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INVITED REVIEW

Are "mystical experiences" essential for antidepressant actions of ketamine and the classic psychedelics?

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Abstract

The growing interest in the rapid and sustained antidepressant effects of the dissociative anesthetic ketamine and classic psychedelics, such as psilocybin, is remarkable. However, both ketamine and psychedelics are known to induce acute mystical experiences; ketamine can cause dissociative symptoms such as out-of-body experience, while psychedelics typically bring about hallucinogenic experiences, like a profound sense of unity with the universe or nature. The role of these mystical experiences in enhancing the antidepressant outcomes for patients with depression is currently an area of ongoing investigation and debate. Clinical studies have shown that the dissociative symptoms following the administration of ketamine or (*S*)-ketamine (esketamine) are not directly linked to their antidepressant properties. In contrast, the antidepressant potential of (*R*)-ketamine (arketamine), thought to lack dissociative side effects, has yet to be conclusively proven in large-scale clinical trials. Moreover, although the activation of the serotonin 5-HT_{2A} receptor is crucial for the hallucinogenic effects of psychedelics in humans, its precise role in their antidepressant action is still under discussion. This article explores the importance of mystical experiences in enhancing the antidepressant efficacy of both ketamine and classic psychedelics.

Keywords Arketamine · Depression · Dissociation · Esketamine · Hallucination · Ketamine · Psilocybin · Psychedelics

Introduction

Major depressive disorder (MDD), one of the most common psychiatric disorders, is characterized by persistent low mood (heightened negative emotions) or anhedonia (diminished positive emotions). Currently, treatments for depression include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other antidepressants. However, significant concerns exist regarding these antidepressants. They are effective for approximately one-third of MDD patients, leaving a substantial portion exhibiting treatment-resistant depression (TRD) [1, 2]. Additionally, these medications often require several weeks to manifest their full effects, which can be particularly problematic for individuals with severe depression or suicidal thoughts. Furthermore, antidepressants can cause various side effects such as gastrointestinal (GI) issues (e.g., nausea, vomiting, or diarrhea), weight gain, sexual dysfunction, sleep disturbances, and emotional blunting [3–5]. These side effects frequently lead to poor adherence and discontinuation of treatment. Consequently, there is a critical unmet medical need to develop new antidepressants that can rapidly alleviate depressive symptoms, including in patients with TRD [6, 7].

Ketamine (Fig. 1), originally known for its use as an anesthetic, has emerged as a significant treatment option for depression, particularly for cases with TRD including MDD and bipolar disorder (BD) [8–20]. One of the most notable features of ketamine in treating depression is its rapid onset of action. Unlike current antidepressants that can take weeks to show effects, ketamine can produce noticeable improvements in mood within hours or days. In addition, ketamine has been found to be particularly effective in individuals with TRD [21–24]. A recent study demonstrated that intravenous ketamine infusion is non-inferior to electroconvulsive therapy (ECT) as therapy for TRD without psychosis [25]. Furthermore, a comprehensive meta-analysis revealed that ECT is not superior to ketamine in the treatment of TRD, and that ketamine showed a significant rapid antidepressant effect over ECT [26].

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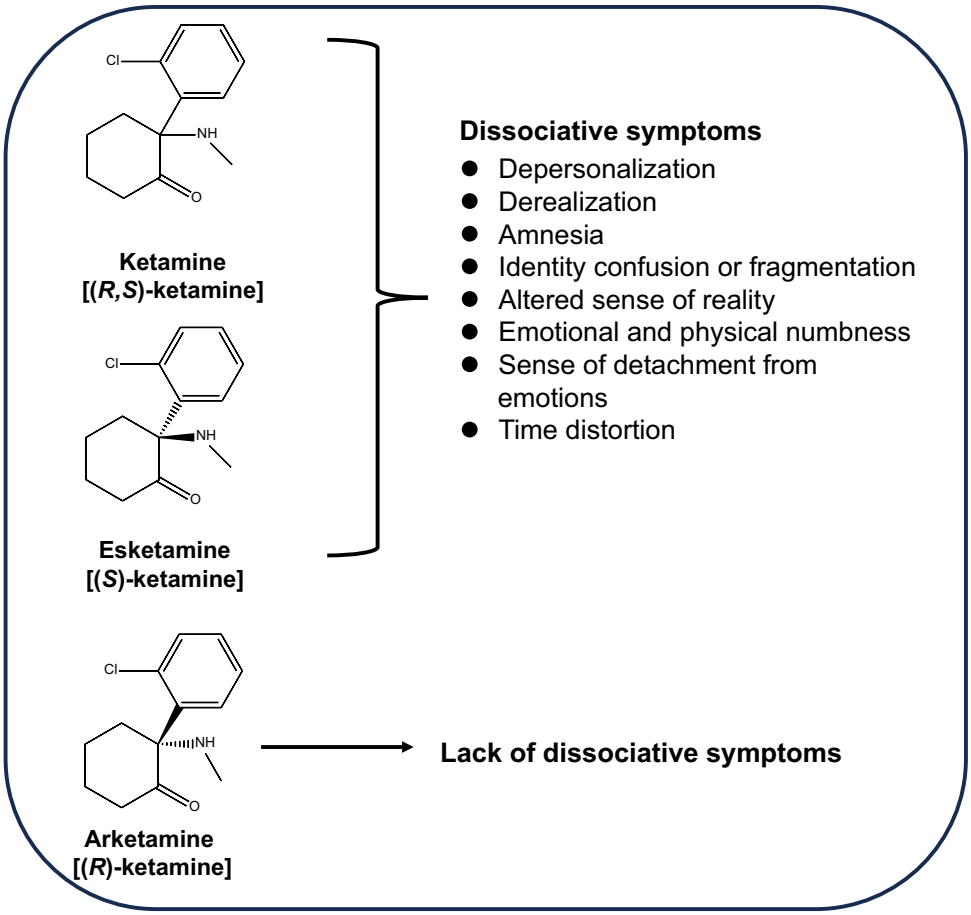

Fig. 1 Chemical structures and dissociative symptoms of ketamine and its enantiomers. The figure illustrates the chemical structures of ketamine (racemic mixture), along with its two enantiomers: esketamine and arketamine. Clinical studies indicate that both ketamine and esketamine can induce dissociative symptoms in healthy volunteers and patients with MDD or BD. Conversely, arketamine is less likely to provoke dissociative symptoms at therapeutic doses. The potential mechanism underlying these dissociative symptoms is attributed to the inhibition of NMDAR by ketamine and esketamine

Consequently, it is recommended that ketamine should be considered on par with ECT for the short-term management of depressive symptoms in outpatients with TRD [27]. Nonetheless, it is important to note that ketamine can cause side effects including dissociation, hallucinations, dizziness, elevated blood pressure during administration, and the potential for abuse with repeated use [8, 28].

The use of classic psychedelics such as psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) (found in magic mushrooms), lysergic acid diethylamide (LSD), and *N*,*N*-dimethyltryptamine (DMT) (found in ayahuasca) (Fig. 2) in treating severe depression represents a growing area of interest in psychiatric research [29–34]. Like ketamine, psychedelics such as psilocybin can produce rapid and sustained antidepressant actions in TRD patients, including MDD and BD [35–39]. It is also currently unclear whether mystical experiences induced by psychedelics are associated with their antidepressant actions in patients with MDD [40–42].

In this review, the author explores the relationships between the robust antidepressant effects of ketamine and psychedelics and the mystical experiences that accompany their application in the treatment of depression.

Dissociative and antidepressant effects of ketamine and its enantiomers

Preclinical studies

Ketamine is a racemic mixture of (*R*)-ketamine (arketamine) and (*S*)-ketamine (esketamine) (Fig. 1). Esketamine shows a higher affinity for the *N*-methyl-D-aspartate receptor (NMDAR) than arketamine. Despite having a lower NMDAR affinity, arketamine demonstrates more potent and sustained antidepressant-like effects in various animal models of depression [43–50]. Additionally, compared to ketamine and esketamine, arketamine's side effects, such as hyperlocomotion, prepulse inhibition, and abuse liability, are less severe in rodents and monkeys [44, 47, 51–53]. Thus, arketamine may emerge as a novel antidepressant with fewer side effects than ketamine and esketamine.

Non-competitive NMDAR antagonists such as phencyclidine (PCP) and ketamine are known for inducing dissociative symptoms in humans. These symptoms include altered perceptions of time, space, and the environment, leading to feelings of disconnection from surroundings and distorted spatial awareness. A notable dissociative effect

