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Psychedelic assisted therapy for major depressive disorder: Recent work and clinical directions

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Abstract

Psychedelic substances such as psilocybin and ketamine may represent the future of antidepressant treatment, due to their rapid and prolonged effects on mood and cognition. The current body of psychedelic research has focused on administration and treatment within a psychiatric context. Here, instead, we put to the test the contention that it is necessary to evaluate the current state of this literature from a broader biopsychosocial perspective. Examining these arguably neglected social and psychological aspects of psychedelic treatment can provide a more holistic understanding of the interplay between the interconnected domains. This review of six major clinical trials applies a biopsychosocial model to evaluate the antidepressant effects of psilocybin and ketamine assisted therapy. We conclude that combination psychedelic treatment and psychotherapy facilitate more enduring and profound antidepressant effects than produced by ketamine or psilocybin alone. Emphasising the advantages of therapeutic intervention will encourage those who

may attempt to self-medicate with psychedelics to instead seek a framework of psychological support, minimising associated risks of unregulated use.

Major depressive disorder (MDD) is a substantial public health issue, affecting over 300 million people worldwide (Jakobsen, Gluud, & Kirsch, 2019). It is characterised by feelings of hopelessness, apathy, anxiety, and has a highly recurrent nature (Kupfer, Frank, & Phillips, 2012). Despite the moderate success of conventional antidepressants, their efficacy is mixed (Read & Williams, 2018). In the search for new treatments, substances such as ketamine and psilocybin are enjoying renewed interest (Carhart-Harris & Goodwin, 2017).

Here, we examine first social factors shaping the current landscape of psychedelic treatment research. Early psychedelic research focused on their efficacy from a medical perspective (see Garcia-Romeu & Richards, 2018; George, Michaels, Sevelius, & Williams, 2020). However, newer studies examine their efficacy within a psychotherapeutic framework, as well as more general social perceptions of psychedelic therapy (Carhart-Harris & Goodwin, 2017; Carhart-Harris et al., 2021; Davis et al., 2021; Murrough et al., 2013; Phillips et al., 2019; Wilkinson et al., 2017; see Table 1). This review compares the biological efficacy of two specific psychedelic treatments, ketamine, and psilocybin, with conventional antidepressants. We focus in on seven major clinical trials that investigate the antidepressant effects of psilocybin and ketamine assisted therapy amongst patients with MDD. We offer conclusions about the impact of therapeutic intervention on treatment response, emphasising the importance of exploring the psychological dimensions of psychedelic therapy in future research.

Table 1.

Summary of recent clinical trials

Ketamine Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
Wilkinson et al. (2017)	Open-label trial, 3.5 months 16 participants (aged 18–65 years) Treatment	4 × ketamine infusions (0.5 mg kg^{-1}) over 2 weeks	4 × CBT sessions over 2 weeks 12 × CBT sessions for additional 8 weeks	Response rate: 1 day post-treatment: 50% Remission rate: 1 day post-treatment:	8 weeks post-treatment: 25% 3 months post-treatment: 62%

Ketamine Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
	-resistant MDD			44% 1 month post-treatment: 38% 2 months post-treatment: 25%	
Murrough et al. (2013)	RCT, (one day of treatment, follow up 4 weeks from start of trial) 47 participants (aged 21–80 years) Treatment-resistant MDD	Treatment: 1 × ketamine infusion (0.5 mg kg^{-1}) Control: Active placebo	No psychotherapeutic support provided	Response rate: 1 day post-treatment: 64% 1 week post-treatment: 51% Remission rate: Not provided	5 weeks post-treatment: 58%
Phillips et al. (2019)	Multi-phase clinical trial, 6 weeks	Phase 1: 6 × ketamine infusions	No psychotherapeutic support provided	Phase 1: Response rate: 59%	Informal follow-up 3 weeks post-treatmen

Ketamine Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
	39 participants (aged 18–65 years) Treatment-resistant MDD	(0.5 mg kg^{-1}) over 2 weeks Phase 2: 4 × ketamine infusions (0.5 mg kg^{-1}) over 4 weeks		Remission rate: 23% Phase 2: Response rate: 91%	t: 100% relapse

Psilocybin Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
Carhart-Harris and Goodwin, 2017	Open-label trial, 6 months 19 participants (aged 31–64 years) Treatment-resistant MDD	2 × oral psilocybin (10 and 25 mg) over 1 week	Facilitators: highly trained 4 h preparation session 2 × 4–6 h in-session emotional support 3 × integration sessions	Response rate: 5 weeks post-treatment: 47% 6 months post-treatment: 66% Remission rate: 5 weeks post-	6 months post-treatment: 33%

Psilocybin Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
				treatment: 21%	
Carhart-Harris et al. (2021)	RCT, 9 weeks 30 participants (aged 18–80 years) MDD (treatment-resistance not reported)	Treatment: 2 × oral psilocybin (25 mg) over 3 weeks Control: SSRI	Facilitators: highly trained 4 h preparation session 2 × 4–6 h in-session emotional support 6 × integration sessions	Response rate: 6 weeks post-treatment: 70% Remission rate: 6 weeks post-treatment:57 %	Not reported
Davis et al. (2021)	RCT, 5 weeks 27 participants (aged 21–75 years) MDD (treatment-resistance not reported)	2 × oral psilocybin (20 and 30 mg) over 1 week	Facilitators: highly trained 8 h of preparation sessions 2 × 4–6 h in-session emotional support	Response rate: 1 week post-treatment: 71% 4 weeks post-treatment 71% Remission rate: 1 week post-	Not reported

