelics are associated with a decrease in the processing of negative emotional stimuli [87,90]. Carhart-Harris and Friston [91] proposed an influential formulation for the actions of psychedelics in psychiatric disorders known as relaxed beliefs under psychedelics (REBUS) [91]. The formulation unifies neurobiological and psychological processes and argues that, when administered in sufficient doses, psychedelics have the potential to dysregulate the neurological systems encoding beliefs and habits [91]. It is argued that this could facilitate their psychological therapeutic effectiveness in psychiatric disorders characterized by rigid ruminations, such as TRD [92]. However, REBUS remains a largely hypothetical model and requires further investigation and clarification [93].

For centuries, psychedelics have been used to experience a self-transcendent and mystical or spiritual state [94]. This state was reported as having substantial personal and psychological meaning in recipients lives when induced by psilocybin [95]. A previous systematic review suggested that mystical experiences were a significant predictor of improved therapeutic outcomes [20]. However, mystical experiences are difficult to measure and subject to a range of biases, as they often rely on self-reports from recipients participating in religious and spiritual events, arguably reducing their credibility. It has been hypothesized that mystical experiences could simply act as a biomarker of 5-HT_{2A} receptor activation. Therefore, any association could be correlational rather than causal and therefore not necessary for enduring therapeutic effects [96]. Nevertheless, further research is needed to explore these psychological mechanisms in TRD populations.

2. Rationale

Over the past decade, there has been a resurgence of clinical research into the antidepressant effects of psychedelics and especially psilocybin. There are a few studies that have explored the effects of psilocybin in MDD, with initial evidence

from systematic reviews suggesting that psilocybin is effective and well-tolerated [20,48,84]. Although only a few published studies have assessed the efficacy of psychedelics in TRD, early evidence is promising.

This review will focus on classic serotoninergic psychedelics, as well as MDMA due to its high affinity for 5-HT, as newly emerging research indicates that serotoninergic psychedelics could hold great promise for targeting TRD. Given the emerging nature of research on LSD, MDMA and ayahuasca in TRD, our preliminary literature search indicated that the volume of relevant, high-quality studies currently available may not be sufficient to support the rigorous criteria of a full systematic review. As such, we opted for a more exploratory literature review approach to provide a comprehensive overview of the existing findings.

Psilocybin for TRD has received special attention, with the first randomized controlled trial (RCT) published less than a year ago showing very promising findings [47]. Since there are no systematic reviews on the efficacy of psilocybin in TRD, we conducted a systematic search to summarize existing research.

3. Systematic review on psilocybin

3.1. Methods

Full details of the search are reported here, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [97]. A protocol of the review was pre-registered on International prospective register of systematic reviews (PROSPERO; CRD42023429969).

3.1.1. Eligibility criteria

Studies were eligible for inclusion if (i) adult human participants were assessed, (ii) the study design was a randomized controlled or open label trial, (iii) study participants had TRD, defined using an evidence-based and operational definition of no improvement despite two or more adequate courses, in terms of dose and duration (at least 6 weeks), of different classes of antidepressants [9,98].

3.1.2. Search strategy

Key search terms were entered into the following databases: MEDLINE, EMBASE, and PsycINFO (all dates from inception to June 2023). The reference lists of key papers were also hand searched to identify any further studies eligible for screening. The following search terms were used: ('psilocybin') AND ('Treatment-resistant depress*' OR 'Treatment resistant depress*' OR 'TRD' OR 'Major depressive disorder' OR 'depress*'). English papers with an available title and abstract were screened independently by two reviewers (RHT and MK) using Rayyan, an open-source review management software [99]. Reviewers were blinded to one another's selections and then unblinded to identify and discuss disparities and reach a consensus with the support of the senior author (AHY). Where full-text papers could not be identified, authors were contacted. This process was then repeated for the full-text screenings and data extraction. Data extracted included study design, dosage, outcomes, and population.

3.1.3. Analysis

Due to a paucity of clinical research, a quantitative meta-analysis was not considered appropriate. The synthesis without meta-analysis (SWiM) reporting guidelines [100] were used to guide and promote clear and comprehensive reporting of the narrative synthesis.

3.1.4. Risk of bias

Risk of bias (RoB) for included studies was independently assessed by RHT, DT, and MK, and any discrepancies were resolved by consensus with the senior author (AHY). Due to the present review including both randomized and non-randomized controlled studies, two RoB tools were employed, each designed to assess for studies using a different study design. The ROBINS-I tool [101] was used to evaluate RoB in non-randomized controlled studies, and the Revised Cochrane Risk of Bias Tool was utilized to assess randomized trials [102]. Studies assessed using the ROBINS-I tool received an overall rating of 'Low risk,' 'Moderate risk,' 'Serious risk' or 'Critical risk' of bias. Studies assessed using the Revised Cochrane Risk of Bias Tool received an overall rating of 'Low risk,' 'Some concerns' or 'High risk.'

3.2. Results

3.2.1. Study selection

The search resulted in 1343 records. As demonstrated in the PRISMA flow chart (Figure 1), after duplicates were removed, the titles and abstracts of 697 studies were screened for inclusion.