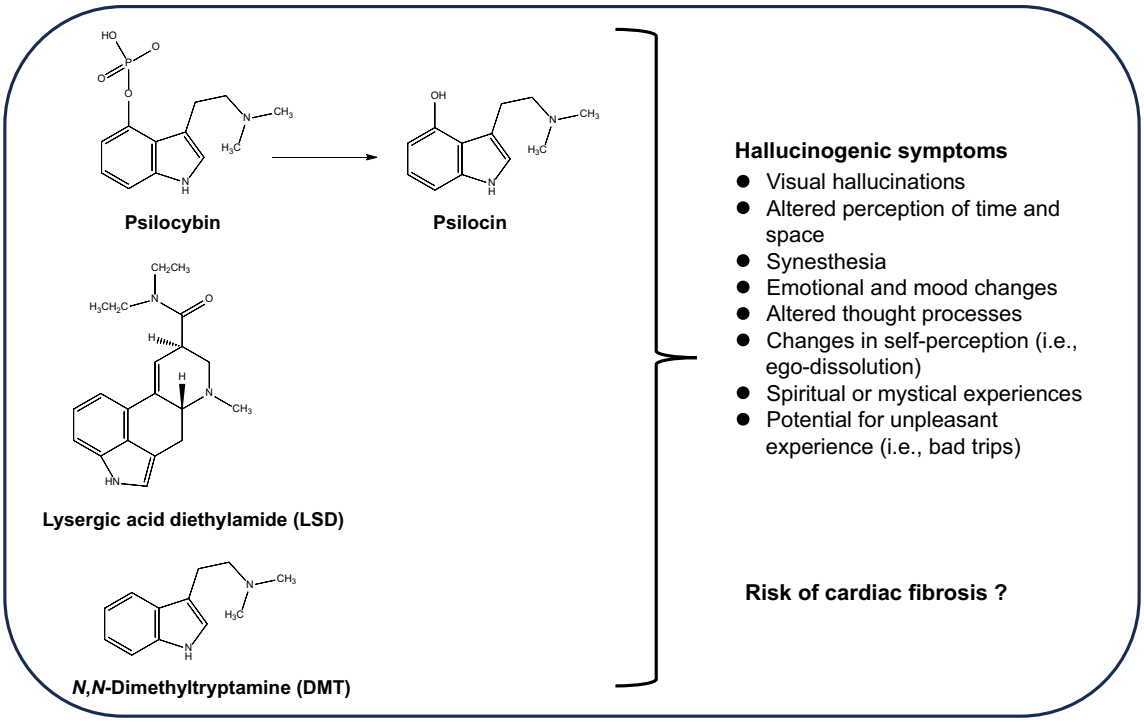

Fig. 2 Chemical structures of classic psychedelics, their hallucinogenic symptoms, and risk of cardiac fibrosis. This figure displays the chemical structures of classic psychedelics, including psilocybin and its primary metabolite psilocin, lysergic acid diethylamide (LSD), and *N*,*N*-dimethyltryptamine (DMT). Psilocybin, found in magic mushrooms, is metabolized into the pharmacologically active compound psilocin. LSD, a synthetic psychedelic, was developed at Sandoz laboratories in Switzerland. DMT, structurally similar to 5-hydroxytryptamine (5-HT: serotonin), occurs naturally in various plants and animals, including humans. In South American indigenous cultures, it is traditionally ingested in the form of ayahuasca, a ceremonial spiritual medicine. These serotonergic classic psychedelics, known for inducing mystical experiences, primarily exert their effects through the activation of the 5-HT_{2A} receptor. Stimulation of the 5-HT_{2B} receptor by psilocin and LSD may potentially increase the risk of cardiac fibrosis [143]

is a sense of detachment or estrangement from oneself, sometimes culminating in an out-of-body experience [8, 54, 55] (Fig. 1). However, the precise molecular and cellular mechanisms behind ketamine-induced dissociation are not fully understood.

Assessing dissociative symptoms in humans relies heavily on self-reporting of mental states, making it challenging to replicate these conditions for behavioral tests in rodents [56]. In 2020, Vesuna and colleagues [57] reported a significant discovery: oscillation rhythms in layer 5 neurons of the retrosplenial cortex are crucial for dissociation-like experiences induced by ketamine, PCP, or dizocilpine. In contrast, memantine, a low-affinity non-competitive NMDAR antagonist that does not cause dissociation in humans, did not induce these oscillation rhythms. They also performed behavioral tests on mice to assess dissociation-like symptoms. Their findings suggest that 1–3 Hz oscillation rhythm in the retrosplenial cortex is essential for inducing dissociation-like behaviors in mice due to ketamine [57], though further detailed research is required.

In 1989, Olney and colleagues [58] demonstrated that NMDAR antagonists like PCP, ketamine, and dizocilpine induce neuropathological changes (specifically, neuronal vacuolization) in the rat brain's retrosplenial cortex. The severity of these changes correlated with each compound's potency at the NMDAR. Dizocilpine and ketamine, as well as esketamine, significantly induced the expression of heat shock protein HSP-70, a marker for neuronal injury, in the retrosplenial cortex of the rat brain. In contrast, arketamine did not trigger HSP-70 expression in this region [59]. The neuropathological alterations observed in the retrosplenial cortex following PCP, ketamine, and esketamine injections might be linked to their dissociative side effects. Future studies, particularly focusing on the two enantiomers of ketamine, would be invaluable in confirming the role of NMDAR in the induction of dissociation-like behaviors and oscillation rhythms in the layer 5 neurons of the retrosplenial cortex [56].

Clinical studies

Dissociative symptoms and antidepressant effects after injection of ketamine or esketamine

In 1997, Vollenweider and colleagues [60] found that increases in glucose utilization in the frontal and left temporal cortex, induced by esketamine, were correlated with ego disintegration and hallucinations in healthy volunteers. In contrast, equivalent doses of arketamine reduced glucose utilization in various brain regions. Notably, arketamine did not trigger psychotic or dissociative symptoms but rather induced relaxation. This study indicates that the esketamine-induced metabolic hyperactivity in the frontal areas resembles the metabolic alterations observed in acute psychotic episodes in patients with schizophrenia. Additionally, it suggests that arketamine is unlikely to cause schizophrenia-like symptoms in healthy individuals.

In 2014, Luckenbaugh and colleagues [61] reported a significant link between ketamine-induced dissociative side effects and its antidepressant efficacy in patients with TRD ($n = 108$). They found a notable association between increased scores on the Clinician-Administered Dissociative States Scale (CADSS) at 40 min and the improvement in the Hamilton Depression Rating Scale (HDRS) scores at 230 min and day 7 following ketamine administration. However, they observed no correlation between changes in the Young Mania Rating Scale (YMRS) or the Brief Psychiatric Rating Scale (BPRS) positive symptom scores at 40 min and HDRS improvement at any time point with ketamine.

In 2018, Niciu and colleagues [62] reported that shifts in depersonalization items on the CADSS, indicative of dissociative side effects, were correlated with changes in depressive symptoms. Additionally, a 2019 study, which analyzed YouTube videos of depressed patients receiving ketamine infusions, suggested that a self-reported feeling of lightness or floating was linked to relief from depressive symptoms [63]. Conversely, Wilkinson and colleagues [64] found no correlation between CADSS scores and the antidepressant effects of ketamine in TRD patients ($n = 54$). These findings highlight the inconsistent nature of the relationship between ketamine-induced dissociation and its antidepressant effects.

An analysis using three trials showed that the antidepressant effects of ketamine in TRD patients (38 with MDD and 44 with BD) are not mediated by the dissociative depersonalization subtype symptom of floating [65]. In a subsequent study, Ballard and Zarate [66] concluded that dissociation is not a necessary component for the antidepressant actions of ketamine. Moreover, a systematic review encompassing 21 studies revealed that total score for ketamine-induced CADSS does not consistently correlate with its antidepressant outcomes [67]. Overall, it appears that ketamine-induced dissociation is not essential for its antidepressant actions, though additional research is required to fully comprehend the relationship between dissociation and the antidepressant effects of ketamine.

In 2019, esketamine nasal spray was approved for TRD in the United State (US) of America and Europe, despite concerns regarding its efficacy and Food Drug Administration (FDA) approval [68]. A recent study utilizing data from the US Food and Drug Adverse Event Reporting System (FAERS) highlighted potential adverse effects and risks associated with the clinical use of esketamine, particularly focusing on its long-term effectiveness, potential for addiction, and suicidal risks [69]. It found the most significant indications for dissociation, dissociative disorder, and sedation. Alarmingly, the frequencies of suicidal ideation and attempt were relatively high, underscoring the need for caution when using esketamine in clinical settings [69]. Therefore, while esketamine nasal spray offers rapid antidepressant benefits, it also introduces various adverse effects and potential hazards.

Meta-analyses revealed that the antidepressant effectiveness of esketamine nasal spray is less pronounced compared to intravenous ketamine injections [70, 71]. The reasons for this difference remain uncertain, but aspects such as the lower bioavailability of the nasal spray [9] and the lack of the arketamine enantiomer in the esketamine formulation could be contributing factors. A comparative study of esketamine and arketamine in MDD patients is crucial to determine which enantiomer significantly contributes to ketamine's antidepressant effects. In 2022, Chen and colleagues [72] reported that the antidepressant effects of esketamine nasal spray in TRD patients were not correlated with dissociative symptoms. In the TRANSFORM-2 study, the response rate at day 2 and day 28 was similar regardless of whether patients experienced significant dissociation following the first dose. Moreover, dissociation scores did not influence the reduction in depression score at day 2 or 28 in TRANSFORM-2, nor did they affect the time to depression relapse in the SUSTAIN-1 trial. This evidence from two phase 3 trials indicates that the antidepressant effects of nasal esketamine spray do not dependent on its dissociative symptoms [72].

Taken together, these findings suggest that the antidepressant effects of both ketamine and esketamine are independent of their dissociative symptoms. Considering the role of NMDAR inhibition in the side effects (such as dissociative symptoms) of NMDAR antagonists [73, 74], it seems unlikely that NMDAR plays a crucial role in the antidepressant effects of ketamine [9–11, 13–17, 75].

Arketamine

Arketamine is known for its greater and more enduring antidepressant-like effects in various animal models of

depression. However, there are relatively few studies exploring its antidepressant effects in TRD patients. A pioneering open-label pilot study in Brazil revealed that a single intravenous injection of arketamine (0.5 mg/kg, 40 min) elicited rapid and sustained antidepressant effects in a small group of female TRD patients ($n=7$) [76]. In contrast, a subsequent placebo-controlled pilot study in Brazil indicated that arketamine did not significantly outperform a placebo in TRD patients ($n=10$) [77]. Additionally, the same research team in Brazil reported that arketamine at doses at 0.5 and 1.0 mg/kg had rapid-acting antidepressant effects in a small cohort of patients ($n=6$) with bipolar depression [78]. Across these three studies, the reported side effects (i.e., dissociation) of arketamine were very low [76–78].

In 2021, Perception Neuroscience, based in New York, US, released data of a phase 1 single ascending dose study of PCN-101 (arketamine) involving healthy adult volunteers [79]. The study found that intravenous arketamine was safe and well tolerated at all tested doses, up to 150 mg, and there were no serious adverse events reported. Notably, it was observed that significantly higher doses of arketamine were required to induce perceptional changes (a type of dissociation side effect) compared to esketamine.

