

Exploring the Therapeutic Potential of Psilocybin and Ketamine in Major Depressive Disorder including Treatment-Resistant Depression: A Narrative Review

Badanie Potencjału Terapeutycznego Psylocybiny i Ketaminy w Leczeniu Depresji Klinicznej, w tym Lekoopornej: Narracyjny Przegląd Literatury

**Christian S. Skowron^{1*}, Urszula Milkowska², Gabriela Maria Piech³,
Igor Lis³, Piotr Kurzyna²**

¹*University of Białystok*

²*Medical University of Białystok*

³*Regional Medical Chamber in Białystok*

*Correspondence: 

Abstract:

Major depressive disorder (MDD), including treatment-resistant depression (TRD), represents significant global health challenges with conventional therapies often yielding suboptimal outcomes. This narrative review examines the therapeutic potential of psilocybin and ketamine, two novel agents offering distinct mechanisms of action compared to traditional monoamine-based or monoamine reuptake inhibitor antidepressants. Psilocybin, a 5-HT_{2A} receptor agonist, induces rapid and sustained antidepressant effects with some clinical trials demonstrating response rates of 54-71% in MDD. Ketamine, an NMDA receptor antagonist, exerts rapid antidepressant effects via glutamatergic signalling pathways, showing particular efficacy in reducing suicidal ideation within hours. While psilocybin requires structured psychotherapeutic support during its acute psychedelic effects, ketamine offers flexible administration routes (intranasal, intravenous, subcutane-

ous), some of which can be applied immediately in an emergency setting. Safety profiles for both compounds are favourable in controlled settings with transient adverse effects such as dissociation or nausea. However, current research faces limitations including small sample sizes, blinding challenges, and heterogeneity in trial design and therapeutic protocols. Despite these constraints, psilocybin and ketamine represent a paradigm shift in depression treatment. Future directions require large-scale trials, standardized protocols and long-term safety assessments to optimize their integration into clinical practice. These agents hold promise for reshaping therapeutic approaches to MDD, particularly for patients unresponsive to conventional therapies (TRD).

Keywords: psilocybin, ketamine, major depressive disorder, treatment-resistant depression, psychedelics

Streszczenie:

Depresja kliniczna (MDD), w tym depresja lekooporna (TRD), stanowi poważne wyzwanie zdrowotne, a konwencjonalne terapie często przynoszą niewystarczające efekty. W niniejszym narracyjnym przeglądzie omówiliśmy potencjał terapeutyczny psylocybiny i ketaminy, dwóch nowatorskich środków oferujących odmienne mechanizmy działania w porównaniu z tradycyjnymi antydepresantami opartymi na monoaminach. Psylocybina, agonista receptora 5-HT_{2A}, wywołuje szybkie i długotrwałe działanie przeciwdepresyjne, a niektóre badania kliniczne wykazały skuteczność na poziomie 54-71% w depresji klinicznej. Ketamina, antagonist receptoru NMDA, wywiera szybkie działanie przeciwdepresyjne poprzez szlaki sygnałowe glutaminergiczne, wykazując szczególną skuteczność w zmniejszaniu myśli samobójczych w ciągu kilku godzin. Podczas gdy terapia psylocybiną wymaga ustrukturyzowanego wsparcia psychoterapeutycznego, oraz odpowiedniej przestrzeni, w czasie w którym pacjenci znajdują się w stanie psychodelicznym, ketamina może być podawana w zróżnicowany sposób (donosowo, dożylnie, podskórnie). Profil bezpieczeństwa obu związków jest korzystny w kontrolowanych warunkach z przejściowymi działaniami niepożądanymi, takimi jak dysocjacja lub nudności. Jednak obecne badania napotykają ograniczenia, w tym małe rozmiary grup badawczych i kontrolnych, wyzwania związane z zaślepianiem i zróżnicowaniem protokołów terapeutycznych. Pomimo tych ograniczeń psylocybina i ketamina zmieniają wcześniej obowiązujący paradygmat w leczeniu depresji. Przyszłe kierunki rozwoju wymagają badań wielkoskalowych, ustandaryzowanych protokołów i długoterminowych ocen bezpieczeństwa w celu odpowiedniego zintegrowania ich z praktyką kliniczną. Zastosowanie tych środków stanowi

szansę do usprawnienia leczenia depresji klinicznej, szczególnie w przypadku pacjentów nieodpowiadających na konwencjonalne terapie (TRD).

Słowa kluczowe: psylocybina, ketamina, depresja kliniczna, depresja lekooporna, psychodeliki

1. Introduction

1.1 Major Depressive Disorder and Treatment-Resistant Depression

Major Depressive Disorder (MDD) is one of the most prevalent psychiatric conditions worldwide, affecting approximately 280 million people and ranking as a leading cause of disability globally (1,2). In short, MDD is characterized by persistent feelings of sadness, anhedonia and a range of other symptoms that significantly impair daily functioning (3). Moreover, this condition substantially increases morbidity and mortality risk with suicide being a particularly concerning outcome (2,4). Approximately one-third of individuals with MDD suffer from Treatment-Resistant Depression (TRD), typically defined as an inadequate response to at least two trials of antidepressant medications (5,6). These patients experience prolonged suffering, marked decreases in quality of life and impose significant burdens on healthcare systems (6).

The neurobiological underpinnings of MDD involve dysregulation across multiple systems, including monoamine neurotransmission, hypothalamic-pituitary-adrenal axis functioning, neuroplasticity mechanisms and inflammatory processes (3,7). Psychological factors, including maladaptive cognitive patterns, early life adversity and ongoing psychosocial stressors, interact with these biological vulnerabilities in complex ways (8). This multifactorial etiology contributes to the heterogeneity of depression presentations and helps us explain why no single treatment approach is universally effective (2,7).

