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Treatment-Resistant Depression: A Literature Review of Innovative and Emerging Treatment Strategies

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ABSTRACT

Introduction and objective: Major depressive disorder (MDD) is a heterogeneous psychiatric condition characterized by affective, cognitive and somatic symptoms that considerably impair daily functioning. It is defined clinically by prolonged low mood, diminished interest or pleasure, and a range of associated disturbances, including changes in cognitive skills, appetite, and sleep patterns. Although many treatment strategies are well-established and available, not all patients achieve satisfactory improvement. Treatment-resistant depression (TRD), often defined as insufficient response to at least two antidepressant trials of proper dose and duration, represents a major therapeutic challenge. This review aims to present and assess emerging treatment strategies for TRD, focusing on their mechanisms, effectiveness and safety.

Brief description of the state of knowledge: Recent advances in the understanding of depression pathophysiology have initiated the development of new therapeutic approaches

targeting various systems thought to be involved in mood regulation. Glutamatergic modulators, such as ketamine and esketamine, have demonstrated prompt antidepressant effects, particularly in patients with severe or refractory symptoms. Neuromodulatory techniques, including repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), remain important treatment options with growing research interest. Simultaneously, heightened attention has been directed toward psychedelic-assisted therapies, especially psilocybin, which may produce sustained antidepressant effects through modulation of various neural networks. Additionally, invasive interventions such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are being studied for resistant cases, although their use remains limited.

Summary: Emerging therapies for TRD offer promising alternatives to conventional treatment strategies, particularly for patients not responding to routine interventions. Further research is crucial for the optimization of therapeutic outcomes and integration of those novel approaches into clinical practice.

Keywords: treatment-resistant depression, TRD, ketamine, esketamine, glutamatergic modulators, repetitive transcranial magnetic stimulation, rTMS, electroconvulsive therapy, neuromodulation, psychedelic therapy, psilocybin, vagus nerve stimulation, deep brain stimulation

Introduction and purposes

Major depressive disorder (MDD) is a common and disabling psychiatric condition manifesting with constant low mood, anhedonia, cognitive impairment, loss of interest in previously enjoyed activities, sleep disturbances and suicidal thoughts In 2018, major depressive disorder was ranked third in terms of disease burden worldwide according to the WHO, and by 2030 it is predicted to rank first [1] . Beyond its role in quality of life, depression is linked with increased morbidity and a higher risk of suicide, which emphasizes the urgent need for effective therapeutic strategies.

Despite the availability of various pharmacological and non-pharmacological treatments, including numerous varieties of antidepressant medication and diverse forms of psychotherapy,

a substantial share of patients still fail to achieve remission. Although the widely available, conventional antidepressants, which primarily target monoaminergic neurotransmission, show effectiveness for many individuals, in some of them the treatment response is delayed, incomplete, or even absent. Therefore, a considerable proportion of patients experience persistent depressive symptoms despite standard therapeutic interventions.

Treatment-resistant depression (TRD) does not have a specific definition in common literature, but is most frequently defined as a form of major depressive disorder in which patients do not respond properly to at least two antidepressants administered at correct doses within the duration of one major depressive episode [2]. Patients with treatment-resistant depression show higher rates of psychiatric and somatic coexisting conditions, larger and more persistent functional impairment and generate significantly greater use of healthcare resources, resulting in elevated medical and psychiatric treatment costs [3]. TRD presents a major clinical challenge and points to the limitations of traditional approaches.

Improved understanding of the complex neurobiology of depression has contributed to the emergence of innovative treatment strategies, some of which are targeted at alternative neural pathways. These approaches include glutamatergic modulators such as ketamine and esketamine, neuromodulatory interventions including repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), as well as various augmentation strategies. In addition, psychedelic-assisted therapies, including agents such as psilocybin, have gained an increasing research interest and show promising potential as new treatment options for patients with treatment-resistant depression.

In light of ongoing developments in this field, this literature review attempts to provide an overview of emerging therapeutic approaches for treatment-resistant depression and to summarize current evidence regarding their efficacy and clinical potential.

Methods

This systematic review was prepared to recognize and synthesize current evidence regarding emerging therapeutic approaches for treatment-resistant depression (TRD). Literature search was performed using the PubMed and Google Scholar databases.