Psilocybin Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
				treatment: 58% 4 weeks post-treatment: 54%	
Gukasyan et al. (2022)	RCT, 12 months 27 participants (aged 21–75 years) Moderate to severe MDD	2 × oral psilocybin at 20mg/70 kg, and then 30mg/70 kg 2 weeks apart	6–8 h of preparatory sessions	Response rate: 4 weeks post treatment: 71%, 3 months post-treatment 67%, 6 months post treatment 79%, 12 months post treatment 75%	Not reported
			Facilitators: highly trained 6–8 h of initial preparation sessions Follow up visits 1–2 h every 3 months, after 1 day and 1	Remission rate: 4 weeks post treatment, 54%, 3 months post treatment 54%, 6 months post treatment 71%, 12 months post	

Psilocybin Study	Design and participants	Treatment	Psychotherapeutic support	Antidepressant effects	Relapse rate
			week initial follow up	treatment 58%.	

The socio-political history of psychedelic research

From the early 1900s to the 1970s, psychedelics generated excitement in Western countries for their potential to treat multiple mental health disorders, including depression (Carhart-Harris & Goodwin, 2017). At its peak in the 1950s–1970s, tens of thousands of patients are estimated to have undergone 'psychedelic psychotherapy', a unique form of drug assisted psychotherapy (Nutt & Carhart-Harris, 2021). In a recent meta-analysis of studies treating mood disorders with psychedelic therapy during this period, almost 80% of participants demonstrated 'clinically judged improvement' following treatment (Rucker, Jelen, Flynn, Frowde, & Young, 2016). However, such research was often not carefully monitored, with subjects given different doses, and little consistency in research protocol (Nutt & Carhart-Harris, 2021).

However, socio-political upheaval in the 1960s led to increasing legal prohibition of psychedelics, with many governments assigning them to the most restricted category of illicit substance (Nichols, 2016). Due to these restrictions, psychedelic research was increasingly difficult, eventually falling into a 25-year hiatus (Carhart-Harris & Goodwin, 2017). The US Government's "War on Drugs" in the 1970s and 80s further criminalised psychedelic usage, whether it be recreational or clinical. Yet rather than eliminating their existence, it forced these substances underground where they were embraced by various counterculture movements (Wesson, 2011). To this day, unregulated recreational use is still prevalent within various typically young, socio-politically alternative demographics (Duff, 2005; Kunst & Gebhardt, 2018).

In recent decades, methodological and neurobiological advances have allowed for safer administration of psychedelics in therapeutic contexts, leading to a resurgence of research and practice (Carhart-Harris & Goodwin, 2017). However, the historical criminalisation of psychedelics has significantly influenced public attitudes towards these substances (Belouin & Henningfield, 2018). A recent global survey found that, of 85,000 people who had never taken psychedelic drugs, only 18% would openly seek psychedelic-assisted therapy as treatment for depression (Winstock et al., 2019). Earleywine, Altman, and De Leo (2021) presented depressed participants with information regarding the advantages and disadvantages of each of Cognitive Behavioural Therapy (CBT), ketamine and CBT-ketamine combined therapy. Despite having received balanced information, participants overwhelmingly rated CBT as the most credible treatment, followed by combined therapy, and then ketamine in its own right. Given the established correlation between perceived

treatment credibility and subsequent therapeutic outcome, Earleywine et al. (2021) emphasised the need to understand social and individual perceptions of psychedelic treatments. These findings also suggest that emphasising the therapeutic component of psychedelic therapy (such as CBT) could be an important part of fostering public perception of this treatment as credible.

Current methodological limitations

Widespread criminalisation largely prevented the production of medical-grade psychedelics, making the sourcing of regulated products difficult for clinicians (Belouin & Henningfield, 2018). Financing of clinical trials has relied largely on philanthropic and private industry interest, leading to several methodological limitations (Nutt & Carhart-Harris, 2021). Firstly, the cost of larger scale studies has led to restricted sample sizes in most clinical trials (Hall, 2021). Petranker, Anderson, and Farb (2020) suggests this limitation reduces the reliability and generalisability of clinical findings to date. Due to the reduced sample sizes, limited inference can be made on their efficacy. Petranker et al. (2020) note that subsequent use of cross-over studies, as opposed to parallel-group design, has led to inconsistencies in dosing levels, limiting opportunity for between-group comparisons.