In January 2023, a press release reported that the phase 2a trial of PCN-101 (arketamine) in TRD patients did not achieve statistical significance on the primary endpoint [79]. However, in June 2023, further analysis from the phase 2a trial data revealed differences between the US and Europe cohorts. Specifically, the US subgroup showed clinically meaningful improvement in depression scores for up to two weeks following a single intravenous infusion of arketamine (60 mg, 40 min). Importantly, arketamine was generally well tolerated in this trial, with no serious adverse events and an acceptable safety profile. There were no significant differences in sedation and dissociative symptoms between the arketamine and placebo groups. Overall, these findings suggest that arketamine does not produce dissociative side effects in humans at doses effective for treating depression. To further investigate the role of dissociative symptoms in ketamine's antidepressant effects, conducting a double-blind, randomized controlled trial is necessary. This study would compare the effects of arketamine with a placebo (or esketamine) in TRD patients with MDD or BD.

Hallucinogenic and antidepressant effects of classic psychedelics

Findings from preclinical studies

Psychedelics such as psilocybin primarily act on the 5-hydroxytryptamine (5-HT) 5-HT_{2A} receptors in the brain, leading to alterations in perception, thought, and mood [80]. Head-twitch response (HTR) is a rapid, rotational head movement observed in rodents after administration of 5-HT_{2A} receptor agonists such as psilocybin and LSD. The potency of psychedelics determined via mouse HTR is highly correlated with potencies to elicit hallucinations in humans [81]. Furthermore, HTR induced by psychedelics in mice could be blocked by potent 5-HT_{2A} receptor antagonists or deletion of the 5-HT_{2A} receptor gene [82–85]. Thus, it is likely that 5-HT_{2A} receptor could play a role in HTR induced after administration of psychedelics. A recent study showed that the 5-HT_{1A} receptor agonist 8-OH DPAT attenuated psilocybin-induced HTR in mice [86], suggesting inhibitory effects of 5-HT_{1A} receptor for the HTR caused by psychedelics. Furthermore, unlike esketamine and the selective NMDAR antagonist dizocilpine, psilocybin did not induce HSP-70 expression in the rat retrosplenial cortex [87], indicating that psilocybin could be a safer option for clinical applications in comparison to esketamine.

In terms of potential antidepressant-like effects of psilocybin, the data are mixed regarding the role of 5-HT_{2A} receptor activation. This uncertainty arises in part from research utilizing rodents that lack depression-like behaviors, potentially limiting accurate predictions about the clinical effectiveness of antidepressant candidates [88–90]. One study showed that 5-HT_{2A} receptor antagonist ketanserin did not block antidepressant-like effects of psilocybin in chronically stressed male mice with depression-like behaviors [91], suggesting that altered perception may not be necessary for its antidepressant actions.

It is currently unclear if 5-HT_{2A} receptor can mediate antidepressant effects of psychedelics such as psilocybin, because several non-hallucinogenic analogs of psychedelics with antidepressant-like properties have been developed [92–94]. In 2023, Qu and colleagues [95] compared the effects of DOI (2,5-dimethoxy-4-iodoamphetamine: a hallucinogenic psychedelic drug with potent 5-HT_{2A} receptor agonism), lisuride (non-hallucinogenic psychedelic analog with 5-HT_{2A} and 5-HT_{1A} receptor agonisms), and arketamine on depression-like behavior and the decreased dendritic spine density in the brain of lipopolysaccharide (LPS)-treated mice. Both lisuride and arketamine ameliorated the increased immobility time of forced swimming test (FST), and the decreased dendritic spine density in the medial prefrontal cortex (PFC) and hippocampus of LPS-treated mice. In contrast, DOI did not improve these changes of LPS-treated mice. This study suggests that 5-HT_{2A} receptor may not play a major role in rapid-acting antidepressant actions of psychedelics although further detailed studies is needed. In addition, it is likely that potent 5-HT_{1A} receptor agonism of lisuride plays a role in a lack of HTR in rodents [86, 95]. Unfortunately, the effects of psilocybin with antidepressant effects in depressed patients were not investigated in this study [95].

Subsequently, Liu and colleagues [96] reported that pretreatment (6 days before LPS) with arketamine, but not DOI and lisuride, ameliorated body weight loss, splenomegaly, the increased immobility time of FST, and the decreased expression of synaptic protein in the PFC of LPS-treated mice. Furthermore, pretreatment with arketamine, but not DOI and lisuride, significantly ameliorated the increased FST immobility time, the reduced sucrose preference in the sucrose preference test, and the decreased expression of synaptic protein in the PFC of CRS (chronic restrain stress)-exposed mice. Unlike to arketamine, both DOI and lisuride do not exhibit long-lasting prophylactic effects in mouse models of depression.

A recent study demonstrated that LSD and psilocin, the primary metabolite of psilocybin, bind directly to TrkB (a receptor for brain-derived neurotrophic factor [BDNF]), exhibiting affinities that are 1,000-fold higher than those of other antidepressants [97]. Furthermore, the study revealed that psychedelics and antidepressants bind to distinct, yet partially overlapping, sites within the transmembrane domain of TrkB dimers [97]. Given the established importance of BDNF–TrkB signaling in the rapid and sustained antidepressant-like effects observed with ketamine and arketamine [44, 46, 49, 98–101], these findings are particularly intriguing. They suggest that high-affinity TrkB positive allosteric modulators, which do not activate the 5-HT_{2A} receptor, may maintain the antidepressant potential of psychedelics without inducing hallucinogenic effects [102]. Consequently, there is an ongoing debate over the role of 5-HT_{2A} receptor in the antidepressant actions of psychedelics such as psilocybin.

Findings from clinical studies

The unique subjective experiences induced by psychedelics like psilocybin are characterized by phenomena such as ego dissolution (loss of self-awareness), indescribable insights, and a profound sense of unity and connection with others (Fig. 2) [36, 103–105]. Psilocybin, upon ingestion, is converted by the body into psilocin (4-hydroxy-*N,N*-dimethyltryptamine: 4-hydroxy DMT), the pharmacologically active compound, which predominantly binds to the 5-HT_{2A} receptor (Fig. 2).

The hallucinogenic effects of psychedelics like psilocybin and LSD in health volunteers are known to be mediated by the 5-HT_{2A} receptor, as evidenced by the fact that these effects can be inhibited by the 5-HT_{2A} receptor antagonist ketanserin [106–108]. A study employing positron emission tomography (PET) revealed a strong correlation between the intensity of psychedelic experiences, 5-HT_{2A} receptor occupancy, and plasma psilocin levels [109]. Thus, activation of the 5-HT_{2A} receptor is likely a contributing factor to the hallucinogenic effects of psychedelics in humans. Research showed that a strong of oceanic boundlessness, akin to mystical-type experiences, under psilocybin was predictive of an antidepressant response in TRD patients ($n = 20$) [110]. This suggests that the nature of the acute mystical experiences plays a crucial role in mediating the long-term antidepressant effects. However, it remains uncertain whether 5-HT_{2A} receptor activation also plays a role in the potential antidepressant actions of psychedelics.

In 2022, Gukasyan and colleagues [111] conducted a 12-month prospective follow-up study examining the effectiveness and safety of psilocybin-assisted therapy for patients with severe MDD ($n = 24$). Significant reductions from baseline in HAMD scores were noted at 1, 3, 6, and 12 months. At the 12-month mark, the treatment response (defined as a greater than 50% reduction in HAMD score from baseline) was 75%, and remission rate was 58%. Notably, participants' reports of personal meaning, spiritual experiences, and mystical experiences following sessions were linked to enhanced well-being at 12 months, yet these did not correlate with improvement in depression. In a comprehensive naturalistic study, involving individuals ($n = 302$) who planned to undergo a psychedelic experience, several factors were found to significantly influence changes in depressive symptoms [112]. These factors included the individuals' medicinal motivations, their history of previous psychedelic use, the dosage of the drug, and the nature of the acute psychedelic experience, particularly the occurrence of an emotional breakthrough [112]. Moreover, a placebo-controlled, double-blind, randomized trial revealed that the subjective effects experienced from a single dose of psilocybin in MDD patients (n = 52) were not associated with a reduction in depressive symptoms two weeks after treatment [113].

In a 2023 exploratory placebo-controlled study involving moderate to severe patients ($N = 19$) with MDD, improvements in depression and anxiety were observed following both placebo and psilocybin treatments, with no significant differences between the two groups [114]. The psilocybin treatment showed high response (66.7%) and remission rates (46.7%). However, the intensity of mystical experiences during psilocybin administration did not correlate with subsequent antidepressant effects [114]. Therefore, it appears unlikely that psilocybin-induced mystical experiences contribute to its antidepressant effects in MDD patients, although it is important to note the sample sizes of these studies.

In 2023, Rosenblat and colleagues [115] reported a groundbreaking case: an adult with TRD who received psilocybin therapy following premedication with trazodone, a potent 5-HT_{2A} receptor antagonist. This case raises the possibility that the antidepressant effects of psilocybin may not solely depend on 5-HT_{2A} receptor activation or its psychedelic properties. However, further research is necessary

to fully understand the role of 5-HT_{2A} receptor activation and its psychedelic impact in antidepressant mechanism of psychedelics like psilocybin.

To delve deeper into the role of the 5-HT_{2A} receptor in psilocybin's antidepressant effects, a comprehensive study design is proposed: a double-blind, randomized controlled trial comparing the effects of psilocybin with and without the 5-HT_{2A} receptor antagonists such as ketanserin and volinanserin (MDL 100,907). Additionally, a similar ongoing study (NCT05710327) is examining the effects of psilocybin (25 mg) combined with risperidone (1 mg), which blocks dopamine D_2 and 5-HT_{2A} receptors, in TRD patients [116].

There are currently a limited number of studies indicating the antidepressant effects of LSD and DMT in patients with MDD. A randomized, placebo-controlled crossover study found that LSD treatment (200 µg across two sessions) significantly alleviated anxiety and depressive symptoms in patients ($n=42$), some of whom had a life-threatening illness [117]. Notably, positive acute subjective drug effects and mystical-type experiences in the first session correlated with long-term reductions in anxiety symptoms [117]. Another randomized, placebo-controlled crossover study revealed that a low dose of LSD (26 µg) decreased depressive scores in depressed patients, albeit with various subjective effects [118]. Additionally, an open-label study reported that a single dose of ayahuasca produced rapid antidepressant effects in six inpatients with depression [119]. More recently, an open-label study demonstrated that DMT treatment (initially 0.1 mg/kg, followed by 0.3 mg/kg) lowered depressive scores in seven MDD patients, though it increased blood pressure, heart rate, anxiety, psychedelic, and psychotomimetic effects [120]. Given the scarcity of research, the extent to which mystical experiences induced by LSD or DMT contribute to their antidepressant effects in depressed patients remains uncertain.