The following keywords were used in various combinations: “treatment-resistant depression,” “TRD,” “ketamine,” “esketamine,” “glutamatergic modulators,” “repetitive transcranial

magnetic stimulation," "rTMS," "electroconvulsive therapy," "neuromodulation," "psychedelic therapy," and "psilocybin", „vagus nerve stimulation", „deep brain stimulation"

Ketamine

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a rapid-acting antidepressant in patients with treatment-resistant depression [4]. The antidepressant effects of ketamine are believed to result mainly from the modulation of glutamatergic neurotransmission. By blocking NMDA receptors on inhibitory neurons, ketamine leads to increased glutamate release and activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [5]. This process causes downstream pathways linked with synaptic plasticity, including increased expression of brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin (mTOR) pathway [5]. Finally, this reaction promotes synaptogenesis and strengthening of neural connections in regions of the brain that partake in mood regulation [5].

Unlike conventional antidepressants, which typically require several weeks to result in clinical improvement, ketamine has been shown to induce remarkably quick effects. Various randomized controlled trials have shown that intravenous ketamine leads to a rapid and meaningful reduction in depressive symptoms in patients with treatment-resistant depression, with improvement noted as early as a few hours following infusion [6]. Reported response rates after a single infusion range from approximately 50% to 70% within the first two to three days, a number considerably higher than those observed with conventional therapies [7]. In other studies, treatment with ketamine was associated with a substantial decrease in MADRS scores compared with placebo, indicating a clinically meaningful improvement in depressive symptoms [8].

Despite the impressive and swift onset of action, the antidepressant effects of a single ketamine infusion are often transient. In many patients, symptom improvement begins to diminish after several days to one week. Therefore, multiple dose protocols have also been investigated in clinical trials, with repeated infusions delivered over a number of days or weeks. These studies show the possibility that recurrent dosing may prolong the response and improve outcomes in patients with TRD [9].

In addition to questions regarding the durability of its antidepressant effects, concerns have also been raised about the safety of ketamine treatment. Although ketamine is generally well tolerated when administered in controlled clinical settings, it is associated with several temporary adverse effects. The most commonly reported include dissociation, nausea, headache and dizziness as well as short increases of blood pressure, which typically happen right after administration and settle within a few hours [9]. Furthermore, the potential for abuse remains an important aspect due to ketamine's psychoactive properties. Long-term safety data regarding repeated administration are still limited, and more research is needed to understand the potential consequences of longer treatment courses [9]. The promising antidepressant effects of ketamine have also led to the development of intranasal esketamine, the S-enantiomer of ketamine, which has also been investigated in several clinical trials for the treatment of resistant depression.

Esktamine

Esketamine is the S-enantiomer of ketamine, which exhibits a higher affinity for the NMDA receptor compared with the racemic form of ketamine [10] Due to its pharmacological properties and potential for prompt antidepressant effects, intranasal esketamine has been introduced as a new treatment option for patients with treatment-resistant depression. The intranasal route of administration allows for easier use compared with intravenous ketamine infusions.

Large clinical trials have demonstrated the efficacy of intranasal esketamine in reducing depressive symptoms in patients with treatment-resistant depression. In the TRANSFORM-2 trial, patients receiving intranasal esketamine in combination with an oral antidepressant showed markedly greater reductions in MADRS scores compared with those receiving placebo and an oral antidepressant [11]. In addition to the TRANSFORM studies, another randomized trial comparing esketamine nasal spray with extended-release quetiapine showed notably higher remission rates and greater reductions in depressive symptoms in the esketamine group [12]. As for the comparison between ketamine and its S-enantiomer, a randomized study established that antidepressant effects of esketamine were not inferior to those observed with intravenous ketamine, showing that both therapeutic approaches may come with similar short-term improvements in depressive symptoms [13].

Evidence from maintenance studies also suggest that continued treatment with intranasal esketamine may be necessary to uphold its antidepressant effects. In the SUSTAIN-1 trial, patients who achieved a clinical response or remission and continued the treatment in combination with an oral antidepressant had a considerably lower risk of relapse compared with those who were switched to placebo while continuing oral antidepressant therapy [14].

Intranasal esketamine may be associated with similar adverse effects to ketamine, including dissociation, dizziness, nausea, temporary increases in blood pressure [9]. Due to its psychoactive properties and safety concerns, esketamine administration is restricted to certified healthcare settings where patients can be monitored after each dose.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that changes neuronal activity in targeted cortical regions through rapidly changing magnetic fields generated by a coil placed on the scalp. These magnetic pulses induce small electrical current in the cortical tissue below it, consequently influencing neuronal excitability and synaptic activity [15] . rTMS may either increase or decrease cortical excitability. In the treatment of treatment-resistant depression (TRD), the most commonly used protocol involves high-frequency stimulation of the dorsolateral prefrontal cortex, which is a brain region involved in the regulation of mood and cognitive control [15] . Evidence from randomized controlled trials and meta-analyses shows that rTMS represents an effective and well-tolerated therapeutic option for patients with TRD, leading to reductions in depressive symptoms with a desirable safety profile compared with more invasive neuromodulatory interventions [16]. In addition, the development of accelerated stimulation protocols, such as theta burst stimulation (TBS), has augmented the clinical utility of rTMS by reducing the duration of treatment while sustaining comparable effectiveness [17].