1.2 Current treatments

Current standard treatments for MDD include pharmacotherapy, psychotherapy, or a combination of the two. First-line pharmacological interventions typically involve 2 main antidepressant groups: selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (9,10). While these medications demonstrate positive effects in large clinical trials, response rates in real-world settings remain sub-optimal with approximately 30-50% of patients failing to achieve adequate response to basic treatments and even fewer achieving complete remission (11).

Evidence-based psychotherapies for depression include cognitive-behavioural therapy (CBT), interpersonal therapy and behavioural activation. These approaches target maladaptive thought patterns, interpersonal difficulties, and behavioural withdrawal that maintain depressive states (10). While effective for many patients, psychotherapy alone may be insufficient for more severe or treatment-resistant cases (10,12).

For TRD, treatment options mainly include switching or combining antidepressants, augmentation with atypical antipsychotics or mood stabilizers as well as neuromodulation approaches such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) (5,13). ECT is considered as one of the most effective interventions for severe TRD, however it is limited by concerns about cognitive side effects, stigma and access issues (14). Despite these advanced options, more and more patients continue to experience devastating symptoms, which highlights the urgent need for novel treatment approaches with different mechanisms of action (13). For this reason – with hopes of generating some insights – we wanted to review current evidence and examine methodological limitations regarding 2 promising psychedelic agents: psilocybin and ketamine.

1.3 The emergence of psychedelics as new treatments

During the last 10 years we witnessed a renaissance in research examining the therapeutic potential of psychedelics for psychiatric cases, particularly depression. This shift follows decades of regulatory restrictions that stopped permitting research initiated between 1950s and 1960s. (15,16).

Among psychedelic compounds, psilocybin has emerged as a prominent candidate for depression treatment. It is an active ingredient in “magic mushrooms” and belongs to the family of substances known as: classic serotonergic psychedelics (also referred to as hallucinogen psychedelics), which produce profound alterations in perception, cognition and mood through 5-HT_{2A} receptor agonism. Modern clinical trials showed that psilocybin can produce rapid and sustained antidepressant effects when administered in a controlled therapeutic environment with psychological support, which established it as a promising agent in treating MDD (15,17).

Ketamine belongs to the family of dissociative psychedelics and is known for producing dissociative effects, which share some phenomenological features with psychedelic experiences. Originally developed as an anaesthetic, ketamine’s antidepressant properties were discovered accidentally. Then, after several clinical trials, esketamine (the S-enantiomer of ketamine) was approved by U.S. Food and Drug Administration as a nasal spray

for TRD to be used in conjunction with an oral antidepressant, and became another novel antidepressant treatment approved (18–20).

Both psilocybin and ketamine represent a paradigm shift in depression treatment and offer mechanisms of treatment different from conventional monoamine-based approaches. They appear to work through effects on neuroplasticity, neural network connectivity and glutamatergic signalling that may allow them to directly address neurobiological dysfunctions associated with depression, although the exact mechanism still remains unknown. Additionally, the subjective experiences they produce (psilocybin in particular) may facilitate psychological insights and emotional breakthroughs which contribute to their therapeutic effects. It may suggest a synergy between biological and psychological mechanisms that are not typically observed with conventional treatments (15).

2. Pharmacology and Possible Mechanisms of Action

2.1 Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a prodrug that is metabolized to the active compound psilocin upon ingestion. Psilocin acts primarily as a serotonin 5-HT_{2A} receptor agonist, but it also has affinity for other serotonin receptor subtypes. The 5-HT_{2A} receptors are heavily concentrated in cortical regions involved in perception, mood regulation and higher cognitive functions, helping explain the profound perceptual, emotional and cognitive effects of psilocybin (21).

Unlike conventional antidepressants that primarily modulate monoamine levels, psilocybin appears to work through unique mechanisms involving altered brain network connectivity. Studies suggest that psilocybin decreases activity in the Default Mode Network (DMN), a brain network involved in self-referential processing that is often hyperactive in depression. This DMN modulation might disrupt the rigid and negative thought patterns characteristic of depressive states (22,23).

Emerging evidence indicates that psilocybin enhances neuroplasticity, promoting the growth of new neural connections. This effect may create a window of heightened adaptability during which maladaptive thought patterns can be more effectively modified, especially with concurrent psychological support. In addition, the acute psychedelic experience itself may facilitate emotional breakthroughs and insights that contribute to therapeutic change, with studies showing correlations between the quality of the subjective experience and clinical outcomes (24,25).

2.2 Ketamine

Ketamine's pharmacological profile differs substantially from both conventional antidepressants and psilocybin. It acts primarily as an N-methyl-D-aspartate (NMDA) receptor antagonist in the glutamatergic system, however it also interacts with opioid receptors and monoamine transporters. This complex pharmacology contributes to both its therapeutic effects and side effect profile (26). The antidepressant mechanism of ketamine appears to involve a cascade of events following NMDA receptor blockade. This blockade leads to increased glutamate release and subsequent activation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptor stimulation triggers downstream signalling pathways, including brain-derived neurotrophic factor (BDNF) release and mammalian target of rapamycin (mTOR) activation, ultimately enhancing synaptic plasticity and synaptogenesis (27). Kopelman et al. specifically examined neuroplasticity changes following ketamine administration in patients with TRD, finding measurable alterations that correlated with clinical response. These findings provide evidence supporting the neuroplasticity hypothesis of ketamine's antidepressant action, suggesting that structural and functional brain changes may underlie its therapeutic effects (28).