A lack of cross-cultural research on psychedelic efficacy offers a particularly important limitation to existing research. Researchers have pointed out the euro-centric and medicalized approach to understanding psychedelic drugs, and lack of diversity in clinical trials (George et al., 2020; Williams, Reed, & George, 2021). There has also been a failure to consider their longstanding medicinal usage in Indigenous contexts the world over (George et al., 2020; Kemprai et al., 2020; Williams et al., 2021). The Yoruba women of West Africa (Williams, 2018), and Zulu and Xhosa groups from Southern Africa (Sobiecko, 2002), for example, have used plants with psychoactive substances for purposes of healing as well as spiritual enrichment (see Williams et al., 2021). George et al. (2020) in particular have pointed out the implications that this restricted perspective can have. This renders an important shortcoming of extant research in western contexts, given the longstanding utilization of these plants around the world. In current western understanding, there is therefore limited consideration of how their usage differentially affect peoples in cross-cultural contexts.

Social perceptions and self-medication

The therapeutic potential of psychedelics is becoming more widely publicised, yet the treatment modality is not yet widely accessible (Hutchison & Bressi, 2021; Williams & Labate, 2020). Enthusiastic members of the public may choose to take experimental dosing into their own hands (Luoma, Chwyl, Bathje, Davis, & Lancelotta, 2020). Arguably, emphasis on the biological potential of psychedelics, without conveying the importance of concurrent therapeutic support, risks fostering a perception that members of the general public can self-medicate and achieve the same results. This risk is exacerbated by the fact that most clinical trials and literature reviews include details of dosage levels and administrative procedures (see Table 1). Additionally, studies have found depression to be one of the most consistent

predictors of substance use disorder (Dierker, Selya, Lanza, Li, & Rose, 2018). Given the known dangers of unregulated or prolonged use of psychedelics, it is essential to implement harm reduction models in this interim phase. Indeed, Luoma et al. (2020) argue that mental health professionals have an ethical obligation to be trained in how to manage the psychological effects of unregulated psychedelic usage amongst potential clients. They advise that once psychologists become aware of their clients' use of these substances, meeting with them before and after personal administration could minimise the associated risks and maximise any therapeutic benefit. Harm reduction procedures are an integral component of psychedelic trials and conveying this to the public could also serve to de-stigmatise this treatment modality, as well encourage safe practice amongst those who choose to self-medicate (Gorman et al., 2021; Pilecki, Luoma, Bathje, Rhea, & Narloch, 2021; Rea & Wallace, 2021).

It is clear that thorough and empirically validated research is helping to re-establish public perceptions of psychedelic treatment as credible. Consideration must be given to methodological limitations within this field, with a focus on increasing sample size and participant diversity. Highlighting the important role of therapeutic intervention could be an important way to foster public perceptions of this modality as valid, safe, and effective, as many emergent studies have suggested (see below). Additionally, the resurgence of psychedelic research might encourage self-medication, so implementing a harm-reduction model and emphasising the importance of the therapeutic component could mitigate the risks associated (Gorman et al., 2021; Pilecki et al., 2021; Rea & Wallace, 2021).

Part two: biological factors in psychedelic therapy

Here we discuss the biological aspects of psilocybin, ketamine, and conventional antidepressants, offering a comparative analysis of each. These three treatments will be evaluated in terms of onset and duration of antidepressant effect, the likelihood of treatment-resistance and the incidence of adverse side-effects. Based on an analysis of current work, recommendations regarding the ideal recipients of each substance will be made. This section will conclude with a discussion of the neural mechanisms underlying each of these three substances, and how this might impact their interaction with psychotherapy, which will provide context for the integrative treatment argument that follows.

Current treatments for major depressive disorder

MDD is characterised by a distinguishable negative shift in mood, pleasure and activity level that endures for at least two weeks (Otte et al., 2016). It is one of the leading causes of disability worldwide (Marcus, Yasamy, van Ommeren, Chisholm, & Saxena, 2012). Daily administration of Selective Serotonin Reuptake Inhibitors (SSRIs) is currently a first-line treatment for depression (Carhart-Harris et al., 2021). SSRIs appear to act on the postsynaptic serotonergic and noradrenergic systems by blocking reuptake, thereby reducing symptoms of depression such as stress, aggression, and anxiety (Morilak & Frazer, 2004). As mentioned, Earleywine et al. (2021) found that people are more comfortable with these conventional antidepressants, given their less turbulent socio-political history. However,

emerging comparison studies between traditional SSRIs and psychedelics are increasingly pointing to the antidepressant potential of psilocybin and ketamine (Petranker et al., 2020).

Psilocybin is a naturally occurring plant alkaloid with the ability to alter states of consciousness and blur perceptual boundaries (Carhart-Harris & Goodwin, 2017). A synthetic form of psilocybin is most commonly used in clinical contexts and is typically administered via oral capsules. Functional neuroimaging studies indicate that psilocybin acts on both the serotonergic and glutamatergic neurotransmitter systems (Vollenweider & Kometer, 2010), though more research is needed to understand its precise neural mechanisms. Ketamine is recognised as both a psychedelic and a dissociative anaesthetic and can induce psychedelic states without producing the same "trip" effect as psilocybin (Dore et al., 2019). In clinical contexts, it is predominantly administered in subanesthetic doses via intravenous infusion (Aleksandrova, Phillips, & Wang, 2017). Growing evidence suggests ketamine acts via the glutamatergic system, and its antidepressant effect is thought to (at least partially) arise from its ability to restore the integrity of neural circuits, which are often impacted during depression (Vollenweider & Kometer, 2010).