Early works, evaluating the efficacy of rTMS in TRD demonstrated that high-frequency stimulation of the left dorsolateral prefrontal cortex produced significantly greater reductions in depressive symptom severity compared with sham stimulation in patients who had not responded to adequate antidepressant treatment [18]. These findings were later supported by larger randomized clinical trials examining modern stimulation protocols, such as the THREE-D trial. That trial showed comparable efficacy of theta burst stimulation and conventional rTMS in patients with depression [19].

Evidence for the use of rTMS in treatment-resistant depression has been further strengthened by meta-analyses. These analyses indicate that active rTMS causes a drop in the severity of depressive symptoms compared with placebo across diverse patient populations and protocols [20]. Importantly, available data also suggest that the antidepressant effects of rTMS may be maintained in some individuals with repeated treatment courses following the acute treatment phase [21].

In recent years, research has focused on optimizing stimulation guidelines to improve the usage and accessibility of rTMS. One of such developments is intermittent theta burst stimulation (iTBS), a form of stimulation that delivers bursts of high-frequency pulses over a shorter treatment duration. Trials and subsequent analyses have demonstrated that iTBS achieves antidepressant effects comparable to those of conventional high-frequency rTMS while reducing the length of single treatment sessions [19].

One of the major advantages of rTMS is its favorable safety profile. The most commonly reported adverse effects include scalp discomfort or headache at the site of stimulation, which are generally temporary and resolve on their own [22]. Unlike electroconvulsive therapy (ECT), rTMS does not require general anesthesia and moreover, it is not associated with cognitive impairment, which makes it an option worth considering for many patients with TRD. The risk of serious adverse events, such as seizures, is believed to be very low when the safety standards are followed [22].

Electroconvulsive therapy

Although electroconvulsive therapy does not strictly belong to novel and emerging treatment strategies, it still remains one of the most effective therapeutic approaches for treatment-resistant depression. Furthermore, it continues to serve as an important benchmark for evaluating newer strategies. Despite being introduced several decades ago, ECT demonstrates consistently high response and remission rates, particularly in patients with severe, psychotic, or life-threatening depression, especially those with high suicidal risk [23].

The antidepressant efficacy of ECT is generally considered superior to that of pharmacotherapy and comparable or, in some cases, greater than that of neuromodulatory techniques such as rTMS. However, its use is often limited by several practical considerations. ECT requires general anesthesia and specialized medical infrastructure, which may limit its availability for some patients. In addition, concerns about cognitive adverse effects, especially transient

memory impairment, remain a significant aspect, often discouraging the medical professionals and patients from accepting of the treatment [24].

In the context of emerging therapies for treatment-resistant depression, ECT provides a valuable reference point for efficacy, especially when assessing rapid-acting interventions such as ketamine or novel neuromodulation strategies. While newer treatments may offer advantages in terms of tolerability, accessibility, or patient preference, only a few have consistently demonstrated antidepressant effects of similar magnitude to ECT in severe cases of depression. Thus, current research efforts focus on developing approaches that can replicate the efficacy of ECT while minimizing its limitations. This includes advances in neuromodulation techniques, such as optimized rTMS protocols, as well as pharmacological innovations, including glutamatergic agents and psychedelic-assisted therapies.

Psychedelic-assisted therapies

Psychedelic-assisted therapies have emerged as one of the most controversial as well as most intensively researched new approaches in the treatment of depression, including treatment-resistant depression (TRD). Among classic psychedelics, psilocybin is currently the most studied compound and has generated the strongest clinical evidence so far. Interest in this field has been driven by the observation that unlike conventional antidepressants, psychedelics may produce a quick and in some cases also sustained antidepressant effects after one or only a few administrations [25]. That differentiates them from standard monoaminergic treatments, which typically require daily dosing lasting over a few weeks in order to yield any noticeable improvement. In the context of TRD, where delayed response and frequent treatment failure are major clinical problems, such a rapid-acting effect has attracted a deserved attention.