3. Efficacy in MDD and TRD

3.1 Psilocybin

The efficacy of psilocybin-based treatments for treating MDD as well as TRD (all studies included in this review examined only one of the two, never both) have consistently been shown as promising in clinical trials. Davis et al. conducted a randomized, waiting-list controlled clinical trial of 2, day-long, therapy-assisted psilocybin sessions in patients with MDD ($N=27$), finding that 71% of participants showed a clinically significant response, and 54% met criteria for remission, at four weeks post-treatment. The doses were moderately high (20 mg/70 kg, or ~ 0.285 mg/kg of body weight) for the first session, and high (30 mg/70 kg, or ~ 0.428 mg/kg) for the second session, and were administered a mean 1.6 weeks apart, for each participant (29). In another study von Rotz et al. lead a placebo-controlled, double-blind, randomized clinical trial of a single, moderately low dose of psilocybin (0.215 mg/kg of body weight, or ~ 15 mg/70 kg) in a supportive psychological setting for patients diagnosed with MDD ($N=52$). Their results showed 54–58% (depending on the used scale) treatment response in the psilocybin group compared to 12–16% in the placebo group, and 46–54% remission in the psilocybin group compared to 12% in the placebo group, at 14 days post-intervention (30). Gukasyan et al. conducted

a randomized, waiting-list controlled trial in patients with MDD ($N=27$), where participants received two doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) with supportive therapy. Of the 24 participants who completed treatment, 75% met criteria for response and 58% for remission, at 12 months post-treatment (31). This longitudinal data is particularly valuable in assessing the durability of psilocybin's antidepressant effects, and, when contrasted with results from the two previously mentioned studies, might suggest that a second, higher dose may contribute to this long-lasting clinical benefit. Results from these studies suggest psilocybin as more advantageous over conventional antidepressants, given the latter typically achieve response rates of 40-50% and remission rates of 30-40% in similar populations (32).

Carhart-Harris et al. ran an open-label feasibility trial of psilocybin with psychological support in patients with TRD ($N=12$). Participants received two oral doses of psilocybin in a supportive setting: a low dose (10 mg, or, assuming 70 kg of body weight, ~ 0.143 mg/kg) followed by a high dose (25 mg, or ~ 0.357 mg/kg with the same assumption), administered 1 week apart. The study found that 67% of patients met criteria for an antidepressant response one week after treatment, and 42% remained in remission three months later, although at this point 5 patients (42%) have also relapsed (33). Their subsequent six-month follow-up study expanded the sample to $N=20$ patients, and indicated that 45% (= 9) initially met response criteria at 5 weeks, and 30% (= 6) of these maintained their response at 6 months without additional sanctioned treatment, suggesting durable effects in 30% of the full cohort (34). Goodwin et al. conducted a phase 2, double-blind, randomized trial of a single, therapy-assisted psilocybin session in adults with TRD ($N=233$). Participants received a single oral dose of 25 mg ($n=79$), 10 mg ($n=75$), or 1 mg ($n=79$; ~ 0.014 mg/kg assuming 70 kg of body weight; dose not producing observable psychoactive effects) of synthetic psilocybin (COMP360), accompanied by psychological support. At week 3 response and remission rates in the 25 mg group were 37% and 29%, respectively, although sustained response at 12 weeks was not statistically significant (35). Carhart-Harris et al. carried out a double-blind, phase 2 trial ($N=59$) comparing psilocybin ($n=30$) with escitalopram ($n=29$) in patients with moderate-to-severe depression. Psilocybin was administered in 2 sessions, 3 weeks apart. Patients in the psilocybin group received an oral dose of 25 mg per session, and the escitalopram group received an oral dose of 1 mg per session (non-active dose, control). Additionally, patients in the psilocybin group self-administered daily placebo for the remaining duration of the study (6 weeks). Similarly, the escitalopram group self-administered 10 mg escitalopram daily for 3 weeks after the first session, with an increase to 20 mg daily for 3 weeks af-

ter the second session. While the primary outcome did not differ significantly between groups at week 6, the psilocybin group was associated with higher response (70%) and remission (57%) rates compared to escitalopram (48% and 28%, respectively), and with improvements in several other secondary measures, including well-being. Participants in both groups received psychological support. However it seems that the specific form of support during the psilocybin sessions could have potentially been different from the studies already mentioned, which in turn could have influenced the results (36). Goodwin et al. also led an exploratory open-label study examining psilocybin administration in TRD patients who continued their SSRI medication ($N=19$). Participants received a single 25 mg dose of psilocybin (~ 0.357 mg/kg for a 70 kg adult) while maintaining stable SSRI treatment. At week 3, rates of both response and remission were 42% (37). The authors of these four studies did not mention adjusting the psilocybin doses to patients' body mass, which introduces uncontrolled variables, negatively impacting the strength of conclusions which can be drawn (33–37).

Collectively, these studies provide some evidence for psilocybin's efficacy in treating MDD, including TRD, with desired effects that appear to be rapid in onset, substantial in magnitude and potentially longer-lasting than conventional treatments. However, as will be discussed in section 5 of this paper, inferring from these results requires a careful consideration of, among other things, the different designs of these trials.

3.2 Ketamine

Clinical trials have consistently demonstrated ketamine's efficacy for MDD, including TRD, with evidence for rapid effects in reducing depressive symptoms, especially suicidal ideation. Studies included below encompass various ketamine formulations, routes of administration, and dosing protocols, providing an image of ketamine's efficacy.