Furthermore, recent studies have highlighted non-hallucinogenic compound lisuride, which shows antidepressant-like effects in preclinical models [95, 121]. A notable study from Japan demonstrated that lisuride maleate (0.075 mg/day over 12 weeks) improved depressive symptoms in patients suffering from post-stroke depression [122]. This study demonstrated that the antidepressant effects of lisuride in these patients do not have a rapid onset. Given lisuride's established use in treating Parkinson's disease, it is intriguing to consider its potential in treating MDD patients.

Conclusion remarks and future directions

A wealth of clinical evidence suggests that the dissociative symptoms triggered by ketamine or esketamine might not be crucial for their antidepressant effects in patients with TRD, including MDD or BD. If large-scale clinical trials confirm the antidepressant efficacy of arketamine in TRD patients, this could indicate that ketamine-induced dissociation is not essential for its robust antidepressant effects. Currently, clinical trials investigating arketamine for depression are being conducted by several pharmaceutical companies, including Perception Neuroscience (USA), Otsuka (Japan), HengRui (China), and Nhwa (China) [15].

The precise role of 5-HT_{2A} receptor activation and its associated hallucinogenic effects in the antidepressant action of psychedelics remains unclear. A recent study has shown that psilocybin, unlike lisuride, can induce antidepressant-like effects in 5-HT_{2A} receptor knock-out mice subjected to repeated swimming stress (10 min daily for five consecutive days) [123]. This implies that the antidepressant-like effects of psilocybin might not involve the 5-HT_{2A} receptor. Furthermore, recent clinical studies suggest there is no significant relationship between the hallucinogenic and antidepressant effects of psilocybin [111, 113–115]. Investigating whether the antidepressant effects of psychedelics like psilocybin can be inhibited by treatment with 5-HT_{2A} receptor antagonist in depressed patients is a topic of significant interest. Furthermore, clinical trials investigating new non-hallucinogenic psychedelics for the treatment of depression are garnering significant interest [124–126].

The molecular mechanisms driving the potent antidepressant effects of serotonergic psychedelics are not yet fully understood. These classic psychedelics are known to primarily influence the serotonergic system in the brain, but they also exert significant effects on the GI tract. Given that GI tract is home to a vast array of 5-HT receptors, psychedelics can induce a range of effects, including altered gut motility. This can manifest as symptoms such as nausea, vomiting, diarrhea, or altered perception of GI sensations [127–129]. Recent studies demonstrated that the gut–brain axis via the vagus nerve plays a crucial role in the stress resilience of the serotonergic entactogen 3,4-methylenedixoymethamphetamine in rodents [130, 131]. Moreover, various studies propose that the gut–brain axis might also play a role in the antidepressant-like actions of ketamine and arketamine [132–137]. Considering that over 95% of the body's 5-HT is found in the GI tract [138, 139], the role of 5-HT in this region and its subsequent impact on the gut–brain axis are important factors to consider in understanding the antidepressant mechanisms of ketamine and serotonergic psychedelics [140, 141].

Finally, the use of ketamine and psychedelics for depression therapy, while showing promise, raises several major concerns: First, ketamine and psychedelics can induce significant side effects, including psychotomimetic and dissociative symptoms, and hallucinogenic effects during the acute phase of the experience. The primary challenge in blind studies is preserving their blind aspect. Due to the distinct mystical experience often induced by ketamine and

psychedelics, participants and researchers may easily deduce whether they have received the actual substance or a placebo. Long-term effects and the potential for psychological harm in vulnerable individuals are not fully understood. A recent study, analyzing data from the US FAERS, underscored potential negative outcomes and hazards (i.e., dissociation, sedation, suicidal ideation, suicidal attempt) linked to the clinical application of esketamine nasal spray [69]. Additionally, a recent longitudinal observational study, which included samples from adult populations in the US and UK (total 9,732 participants), revealed correlations between the use of psychedelic and the occurrence of unusual visual experiences that manifest after the acute pharmacological effects have diminished [142]. Recent research indicated that prolonged microdosing of psychedelics like psilocybin and LSD, over several months or more, may increase the risk of cardiac fibrosis [143]. This is attributed to the stimulation of the 5-HT_{2B} receptor by these substances, potentially leading to the development of fibrosis [143]. Second, ketamine and psychedelics can trigger or exacerbate psychotic episodes in individuals with a personal or family history of psychiatric disorders. A prior investigation demonstrated that the repeated administration of esketamine, as opposed to arketamine, augmented locomotor activity in mice following additional methamphetamine exposure [144], indicating an elevated likelihood of psychosis in subjects treated with esketamine. Third, both ketamine and psychedelics generally have a potential for addition. There is concern about their misuse outside a therapeutic context. A study, analyzing data from the US FAERS, highlighted the potential risk of abuse associated with the clinical use of esketamine nasal spray [69]. Fourth, the necessity of psychotherapy in conjunction with psychedelic treatment remains a question [145–148]. Finally, the off-label use of ketamine and psychedelics challenges current medical, ethical, and societal norms around drug use and mental health treatment, requiring careful consideration and potentially new frameworks for understanding and managing mental health.

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Author contributions KH is the sole author that conceived, drafted, and approved the final version of this work.

Declarations

Competing interest Dr. Hashimoto serves as one of the editors of this journal. Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-Ketamine in the treatment of psychiatric diseases," "(*S*)-norketamine and salt thereof as pharmaceutical," "*R*-Ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder," "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases," and "*R*-Ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder" by the Chiba University. Dr. Hashimoto has also received speakers' honoraria, consultant fee, or research support from Abbott, Boehringer-Ingelheim, Daiichi-Sankyo, Meiji Seika Pharma, Seikagaku Corporation, Dainippon-Sumitomo, Taisho, Otsuka, Murakami Farm, and Perception Neuroscience.

References

1. Fava M (2003) Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53(8):649–659. https://doi.org/10.1016/s0006-3223(03)00231-2
2. Voineskos D, Daskalakis ZJ, Blumberger DM (2020) Management of treatment-resistant depression: challenges and strategies. Neuropsychiatr Dis Treat 16:221–234. https://doi.org/10.2147/NDT.S198774
3. Kelly K, Posternak M, Alpert JE (2008) Toward achieving optimal response: understanding and managing antidepressant side effects. Dialog Clin Neurosci 10(4):409–418. https://doi.org/10.31887/DCNS.2008.10.4/kkelly
4. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA (2016) The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom 85(5):270–288. https://doi.org/10.1159/000447034
5. Oliva V, Lippi M, Paci R, Del Fabro L, Delvecchio G, Brambilla P, De Ronchi D, Fanelli G, Serretti A (2021) Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 109:110266. https://doi.org/10.1016/j.pnpbp.2021.110266
6. Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R (2023) Novel and emerging treatments for major depression. Lancet 401(10371):141–153. https://doi.org/10.1016/S0140-6736(22)02080-3
7. Hashimoto K (2023) Neuroinflammation through the vagus nerve-dependent gut-microbiota-brain axis in treatment-resistant depression. Prog Brain Res 278:61–77. https://doi.org/10.1016/bs.pbr.2023.01.003
8. Domino EF (2010) Taming the ketamine tiger. Anesthesiology 113(3):678–84. https://doi.org/10.1097/ALN.0b013e3181ed09a2
9. Hashimoto K (2019) Rapid-acting antidepressant ketamine, its metabolites and other candidates: a historical overview and future perspective. Psychiatry Clin Neurosci 73(10):613–627. https://doi.org/10.1111/pcn.12902
10. Yang C, Yang J, Luo A, Hashimoto K (2019) Molecular and cellular mechanisms underlying the antidepressant effects of