From these, four articles reporting on three studies were eligible for inclusion. Specifically, Carhatt-Harris et al. [103] is an updated and extended 6-month follow-up to Carhart-Harris et al. [30], with an increased sample size.

3.2.2. Study characteristics

Table 1 provides a summary of the key study characteristics.

All trials included participants with a diagnosis of TRD as confirmed using medical records or a Mini-International Neuropsychiatric Interview. All trials defined TRD as no response to two or more antidepressant medications within the current episode for more than 6 weeks [30,103] or 8 weeks or more [47,104]. Only one trial [104] included participants who were currently taking an SSRI.

3.2.3. Risk of bias

The RoB assessment is presented in the appendix (Table S1). All studies received a judgment of 'moderate risk', other than Goodwin et al. [47] which received a judgment of 'Some concerns'. However, due to a paucity of research, trials with varying study designs were included in the present review, and therefore different risk of bias assessment tools were used, limiting comparability of overall RoB judgments. Goodwin et al. [47] recruited a larger sample and employed double-blinding and a control condition. Therefore, the present review emphasizes the outcomes of this trial.

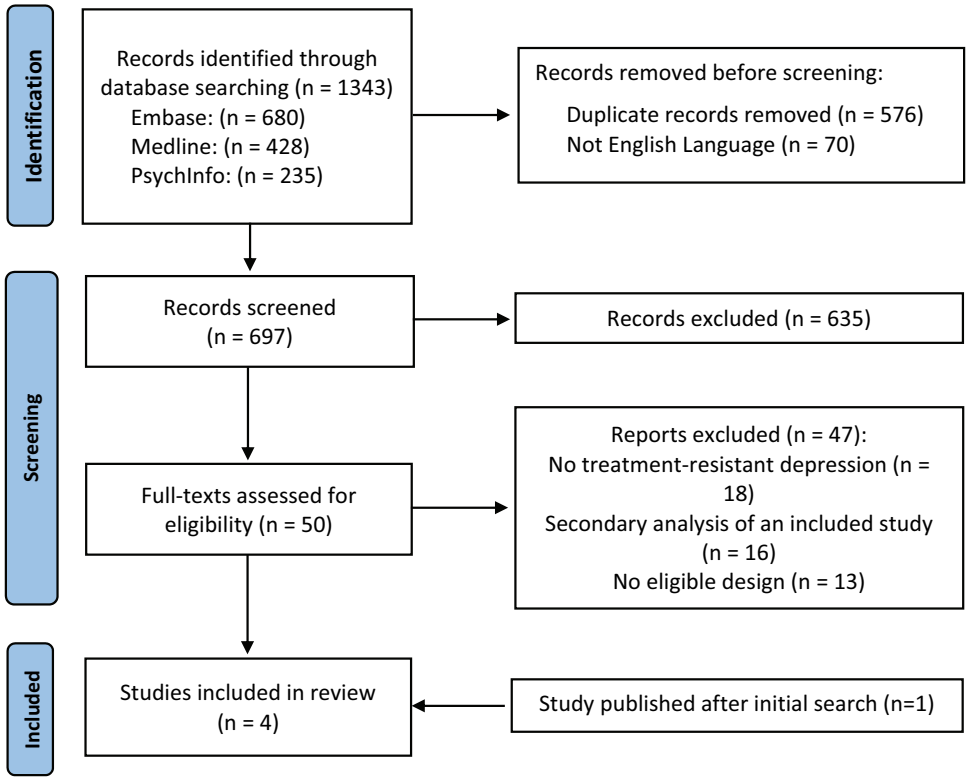

Figure 1. PRISMA flowchart.

3.2.4. Outcomes

The objective of the present review was to systematically identify, collate, and critically analyze the methods and outcomes of all published clinical trials administering psilocybin to patient groups with TRD. The primary outcome was a change in depressive symptom score as assessed using pre-/post-measurement on standard instruments such as the Montgomery-Åsberg Depression Rating Scale or equivalent. Three studies were identified and included. Only one trial [47] was a randomized controlled trial. All other trials were open label [30,103,104]. All trials included some form of psychological support.

3.3. Findings on psilocybin

A summary of findings for psilocybin trials in TRD is presented in Table 1. As the first psilocybin in TRD trial, Carhart and colleagues [30] recruited only 12 participants to their single-arm, open label feasibility pilot study. Due to the small sample size, the results use the Hedges' g formula to report effect sizes. Change in severity of depression was measured using the 16-item Quick Inventory of Depressive Symptoms (QIDS-SR16) from baseline to week 1 (marked reduction, Hedges' $g = 3.1$), week 5 (marked reduction, Hedges' $g = 2.7$) and 3 months (sustained reduction, Hedges' $g = 2.0$). A follow-up of this study with more participants reported a sustained reduction at 3 months (Cohen's $d = 1.5$) and 6 months (Cohen's $d = 1.4$) [103]. This trial was limited by the small sample size, the open-label design and the absence of a control condition. However, it was designed to act as a proof-of-principle study and did provide preliminary support for the efficacy and safety of psilocybin.