Multiple large-scale studies of esketamine nasal spray have provided more statistically robust data compared to psilocybin studies. Ionescu et al. conducted a phase 3, double-blind, randomized, placebo-controlled trial (ASPIRE II) to evaluate the efficacy of esketamine nasal spray in the rapid reduction of depressive symptoms in adults with MDD who exhibited active suicidal ideation with intent. Participants ($N=230$) were randomized 1:1 to receive either 84 mg esketamine or placebo nasal spray twice weekly for four weeks, alongside comprehensive standard-of-care treatment, which included hospitalization and newly initiated or optimized oral antidepressants. These antidepressants were: sertraline, fluoxetine, venlafaxine XR, duloxetine, mirtazapine, bupropion SR or XL, and they were selected based on clinical judgment and guidelines,

and participants were required to begin or adjust one of these medications at the start of the double-blind treatment period. At 24 hours post-first intranasal dose, the esketamine group showed a significantly greater reduction in mean depressive symptoms scores compared to placebo. At this time point, remission rates were 11.3% higher in the esketamine group. Response rates also favoured esketamine throughout the double-blind phase, although not all differences were statistically significant (38). In their phase 3, randomized withdrawal trial (SUSTAIN-1), Daly et al. evaluated the efficacy of esketamine nasal spray in sustaining antidepressant effects among adults with TRD ($N=297$). Following a 16-week open-label induction and optimization phase with esketamine (56 mg or 84 mg) plus a new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine ER), 297 patients who achieved stable remission or response were randomized to either continue esketamine treatment or switch to placebo nasal spray, while maintaining the oral antidepressant. Among those in stable remission, relapse occurred in 26.7% of the esketamine group compared to 45.3% in the placebo group. For patients with stable response, but not remission, relapse rates were 25.8% versus 57.6%, respectively (39). Fedgchin et al. and Popova et al. examined fixed-dose and flexible-dosed esketamine nasal spray respectively, as an adjunct to newly initiated oral antidepressants (duloxetine, escitalopram, sertraline, or venlafaxine XR) in adults with TRD, in their TRANSFORM-1 and TRANSFORM-2 trials. Compared to placebo both trials reported higher response and remission rates for esketamine-treated patients, with improvements apparent as early as 24 hours. However, a statistically significant decrease in depressive symptoms at day 28 was only achieved in the TRANSFORM-2 trial for the esketamine group compared to the placebo group. The flexible-dose design may have contributed to more robust outcomes in Popova et al., suggesting potential benefits of individualized titration in optimizing antidepressant response (40,41).

Several studies investigated intravenous ketamine for TRD (28,42–45). For example, in a randomized, double-blind, placebo-controlled trial, Ionescu et al. evaluated the antidepressant and anti-suicidal effects of repeat-dose intravenous ketamine in outpatients with TRD and chronic suicidal ideation. Participants ($N=26$) were randomized to receive six infusions of either ketamine ($n=13$; 0.5 mg/kg) or saline placebo ($n=13$) over a three-week period, alongside their existing antidepressant regimens. The study found no significant differences between groups in depression severity or suicidal ideation over the course of treatment. Post-infusion, response rates were 25% in the ketamine group and 33% in the placebo group, with remission observed in 17% and 8%, respectively. Absence of suicidal ideation was reported by 42% of ketamine recipients and

25% of those receiving placebo, though these differences did not reach statistical significance. At three-month follow-up, outcomes remained similar across groups (42). These findings suggest that standard-dose ketamine may offer limited additional benefit for this high-risk population struggling with chronic suicidal ideation. Alternative administration routes have been explored to increase accessibility and practicality. In a phase 3, double-blind, randomised controlled trial (KADS), Loo et al. evaluated the efficacy of repeated subcutaneous racemic ketamine injections in TRD across two dosing protocols. The trial enrolled 184 participants, with 174 receiving at least one dose of ketamine or midazolam, administered twice weekly for four weeks. In the fixed-dose cohort (0.5 mg/kg), ketamine did not significantly outperform midazolam in achieving remission (6.3% vs 8.8%). Although, in the flexible-dose cohort (0.5–0.9 mg/kg), ketamine demonstrated statistically significant and clinically meaningful improvements, with higher remission (19.6% vs 2.0%, $P = 0.007$) and response rates (29% vs 4%, $P = 0.001$) compared to midazolam. These findings support the antidepressant efficacy of adequately dosed subcutaneous ketamine and highlight the importance of dose individualisation in TRD treatment. However, at follow-up 4-weeks post-treatment, remission rates dropped (ketamine 8%, midazolam 2.1%), suggesting benefits attenuated without ongoing treatment (46). A novel formulation – extended-release ketamine tablets, were studied by Glue et al. in a randomized, placebo-controlled, phase 2 trial (47). This oral formulation could potentially increase accessibility of ketamine treatment by eliminating the need for injections, although in most cases nasal spray may turn out to be the preferred route of administration. Special populations have also been studied. For example Ochs-Ross et al. focused specifically on elderly patients with TRD (48). Their findings on efficacy in this population address an important gap in the literature, as older adults (age ≥ 65) were often excluded from the other clinical trials, despite rates of treatment-resistance within the elder depressed population seem similar to the adult population (approx. 30%) (49).

In sum, these studies provide evidence mostly in favour of ketamine's efficacy in rapidly reducing depressive symptoms in MDD, including in TRD, with effects often observed within hours of administration. The benefits appear to extend (at least somewhat) to patients with suicidal ideation, suggesting a potential role for ketamine in emergency psychiatric care, however more research would be helpful.