ketamine enantiomers and its metabolites. Transl Psychiatry 9(1):280. https://doi.org/10.1038/s41398-019-0624-1
11. Hashimoto K (2020) Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (*R*)-ketamine. Biochem Pharmacol 177:113935. https://doi.org/10.1016/j.bcp.2020.113935
12. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, Brietzke E, Dodd S, Gorwood P, Ho R, Iosifescu DV, Lopez Jaramillo C, Kasper S, Kratiuk K, Lee JG, Lee Y, Lui LMW, Mansur RB, Papakostas GI, Subramaniapillai M, Thase M, Vieta E, Young AH, Zarate CA Jr, Stahl S (2021) Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am J Psychiatry 178(5):383–399. https://doi.org/10.1176/appi.ajp.2020.20081251
13. Wei Y, Chang L, Hashimoto K (2022) Molecular mechanisms underlying the antidepressant actions of arketamine: beyond the NMDA receptor. Mol Psychiatry 27(1):559–573. https://doi.org/10.1038/s41380-021-01121-1
14. Hashimoto K (2022) Ketamine: anesthetic, psychotomimetic, antidepressant, or anthelmintic? Mol Psychiatry 27(8):3116–3118. https://doi.org/10.1038/s41380-022-01587-7
15. Zhang JC, Yao W, Hashimoto K (2022) Arketamine, a new rapid-acting antidepressant: a historical review and future directions. Neuropharmacology 218:109219. https://doi.org/10.1016/j.neuropharm.2022.109219
16. Zhang K, Yao Y, Hashimoto K (2023) Ketamine and its metabolites: Potential as novel treatments for depression. Neuropharmacology 222:109305. https://doi.org/10.1016/j.neuropharm.2022.109305
17. Hashimoto K (2023) Arketamine for cognitive impairment in psychiatric disorders. Eur Arch Psychiatry Clin Neurosci 273(7):1513–1525. https://doi.org/10.1007/s00406-023-01570-5
18. Johnston JN, Kadriu B, Allen J, Gilbert JR, Henter ID, Zarate CA Jr (2023) Ketamine and serotonergic psychedelics: an update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. Neuropharmacology 226:109422. https://doi.org/10.1016/j.neuropharm.2023.109422
19. Krystal JH, Kaye AP, Jefferson S, Girgenti MJ, Wilkinson ST, Sanacora G, Esterlis I (2023) Ketamine and the neurobiology of depression: Toward next-generation rapid-acting antidepressant treatments. Proc Natl Acad Sci USA 120(49):e2305772120. https://doi.org/10.1073/pnas.2305772120
20. Rossi GN, Hallak JEC, Baker G, Dursun SM, Dos Santos RG (2023) The effects of ketamine and classic hallucinogens on neurotrophic and inflammatory markers in unipolar treatment-resistant depression: a systematic review of clinical trials. Eur Arch Psychiatry Clin Neurosci 273(1):129–155. https://doi.org/10.1007/s00406-022-01460-2
21. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63(8):856–864. https://doi.org/10.1001/archpsyc.63.8.856
22. Su TP, Chen MH, Li CT, Lin WC, Hong CJ, Gueorguieva R, Tu PC, Bai YM, Cheng CM, Krystal JH (2017) Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. Neuropsychopharmacology 42(13):2482–2492. https://doi.org/10.1038/npp.2017.94
23. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, Ionescu DF, Mathew SJ, Chang LC, Iosifescu DV, Murrough J, Debattista C, Schatzberg AF, Trivedi MH, Jha MK, Sanacora G, Wilkinson ST, Papakostas GI (2020) Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry 25(7):1592–1603. https://doi.org/10.1038/s41380-018-0256-5
24. Price RB, Kissel N, Baumeister A, Rohac R, Woody ML, Ballard ED, Zarate CA Jr, Deakin W, Abdallah CG, Feder A, Charney DS, Grunebaum MF, Mann JJ, Mathew SJ, Gallagher B, McLoughlin DM, Murrough JW, Muthukumaraswamy S, McMillan R, Sumner R, Papakostas G, Fava M, Hock R, Phillips JL, Blier P, Shiroma P, Šóš P, Su TP, Chen MH, Tiger M, Lundberg J, Wilkinson ST, Wallace ML (2022) International pooled patient-level meta-analysis of ketamine infusion for depression: In search of clinical moderators. Mol Psychiatry 27(12):5096–5112. https://doi.org/10.1038/s41380-022-01757-7
25. Anand A, Mathew SJ, Sanacora G, Murrough JW, Goes FS, Altinay M, Aloysi AS, Asghar-Ali AA, Barnett BS, Chang LC, Collins KA, Costi S, Iqbal S, Jha MK, Krishnan K, Malone DA, Nikayin S, Nissen SE, Ostroff RB, Reti IM, Wilkinson ST, Wolski K, Hu B (2023) Ketamine versus ECT for nonpsychotic treatment-resistant major depression. N Engl J Med 388(25):2315–2325. https://doi.org/10.1056/NEJMoa2302399
26. Shafiee A, Soltani Abhari F, Jafarabady K, Bakhtiyari M (2023) Ketamine versus electroconvulsive therapy for treatment-resistant depression: An updated meta-analysis of randomized clinical trials. Asian J Psychiatry 88:103720. https://doi.org/10.1016/j.ajp.2023.103720
27. Mathew SJ, Jha MK, Anand A (2023) Choosing between ketamine and electroconvulsive therapy for outpatients with treatment-resistant depression-advantage ketamine? JAMA Psychiat 80(12):1187–1188. https://doi.org/10.1001/jamapsychiatry.2023.3979
28. Andrade C (2023) Ketamine for depression – knowns, unknowns, possibilities, barriers, and opportunities. JAMA Psychiat 80(12):1189–1190. https://doi.org/10.1001/jamapsychiatry.2023.3982
29. Anderson BT, Danforth AL, Grob CS (2020) Psychedelic medicine: safety and ethical concerns. Lancet Psychiatry 7(10):829–830. https://doi.org/10.1016/S2215-0366(20)30146-2
30. McClure-Begley TD, Roth BL (2022) The promises and perils of psychedelic pharmacology for psychiatry. Nat Rev Drug Discov 21(6):463–473. https://doi.org/10.1038/s41573-022-00421-7
31. Muttoni S, Ardissino M, John C (2019) Classical psychedelics for the treatment of depression and anxiety: a systematic review. J Affect Disord 258:11–24. https://doi.org/10.1016/j.jad.2019.07.076
32. Vollenweider FX, Preller KH (2020) Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci 21(11):611–624. https://doi.org/10.1038/s41583-020-0367-2
33. Roth BL, Gumpper RH (2023) Psychedelics as transformative therapeutics. Am J Psychiatry 180(5):340–347. https://doi.org/10.1176/appi.ajp.20230172
34. Rodrigues LS, Rossi GN, Rocha JM, L Osório F, Bouso JC, Hallak JEC, Dos Santos RG (2022) Effects of ayahuasca and its alkaloids on substance use disorders: an updated (2016–2020) systematic review of preclinical and human studies. Eur Arch Psychiatry Clin Neurosci 272(4):541–556. https://doi.org/10.1007/s00406-021-01267-7
35. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3(7):619–627. https://doi.org/10.1016/S2215-0366(16)30065-7
36. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR (2021) Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiat 78(5):481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

37. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, Bird C, Blom RE, Brennan C, Brusch D, Burke L, Campbell-Coker K, Carhart-Harris R, Cattell J, Daniel A, DeBattista C, Dunlop BW, Eisen K, Feifel D, Forbes M, Haumann HM, Hellerstein DJ, Hoppe AI, Husain MI, Jelen LA, Kamphuis J, Kawasaki J, Kelly JR, Key RE, Kishon R, Knatz Peck S, Knight G, Koolen MHB, Lean M, Licht RW, Maples-Keller JL, Mars J, Marwood L, McElhiney MC, Miller TL, Mirow A, Mistry S, Mletzko-Crowe T, Modlin LN, Nielsen RE, Nielson EM, Offerhaus SR, O'Keane V, Páleníček T, Printz D, Rademaker MC, van Reemst A, Reinholdt F, Repantis D, Rucker J, Rudow S, Ruffell S, Rush AJ, Schoevers RA, Seynaeve M, Shao S, Soares JC, Somers M, Stansfield SC, Sterling D, Strockis A, Tsai J, Visser L, Wahba M, Williams S, Young AH, Ywema P, Zisook S, Malievskaia E (2022) Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med 387(18):1637–1648. https://doi.org/10.1056/NEJMoa2206443
38. Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, Kakar R, Hassman M, Trivedi RP, Robison R, Gukasyan N, Nayak SM, Hu X, O'Donnell KC, Kelmendi B, Sloshower J, Penn AD, Bradley E, Kelly DF, Mletzko T, Nicholas CR, Hutson PR, Tarpley G, Utzinger M, Lenoch K, Warchol K, Gapasin T, Davis MC, Nelson-Douthit C, Wilson S, Brown C, Linton W, Ross S, Griffiths RR (2023) Single-dose psilocybin treatment for major depressive disorder: a randomized clinical trial. JAMA 330(9):843–853. https://doi.org/10.1001/jama.2023.14530
39. Aaronson ST, van der Vaart A, Miller T, LaPratt J, Swartz K, Shoultz A, Lauterbach M, Sackeim HA, Suppes T (2023) Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: A nonrandomized controlled trial. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2023.4685
40. Olson DE (2020) The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. ACS Pharmacol Transl Sci 4(2):563–567. https://doi.org/10.1021/acsptsci.0c00192
41. Kozak Z, Johnson MW, Aaronson ST (2023) Assessing potential of psilocybin for depressive disorders. Expert Opin Investig Drugs 32(10):887–900. https://doi.org/10.1080/13543784.2023.2273493
42. van den Berg M, Magaraggia I, Schreiber R, Hillhouse TM, Porter JH (2022) How to account for hallucinations in the interpretation of the antidepressant effects of psychedelics: a translational framework. Psychopharmacology 239(6):1853–1879. https://doi.org/10.1007/s00213-022-06106-8
43. Zhang JC, Li SX, Hashimoto K (2014) *R* (-)-ketamine shows greater potency and longer lasting antidepressant effects than *S* (+)-ketamine. Pharmacol Biochem Behav 116:137–141. https://doi.org/10.1016/j.pbb.2013.11.033
44. Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, Hashimoto K (2015) *R*-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry 5(9):e632. https://doi.org/10.1038/tp.2015.136
45. Fukumoto K, Toki H, Iijima M, Hashihayata T, Yamaguchi JI, Hashimoto K, Chaki S (2017) Antidepressant potential of (*R*)-ketamine in rodent models: comparison with (*S*)-ketamine. J Pharmacol Exp Ther 361(1):9–16. https://doi.org/10.1124/jpet.116.239228
46. Yang C, Ren Q, Qu Y, Zhang JC, Ma M, Dong C, Hashimoto K (2018) Mechanistic target of rapamycin-independent antidepressant effects of (*R*)-ketamine in a social defeat stress model. Biol Psychiatry 83(1):18–28. https://doi.org/10.1016/j.biopsych.2017.05.016
47. Chang L, Zhang K, Pu Y, Qu Y, Wang SM, Xiong Z, Ren Q, Dong C, Fujita Y, Hashimoto K (2019) Comparison of antidepressant and side effects in mice after intranasal administration of (*R,* S)-ketamine, *(*R)-ketamine, and *(*S)-ketamine. Pharmacol Biochem Behav 181:53–59. https://doi.org/10.1016/j.pbb.2019.04.008
48. Zhang K, Yang C, Chang L, Sakamoto A, Suzuki T, Fujita Y, Qu Y, Wang S, Pu Y, Tan Y, Wang X, Ishima T, Shirayama Y, Hatano M, Tanaka KF, Hashimoto K (2020) Essential role of microglial transforming growth factor-β1 in antidepressant actions of (*R*)-ketamine and the novel antidepressant TGF-β1. Transl Psychiatry 10(1):32. https://doi.org/10.1038/s41398-020-0733-x
49. Yao W, Cao Q, Luo S, He L, Yang C, Chen J, Qi Q, Hashimoto K, Zhang JC (2022) Microglial ERK-NRBP1-CREB-BDNF signaling in sustained antidepressant actions of (*R*)-ketamine. Mol Psychiatry 27(3):1618–1629. https://doi.org/10.1038/s41380-021-01377-7
50. Huang C, Wu Z, Wang D, Qu Y, Zhang J, Jiang R, Xu X, Xu X, Wang Y, Liu H, He T, Liu C, Chen G, Yang JJ, Hashimoto K, Yang C (2023) Myelin-associated oligodendrocytic basic protein-dependent myelin repair confers the long-lasting antidepressant effect of ketamine. Mol Psychiatry. https://doi.org/10.1038/s41380-023-02288-5
51. Yang C, Han M, Zhang JC, Ren Q, Hashimoto K (2016) Loss of parvalbumin-immunoreactivity in mouse brain regions after repeated intermittent administration of esketamine, but not *R*-ketamine. Psychiatry Res 239:281–283. https://doi.org/10.1016/j.psychres.2016.03.034
52. Hashimoto K, Kakiuchi T, Ohba H, Nishiyama S, Tsukada H (2017) Reduction of dopamine $D_{2/3}$ receptor binding in the striatum after a single administration of esketamine, but not *R*-ketamine: a PET study in conscious monkeys. Eur Arch Psychiatry Clin Neurosci 267(2):173–176. https://doi.org/10.1007/s00406-016-0692-7
53. Bonaventura J, Lam S, Carlton M, Boehm MA, Gomez JL, Solís O, Sánchez-Soto M, Morris PJ, Fredriksson I, Thomas CJ, Sibley DR, Shaham Y, Zarate CA Jr, Michaelides M (2021) Pharmacological and behavioral divergence of ketamine enantiomers: implications for abuse liability. Mol Psychiatry 26(11):6704–6722. https://doi.org/10.1038/s41380-021-01093-2
54. Domino EF, Chodoff P, Corssen G (1965) Pharmacologic effects of CI-581, a new dissociative: anesthetic, in man. Clin Pharmacol Ther 6:279–291. https://doi.org/10.1002/cpt196563279
55. Domino EF (1992) Chemical dissociation of human awareness: focus on non-competitive NMDA receptor antagonists. J Psychopharmacol 6(3):418–424. https://doi.org/10.1177/026988119200600312
56. Hashimoto K (2021) Neural rhythm in the retrosplenial cortex during ketamine-induced dissociation. Eur Arch Psychiatry Clin Neurosci 271(3):583–585. https://doi.org/10.1007/s00406-020-01226-8
57. Vesuna S, Kauvar IV, Richman E, Gore F, Oskotsky T, Sava-Segal C, Luo L, Malenka RC, Henderson JM, Nuyujukian P, Parvizi J, Deisseroth K (2020) Deep posteromedial cortical rhythm in dissociation. Nature 586(7827):87–94. https://doi.org/10.1038/s41586-020-2731-9
58. Olney JW, Labruyere J, Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 244(4910):1360–1362. https://doi.org/10.1126/science.2660263
59. Tian Z, Dong C, Fujita A, Fujita Y, Hashimoto K (2018) Expression of heat shock protein HSP-70 in the retrosplenial cortex of rat brain after administration of (*R,* S)-ketamine and *(*S)-ketamine, but not *(*R)-ketamine. Pharmacol Biochem Behav 172:17–21. https://doi.org/10.1016/j.pbb.2018.07.003

60. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997) Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 7(1):25–38. https://doi.org/10.1016/s0924-977x(96)00042-9
61. Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche NE, Guevara S, Zarate CA (2014) Do the dissociative side effects of ketamine mediate its antidepressant effects? J Affect Disord 159:56–61. https://doi.org/10.1016/j.jad.2014.02.017
62. Niciu MJ, Shovestul BJ, Jaso BA, Farmer C, Luckenbaugh DA, Brutsche NE, Park LT, Ballard ED, Zarate CA Jr (2018) Features of dissociation differentially predict antidepressant response to ketamine in treatment-resistant depression. J Affect Disord 232:310–315. https://doi.org/10.1016/j.jad.2018.02.049
63. Stocker K, Hasler G, Hartmann M (2019) The altered-state-of-consciousness aspect of a feeling of lightness is reported to be associated with antidepressant benefits by depressed individuals receiving ketamine infusions: a systematic analysis of internet video testimonials. Psychother Psychosom 88(3):182–183. https://doi.org/10.1159/000497441
64. Wilkinson ST, Katz RB, Toprak M, Webler R, Ostroff RB, Sanacora G (2018) Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. J Clin Psychiatry 79(4):17m11731. https://doi.org/10.4088/JCP.17m11731
65. Acevedo-Diaz EE, Cavanaugh GW, Greenstein D, Kraus C, Kadriu B, Park L, Zarate CA Jr (2020) Can 'floating' predict treatment response to ketamine? Data from three randomized trials of individuals with treatment-resistant depression. J Psychiatry Res 130:280–285. https://doi.org/10.1016/j.jpsychires.2020.06.012
66. Ballard ED, Zarate CA Jr (2020) The role of dissociation in ketamine's antidepressant effects. Nat Commun 11(1):6431. https://doi.org/10.1038/s41467-020-20190-4
67. Grabski M, Borissova A, Marsh B, Morgan CJA, Curran HV (2020) Ketamine as a mental health treatment: Are acute psychoactive effects associated with outcomes? A systematic review. Behav Brain Res 392:112629. https://doi.org/10.1016/j.bbr.2020.112629
68. Turner EH (2019) Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. Lancet Psychiatry 6(12):977–979. https://doi.org/10.1016/S2215-0366(19)30394-3
69. Jiang Y, Du Z, Shen Y, Zhou Q, Zhu H (2023) The correlation of Esketamine with specific adverse events: a deep dive into the FAERS database. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-023-01732-5
70. Bahji A, Vazquez GH, Zarate CA Jr (2021) Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord 278:542–555. https://doi.org/10.1016/j.jad.2020.09.071
71. Terao I, Tsuge T, Endo K, Kodama W (2024) Comparative efficacy, tolerability and acceptability of intravenous racemic ketamine with intranasal esketamine, aripiprazole and lithium as augmentative treatments for treatment-resistant unipolar depression: a systematic review and network meta-analysis. J Affect Disord 346:49–56. https://doi.org/10.1016/j.jad.2023.11.023
72. Chen G, Chen L, Zhang Y, Li X, Lane R, Lim P, Daly EJ, Furey ML, Fedgchin M, Popova V, Singh JB, Drevets WC (2022) Relationship between dissociation and antidepressant effects of esketamine nasal spray in patients with treatment-resistant depression. Int J Neuropsychopharmacol 25(4):269–279. https://doi.org/10.1093/ijnp/pyab084
73. Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148(10):1301–1308. https://doi.org/10.1176/ajp.148.10.1301
74. Domino EF, Luby ED (2012) Phencyclidine/schizophrenia: one view toward the past, the other to the future. Schizophr Bull 38(5):914–919. https://doi.org/10.1093/schbul/sbs011
75. Zorumski CF, Izumi Y, Mennerick S (2016) Ketamine: NMDA receptors and beyond. J Neurosci 36(44):11158–11164. https://doi.org/10.1523/JNEUROSCI.1547-16.2016
76. Leal GC, Bandeira ID, Correia-Melo FS, Telles M, Mello RP, Vieira F, Lima CS, Jesus-Nunes AP, Guerreiro-Costa LNF, Marback RF, Caliman-Fontes AT, Marques BLS, Bezerra MLO, Dias-Neto AL, Silva SS, Sampaio AS, Sanacora G, Turecki G, Loo C, Lacerda ALT, Quarantini LC (2021) Intravenous arketamine for treatment-resistant depression: open-label pilot study. Eur Arch Psychiatry Clin Neurosci 271(3):577–582. https://doi.org/10.1007/s00406-020-01110-5
77. Leal GC, Souza-Marques B, Mello RP, Bandeira ID, Caliman-Fontes AT, Carneiro BA, Faria-Guimarães D, Guerreiro-Costa LNF, Jesus-Nunes AP, Silva SS, Lins-Silva DH, Fontes MA, Alves-Pereira R, Cordeiro V, Rugieri-Pacheco S, Santos-Lima C, Correia-Melo FS, Vieira F, Sanacora G, Lacerda ALT, Quarantini LC (2023) Arketamine as adjunctive therapy for treatment-resistant depression: a placebo-controlled pilot study. J Affect Disord 330:7–15. https://doi.org/10.1016/j.jad.2023.02.151
78. Bandeira ID, Leal GC, Correia-Melo FS, Souza-Marques B, Silva SS, Lins-Silva DH, Mello RP, Vieira F, Dorea-Bandeira I, Faria-Guimarães D, Carneiro B, Caliman-Fontes AT, Kapczinski F, Miranda-Scippa Â, Lacerda ALT, Quarantini LC (2023) Arketamine for bipolar depression: Open-label, dose-escalation, pilot study. J Psychiatry Res 164:229–234. https://doi.org/10.1016/j.jpsychires.2023.06.028
79. Press release by Perception Neuroscience. https://www.perceptions.com/newsv2
80. Nichols DE (2016) Psychedelics. Pharmacol Rev 68(2):264–355. https://doi.org/10.1124/pr.115.011478
81. Halberstadt AL (2020) Automated detection of the head-twitch response using wavelet scalograms and a deep convolutional neural network. Sci Rep 10(1):8344. https://doi.org/10.1038/s41598-020-65264-x
82. González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q, Sealfon SC, Gingrich JA (2007) Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signaling pathways to affect behavior. Neuron 53(3):439–452. https://doi.org/10.1016/j.neuron.2007.01.008
83. Hanks JB, González-Maeso J (2013) Animal models of serotonergic psychedelics. ACS Chem Neurosci 4(1):33–42. https://doi.org/10.1021/cn300138m
84. de la Fuente RM, Shin JM, Vohra HZ, Hideshima KS, Schneck M, Poklis JL, González-Maeso J (2019) Fully automated head-twitch detection system for the study of 5-HT_{2A} receptor pharmacology *in vivo*. Sci Rep 9(1):14247. https://doi.org/10.1038/s41598-019-49913-4
85. de la Fuente RM, Shah UH, Nassehi N, Jaster AM, Hemanth P, Sierra S, Dukat M, González-Maeso J (2021) Psychedelic-like properties of quipazine and its structural analogues in mice. ACS Chem Neurosci 12(5):831–844. https://doi.org/10.1021/acschemneuro.0c00291
86. Shahar O, Botvinnik A, Esh-Zuntz N, Brownstien M, Wolf R, Lotan A, Wolf G, Lerer B, Lifschytz T (2022) Role of 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A} and TAAR1 receptors in the head twitch response induced by 5-hydroxytryptophan and psilocybin: translational implications. Int J Mol Sci 23(22):14148. https://doi.org/10.3390/ijms232214148
87. Iorgu AM, Vasilescu AN, Pfeiffer N, Spanagel R, Mallien AS, Inta D, Gass P (2023) Psilocybin does not induce the