Goodwin et al. [47] is the largest trial included in the present review, recruiting 233 adults. The trial employed a double-blind study design, with participants blinded to their random allocation to one of the three treatment arms. Each group received a different dose of psilocybin: 25 mg ($n = 79$), 10 mg ($n = 75$), and an active control group who received 1 mg ($n = 79$). Changes in the severity of depression were assessed from baseline to week 3 using the Montgomery–Åsberg Depression Rating Scale (MADRS) total scores. A 25 mg dose of psilocybin but not a 10 mg dose, reduced depression scores significantly more than a 1 mg dose (95% confidence interval [CI]: −10.2 to − 2.9; $p < 0.001$). Across treatment arms, the least-squares mean change at week 3 were − 12.0 points in the 25-mg group, −7.9 in the 10-mg group, and − 5.4 in the 1-mg group. Although the study used a double-blind trial design, the quality of blinding in psychedelic studies can be challenged by the acute subjective psychedelic experience. This trial though is strengthened by its multi-site design, running across 12 countries, therefore resulting in a diverse sample.

Finally, Goodwin et al. [104] ($n = 19$) administered a 25 mg dose of psilocybin as adjunctive to an SSRI. Mean change from baseline to week 3 MADRS total score was − 14.9 (95% CI: −20.7 to − 9.2). The trial is limited by its open-label design, small sample size, and the absence of a control group. Despite these limitations, findings are meaningful: it is the first trial to administer psilocybin in combination with SSRIs to those with TRD and therefore provides preliminary evidence of SSRI withdrawal not being a prerequisite for psilocybin's antidepressant effects.

Table 1. Characteristics and findings of psilocybin studies on treatment-resistant depression.

Study	Population	Design	Dosing & support	Primary outcome	Main findings
[30]*	*N* = 12 HAMD >17 & failure of 2 ADMs of different classes with adequate dosage/duration (at least 6 weeks) in current episode	Open-label	Two sessions, 7 days apart: – 10 mg & 25 mg – 1 preparation session – Nondirective support during dosing session –2 integration sessions post-dosing	QIDS	Treatment effects on the QIDS: 1 week: Marked reduction, Hedges' *g* = 3.1 5 weeks: Marked reduction, Hedges' *g* = 2.7 3 months: Sustained reduction, Hedges' *g* = 2.0; Response: 50%, Remission: 42%
[103]*	*N* = 20 As above	As above	As above	As above	Treatment effects on the QIDS: 3 months: Sustained reduction, Cohen's *d* = 1.5 6 months: Sustained reduction, Cohen's *d* = 1.4 Relapse rate on responders at 6 months: 33%
[47]	*N* = 233 Failure of 2–4 ADMs with adequate dosage/duration (at least 8 weeks) in current episode	Double-blind RCT	One session per group: – 1 mg – 10 mg – 25 mg – Up to 3 preparation sessions – Nondirective support during dosing session – 2 integration sessions post-dosing	MADRS	MADRS reduction per group at 3 weeks: 1 mg: −5.4, Response: 18%, Remission: 8% 10 mg: −7.9, Response: 19%, Remission: 9% 25 mg: −12.0, Response: 37%, Remission: 29% Significant difference in MADRS reduction: – 1 mg <25 mg Sustained response (week 12): 1 mg: 10% 10 mg: 5% 25 mg: 20%
[104]	*N* = 19 HAMD >17 & failure of 2–4 ADMs with adequate dosage/duration (at least 8 weeks), including ongoing SSRI treatment, in current episode	Open-label	One session: – 25 mg, adjunct to an SSRI As above	As above	MADRS reduction at 3 weeks: −14.9 Response: 42%, Remission: 42%

Notes: ADM: Antidepressant medication; HAMD: Hamilton Rating Scale for Depression; QIDS: Quick Inventory of Depressive Symptomatology; MADRS: Montgomery–Åsberg Depression Rating Scale; RCT: Randomized Controlled Trial; TRD: Treatment-Resistant Depression.
*Studies using an overlapping sample; [103] is a 6-months follow-up to [30].

4. Findings on other psychedelic substances

4.1. DMT and ayahuasca

In an exploratory open-label phase 1 study, D'Souza et al. [105] administered 2 intravenous doses of DMT (0.1 mg/kg followed by 0.3 mg/kg) at least 48 h apart to 7 people with TRD. Participants reported a significant reduction in HAMD-17 scores 1 day after DMT, but only following the 0.3 mg/kg session.

One double-blind RCT has explored the efficacy of ayahuasca in TRD [106]. This RCT included 29 participants who received either a single dose of 1 ml/kg of placebo or ayahuasca containing 0.36 mg/kg of DMT. The placebo was designed to mimic the taste and color of ayahuasca. Findings indicate that ayahuasca was effective in reducing depression severity at day 7 compared to placebo (Cohen's *d* = 0.98). Nevertheless, remission rates did not reach statistical significance (*p*s>.05). The characteristics and findings of the studies are presented in Table 2.

Although these studies report significant reductions in depressive symptoms, they present various methodological limitations, including open-label design, small sample size and short follow-up, hence any findings should be interpreted with caution.