Effect onset and duration

A key advantage of both psilocybin and ketamine is that they appear to produce a markedly faster and longer lasting antidepressant effect than conventional antidepressants (Hashimoto, 2020; Wei, Chang, & Hashimoto, 2020). Patients using SSRIs wait between two and four weeks (on average) for symptoms to improve (Mohammed Ali, 2018), with chronic daily doses then required to maintain these effects (Reid & Barbui, 2010). In contrast, a recent trial of psilocybin-assisted therapy for patients with moderate-to-severe MDD found a rapid decrease in depression symptoms within the first day of treatment, with these effects lasting up to four weeks (Davis et al., 2021), or even up to a year (Gukasyan et al., 2022). Similar results have emerged in other trials where, after two doses of psilocybin, antidepressant effects peaked at five to six weeks post-treatment (Carhart-Harris et al., 2021) and were still evident up to six months later (Carhart-Harris et al., 2017). Ketamine appears to act even more rapidly, with several studies showing a reduction in depressive symptoms, as well as suicidality, within hours of a single infusion (Ballard et al., 2014; DiazGranados et al., 2010; Price et al., 2014). These effects typically peak within one to two days and last on average five to eight days (Murrough et al., 2013), though have been reported to endure for up to two weeks (Fond et al., 2014). The most recent of the trials, Gukasyan et al. (2022), reported the longest-running effects, with many participants reporting improved symptoms of MDD 12 months later (Fig. 1).

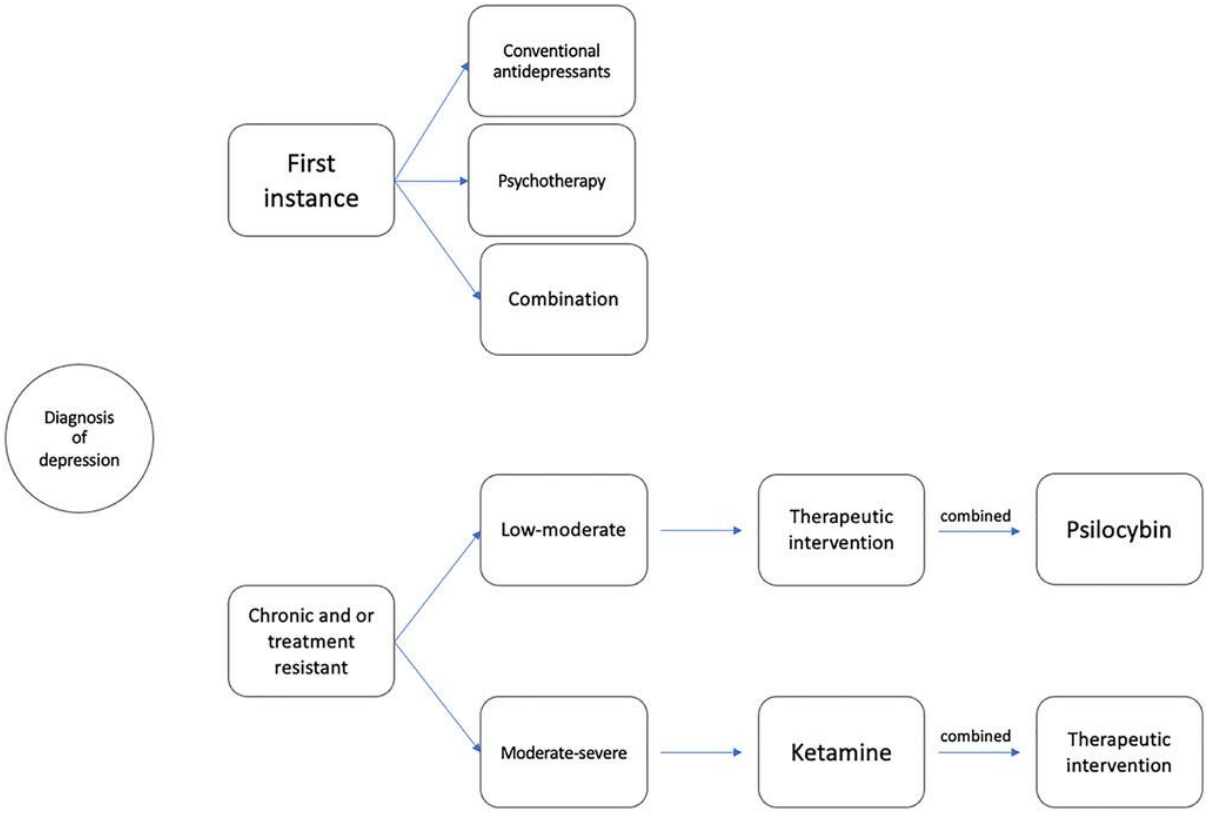

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Fig. 1.