vulnerability marker HSP70 in neurons susceptible to Olney's lesions. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-023-01699-3
88. Hashimoto K, Shirayama Y (2018) What are the causes for discrepancies of antidepressant actions of (2*R*,6*R*)-hydroxynorketamine? Biol Psychiatry 84:e7–e8. https://doi.org/10.1016/j.biopsych.2017.12.007
89. Ma L, Hashimoto K (2022) The role of hippocampal KCNQ2 channel in antidepressant actions of ketamine. Neuron 110:2201–2203. https://doi.org/10.1016/j.neuron.2022.05.027
90. Chang L, Hashimoto K (2022) Comments to behavioral tests for antidepressant-like actions of (2*R*,6*R*)-hydroxynorketamine by Bonaventura et al. Mol Psychiatry. https://doi.org/10.1038/s41380-022-01766-6
91. Hesselgrave N, Troppoli TA, Wulff AB, Cole AB, Thompson SM (2021) Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. Proc Natl Acad Sci USA. https://doi.org/10.1073/pnas.2022489118
92. Cameron LP, Tombari RJ, Lu J, Pell AJ, Hurley ZQ, Ehinger Y, Vargas MV, McCarroll MN, Taylor JC, Myers-Turnbull D, Liu T, Yaghoobi B, Laskowski LJ, Anderson EI, Zhang G, Viswanathan J, Brown BM, Tjia M, Dunlap LE, Rabow ZT, Fiehn O, Wulff H, McCorvy JD, Lein PJ, Kokel D, Ron D, Peters J, Zuo Y, Olson DE (2021) A non-hallucinogenic psychedelic analogue with therapeutic potential. Nature 589(7842):474–479. https://doi.org/10.1038/s41586-020-3008-z
93. Dong C, Ly C, Dunlap LE, Vargas MV, Sun J, Hwang IW, Azinfar A, Oh WC, Wetsel WC, Olson DE, Tian L (2021) Psychedelic-inspired drug discovery using an engineered biosensor. Cell. https://doi.org/10.1016/j.cell.2021.03.043
94. Kaplan AL, Confair DN, Kim K, Barros-Álvarez X, Rodriguiz RM, Yang Y, Kweon OS, Che T, McCorvy JD, Kamber DN, Phelan JP, Martins LC, Pogorelov VM, DiBerto JF, Slocum ST, Huang XP, Kumar JM, Robertson MJ, Panova O, Seven AB, Wetsel AQ, Wetsel WC, Irwin JJ, Skiniotis G, Shoichet BK, Roth BL, Ellman JA (2022) Bespoke library docking for 5-HT_{2A} receptor agonists with antidepressant activity. Nature 610(7932):582–591. https://doi.org/10.1038/s41586-022-05258-z
95. Qu Y, Chang L, Ma L, Wan X, Hashimoto K (2023) Rapid antidepressant-like effect of non-hallucinogenic psychedelic analog lisuride, but not hallucinogenic psychedelic DOI, in lipopolysaccharide-treated mice. Pharmacol Biochem Behav. https://doi.org/10.1016/j.pbb.2022.173500
96. Liu G, Ma L, Qu Y, Wan X, Xu D, Zhao M, Murayama R, Hashimoto K (2023) Prophylactic effects of arketamine, but not hallucinogenic psychedelic DOI nor non-hallucinogenic psychedelic analog lisuride, in lipopolysaccharide-treated mice and mice exposed to chronic restrain stress. Pharmacol Biochem Behav. https://doi.org/10.1016/j.pbb.2023.173659
97. Moliner R, Girych M, Brunello CA, Kovaleva V, Biojone C, Enkavi G, Antenucci L, Kot EF, Goncharuk SA, Kaurinkoski K, Kuutti M, Fred SM, Elsilä LV, Sakson S, Cannarozzo C, Diniz CRAF, Seiffert N, Rubiolo A, Haapaniemi H, Meshi E, Nagaeva E, Öhman T, Róg T, Kankuri E, Vilar M, Varjosalo M, Korpi ER, Permi P, Mineev KS, Saarma M, Vattulainen I, Casarotto PC, Castrén E (2023) Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. Nat Neurosci 26(6):1032–1041. https://doi.org/10.1038/s41593-023-01316-5
98. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475(7354):91–95. https://doi.org/10.1038/nature10130
99. Liu WX, Wang J, Xie ZM, Xu N, Zhang GF, Jia M, Zhou ZQ, Hashimoto K, Yang JJ (2016) Regulation of glutamate transporter 1 via BDNF-TrkB signaling plays a role in the anti-apoptotic and antidepressant effects of ketamine in chronic unpredictable stress model of depression. Psychopharmacology 233(3):405–415. https://doi.org/10.1007/s00213-015-4128-2
100. Sun HL, Zhou ZQ, Zhang GF, Yang C, Wang XM, Shen JC, Hashimoto K, Yang JJ (2016) Role of hippocampal p11 in the sustained antidepressant effect of ketamine in the chronic unpredictable mild stress model. Transl Psychiatry 6(2):e741. https://doi.org/10.1038/tp.2016.21
101. Xie ZM, Wang XM, Xu N, Wang J, Pan W, Tang XH, Zhou ZQ, Hashimoto K, Yang JJ (2017) Alterations in the inflammatory cytokines and brain-derived neurotrophic factor contribute to depression-like phenotype after spared nerve injury: improvement by ketamine. Sci Rep 7(1):3124. https://doi.org/10.1038/s41598-017-03590-3
102. Garcia-Romeu A, Griffiths RR, Johnson MW (2014) Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 7(3):157–164. https://doi.org/10.2174/1874473708666150107121331
103. Griffiths RR, Richards WA, McCann U, Jesse R (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 187(3):268–83; discussion 284–92. https://doi.org/10.1007/s00213-006-0457-5
104. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R (2011) Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology 218(4):649–665. https://doi.org/10.1007/s00213-011-2358-5
105. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D (1998) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. NeuroReport 9(17):3897–3902. https://doi.org/10.1097/00001756-199812010-00024
106. Kometer M, Schmidt A, Jäncke L, Vollenweider FX (2013) Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci 33(25):10544–10551. https://doi.org/10.1523/JNEUROSCI.3007-12.2013
107. Preller KH, Burt JB, Ji JL, Schleifer CH, Adkinson BD, Stämpfli P, Seifritz E, Repovs G, Krystal JH, Murray JD, Vollenweider FX, Anticevic A (2018) Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. Elife 7:e35082. https://doi.org/10.7554/eLife.35082
108. Holze F, Vizeli P, Ley L, Müller F, Dolder P, Stocker M, Duthaler U, Varghese N, Eckert A, Borgwardt S, Liechti ME (2021) Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology 46(3):537–544. https://doi.org/10.1038/s41386-020-00883-6
109. Madsen MK, Stenbæk DS, Arvidsson A, Armand S, Marstrand-Joergensen MR, Johansen SS, Linnet K, Ozenne B, Knudsen GM, Fisher PM (2021) Psilocybin-induced changes in brain network integrity and segregation correlate with plasma psilocin level and psychedelic experience. Eur Neuropsychopharmacol 50:121–132. https://doi.org/10.1016/j.euroneuro.2021.06.001
110. Roseman L, Nutt DJ, Carhart-Harris RL (2018) Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 8:974. https://doi.org/10.3389/fphar.2017.00974
111. Gukasyan N, Davis AK, Barrett FS, Cosimano MP, Sepeda ND, Johnson MW, Griffiths RR (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective

12-month follow-up. J Psychopharmacol 36(2):151–158. https://doi.org/10.1177/02698811211073759
112. Nygart VA, Pommerencke LM, Haijen E, Kettner H, Kaelen M, Mortensen EL, Nutt DJ, Carhart-Harris RL, Erritzoe D (2022) Antidepressant effects of a psychedelic experience in a large prospective naturalistic sample. J Psychopharmacol 36(8):932–942. https://doi.org/10.1177/02698811221101061
113. von Rotz R, Schindowski EM, Jungwirth J, Schuldt A, Rieser NM, Zahoranszky K, Seifritz E, Nowak A, Nowak P, Jäncke L, Preller KH, Vollenweider FX (2022) Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine 56:101809. https://doi.org/10.1016/j.eclinm.2022.101809
114. Sloshower J, Skosnik PD, Safi-Aghdam H, Pathania S, Syed S, Pittman B, D'Souza DC (2023) Psilocybin-assisted therapy for major depressive disorder: an exploratory placebo-controlled, fixed-order trial. J Psychopharmacol 37(7):698–706. https://doi.org/10.1177/02698811231154852
115. Rosenblat JD, Leon-Carlyle M, Ali S, Husain MI, McIntyre RS (2023) Antidepressant effects of psilocybin in the absence of psychedelic effects. Am J Psychiatry 180(5):395–396. https://doi.org/10.1176/appi.ajp.20220835
116. Husain MI, Blumberger DM, Castle DJ, Ledwos N, Fellows E, Jones BDM, Ortiz A, Kloiber S, Wang W, Rosenblat JD, Mulsant BH (2023) Psilocybin for treatment-resistant depression without psychedelic effects: study protocol for a 4-week, double-blind, proof-of-concept randomised controlled trial. BJPsych Open 9(4):e134. https://doi.org/10.1192/bjo.2023.535
117. Holze F, Gasser P, Müller F, Dolder PC, Liechti ME (2023) Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness: a randomized, double-blind, placebo-controlled phase II study. Biol Psychiatry 93(3):215–223. https://doi.org/10.1016/j.biopsych.2022.08.025
118. Molla H, Lee R, Tare I, de Wit H (2023) Greater subjective effects of a low dose of LSD in participants with depressed mood. Neuropsychopharmacology. https://doi.org/10.1038/s41386-023-01772-4
119. Osório Fde L, Sanches RF, Macedo LR, Santos RG, Maia-de-Oliveira JP, Wichert-Ana L, Araujo DB, Riba J, Crippa JA, Hallak JE (2015) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Braz J Psychiatry 37(1):13–20. https://doi.org/10.1590/1516-4446-2014-1496
120. D'Souza DC, Syed SA, Flynn LT, Safi-Aghdam H, Cozzi NV, Ranganathan M (2022) Exploratory study of the dose-related safety, tolerability, and efficacy of dimethyltryptamine (DMT) in healthy volunteers and major depressive disorder. Neuropsychopharmacology 47(10):1854–1862. https://doi.org/10.1038/s41386-022-01344-y
121. Cao D, Yu J, Wang H, Luo Z, Liu X, He L, Qi J, Fan L, Tang L, Chen Z, Li J, Cheng J, Wang S (2022) Structure-based discovery of nonhallucinogenic psychedelic analogs. Science 375(6579):403–411. https://doi.org/10.1126/science.abl8615
122. Hougaku H, Matsumoto M, Hata R, Handa N, Imaizumi M, Sugitani Y, Yoneda S, Etani H, Sueyoshi K, Kusunoki M, Uyama O, Kamada T (1994) Therapeutic effect of lisuride maleate on post-stroke depression. Nihon Ronen Igakkai Zasshi 31(1):52–59. https://doi.org/10.3143/geriatrics.31.52
123. Sekssaoui M, Bockaert J, Marin P, Bécamel C (2024) Antidepressant-like effects of psychedelics in a chronic despair mouse model: is the 5-HT_{2A} receptor the unique player? Neuropsychopharmacology. https://doi.org/10.1038/s41386-024-01794-6
124. Cameron LP, Benetatos J, Lewis V, Bonniwell EM, Jaster AM, Moliner R, Castrén E, McCorvy JD, Palner M, Aguilar-Valles A (2023) Beyond the 5-HT_{2A} receptor: classic and nonclassic targets in psychedelic drug action. J Neurosci 43(45):7472–7482. https://doi.org/10.1523/JNEUROSCI.1384-23.2023
125. Duan W, Cao D, Wang S, Cheng J (2024) Serotonin 2A receptor (5-HT_{2A}R) agonists: psychedelics and non-hallucinogenic analogues as emerging antidepressants. Chem Rev 124(1):124–163. https://doi.org/10.1021/acs.chemrev.3c00375
126. Jaster AM, González-Maeso J (2023) Mechanisms and molecular targets surrounding the potential therapeutic effects of psychedelics. Mol Psychiatry 28(9):3595–3612. https://doi.org/10.1038/s41380-023-02274-x
127. Breeksema JJ, Kuin BW, Kamphuis J, van den Brink W, Vermetten E, Schoevers RA (2022) Adverse events in clinical treatments with serotonergic psychedelics and MDMA: a mixed-methods systematic review. J Psychopharmacol 36(10):1100–1117. https://doi.org/10.1177/02698811221116926
128. Perez N, Langlest F, Mallet L, De Pieri M, Sentissi O, Thorens G, Seragnoli F, Zullino D, Kirschner M, Kaiser S, Solmi M, Sabé M (2023) Psilocybin-assisted therapy for depression: a systematic review and dose-response meta-analysis of human studies. Eur Neuropsychopharmacol 76:61–76. https://doi.org/10.1016/j.euroneuro.2023.07.011
129. Kaminski D, Reinert JP (2023) The tolerability and safety of psilocybin in psychiatric and substance-dependence conditions: a systematic review. Ann Pharmacother 30:10600280231205644. https://doi.org/10.1177/10600280231205645
130. Qu Y, Eguchi A, Wan X, Ma L, Chang L, Shan J, Yang Y, Mori C, Hashimoto K (2023) Repeated use of 3,4-methylenedioxymethamphetamine is associated with the resilience in mice after chronic social defeat stress: a role of gut-microbiota-brain axis. Psychiatry Res 320:115020. https://doi.org/10.1016/j.psychres.2022.115020
131. Qu Y, Eguchi A, Ma L, Wan X, Mori C, Hashimoto K (2023) Role of the gut-brain axis via the subdiaphragmatic vagus nerve in stress resilience of 3,4-methylenedioxymethamphetamine in mice exposed to chronic restrain stress. Neurobiol Dis 189:106348. https://doi.org/10.1016/j.nbd.2023.106348
132. Qu Y, Yang C, Ren Q, Ma M, Dong C, Hashimoto K (2017) Comparison of (*R*)-ketamine and lanicemine on depression-like phenotype and abnormal composition of gut microbiota in a social defeat stress model. Sci Rep 7(1):15725. https://doi.org/10.1038/s41598-017-16060-7
133. Yang C, Qu Y, Fujita Y, Ren Q, Ma M, Dong C, Hashimoto K (2017) Possible role of the gut microbiota-brain axis in the antidepressant effects of (*R*)-ketamine in a social defeat stress model. Transl Psychiatry 7(12):1294. https://doi.org/10.1038/s41398-017-0031-4
134. Huang N, Hua D, Zhan G, Li S, Zhu B, Jiang R, Yang L, Bi J, Xu H, Hashimoto K, Luo A, Yang C (2019) Role of *Actinobacteria* and *Coriobacteriia* in the antidepressant effects of ketamine in an inflammation model of depression. Pharmacol Biochem Behav 176:93–100. https://doi.org/10.1016/j.pbb.2018.12.001
135. Hua H, Huang C, Liu H, Xu X, Xu X, Wu Z, Liu C, Wang Y, Yang C (2022) Depression and antidepressant effects of ketamine and its metabolites: The pivotal role of gut microbiota. Neuropharmacology 220:109272. https://doi.org/10.1016/j.neuropharm.2022.109272
136. Chang L, Wei Y, Hashimoto K (2022) Brain-gut-microbiota axis in depression: a historical overview and future directions. Brain Res Bull 182:44–56. https://doi.org/10.1016/j.brainresbull.2022.02.004
137. Wei Y, Wang T, Liao L, Fan X, Chang L, Hashimoto K (2022) Brain-spleen axis in health and diseases: a review and future perspective. Brain Res Bull 182:130–140. https://doi.org/10.1016/j.brainresbull.2022.02.008
138. Mawe GM, Hoffman JM (2013) Serotonin signalling in the gut–functions, dysfunctions and therapeutic targets. Nat Rev

Gastroenterol Hepatol 10(8):473–486. https://doi.org/10.1038/nrgastro.2013.105
139. Shine JM, O'Callaghan C, Walpola IC, Wainstein G, Taylor N, Aru J, Huebner B, John YJ (2022) Understanding the effects of serotonin in the brain through its role in the gastrointestinal tract. Brain 145(9):2967–2981. https://doi.org/10.1093/brain/awac256
140. Kelly JR, Clarke G, Harkin A, Corr SC, Galvin S, Pradeep V, Cryan JF, O'Keane V, Dinan TG (2023) Seeking the psilocybiome: Psychedelics meet the microbiota-gut-brain axis. Int J Clin Health Psychol 23(2):100349. https://doi.org/10.1016/j.ijchp.2022.100349
141. Kargbo RB (2023) Microbiome: the next frontier in psychedelic renaissance. J Xenobiot 13(3):386–401. https://doi.org/10.3390/jox13030025
142. Simonsson O, Hendricks PS, Stenfors CU, Goldberg SB, Honk L, Osika W (2023) Longitudinal associations between psychedelic use and unusual visual experiences in the United States and the United Kingdom. J Psychopharmacol 23:2698811231218931. https://doi.org/10.1177/02698811231218931
143. Rouaud A, Calder AE, Hasler G (2024) Microdosing psychedelics and the risk of cardiac fibrosis and valvulopathy: comparison to known cardiotoxins. J Psychopharmacol 12:2698811231225609. https://doi.org/10.1177/02698811231225609
144. Tan Y, Hashimoto K (2020) Risk of psychosis after repeated intermittent administration of (*S*)-ketamine, but not (*R*)-ketamine, in mice. J Affect Disord 269:198–200. https://doi.org/10.1016/j.jad.2020.03.040
145. Palitsky R, Kaplan DM, Peacock C, Zarrabi AJ, Maples-Keller JL, Grant GH, Dunlop BW, Raison CL (2023) Importance of integrating spiritual, existential, religious, and theological components in psychedelic-assisted therapies. JAMA Psychiat 80(7):743–749. https://doi.org/10.1001/jamapsychiatry.2023.1554
146. Goodwin GM, Malievskaia E, Fonzo GA, Nemeroff CB (2024) Must psilocybin always "Assist Psychotherapy"? Am J Psychiatry 181(1):20–25. https://doi.org/10.1176/appi.ajp.20221043
147. O'Donnell KC, Anderson BT, Barrett FS, Bogenschutz MP, Grob CS, Hendricks PS, Kelmendi B, Nayak SM, Nicholas CR, Paleos CA, Stauffer CS, Gukasyan N (2024) Misinterpretations and omissions: a critical response to Goodwin and colleagues' commentary on psilocybin-assisted therapy. Am J Psychiatry 181(1):74–75. https://doi.org/10.1176/appi.ajp.20230661
148. Schenberg EE, King F 4th, da Fonseca JE, Roseman L (2024) Is poorly assisted psilocybin treatment an increasing risk? Am J Psychiatry 181(1):75–76. https://doi.org/10.1176/appi.ajp.20230664