4.2. 5-MeO DMT

Reckweg et al. [107] conducted a combined phase 1 and 2 open-label trial to assess the antidepressant effects of 5-MeO-DMT in a vaporized formulation (GH001) in people with TRD. In phase 1, participants (= 8) received 12 mg and 18 mg of GH001, while in phase 2 (= 8) participants received of up to three increasing doses of GH001 (6 mg, 12 mg, and 18 mg) at least 3 h apart. Findings indicate a significant decrease in MADRS scores at 2 h, 1 day and 7 days following GH001 administration in all groups, whilst 87.5% (= 7) of participants in phase 2 study showed remission (MADRS ≤10) at day 7. In phase 1, the remission rates at day 7 were 50% (= 4) in the 12 mg group and 25% (= 2) in the 18 mg group (see Table 2).

4.3. LSD

No studies that assessed the effects of LSD in TRD or MDD were found. Holze et al. [108] recently published a randomized double-blind trial in 44 patients with anxiety, with or without a life-threatening ilness, which indicated significant reductions in the Hamilton Depression Scale 21-item version (HAM-D-21) (Cohen's *d* = −1.1, *p* = .0004) and Beck Depression Inventory (BDI) scores (Cohen's *d* = −.72, *p*=.02) 16 weeks following oral LSD administration (200 µg). In the pilot for this trial, which included people with anxiety associated with life-threatening diseases, the reported depression scores appear to be decreased 2 months following LSD administration (200 µg), although statistical significance was not assessed as depression was a secondary outcome [109].

4.4. Mescaline

Research on the antidepressant effects of mescaline is scarce. A cross-sectional naturalistic study in 452 participants found

Table 2. Characteristics and findings of psychedelic studies on treatment-resistant depression.

Study	Psychedelic	Population	Design	Dosing & support	Primary outcome	Main findings
[105]	DMT (Intravenous)	$N = 7$ HAMD >17 & failure of 2 ADMs with adequate dosage/duration, one of which in current episode	Open-label	Two sessions, fixed order, at least 48 h apart: – 0.1 mg/kg & 0.3 mg/kg – 1 preparation session – Non-directive support during dosing session – 1 debriefing session	HAMD	Next day effects on the HAMD: 0.1: Nominal reduction, not significant 0.3: Significant reduction, Hedge's $g = 0.75$ Significant difference in HAMD reduction: 0.1 mg/kg <0.3 mg/kg
[107]	5-MeO-DMT (Inhalation)	$N = 16$ MADRS >27 & failure of 2 ADMs with adequate dosage/duration or 1 ADM and 1 EBP in current episode	As above	*Phase 1 ($n = 8$; single dose)* One session per group: – 12 mg – 18 mg *Phase 2 ($n = 8$; individualized dose)* Up to three sessions, fixed order, same day, 3 h apart: – 6 mg, 12 mg & 18 mg	*Phase 1*: Safety MADRS *Phase 2*: MADRS	*Phase 1*: 5-MeO-DMT was well tolerated. MADRS reduction at day 7: 12 mg: −21.0, Remission: 50% 18 mg: −12.5, Remission: 25% *Phase 2*: MADRS reduction at day 7: −24.4, Remission: 87.5%
[106]	Ayahuasca (Liquid)	$N = 29$ HAMD >17 & failure of 2 ADMs of different classes with adequate dosage/duration in current episode	Double-blind RCT	One session per group: – 1 ml/kg ayahuasca (0.36 mg/kg of DMT) – 1 ml/kg placebo – Non-directive support during dosing session – 1 debriefing session	HAMD	Significant difference in HAMD reduction at day 7: Ayahuasca < placebo, Cohen's $d = 0.98$

Notes: 5-MeO-DMT: 5-methoxy-N,N-dimethyltryptamine; ADM: Antidepressant medication; DMT: N,N-Dimethyltryptamine; EBP: Evidence-based psychotherapy; HAMD: Hamilton Rating Scale for Depression; MADRS: Montgomery–Åsberg Depression Rating Scale; RCT: Randomized Controlled Trial; TRD: Treatment-Resistant Depression.

that 86% ($n = 184$) of those with self-reported depression stated that their condition improved following mescaline use [110]. However, this study presents important limitations, including cross-sectional design and absence of psychometric assessment and diagnosis validation of depression. The lack of high-quality studies does not allow us to comment on the potential usefulness of mescaline for TRD.

4.5. MDMA

Current evidence on the efficacy of MDMA in depression is limited, with existing RCTs focusing on post-traumatic stress disorder (PTSD) and distress in people with life-threatening conditions.

A phase 3 RCT [111] administered doses ranging from 80-180 mg of MDMA combined with therapy session to 46 participants with severe PTSD. MDMA therapy significantly improved depression assessed using the BDI II ~18 weeks after baseline compared to placebo (Cohen's $d = 0.67$, 95%CI: 0.22, 1.12). Similarly, a cross-over RCT in PTSD ($n = 28$) reported that participants who received a single dose of 40 mg-125 mg of MDMA had reduced depression scores at 12-month follow-up, albeit due to the cross-over design, there was no control group for comparison at this time-point [112]. On the contrary, one small RCT ($n = 18$) found that although MDMA-assisted psychotherapy for distress related to life-threatening conditions improved depression scores, this effect was not superior to placebo [113].