Schematic of novel and conventional MDD treatment pathways

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Treatment resistance

Following treatment with conventional antidepressants, many patients show reduced or remitted depressive symptoms (Morilak & Frazer, 2004). However, around 30–50% of patients do not respond fully and 10–30% are considered treatment-resistant (Al-harbi, 2012). Unfortunately, alternative psychopharmaceuticals treatments for these patients are currently limited. There is growing evidence that ketamine could be effective for this population, with numerous studies reporting substantial reduction and even remission, of depressive symptoms in over 50% of previously treatment-resistant patients (Murrough et al., 2013; Phillips et al., 2019; Wilkinson et al., 2017). Psilocybin is a similarly promising alternative: Carhart-Harris et al. (2016) assessed patients with moderate-to-severe depression, who had not responded to at least two courses of conventional antidepressants within their current depressive episode. It was found that two doses of psilocybin were sufficient to produce rapid and sustained antidepressant effects within around 60% of this sample (Carhart-Harris et al., 2016). It is important to note that chronic SSRI usage could partially mute the antidepressant effects of psilocybin (Bonson & Murphy, 1995). This implies

that chronically medicated, treatment-resistant patients could be difficult to treat with psilocybin and would likely require carefully managed discontinuation of SSRIs prior to receiving this psychedelic treatment (Baldwin, Montgomery, Nil, & Lader, 2005).

Incidence and types of side-effects

Psilocybin and ketamine are also associated with less adverse side-effects than conventional antidepressants (Carhart-Harris et al., 2017; Griffiths et al., 2016; Meikle et al., 2020). In a recent global survey, 50–70% of adult SSRI users reported side-effects such as suicidality, emotional numbness, weight gain and sexual difficulties (Read & Williams, 2018). A similar survey in New Zealand (Cartwright, Gibson, Read, Cowan, & Dehar, 2016) revealed that 27% of SSRI users had experienced addiction to this medication, and 55% had undergone withdrawal effects such as insomnia and suicidal ideation when they ceased usage. These adverse side-effects have been noted to lead to patient adherence issues (Kolovos et al., 2017). In contrast, short-term ketamine usage has not been associated with such side-effects (Short, Fong, Galvez, Shelker, & Loo, 2018). It does typically induce euphoria and a temporary cognitive deficit within hours of administration (Short et al., 2018); however, these are temporary and unrelated to ketamine's antidepressant action, which continues to be effective for days after the infusion (Berman et al., 2000).

Notably, the administration of ketamine does pose moderate physiological risks that necessitates medical supervision (Morgan & Curran, 2011). Ketamine also has moderate potential for facilitating substance use disorder (Schatzberg, 2014), and prolonged recreational use has been associated with bladder and neurological toxicity (Tsai & Kuo, 2015), as well as negative impacts on cognition (Featherstone et al., 2012). Unlike ketamine, psilocybin has a low potential for addiction and toxicity (Gable, 2004), and has not been associated with long-term perceptual or neurological dysfunction (Studerus, Kometer, Hasler, & Vollenweider, 2010). A recent clinical trial by Carhart-Harris et al. (2021) compared psilocybin with a common SSRI and found that while both substances caused headaches and nausea, these side effects were far milder within the psilocybin group. While psilocybin was associated with minor, uncomfortable emotional experiences, these only occurred during the acute dosing session and subsided within hours. Notably, none of the severe physical symptoms or suicidality commonly reported amongst SSRI users (Read & Williams, 2018) were observed for psilocybin.

Treatment suitability for different populations

It is increasingly clear that psilocybin, ketamine, and SSRIs differ in terms of onset and duration of antidepressant action, severity of side-effects, and reversal of treatment-resistance (Schlag, Aday, Salam, Neill, & Nutt, 2022). Consideration of these factors can usefully inform when, and for whom, each treatment is most suitable. While SSRIs are the most common pharmacological treatment for depression (Luo, Kataoka, Ostinelli, Cipriani, & Furukawa, 2020), they take several weeks to work (Harmer, Goodwin, & Cowen, 2009), are ineffective for much of the population (Penn & Tracy, 2012) and can produce adverse effects which often lead to discontinued use (Kelly, Posternak, & Jonathan, 2022). Ketamine could

provide an alternative treatment for patients with markedly treatment-resistant depression, especially in the short-term. Given ketamine's ability to reduce severe depressive symptoms and suicidality within hours (Hashimoto, 2020; Pham & Gardier, 2019; Sahib et al., 2020; Riggs & Gould, 2021), it appears ideal as an emergency response to suicidality, especially in a medical context (Domany, Shelton, & McCullumsmith, 2020; Domany & McCullumsmith, 2021, pp. 1–16). The need to monitor physiological risks within the acute phase of ketamine administration, further affirms it as suitable in a medical context (Ritter, Findeis, & Bauer, 2019).

Psilocybin appears best suited to those seeking out a longer-term alternative to SSRIs. Carhart-Harris et al. (2021) found psilocybin to be just as effective as SSRIs in reducing depressive symptoms, without any of the severe side-effects potential for substance use disorder associated with long-term SSRI usage. Psilocybin could prove useful in combination with therapeutic intervention as a long-term treatment option. Indeed, after four weeks of combined psilocybin treatment and psychotherapy, participants in Davis et al.'s (2021) study reported antidepressant effects approximately two times higher than psychotherapy alone, and four times higher than psychopharmacological treatment alone.