4. Safety and Tolerability

4.1 Psilocybin

Clinical trials have consistently demonstrated that psilocybin-assisted therapy is generally well-tolerated when administered in controlled settings with appropriate psychological support. The safety profile appears favourable, with most adverse events being transient, mild and manageable.

For example, von Rotz et al. reported that adverse events associated with psilocybin were generally mild to moderate, and transient, primarily occurring during the acute drug effects. Common physical side effects included headache, nausea, and dizziness, which typically resolved without intervention. Psychological effects such as anxiety or emotional distress were manageable with psychological support and rarely led to lasting adverse outcomes (30). Papers on other studies included similar reports (29,35). In their open-label trial, Carhart-Harris et al. pointed that although some patients experienced challenging psychological content during the acute effects of psilocybin, these experiences were often considered valuable from a therapeutic perspective when processed with skilled psychological support (33). Their six-month follow-up found no evidence of treatment-emergent psychosis, persistent perceptual effects, or addictive behaviours, addressing common safety concerns about psychedelic compounds (34). Goodwin's et al. 2023 study examined the safety of psilocybin, specifically in patients taking SSRIs, finding no evidence of serotonin syndrome or other concerning drug interactions, which addresses an important safety question for clinical implementation (37). In their comparative trial, Carhart-Harris et. al. found that psilocybin had a more favourable side effect profile than escitalopram, with fewer reports of sexual dysfunction, emotional blunting, and other adverse effects commonly associated with SSRIs (36). This comparative safety data is particularly important for clinical decision-making. Valuable data on longer-term safety was provided by Gukasyan's et al. study. Their 12-month follow-up found no evidence of serious adverse effects or addiction potential with psilocybin treatment over this extended period (31).

It is important to note, that all these studies used extensive screening procedures, for example excluding participants with personal or family history of psychosis or bipolar disorder, as these conditions are considered relative contraindications for psilocybin. The reported favourable safety profile should be taken within the context of the careful and strict selection criteria and the controlled settings in which psilocybin was administered.

4.2 Ketamine

The safety and tolerability of ketamine and esketamine have been thoroughly assessed across multiple clinical trials, revealing a consistent pattern of generally manageable adverse effects that must be balanced against their therapeutic benefits. Understanding these safety considerations is essential for appropriate clinical implementation.

In the ASPIRE II trial, Ionescu et al. reported that the most common adverse events associated with esketamine administered intranasally included dissociation, dizziness, headache, nausea, somnolence, and increased blood pressure (38). In a previous study they also showed that adverse effects did not increase significantly for multiple intravenous doses (42). Several investigations found that these effects were typically transient, occurring during, and shortly after, administration, and resolved without intervention in most cases (28,43–46). Some of the larger esketamine trials, namely Daly's et al. SUSTAIN-1, Fedgchin's et al. TRANSFORM-1, Ochs-Ross's et al. TRANSFORM-3, and Popova's et al. TRANSFORM-2, also found vertigo to occur, typically appearing shortly after dosing and resolving within 1-2 hours (39–41,48). For subcutaneous administrations, Loo et al. found common acute effects including dissociation, dizziness, and elevated blood pressure, which were also more frequently observed at higher doses, but generally resolved within 2 hours. Four participants in the KADS trial discontinued treatment due to adverse events, including rash, anxiety, headache, and worsening depression (46).

The safety of a novel formulation was addressed as well, by Glue et al., who studied extended-release ketamine tablets. Their findings suggested a potentially different side effect profile compared to intravenous, subcutaneous or intranasal administration due to altered pharmacokinetics, and included dizziness, headache and anxiety, but minimal dissociation and sedation and no changes in blood pressure (47).

5. Limitations of current research methods

5.1 Psilocybin

Despite promising results presented in the reviewed studies, the current research on psilocybin for depression has several methodological limitations, which must be considered when interpreting and comparing findings. Acknowledgement of these limitations is meant to inform future research directions and clinical implementation considerations.

Sample size constraints affect most studies in this field. The vast majority of reviewed studies on psilocybin included relatively small numbers of participants (for example 12

in one of Carhart-Harris's et al. study, later expanded to 20) limiting statistical power and the ability to identify predictors of response or perform meaningful subgroup analyses. While the consistency of findings across studies somewhat addresses this limitation, larger trials are needed to establish robust efficacy and safety profiles. The trial performed by Goodwin et al., which included a sample size of more than 200 is a good step forward. Blinding also presents a particular challenge in psilocybin research due to the compound's distinctive psychoactive effects. Goodwin et al. and Carhart-Harris et al. acknowledged that most participants and therapists could correctly guess whether active drug or placebo was administered, potentially introducing expectancy bias (35,36). Various strategies have been employed to address this, including active placebos with mild psychoactive effects and different trial designs, but, as pointed out by van Elk and Fried, perfect blinding remains elusive (50). The influence of expectations is particularly relevant given the significant media attention surrounding psychedelic research. Davis et al. and Gukasyan et al. discussed how participants' expectations of benefit from this highly publicized treatment approach might inflate therapeutic responses (29,31). Distinguishing drug effects from expectancy effects remains methodologically challenging. Selection of control conditions varies across studies. While some, including Von Rotz et al. and Goodwin et al., used placebo controls, others employed waiting lists, or, in the case of open-label studies, did not utilise any control condition at all (30,35). This heterogeneity complicates direct comparisons between studies and meta-analyses of the literature. Long-term follow-up data, while growing, remains limited. Gukasyan et al. provided valuable 12-month follow-up data, and Carhart-Harris et al. reported 6-month outcomes, but many studies have focused on short-term effects, or effects up to 4 weeks, which is also a matter of debate, as to what is considered long-term (31,34). Understanding the durability of psilocybin's antidepressant effects and potential need for treatment maintenance requires extended observation periods. Generalizability concerns arise from the highly selected nature of study populations. Participants typically underwent extensive screening, excluding those with personal or family history of psychosis, serious suicide risk, and various comorbidities common in clinical practice. The intensive psychological support provided in research settings as well as the long duration of sessions (6-8 hours) may also be difficult to replicate in routine care, raising questions about real-world effectiveness. The optimal therapeutic protocol remains undetermined, with variations in dosing, number of sessions and psychological support approaches across studies. Determining the essential components of effective treatment will require dismantling the design of studies.