A couple non-RCT studies have also found significant associations between MDMA use and improvement in depressive symptoms. One small study reported that participants with high depression scores ($n = 20$) (i.e. 63 or more on the depression dimension of brief symptom inventory) experienced an immediate decrease in depressive symptoms following ecstasy use in a social gathering [114]. In addition, although the direction of causality is undetermined, an observational study in a large sample of US adults ($n = 213{,}437$) also found that, like psilocybin, a lifetime use of MDMA is associated with reduced odds of depressive episodes [115].

5. Importance of psychological therapy

Across all of the psychedelic substances discussed, contemporary administration of psychedelics usually involves psychotherapeutic support. It is argued that psychological support is integral to understanding the therapeutic efficacy of psychedelics. Components integral to the experience of psychedelic-assisted therapy include the therapist encouraging and guiding an appropriate and supportive state of mind (set) and environment (setting) [116]. Non-pharmacological variables, including variables measuring components of set and setting, were found to predict how 261 healthy volunteers experienced psilocybin [117].

The psychological effects of psychedelics, such as enhanced trust, feelings of closeness to others, and increased emotional empathy, may promote the delivery and efficacy of psychotherapy [87,88]. Similarly, pre-existing variables might mediate treatment effects and be important for tailoring therapy. Modlin et al. [118] proposed that openness, motivation and affective tolerance, as well as therapeutic alliance and safety factors, can influence readiness to psilocybin therapy and subsequent treatment outcomes.

Secondary analysis of a recent double-blind randomized controlled trial administering psilocybin in a population with depression found that the strength of the therapeutic alliance predicted greater emotional-breakthrough and mystical-type experiences. A weaker alliance ahead of the second psilocybin session predicted higher final depression scores [119]. Interestingly, this trial employed a new psychedelic therapy

model, called 'Accept-Connect-Embody' (ACE), aiming to use the development of a non-directive, open, and safe set and setting to allow the emergence of unconscious psychological phenomena, such as memories and emotions.

Common features of psychotherapy include the exploration and gaining of meaning, emotional skills, and bonds. It has been argued that these are central to the often vulnerable and emotionally heightened experience of a psychedelic experience. Therefore, many existing psychotherapies could be employed to effectively guide and facilitate the administration of psychedelics and bolster the therapeutic effects [120]. However, since most psychedelic studies do not employ specific and formal psychotherapeutic approaches, further research is required before useful comparisons can be drawn between therapies.

6. Limitations of psychedelic research

Although preliminary evidence on the efficacy of psychedelics is promising, high quality RCTs in TRD are still scarce. To our knowledge, no RCTs have explored the efficacy of LSD, DMT, 5-MeO-DMT, mescaline and MDMA in TRD, whilst only one RCT on psilocybin for TRD had a large sample size ($n = 233$ [47]). The RCT that assessed ayahuasca for TRD [106] had a small sample size ($n = 29$) and a short follow-up period of only 7 days.

Most existing studies in psychedelics for TRD were open-label. Non-randomized open-label studies with no control group present various methodological limitations, including expectancy effects and selection bias. These may lead to an over-representation of participants with positive attitudes toward psychedelics and inflate effect sizes. Finally, none of the RCTs for TRD included an antidepressant as a comparator. Therefore, it is unclear whether psychedelics are superior to other antidepressants in TRD. However, a phase 2 RCT comparing the efficacy of psilocybin versus escitalopram in MDD ($n = 59$) found that change in depressive scores at 6 weeks was not significantly different between the two groups [121]. It is also unclear whether the antidepressant effects of psychedelics in TRD are sustained long-term. Existing studies on psychedelics for TRD included a very brief follow-up period of a few days, with the exception of one RCT in psilocybin which had a 3-month follow-up [47].

Integrity of blinding is also a crucial issue in psychedelics. Concealing the allocation group is almost impossible in psychedelic research, due to the pronounced subjective effects of these drugs; a study which involved psilocybin-assisted psychotherapy reports that 93.6% of participants correctly guessed their allocation group [122]. However, this is not unique to psychedelics, as in most RCTs assessing psychological interventions masking participants to their allocation group is also impossible. Failure of blinding could lead to expectancy bias [123,124]. This challenge can be mitigated by having independent and blinded raters.

Finally, there has been substantial disagreement and uncertainty surrounding the optimal delivery of psychedelics and the role of both the psychedelic experience and psychotherapy for the efficacy of these substances. Further, the existing literature has varied considerably in its definitions and delivery of appropriate set, setting, dosage, and outcomes measured [94]. This can complicate drawing clear conclusions and collating data appropriately.

7. Risks and safety

There is a distinction between the risks associated with recreational use of psychedelics and medical use in a controlled supervised environment. Current research suggests that the use of serotoninergic psychedelics in controlled environments is relatively safe and does not lead to dependence [21,48]. Bender and Hellerstein [125] recently reviewed the second-wave clinical data of classical psychedelics to assess their risk-benefit profile. Across all data from all included classical psychedelics, no serious adverse events (SAEs) were reported across trials in classic psychedelics, with 11 of 14 included trials administering psilocybin.