Efficacy of combining psychedelic treatment with psychological support

The comparisons drawn thus far raise an important question regarding the importance of combining psychedelic treatment with psychotherapeutic intervention. Psychotherapy is recommended in combination with SSRIs, as it can help reduce and manage residual symptoms of depression and also minimise the chance of recurrence (Dunlop et al., 2019). SSRI's stimulate the release of brain-derived neurotrophic factor, which activates synaptic plasticity after several weeks (Aleksandrova et al., 2017). This is hypothesised to contribute to their antidepressant effects, as it creates an opportunity to establish new and more adaptive cognitive and behavioural patterns which can be supported through therapy (Craighead & Dunlop, 2014; Letheby, 2021).

The benefits of combination treatment are arguably even more potent for ketamine and psilocybin, due to their faster and more pronounced neuroplastic effects. Like SSRIs, ketamine stimulates synaptic plasticity (Cornwell et al., 2012), however this plasticity has been observed within hours (rather than weeks) of administration (Schwartz, Murrough, & Iosifescu, 2016). This appears to produce temporary, critical periods in which depression-related cognitive impairments can be more easily changed (Lepow, Morishita, & Yehuda, 2021). For example, Bottemanne, Morlaàs, Claret, Fossati, and Schmidt (2021) found that after a single ketamine infusion, patients updated their future-related beliefs more after favourable, and less after unfavourable information. This optimistic cognitive bias then mediated clinical responsiveness after one week of treatment. Their findings suggest that cognitive interventions in this period of plasticity can enhance ketamine's antidepressant effects.

Psilocybin also appears to induce cognitive and emotional flexibility (Preller et al., 2020). At certain dosages, this substance temporarily alters activity in the neural networks underlying

sensory processing (Preller et al., 2020), as well as networks responsible for conscious self-awareness or “ego” (Varley, Carhart-Harris, Roseman, Menon, & Stamatakis, 2020). Consequently, psilocybin can temporarily alter a person's sense of self and their surroundings. This can lead to profound experiences of connectivity to others and the environment (Erritzoe et al., 2019), and may also reduce the rigid thinking patterns common in depression (De Gregorio et al., 2020). Additionally, in contrast to SSRIs which tend to moderate or “blunt” emotional responsiveness when used long-term, psilocybin appears to facilitate emotional catharsis (Carhart-Harris et al., 2014; Cowen & Browning, 2015). For example, Roseman, Nutt, and Carhart-Harris (2018) observed increased amygdala reactivity in depressed patients one day after psilocybin treatment, suggesting that psilocybin facilitated the processing of negative emotional memories. Taken together, this literature implies that psilocybin and ketamine induce a critical period for transforming cognitive, emotional and behaviour patterns, which psychological intervention could then optimise.

Part three: psychological factors in psychedelic therapy

The final section of this review will examine this psychological dimension of psychedelic therapy: specifically, whether psychotherapeutic support does indeed enhance the efficacy of psilocybin and ketamine in treating depression. The importance of the environmental context, and in particular the role of the therapist, will be discussed. Emerging guidelines for this therapeutic component of psychedelic-assisted therapy will then be outlined. Seven clinical trials using ketamine and psilocybin to treat patients with MDD will be reviewed, specifically comparing the extent to which they implemented these guidelines, and the resulting rates of treatment response and relapse. These results are then discussed, to discern the impact of psychological support on treatment outcomes.

The importance of environment

Research is increasingly emphasising the importance of psychological support during the psychedelic experience, in order to reduce associated risks and maximise therapeutic benefits (Carhart-Harris et al., 2021). Historically, psychedelics have been used for centuries by indigenous peoples as a tool for healing and spiritual exploration, with great importance placed on the environment, clear intention, song, and importance of ritual (Loizaga-Velder & Verres, 2014). Modern researchers have similarly found that emotional support, music, and a clear intention to guide the experience can lead to better psychological outcomes (Carhart-Harris et al., 2021).

The role of the therapist

Within this, the role of the therapist facilitating the psychedelic experience is being better understood and appreciated. Research has consistently found the therapist-client relationship to be a major determinant in treatment outcomes within standard psychotherapy (Martin, Garske, & Davis, 2000). Since the early 1960s, researchers have questioned the role of the therapist within the therapeutic potential of psychedelics, asking whether psychedelics were the therapy in and of themselves, or their true potential was in

their ability to catalyse the therapeutic relationship (Phelps, 2017). Yet the restrictions placed on psychedelics have had a significant impact on the study of therapist-related variables within psychedelic research.

In the recent resurgence of this field, the push for highly controlled clinical studies has resulted in therapeutic variables such as effectiveness and competence not being a core focus in many studies (Phelps, 2017). The need to validate the efficacy of psychedelic medicine has overshadowed discussions regarding the importance of therapeutic variables and therapist competencies. Phelps (2017) emphasised the role of the therapist in psychedelic clinical research, noting that the focus on evidence-based, medical model outcomes has distracted from the importance of researching and evaluating the involvement of the therapists within psychedelic research.