The proposed mechanism of action of psilocybin is complex and involves both acute receptor level pharmacology and long-lasting systemic changes in brain function. Psilocybin is a prodrug that is dephosphorylated to psilocin, which acts primarily as an agonist of serotonin 5-HT2A receptors. These receptors are densely expressed in cortical association regions involved in self-reference processing, affective regulation, and cognition. Activation of 5-HT2A signaling is thought to increase cortical excitability and destabilize patterns of network activity that may lie at the basis of depressive cognition, including rumination and cognitive inflexibility [26]. Studies have also suggested that psychedelics promote structural and functional neuroplasticity, with evidence indicating increased dendritic remodeling, synaptic strengthening, and plasticity-related signaling cascades. An influential study published in 2023 suggested that psychedelic-induced plasticity may depend on activation of intracellular 5-

HT2A receptors, offering a biologically possible explanation for the prolonged therapeutic effects that can outlast the acute subjective experience [27]

At the level of brain networks, psychedelic agents appear to briefly change functional organization at a large scale, which may be especially relevant in depression. Neuroimaging research works have reported decreased integrity of rigid network connectivity and increased communication between normally segregated networks, including changes involving the default mode network, salience network, and associative systems. These findings are commonly interpreted as reflecting a temporary relaxation of maladaptive previous assumptions and enhanced neural flexibility. A 2024 study showed that psilocybin produces noticeable desynchronization of normal brain activity patterns [28], while another 2024 study suggested that psilocybin and escitalopram [29] working together may improve depressive states through distinct reconfigurations of the hierarchy of brain dynamics. Although the exact relationship between these network effects and antidepressant response remains unclear, they support the viewpoint that psychedelic therapy may work not simply by improving monoamine deficits, but by allowing for a broader reorganization of pathological emotional and cognitive patterns.

Clinical evidence for psilocybin in depressive disorders is becoming significant, although the evidence base in TRD populations remains more limited than in larger major depressive disorder cohort studies. Early research suggested rapid symptom reduction after psilocybin administered with psychological support, but the most important milestone for TRD was the phase 2 double-blind trial published in the New England Journal of Medicine in 2022. In that study, a single 25 mg dose of synthetic psilocybin caused a notably larger decrease in depression severity at 3 weeks than a 1 mg control dose, whereas the 10 mg dose did not clearly differentiate from control group. The antidepressant effect was therefore dose dependent, and the 25 mg dose proved as the most clinically relevant in that trial [25]. More recently, authors have investigated repeated dosing and long term outcomes, including a 2026 randomized study in JAMA Psychiatry indicating that psilocybin was generally tolerable but a second 25 mg administration did not produce clear additional short-term benefit during the study period [30]. Taken together, these findings suggest that psilocybin can exhibit meaningful antidepressant effects in at least a part of patients with treatment-resistant depression, but the optimal dosing schedule and maintenance strategy remain undiscovered.

Psilocybin has also been studied outside TRD populations, and those data are often discussed because they help to put its antidepressant potential in context. In a important comparative trial, psilocybin-assisted therapy was compared with escitalopram in patients with depression. Although the primary endpoint did not show a statistically significant difference, several secondary outcomes favored psilocybin [31]. These results have often been interpreted with caution, but they strengthened the message that psychedelic therapy may achieve antidepressant effects that are at least clinically comparable to already known pharmacological options in some patients.

Safety-wise, psilocybin appears promising but should not be described as risk-free. In controlled clinical environments, the most commonly reported adverse effects are temporary and include anxiety during the acute experience, headache, nausea, mild increases in blood pressure and heart rate, fatigue, and vomiting [32]. Serious medical toxicity is rare in supervised trials, and psilocybin does not appear to cause dependence. However, important safety considerations remain. Trials and recent safety reviews have noted episodes of transient suicidal thoughts, worsening depression, severe anxiety, perception disturbances, and rare concerns about psychotic or manic reactions, particularly in susceptible individuals [33]. Accordingly, modern studies usually exclude patients with current psychotic disorders, bipolar disorder, or significant instability, and they focus on careful screening, psychological support, and controlled settings of administration.

Although psilocybin remains the leading substance in depression research, other classic psychedelics are also being investigated. Ayahuasca, a psychedelic brew containing N,N-dimethyltryptamine (DMT) together with monoamine oxidase-inhibiting beta-carbolines, has shown rapid antidepressant effects in a randomized placebo-controlled trial in treatment-resistant depression [34]. It should be noted that the available studies remain relatively small. DMT itself has attracted growing interest because of its very short duration of action, which may make it more practical for medical settings than psilocybin. By contrast, evidence for LSD in depression is still less developed, despite increasing research activity. At present, LSD is more often discussed as a relevant comparator or as an investigational option rather than as a treatment for TRD. Overall, the current literature suggests that psilocybin remains the most clinically advanced classic psychedelic for depressive disorders, while DMT and ayahuasca may represent important next-generation candidates requiring further research in larger trials.