Furthermore, two of the papers included in the present review [30,103] on psilocybin for TRD report that psilocybin was generally well tolerated, and no SAEs or unexpected adverse events (UAEs) occurred. Adverse reactions included transient headache, anxiety, nausea and thought disorder. Goodwin et al. [47] report that SAEs on day 1 were reported by 4% of the participants in the 25-mg group, 8% of participants in the 10-mg group, and 1% in the 1 mg group . From day 2 up to week 3, SAEs reported by 9%, 7% and 1% of participants in the 25-mg 10-mg and 1-mg group, respectively. These included suicidal ideation, self-injury and hospitalization for depression. Goodwin et al. [104] report that 2 participants had increased blood pressure which was considered severe and possibly related to psilocybin, and one participant experienced chest heaviness. These reactions were treated with clonidine. Although none of the included studies compared psilocybin with other medications, this increase in adverse events (AEs) may not be specific to psilocybin. For instance, a trial that compared psilocybin with escitalopram in depression reported the number of participants reporting AEs was similar in the two groups (87% and 83%) [121]. Studies that included DMT, 5-MeO-DMT, LSD and ayahuasca also report mostly mild AEs [105,107,109], with the exception of one SAE following LSD (anxiety and delusions) [108] and another SAE following DMT, which involved significant asymptomatic bradycardia and hypotension [105]. Palhano-Fontes et al. [106] mention that participants had a psychiatric evaluation following ayahuasca dosing and 4 of the 14 participants had to remain in the hospital ward for a week, without providing further details.

The potential long-term risks associated with psychedelics are poorly understood and warrant further research. There is also very little research exploring and reporting on the adverse reactions and risks associated with psychedelics and serious psychiatric disorders. For instance, it is not yet well determined whether psilocybin therapy for depression can increase the risk of mania or psychosis [126]. It is also unclear to what extent the increased suicidality and self-harming reported in studies [47] is attributed to psychedelics or TRD per se.

A potential adverse effect is hallucinogen persisting perception disorder (HPPD). HPPD is a rare DSM-5 disorder in

which a person who has had a prior exposure to a hallucinogen drug experiences a total or partial recurrence of visual hallucinations or perceptual disturbances long after the exposure [1]. Although DSM-5 suggests a prevalence of 4.2% among individuals who use psychedelics, HPPD has not yet been documented in contemporary psychedelic studies. HPPD may be partially associated with preexisting psychiatric comorbidity, such as individual or family history of anxiety [127]. As newly emerging clinical trials diversify patient groups and administer psychedelics to those with more serious psychiatric symptomatology, it will be important to consider a possible increase in the occurrence of these more serious and longer enduring AEs.

Nevertheless, there are notable risks when psychedelics are used as recreational drugs in uncontrolled settings without a therapist. For instance, in online survey data from 1993, 39% of individuals who had tried psilocybin mushrooms outside of clinical settings rated the experience among the top five most challenging of their life and 10.7% reported having put themselves or others at risk of physical harm [128].

Baseline traits and biomarkers are being studied and could be used to prevent adverse reactions [129–131]. The evidence suggests that targeting psychological processes and administering psychedelics in a controlled environment alongside psychological therapy are critical components of psychedelics research and can further minimize potential risks.

8. Conclusions

The present paper reviewed serotoninergic psychedelics, with the main focus on psilocybin for TRD. Preliminary evidence provided by one double-blind RCT and two open label studies suggest that psilocybin produces significant and sustained antidepressant effects in TRD. One RCT on ayahuasca also reported promising findings, although based on a small sample and short follow-up. Although initial findings are encouraging, further adequately powered RCTs with longer follow-ups are required to establish the potential efficacy of psychedelics for TRD.

9. Expert opinion

9.1. Key findings and weaknesses

Over the past decade, there has been a resurgence of psychedelics in psychiatric research, with psychedelics representing a new era in the treatment for TRD.

Psilocybin in particular may become a new treatment option for TRD, with preliminary research suggesting rapid antidepressant effects that sustained for at least 3 months and remission incidence of 29% at 3 weeks [47]. These findings are very encouraging considering that the participants included had not responded to at least 2 antidepressant agents. Two open-label feasibility trials have also reported meaningful results. Furthermore, antidepressants may take several weeks to produce a significant effect [132], thus rapid antidepressant agents such as psilocybin could have real advantages for TRD. Due to the lack of evidence on other serotoninergic psychedelics (i.e. ayahuasca, DMT, 5-MeO-DMT, mescaline, MDMA), psilocybin currently seems to be the most promising one for TRD. Nevertheless, existing studies present various methodological limitations including blinding concerns and expectancy effects. However, these are not unique to psychedelics, as in most studies involving psychological interventions participants are also aware of their allocation group. Evidence on other serotoninergic psychedelics, apart from psilocybin, for TRD is limited. One small sample RCT reported that ayahuasca had significant antidepressant effects in people with TRD, whilst double-blind RCTs on LSD, DMT, 5-MeO-DMT, MDMA and mescaline for TRD have yet to be published. In addition, the psychological, pharmacological and neurocognitive mechanisms of psychedelics for TRD are yet to be clearly delineated. Further research is needed to explore the long-term effects of psychedelics on TRD.