Despite these limitations, the consistency of positive findings across studies with different designs and research teams suggests that psilocybin's antidepressant effects are robust. However, addressing these methodological challenges in future research will be essential for establishing psilocybin as a robust treatment option for depression.

5.2 Ketamine

Several methodological constraints limit the extendibility of ketamine research findings. Sample sizes in key trials remain modest, particularly for novel formulations – for example Glue et al. included 168 participants in their tablet study, while Zolghadriha et al. enrolled 89 patients, limiting subgroup analyses and statistical inferences (45,47). However, even these trials achieve sample sizes considerably larger compared to most psilocybin trials, and thus provide greater extendibility of findings through statistical relevance. One reason for this may be that psilocybin is treated more cautiously and as a result researchers include more strict screening protocols. This, in turn, could be due to psilocybin's controversial political and legal history (15,51). Though, this is merely our speculation.

Blinding challenges persist due to ketamine's unique and acute psychoactive effects; Loo et al. used midazolam as an active control but noted 78% of participants correctly guessed their treatment arm, potentially deflating placebo responses (46). Heterogeneous control conditions and trial design complicate cross-trial comparisons – Pattanasari et al. used saline placebo as a control for daily IV ketamine, whereas Daly et al. compared intranasal esketamine to placebo nasal spray alongside oral antidepressants (39,44). Population generalizability is constrained by wide exclusion criteria. Ohtani et al. excluded patients with personality disorders, while Ionescu et al. focused exclusively on acutely suicidal individuals, limiting understanding of ketamine's effectiveness in complex comorbid cases (38,43). Industry sponsorship introduces potential bias, with many ketamine studies funded by pharmaceutical companies, including one pharmaceutical company's pivotal esketamine trials (40,41). Dosing variability further complicates clinical translation. Kopelman et al. employed single IV doses, whereas Ionescu et al. tested repeated administrations without consensus on optimal frequency (28,42). The lack of standardized psychological support protocols – ranging from minimal monitoring to structured therapy – creates uncertainty about essential treatment components. These limitations underscore the need for large, independently funded trials comparing administration methods and frequency across diverse populations with long-term follow-up.

6. Clinical Considerations and Possible Future Directions

The emergence of psilocybin and ketamine as novel treatments for depression presents both opportunities and challenges for clinical practice. Although their efficacy profiles are promising, several considerations regarding implementation must be addressed to optimize therapeutic outcomes and ensure patient safety. Both compounds require specialized administration protocols that differ significantly from conventional antidepressant treatments, necessitating systemic changes in healthcare delivery. For psilocybin-assisted therapy, the intensive psychotherapeutic framework poses logistical challenges. Current studies use dedicated clinical spaces, extended session durations (6-8 hours) and teams of trained therapists – resources that may not be readily available in standard mental health settings. Ketamine’s various administration routes (intravenous, intranasal, subcutaneous) provide flexibility but require careful consideration of adverse effects. Future research could utilise head-to-head comparisons between psilocybin and ketamine, as their distinct mechanisms and effect profiles may suit different patient subgroups. The development of standardized protocols for “set and setting” optimization, particularly for psilocybin (but also for other psychedelic hallucinogens like LSD and DMT), requires international consensus among researchers. To that end designing and conducting trials on different therapeutic contexts for psilocybin sessions with standardized dosing regimens, could help in achieving a solution. Tracking outcomes with longitudinal studies will be essential to fully understand the durability of treatment effects and long-term safety profiles.

7. Conclusions

The accumulated evidence from clinical trials strongly supports both psilocybin and ketamine as valuable additions to the depression treatment repertoire. Psilocybin demonstrates remarkable potential for producing sustained antidepressant effects through a model combining pharmacological action with psychotherapeutic support in a unique way. Its ability to induce and facilitate psychological breakthroughs offers a paradigm-shifting approach to depression treatment, particularly for patients who have not responded to conventional therapies. However, safety may differ for populations excluded from the reviewed studies during their respective screening processes. Ketamine and its enantiomer esketamine provide crucial rapid-onset intervention capabilities, filling a need in urgent suicidality management. The established efficacy across diverse administration routes and some patient populations underscores its versatility, though requires

careful safety monitoring, especially in the long-term. The development of novel formulations aims to optimize efficacy and practicality in clinical implementation. Both treatments challenge traditional diagnostic and treatment paradigms, emphasizing the need for updated clinical guidelines. Their distinct mechanisms of action highlight the extremely varied nature of depression's pathophysiology and the importance of personalized approaches to treatment. While significant challenges remain in scaling these interventions, the therapeutic potential they represent justifies a continued and increased investment in their research.

As these novel approaches transition from research settings to clinical practice, maintaining scientific rigor will be essential to realizing their full public health potential. The coming decade will likely see these treatments evolve from experimental interventions to mainstream options, fundamentally reshaping the landscape of depression care.