In summary, psychedelic-assisted therapies represent a highly promising but still evolving area in the management of TRD. Their advantage stems from a combination of rapid antidepressant action, potential durability after limited dosing, and a mechanistic profile that appears to go above traditional monoaminergic models towards neuroplasticity, network reorganization, and psychological flexibility. Nevertheless, important questions remain regarding patient selection, durability of benefit, comparing efficacy against established treatments and long-term safety. For these reasons, psychedelic therapies should currently be viewed as emerging interventions with meaningful potential, but not yet as routine standard treatment.

Vagus nerve stimulation and deep brain stimulation

Beyond non-invasive neuromodulation approaches such as rTMS, more invasive brain stimulation techniques have also been explored in treatment-resistant depression, particularly in patients with frequently relapsing illness. Among these, vagus nerve stimulation (VNS) and deep brain stimulation (DBS) represent important but still specialized strategies. Although both methods have shown antidepressant potential, their clinical role remains more limited than that of other emerging therapies because of their invasive nature, higher cost, and the need for surgery.

Vagus nerve stimulation involves implantation of a pulse generator connected to the left cervical vagus nerve, providing intermittent electrical stimulation over long periods. Its antidepressant mechanism is not fully understood, but available evidence suggests that VNS primarily acts through afferent vagal fibers projecting to the nucleus tractus solitarius and then to brainstem and forebrain networks involved in mood regulation [35].

Clinically, VNS appears to have a relatively slow onset but may provide sustained benefit in a subset of patients with severe TRD. Earlier short-term trials produced various findings, but more recent long-term and controlled studies have strengthened the case for VNS in treatment-resistant major depression. In particular, a one-year randomized trial found that VNS was safe and effective in this population, and a related analysis reported improvements in daily functioning and quality of life [36]. These data fit the view that VNS may be more valuable as a long-term neuromodulation strategy than as a rapid-acting intervention. VNS is generally considered well tolerated, although adverse effects related to both implantation and active stimulation are common. The most frequently reported problems include hoarseness, throat discomfort, cough, dyspnea, and voice alteration during stimulation. Serious complications

such as infection or revision surgery are less common but remain important when investigating the risk to benefit ratio of this treatment [37]

Deep brain stimulation is an even more invasive neuromodulation technique and remains investigated in depression. It involves a stereotactic implantation of electrodes into specific neural targets followed by chronic electrical stimulation delivered by an implanted pulse generator. In TRD, several anatomical targets have been explored, including the subcallosal cingulate cortex, ventral capsule, ventral striatum, nucleus accumbens, and medial forebrain bundle. The theoretical mechanism for DBS is that severe depression reflects dysfunctional activity within distributed cortical and limbic and reward-related circuits, and that direct modulation of these networks may help to restore emotional processing [38].

The clinical efficacy of DBS has been promising but inconsistent. Open-label studies and long-term follow-up reports have suggested substantial benefit in carefully selected patients, but randomized sham-controlled trials have not always shown meaningful improvement [38]. Recent reviews and meta-analyses therefore conclude that DBS still has therapeutic potential, but that the evidence remains insufficient for routine use outside highly specialized centers and research settings. Patient safety is also a major issue for DBS. In addition to neurosurgical risks such as hemorrhage, infection, and technical complications, psychiatric adverse effects including anxiety, hypomania, emotional blunting, and suicidality have been reported [39].

Overall, both VNS and DBS illustrate the growing interest in circuit-based models of depression. While neither currently hold a central place in standard TRD treatment algorithms, both remain important for understanding future directions in neuromodulation for the most refractory patients.

Summary

The expanding range of therapeutic strategies for treatment-resistant depression reflects a shift toward more diverse and mechanism-based approaches. Pharmacological innovations such as ketamine and esketamine, neuromodulatory techniques including rTMS and ECT, as well as emerging interventions like psychedelic-assisted therapies and invasive stimulation methods, highlight the broad complexity of the disorder and the need for tailoring treatment options to individual patient characteristics. Together, these approaches broaden the available options beyond conventional therapies.

Despite promising findings, many of these strategies are limited by issues related to accessibility, safety, and the persistence of their effects. Moreover, diversity across studies makes it difficult to compare outcomes and establish new and reliable treatment algorithms. Additional studies are therefore necessary to define the role of these interventions and to improve outcomes for patients with the largest unmet needs.

Disclosure:

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