Psychological variables, such as mind-set, setting and openness also seem to influence the psychedelic experience [117,129–131] and targeting those may improve treatment outcomes. Due to the importance of psychological factors, psychedelic studies often involve psychotherapeutic support [30,47,104,111]. The emphasis on psychedelic-assisted psychotherapy constitutes a paradigm shift in depression research, and it could maximize the therapeutic benefits of psychedelics and mitigate risks.

It could be argued that the main effects of psychedelics are induced by the integrated psychological support. Nevertheless, in most studies, psychological support only includes sessions that aim to prepare participants, as well as guide them during and after their psychedelic experience. Therefore, this alone is unlikely to be responsible for the observed antidepressant effects.

Psychedelic use for TRD also presents limitations that need to be considered. Psilocybin is known to be a very short-acting substance, the half-life of which is estimated between 66–132 min [31]. Given the lack of longitudinal research, it is possible that relatively frequent psilocybin administrations would be required to maintain the antidepressant effect. Long-term clinical issues remain to be investigated and existing pharmacological options such as antidepressants require daily administration. Although in psychedelic studies participants are often asked to discontinue antidepressant treatments, preliminary findings are suggesting that this is not required [104]. Finally, ayahuasca has a diverse pharmacological profile, due to being a brew of different psychoactive substances including DMT and β-carboline alkaloids that are MAO-A inhibitors. This makes it challenging to control its consistency and potential drug interactions. MAO inhibitors can interact with other psychotropic substances, such as SSRIs [133] and result in adverse reactions. This can render the therapeutic use of ayahuasca more problematic and challenging to research compared to other classic psychedelics, such as psilocybin.

Although initial outcomes look promising and attitudes are shifting, the potential effectiveness of psychedelics may depend on individual traits. For example, personality traits and temperament may mediate effects. More specifically, it has been reported that openness to experience predicted well-being changes following psychedelic use, whilst positive mind-set was associated with less challenging psychedelic experiences [130,131]. Targeting these may optimize

Table 3. Currently registered psilocybin studies on treatment-resistant depression.

Registry Identifier	Investigator(s)/ Country	*N*	Design/Phase	Psilocybin	Therapy support	Comparator(s)	Primary endpoint	Follow-up	Status	Expected end date
NCT04433845*	Scott T. Aaronson USA	15	Open label Phase II	Single dosing 25 mg	No	n/a	MADRS Week 3	3 weeks	Recruitment completed	15/04/2023
NCT05029466 CTA: 253490	Joshua Rosenblat Canada	30	Open-label with random allocation Phase II	Single dosing, plus up to 2 doses upon relapse 1. Immediate 2. Delayed dosing *(dose not defined)*	No	n/a	Retention C-SSRS Safety 6 months	6 months	Recruitment completed	22/07/2023
NCT04519957 EudraCT: 2020–001348–25	COMPASS Pathways USA/UK/Ireland/ Netherlands/Czech Republic	66	RCT follow-up Phase II	Single dosing 1. 10 mg 2. 25 mg		Psilocybin 1 mg (active control)	Service use Hospital admissions Suicidality MADRS Week 52	52 weeks	Recruitment completed	11/08/2023
NCT04433858	Scott T. Aaronson USA	27	Open-label Phase II	Single dosing 25 mg	No	n/a	MADRS Week 3	3 weeks	Recruitment completed	24/10/2023
NCT04959253 EudraCT: 2018–003573–97	James Rucker Allan H. Young UK	60	RCT Phase II	Single dosing 25 mg	Yes	Placebo	MADRS Week 3	6 weeks	Recruiting	01/11/2023
ACTRN12621001097831	Susan Rossell Australia	15	Open label Phase II	Double dosing (6 weeks apart) 25 mg + 11 sessions of integrative psychotherapy	Yes	n/a	QIDS Week 3 & 20	26 weeks	Recruiting	31/12/2023
NCT05220410	Scott T. Aaronson USA	20	Open label Phase II	Single dosing 25 mg	No	n/a	C-SSRS Week 12	12 weeks	Recruiting	01/2024
NCT04670081 EudraCT: 2019–003984–24	Gerhard Gründer Lea Mertens Germany	144	RCT Phase II	Double dosing (6 weeks apart) 1. 25 mg +25 mg 2. 25 mg +5 mg 3. 5 mg +25 mg	Yes	Nicotinamide 100 mg (placebo)	HAMD Week 6	12 months	Recruiting	01/03/2024
NCT05581797	Cameron Lacey New Zealand	20	Open label Phase II	Double dosing (1 week apart) 25 mg + 8 sessions of interpersonal psychotherapy	Yes	n/a	Feasibility Week 0 Retention Week 10 HAMD Week 18	18 weeks	Enrolling by invitation	03/2024
NCT05381974	Sharmin Ghaznavi USA	20	Open label Phase II	Single dosing 25 mg	No	n/a	MGH-RQ Week 12	12 weeks	Recruiting	30/06/2024
NCT05624268	COMPASS Pathways USA	378	RCT Phase III	Single dosing 25 mg	Yes	Placebo	MADRS Week 6	6 weeks	Recruiting	10/2024
NCT05383313 EudraCT: 2018–004480–31	Vivian Winkler Nikola Leca Czech Republic	60	RCT Phase II	Single dosing 25 mg	No	– Ketamine 250 mg – Midazolam 5 mg (placebo)	MADRS Day 1	3 months	Recruiting	30/04/2025
NCT05711940	COMPASS Pathways USA	568	RCT Phase III	Single dosing 1. 10 mg 2. 25 mg	Yes	Psilocybin 1 mg (active control)	MADRS Week 6	6 weeks	Recruiting	05/2025