Declarations of interest: The authors declare that they have no conflict of interest.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Authors contributions: Christian S. Skowron: study conceptualization, formal analysis, writing of the original draft, and final draft review and editing; Urszula Miłkowska: final draft review and editing; Gabriela Maria Piech: writing of the original draft, and final draft review and editing; Igor Lis : writing of the original draft, and final draft review and editing; Piotr Kurzyrna: formal analysis, final draft review and editing

References:

1. Maldonado-García JL, García-Mena LH, Mendieta-Cabrera D, Pérez-Sánchez G, Becerril-Villanueva E, Alvarez-Herrera S, et al. Use of Extracellular Monomeric Ubiquitin as a Therapeutic Option for Major Depressive Disorder. *Pharmaceuticals*. 2024 Jun 27;17(7):841.
2. Kim KY, Shin KY, Chang KA. Potential Inflammatory Biomarkers for Major Depressive Disorder Related to Suicidal Behaviors: A Systematic Review. *Int J Mol Sci*. 2023 Sep 9;24(18):13907.
3. Gong X, Chang R, Zou J, Tan S, Huang Z. The role and mechanism of tryptophan - kynurenine metabolic pathway in depression. *Rev Neurosci*. 2023 Apr 25;34(3):313–24.
4. Obuobi-Donkor G, Nkire N, Agyapong VIO. Prevalence of Major Depressive Disorder and Correlates of Thoughts of Death, Suicidal Behaviour, and Death by Suicide in the Geriatric Population—A General Review of Literature. *Behav Sci*. 2021 Oct 21;11(11):142.
5. Veluri N, Mansuri Z. How effective are ketamine or esketamine in treatment-resistant depression? *Eur Psychiatry*. 2021 Aug 13;64(Suppl 1):S330.

6. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv Wash DC*. 2014 Aug 1;65(8):977–87.
7. Ivanets NN, Svistunov AA, Chubarev VN, Kinkulkina MA, Tikhonova YG, Syzrantsev NS, et al. Can Molecular Biology Propose Reliable Biomarkers for Diagnosing Major Depression? *Curr Pharm Des*. 2021;27(2):305–18.
8. Remmers MCC, Reijs RP, Hoebe CJP. Defining and distinguishing early life stress, trauma, adversity, toxic and chronic stress and allostatic load: a descriptive review. *Scand J Public Health*. 2024 Aug 1;14034948241260105.
9. Khalifa MA, Salaheldin AO, Elsead JA, Aboud FA, Korim BM, Abdalstar SS, et al. Assessing the Impact of Gepirone on Major Depressive Disorder - A systematic review and meta analysis. *Alzheimers Dement*. 2025 Jan 9;20(Suppl 8):e095197.
10. van Hees MLJM, Rotter T, Ellermann T, Evers SMAA. The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: a systematic review. *BMC Psychiatry*. 2013 Jan 11;13:22.
11. Pappa *Sofia, Shah M, Young S, Anwar T, Ming T. CLINICAL AND ECONOMIC BURDEN OF MAJOR AND TREATMENT- RESISTANT DEPRESSION IN A POPULATION-BASED STUDY COHORT OF 110.000 PATIENTS. *Int J Neuropsychopharmacol*. 2025 Feb 12;28(Suppl 1):i20.
12. Di Salvo G, Perotti C, Ricci V, Maina G, Rosso G. Efficacy and suitability of adding short-term psychodynamic psychotherapy (STPP) to pharmacotherapy in patients with depressive disorders: a systematic review. *Trends Psychiatry Psychother*. 2024 Apr 30;
13. Schlaepfer TE, Agren H, Monteleone P, Gasto C, Pitchot W, Rouillon F, et al. The hidden third: improving outcome in treatment-resistant depression. *J Psychopharmacol Oxf Engl*. 2012 May;26(5):587–602.
14. Youssef NA, McCall WV. Relapse prevention after index electroconvulsive therapy in treatment-resistant depression. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr*. 2014 Nov;26(4):288–96.
15. Torres S. Psychedelics: A new era of treatment? *Eur Psychiatry*. 2021 Aug 13;64(Suppl 1):S483.
16. Bright S, Williams M, Caldicott D. Should addiction researchers be interested in psychedelic science? *Drug Alcohol Rev*. 2017 May;36(3):285–7.
17. Forstmann M, Sagioglou C. New Insights Into the Clinical and Nonclinical Effects of Psychedelic Substances: An Integrative Review. *Eur Psychol*. 2022 Oct;27(4):291–301.
18. Stewart LH. The dissociative psychedelic renaissance. *J Psychedelic Stud*. 2018 Dec;2(2):61–3.
19. Bartoli F, Cavaleri D, Riboldi I, Crocamo C, de Filippis R, Zandonella Callegger R, et al. The Resistant Depression Response to Esketamine Assessing Metabolomics (ReDREAM) Project—Untargeted Metabolomics to Identify Biomarkers of Treatment Response to Intranasal Esketamine in Individuals with Treatment-Resistant Depression: A Study Protocol. *Alpha Psychiatry*. 2024 Aug 1;25(4):555–60.
20. de Filippis R, De Fazio P. Esketamine nasal spray in severe bipolar depression with borderline personality disorder and history of multiple substance abuse: A case report. *Bipolar Disord*. 2023 Sep;25(6):524–6.
21. Thaiboonruang N, Lohitnavy M, Lohitnavy O. Pharmacokinetics of Psilocybin, a Tryptamine Alkaloid in Magic Mushroom (*Psilocybe cubensis*): A Systematic Review. *J Psychoactive Drugs*. 2024 Sep 10;1–13.