Johnson, Richards, and Griffiths (2008) developed guidelines for providing psychological support during psychedelic treatment. The core aspects of these guidelines are (1) allocation of one or more experienced therapists to support the patient before, during and after treatment. (2) Preparation: which involves getting to know the patient's background, building trust, and communicating about how to navigate the acute dosing phase. (3) Support: being physically and emotionally present for the patient during the dosing sessions. It involves non-directive emotional support, such as reassurance and empathetic listening. (4) Integration: non-judgmental listening to the patient's summary of their psychedelic experience, which may include interpreting its content and offering potential meaning. Integration can also involve providing advice and consultation for cultivating positive changes in the patient's life and perspective. These guidelines provide a useful lens through which to analyse the methodology of recent clinical trials, to then ascertain the extent of their focus on psychological support and assess what effect this had on reported treatment outcomes.

A review of recent clinical trials

The results of a review of recent clinical trials using ketamine or psilocybin to treat MDD are summarised in Table 1. Studies were selected based on the following criteria: clinical trials with human participants; administration of ketamine or psilocybin to treat MDD (preferably treatment-resistant); clear presence or absence of adjacent psychotherapeutic support (such as CBT); absence of concurrent non-psychotherapeutic intervention (such as transcranial magnetic stimulation).

Comparison of ketamine trials

In comparing the three trials of ketamine in Table 1, it is important to note that all participants presented with high severity of treatment resistant MDD at baseline. Murrough et al. (2013) investigated the antidepressant impacts of a single ketamine infusion on participant's depressive symptoms. Although they were medically monitored during the dosing session, participants received no psychotherapeutic support during the study. Results indicated that ketamine was associated with a rapid-onset antidepressant effect: one day post-infusion, 64% of the ketamine group showed at least 50% reduction in depressive

symptoms. One week later, 51% still maintained this level of treatment response, however the relapse rate steadily increased and at 5 weeks post-treatment, approximately 58% of these participants again experienced depressive symptoms.

Phillips et al. (2019) conducted a similar trial, but utilised a more intensive dosing regime, involving thrice-weekly ketamine infusions over two weeks. Notably, this study also provided no adjacent psychological intervention. Their results showed a cumulative antidepressant effect of these repeated doses: at the end of two weeks more than half of participants (59%) displayed a 50% reduction in depressive symptoms, and almost a quarter (23%) were in remission. These responders then received once-weekly maintenance ketamine infusions for four weeks, by the end of which 91% had maintained an antidepressant response. However, an informal follow-up of a subset of participants found that within 3 weeks of their final ketamine infusion, all had relapsed and were displaying severe depressive symptoms.

In contrast, Wilkinson et al. (2017) administered ketamine in combination with cognitive behavioural therapy (CBT). Over two weeks, participants were given four ketamine infusions (0.5 mg kg^{-1}) and concurrent, twice-weekly CBT. This psychological intervention was based on Beck's model (Disner, Beevers, Haigh, & Beck, 2011) and focused on (1) psychoeducation, (2) cognitive restructuring, and (3) behavioural modification. Immediately post-treatment, half of the participants had at least a 50% reduction in depressive symptoms. This is a roughly equivalent response rate to both Murrough et al.'s (2013) and Phillips et al. (2019) studies. In the second phase of Wilkinson et al.'s (2017) trial, they ceased ketamine administration but continued to provide 12 sessions of CBT for a further eight weeks, to determine its efficacy in prolonging ketamine's antidepressant effect. The results were supportive, showing a markedly lower relapse rate (25%) for an even longer duration (eight weeks) than the prior two studies. Furthermore, their participants took over twice as long (three months) to relapse into depression, compared to the non-CBT studies (3–5 weeks). Wilkinson et al. (2017) noted that most participants relapsed after completing weekly CBT treatment, suggesting that ongoing psychotherapy was effective in sustaining ketamine's antidepressant effect.

Comparison of psilocybin trials

Three (with a fourth being a follow-up) trials of psilocybin-assisted treatment for depression were reviewed in Table 1. All recruited participants with a comparable severity of depression, however these trials differed in the strengths of psilocybin administered, and the extent to which they adhered to Johnson et al.'s (2008) aforementioned guidelines for psychological support. Carhart-Harris et al. (2017) administered the lowest levels of psilocybin (a 10 and 25 mg dose) seven days apart to participants with treatment-resistant depression. They successfully applied Johnson et al.'s (2008) guidelines, by (1) allocating a pair of well-trained facilitators to support the patient throughout treatment; (2) providing preparation sessions beforehand to establish trust and communicate about treatment expectations; (3) offering high-quality emotional and physical support during the acute dosing sessions; and (4) providing integration sessions for participants to process their experience. Carhart-Harris

et al. (2017) observed a rapid and sustained antidepressant effect that peaked at five weeks post-treatment, with almost half (47%) of participants showing at least a 50% reduction in depressive symptoms, and 21% going into remission. At six months post-treatment, 66% of these responders maintained a significant antidepressant response and only one-third (33%) had relapsed.