(*Continued*)

Table 3. (Continued).

Registry Identifier	Investigator(s)/ Country	*N*	Design/Phase	Psilocybin	Therapy support	Comparator(s)	Primary endpoint	Follow-up	Status	Expected end date
ACTRN12623000667617	Susan Rossell Australia	160	RCT Phase II	Multiple dosing (4–17 weeks apart) 1. 3 × 25 mg + PAP 2. 2 × 25 mg + PAP	Yes	Placebo + PAP	MADRS Week 5 & 17	12 months	Recruiting	30/06/2025
ACTRN12623000618651	Sean Hood Australia	60	RCT Phase II	Double dosing (3 weeks apart) 25 mg + PAP with therapist and a family member	Yes	Double dose 25 mg + PAP with therapist (active control)	HAMD Week 6	12 months	Not yet recruiting	01/09/2025
NCT05710237 CTA: 270065	Ishrat Husain Nicole Ledwos Canada	60	RCT Phase II	Single dosing 1. 25 mg + Risperidone 1 mg 2. 25 mg + Placebo	Yes	Risperidone 1 mg + Placebo	Retention Safety Week 4 MADRS Day 7	4 weeks	Not yet recruiting	02/2026

Notes: *:Treatment-resistant bipolar depression (type II).

Trial registries searched: Clinical Trials: https://clinicaltrials.gov/, WHO: https://trialsearch.who.int/AdvSearch.aspx, EU: https://www.clinicaltrialsregister.eu/ctr-search/search, UK: https://www.isrctn.com/, Canada: https://health-products.canada.ca/ctdb-bdec/, Australia: https://www.anzctr.org.au/Default.aspx.

C-SSRS: Columbia-Suicide Severity Rating Scale; HAMD: Hamilton Rating Scale for Depression; QIDS: Quick Inventory of Depressive Symptomatology; MADRS: Montgomery–Åsberg Depression Rating Scale; MGH-RQ: Massachusetts General Hospital Rumination Questionnaire; RCT: Randomized Controlled Trial; PAP: Psychedelic-assisted Psychotherapy.

preparation for psychedelic therapy and subsequent treatment outcomes. Similarly, adopting a personalized approach to psychedelic therapy may also be more beneficial for participants who do not possess these supporting characteristics.

9.2. Future research and implications

Although preliminary findings on psilocybin are encouraging, only three studies were included in the present systematic review, limiting conclusions. Further large-scale, double-blind RCTs as well as mechanistic studies are needed to establish the efficacy, safety, long-term outcomes, and mechanisms of psychedelics. Future studies should also compare the efficacy of psychedelics with antidepressants in TRD. Targeting psychological factors, such as openness and mind-set, can improve psychedelic experience and subsequent outcomes.

As presented in Table 3, it is exciting to observe numerous ongoing RCTs on psilocybin for TRD, which will update and extend the preliminary but promising outcomes presented in this review, as well as improving our understanding of psychedelic action.

Beyond antidepressant effects, there are anxiolytic and anti-addictive effects are further explored. Although we did not have the scope to discuss further effects in the present paper, psychedelic therapy holds promise for other psychiatric conditions including PTSD [111], anorexia [134], addiction [135], borderline personality disorder [136] and bipolar depression.

Although bipolar depression can be difficult to treat, the associated risk of possible onset of mania and hypomania has resulted in caution. A recent study, published as an abstract, reported preliminary findings indicating that participants with bipolar II TRD responded to 25 mg of psilocybin with no UAEs and no recorded onset of mania or hypomania [137]. At the three-week follow-up point, 11 of 14 participants (78.6%) met remission criteria (MADRS ≤10). Although the details of the full trial are yet to be published, and the study was small with an open-label design, these results are compelling, demonstrating feasibility and safety, and warrant further attention.

Australia recently legalized the medical use of psilocybin for TRD and MDMA for PTSD, whilst in Oregon U.S.A. the first psilocybin services centers are expected to open this year. Legalization for medical purposes is a turning point which can shift attitudes and accelerate research. It is anticipated that psychedelic research will broaden over the next decade, and the emergence of new evidence may result in shifting clinical guidelines and legalization of psychedelics for mental health in more countries.

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