22. Carhart-Harris RL, Leech R, Erritzoe D, Williams TM, Stone JM, Evans J, et al. Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis. *Schizophr Bull.* 2013 Nov;39(6):1343–51.
23. Siegel JS, Subramanian S, Perry D, Kay BP, Gordon EM, Laumann TO, et al. Psilocybin desynchronizes the human brain. *Nature.* 2024;632(8023):131–8.
24. Zhao X, Du Y, Yao Y, Dai W, Yin Y, Wang G, et al. Psilocybin promotes neuroplasticity and induces rapid and sustained antidepressant-like effects in mice. *J Psychopharmacol Oxf Engl.* 2024 May;38(5):489–99.
25. Kinderlehrer DA. Mushrooms, Microdosing, and Mental Illness: The Effect of Psilocybin on Neurotransmitters, Neuroinflammation, and Neuroplasticity. *Neuropsychiatr Dis Treat.* 2025 Jan 29;21:141–55.
26. Kritzer MD, Mischel NA, Young JR, Lai CS, Masand PS, Szabo ST, et al. Ketamine for treatment of mood disorders and suicidality: A narrative review of recent progress. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr.* 2022 Feb;34(1):33–43.
27. Kang MJY, Hawken E, Vazquez GH. The Mechanisms Behind Rapid Antidepressant Effects of Ketamine: A Systematic Review With a Focus on Molecular Neuroplasticity. *Front Psychiatry.* 2022 Apr 25;13:860882.
28. Kopelman J, Keller TA, Panny B, Griffio A, Degutis M, Spotts C, et al. Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. *Transl Psychiatry.* 2023 May 9;13:159.
29. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2021 May 1;78(5):481–9.
30. von Rotz R, Schindowski EM, Jungwirth J, Schuldt A, Rieser NM, Zahoranszky K, et al. Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. *eClinicalMedicine.* 2023 Feb 1;56:101809.
31. Gukasyan N, Davis AK, Barrett FS, Cosimano MP, Sepeda ND, Johnson MW, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *J Psychopharmacol (Oxf).* 2022 Feb 1;36(2):151–8.
32. Pigott HE, Kim T, Xu C, Kirsch I, Amsterdam J. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. *BMJ Open.* 2023 Jul 25;13(7):e063095.
33. Carhart-Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry.* 2016 Jul 1;3(7):619–27.
34. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl).* 2018 Feb 1;235(2):399–408.
35. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N Engl J Med.* 2022 Nov 2;387(18):1637–48.

36. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of Psilocybin versus Escitalopram for Depression. *N Engl J Med*. 2021 Apr 14;384(15):1402–11.
37. Goodwin GM, Croal M, Feifel D, Kelly JR, Marwood L, Mistry S, et al. Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2023 Sep;48(10):1492–9.
38. Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021 Jan 1;24(1):22–31.
39. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2019 Sep 1;76(9):893.
40. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *Int J Neuropsychopharmacol*. 2019 Oct 1;22(10):616–30.
41. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry*. 2019 Jun 1;176(6):428–38.
42. Ionescu DF, Bentley KH, Eikermann M, Taylor N, Akeju O, Swee MB, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. *J Affect Disord*. 2019 Jan;243:516–24.
43. Ohtani Y, Tani H, Nomoto-Takahashi K, Yatomi T, Yonezawa K, Tomiyama S, et al. Efficacy and safety of intravenous ketamine treatment in Japanese patients with treatment-resistant depression: A double-blind, randomized, placebo-controlled trial. *Psychiatry Clin Neurosci*. 2024 Dec;78(12):765–75.
44. Pattanaseri K, Lortrakul J, Jaisin K, Srifuengfung M, Sa-Nguanpanich N, Viravan N, et al. A randomized controlled pilot study of daily intravenous ketamine over three days for treatment-resistant depression. *BMC Psychiatry*. 2024 Jul 18;24(1):512.
45. Zolghadriha A, Anjomshoa A, Jamshidi MR, Taherkhani F. Rapid and sustained antidepressant effects of intravenous ketamine in treatment-resistant major depressive disorder and suicidal ideation: a randomized clinical trial. *BMC Psychiatry*. 2024 May 7;24(1):341.
46. Loo C, Glozier N, Barton D, Baune BT, Mills NT, Fitzgerald P, et al. Efficacy and safety of a 4-week course of repeated subcutaneous ketamine injections for treatment-resistant depression (KADS study): randomised double-blind active-controlled trial. *Br J Psychiatry J Ment Sci*. 2023 Dec;223(6):533–41.
47. Glue P, Loo C, Fam J, Lane HY, Young AH, Surman P, et al. Extended-release ketamine tablets for treatment-resistant depression: a randomized placebo-controlled phase 2 trial. *Nat Med*. 2024 Jul;30(7):2004–9.
48. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression—TRANSFORM-3. *Am J Geriatr Psychiatry*. 2020 Feb;28(2):121–41.

49. Knochel C, Alves G, Friedrichs B, Schneider B, Schmidt-Rechau A, Wenzler S, et al. Treatment-resistant Late-life Depression: Challenges and Perspectives. *Curr Neuropsychopharmacol*. 2015 Oct 13;13(5):577–91.
50. van Elk M, Fried EI. History repeating: guidelines to address common problems in psychedelic science. *Ther Adv Psychopharmacol*. 2023 Jan 1;13:20451253231198466.
51. Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society*: Second Edition. Aeon Books; 2020. 402 p.