Davis et al. (2021) (and its accompanying follow-up Gukasyan et al., 2022) administered the highest doses of psilocybin (25 and 30 mg) two weeks apart. Supportive psychotherapy was also given. Preparatory meetings and in-session support were provided, with highly trained clinicians and researchers. Additionally, after the acute dosing treatments, no sessions were provided for the express purpose of assisting participants in integrating their experience. This trial reported a stronger overall antidepressant effect than Carhart-Harris et al.'s (2017) trial: four weeks post-treatment, 71% of participants showed at least 50% reduction in depressive symptoms, and 54% were in remission. However, these results could be partially attributed to the higher doses of psilocybin given in this trial. A follow up study (Gukasyan et al., 2022), reported long-lasting therapeutic effects at 3, 6, and up to 12 months later. Participants reported for follow-up visits every 3 months, each lasting for 2 h. This suggests that combination of preparatory sessions, psychological support by highly trained professionals, and higher doses offer the highest potential for large and long-lasting therapeutic benefit.

Carhart-Harris et al. (2021) administered an intermediate dosage of psilocybin (two 25 mg doses), three weeks apart. They also provided the highest level of psychological support of the three trials reviewed there. As in Carhart-Harris et al.'s (2017) study, they implemented all of Johnson et al.'s (2008) guidelines, however they provided even more frequent and intensive integration sessions to assist participants to consolidate their experience and move towards their therapeutic goals. These sessions involved open, attentive listening to the participant's psychedelic account. Participants were also offered visualisation exercises to re-access the emotions they had experienced during the psilocybin session, which could then be discussed and further processed. Additionally, these facilitators were highly trained and had access to supervision with an expert in psychedelic-assisted therapy. Carhart-Harris et al. (2021) found that at six weeks post-treatment, 70% of participants showed substantial reduction in depressive symptoms, and 57% were in remission. These effects were equivalent or superior to those reported in the two prior studies and endured to an even later time point (six weeks compared to 4–5 weeks). This trial did use a higher cumulative dose of psilocybin than in Carhart-Harris et al. (2017), which could explain their stronger results. However, this dose was not as strong as in Davis et al.'s (2021) trial, and nonetheless produced comparatively more enduring antidepressant effects. An overall comparison of these results indicates that psilocybin treatment, when combined with rigorous psychological support, produces more enduring antidepressant effects.

Limitations and future directions

It is possible that personality is a potential confounding variable that influences sample bias in psychedelic research. Psilocybin has been found to increase trait openness, which

encompasses imagination, curiosity and a willingness to embrace new things (MacLean, Johnson, & Griffiths, 2011). However, it is possible that individuals willing to participate in psychedelic clinical trials are already high in trait openness at baseline (see McGovern, Leptourgos, Hutchinson, & Corlett, 2022). Similarly, prior recreational psychedelic use could be an unaccounted confounding variable, as it may predispose participants to the pleasurable effects of the substances, thus enhancing the significance of symptom improvement (Mahapatra & Gupta, 2016). The second limitation to consider, is the pervasive lack of cultural diversity, and western medicalized scope of many clinical psychedelic trials (see George et al., 2020; Williams et al., 2021). An approach which prioritizes greater participatory action approach to future research, whereby various communities are invited to engage more actively with the process and outcome of the trials would be beneficial for future research (Williams, Gooden, & Davis, 2012). This could encourage communities who were previously less inclined or able to participate, to partake in the next wave of this research. Additionally, it remains unclear how sociocultural factors such as education, social networks and socioeconomic background might influence substance efficacy and treatment outcomes. A greater focus on both the risk and protective aspects of these sociocultural factors could assist the development of a more in-depth and complete understanding of moderating environmental variables. Lastly, the amount of psychotherapy received by participants was difficult to compare across the clinical trials reviewed above. Specifically, this variable is not yet able to be controlled for across studies, in the same way as the substance dosage. The marked variance in type, intensity and duration of psychotherapy across each trial, made it difficult to determine the extent to which this variable contributed to the improvement of depressive symptoms in participants. Future trials should begin by describing their therapeutic interventions in more detail, to increase replicability. This could lead to a new focus on comparing the outcomes of different amounts of therapeutic intervention, in order to identify an ideal therapeutic intervention structure that could be applied more consistently in future research.

Conclusion

This review has examined the psychedelic treatment of MDD from a multifactorial perspective. A comparison of recent clinical trials shows that the psychological component of psychedelic treatment is vital for sustaining antidepressant outcomes. This aligns with the emerging biological understanding of these substances, specifically, their capacity to induce a period of neural plasticity that enhances the opportunity for emotional, cognitive, and behavioural repatterning. Given the bias towards a medical treatment model caused by the socio-political history of psychedelics, as well as flat out ignorance of their longstanding medicinal uses in cultures across the world, future research would benefit from more deliberately considering the importance of combined psychological and psychedelic therapy. Arguably, as these substances become increasingly legalised in a medical context, and thereby accessible to the public, psychedelic therapy will become less stigmatised. Until then, acknowledgment in clinical research and by practitioners of the dual importance of biological

and psychological factors, could help to present a united front that actively works to align public perception of psychedelic treatment with its true therapeutic potential.

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