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Novel treatments of depression: bridging the gap in current therapeutic approaches

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Abstract

Depression poses a significant global health burden, yet current therapeutic approaches focusing on monoaminergic neurotransmission often fall short of achieving full remission and managing acute episodes effectively. This article explores novel treatment avenues beyond conventional monoaminergic approaches, focusing on emerging strategies targeting glutamatergic modulation, electrophysiological/magnetic brain stimulation techniques, anti-inflammatory agents, gut-brain axis interventions, gamma-aminobutyric acid (GABA) modulation, and psychedelic-assisted therapy. Through a narrative review of recent literature, this paper elucidates the mechanisms, clinical efficacy, safety profiles, and future directions of these innovative treatments. These insights offer valuable perspectives for advancing depression management and bridging existing therapeutic gaps.

Keywords

Depression, therapeutic approaches, glutamatergic modulation, brain stimulation, anti-inflammatory agents, gut-brain axis, GABA modulation, psychedelic-assisted psychotherapy

Introduction

Depression, a pervasive mental health disorder, continues to exact a profound toll on global well-being, affecting millions of individuals across diverse demographics. According to the World Health Organization (WHO), depression is a leading cause of disability worldwide, with an estimated 280 million people grappling with its debilitating effects as of the most recent global health assessment [1].

The conventional understanding of depression, as posited by the monoamine hypothesis, has long shaped the landscape of antidepressant pharmacotherapy. This theory implicates imbalances in neurotransmitters, particularly serotonin, norepinephrine, and dopamine, as the primary culprits in the pathophysiology of depression [2]. While this framework has guided the development of various antidepressant medications over the past several decades, the persistence of treatment-resistant

depression (TRD) and the significant limitations associated with existing therapies underscore the complexity of the disorder and the need for innovative treatment strategies.

Despite the availability of a diverse array of antidepressants, ranging from selective serotonin reuptake inhibitors (SSRIs) to tricyclic antidepressants (TCAs), a substantial proportion of individuals with depression do not achieve full remission with current treatments [3]. Moreover, the delayed onset of therapeutic effects, a common characteristic of traditional antidepressants, poses a significant challenge in the management of acute depressive episodes. The side effect profiles of these medications, including weight gain, sexual dysfunction, and gastrointestinal disturbances, further limit their tolerability and long-term adherence [4].

The recognition of these therapeutic gaps, coupled with a deepened understanding of the multifactorial nature of depression, has spurred a growing interest in exploring novel treatments. The imperative to develop interventions that not only address the limitations of current therapeutics but also target novel pathways and mechanisms associated with depression underscores the urgency to innovate in the realm of mental health. As we delve into the intricate web of neural, inflammatory, and gut-brain axis connections implicated in depression, this narrative review aims to unravel and evaluate the latest advancements in the quest for novel treatments of depression.

Methodology

We initially did a scoping search of PubMed to identify novel treatment strategies for depression in humans used in the last 10 years. Both unipolar and bipolar depression diagnoses were included in the scoping search. The search strategy included searching for medical subject headings (MeSH) terms "major depressive disorder" OR "bipolar disorder" AND the term "treatment" in the Title/Abstract. After creating a list of novel treatment strategies, a focused search was done on PubMed with MeSH terms "major depressive disorder" AND "X", where "X" included each treatment strategy from the list created. Initially, systematic review and meta-analysis filters were used to identify such study types. Other filters like randomized control trials or clinical trials were used if these were unavailable. We reviewed papers on the efficacy of the novel treatments. This search strategy was used as the scope of this paper was to do a narrative review rather than a systematic review.

Treatment modalities

Pharmacologic agents

Ketamine/Esketamine

In the last decade, the discovery of rapid antidepressant effects of subanesthetic doses of ketamine has shifted the focus from the traditional monoaminergic hypothesis of depression. Glutamatergic dysfunction is increasingly being implicated in the pathophysiology of depression [5]. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is involved in various neural processes, including synaptic plasticity, learning, and memory. Synaptic plasticity is crucial for normal cognitive and emotional functioning [6].

The *N*-methyl-*D*-aspartate (NMDA) and alpha amino-3-hydroxy-5-methyl-4-isoxzole propionic acid (AMPA) receptors are types of glutamate receptors that are involved in synaptic plasticity, learning, and memory. Changes in the function or expression of these receptors may disrupt these processes and contribute to depressive symptoms [6]. Glutamate is also linked to the expression of neurotrophic factors, which support the growth, survival, and function of neurons. Reduced levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), have been implicated in depression [7]. The success of ketamine in rapidly alleviating depressive symptoms is thought to be related to its modulation of the glutamatergic system through NMDA antagonism and activation of AMPA receptors [8].

In clinical practice, ketamine is typically used to treat depression through intravenous, intramuscular, or intranasal administration. The intravenous dosage commonly ranges around 0.5 mg/kg, delivered over

30–40 minutes under blood pressure, heart rate, and temperature monitoring. It can be administered either independently or alongside another antidepressant. For patients who do not respond to the standard 0.5 mg/kg dose, a higher dosage of 0.75 mg/kg or 1 mg/kg may be considered suitable [9]. Several randomized controlled trials (RCTs) have demonstrated the effectiveness of a single intravenous infusion of ketamine in treating depression that is resistant to standard treatments [5, 10]. A meta-analysis of 36 RCTs, which included nine trials using esketamine and the remainder using racemic ketamine, indicated that treatment with any form of ketamine was linked to improved response rates [pooled rate ratios (RAR) = 2.14; 95% confidence interval (CI): 1.72–2.66; I^2 = 65%], higher rates of remission (RAR = 1.64; 95% CI: 1.33–2.02; I^2 = 39%), and reduction in depression severity [Cohen's standardized mean difference (d) = –0.63; 95% CI: –0.80 to –0.45; I^2 = 78%] compared to placebo. There was no significant association found between either form of ketamine treatment and dropouts due to adverse events (RAR = 1.56; 95% CI: 1.00–2.45; I^2 < 1%), or with the overall number of adverse events reported per participant (RAR = 2.14; 95% CI: 0.82–5.60; I^2 = 62%) compared to placebo [11]. The role of ketamine in adolescent and geriatric depression is less well-defined. A systematic review of 13 studies for depression in ages ≤ 18 and ≥ 60 years found that ketamine treatments resulted in rapid antidepressant effects (≤ 2 weeks latency), with better outcomes following larger, repeated doses and in open-label rather than blinded settings. The heterogeneity and poor quality of included studies limit the conclusions of this review [12].

The US Food and Drug Administration (FDA) approved intranasal esketamine (the *S*-enantiomer of ketamine) in 2019 for treating adults with TRD [13]. Its efficacy in TRD has been demonstrated in several short-term RCTs [14, 15]. A double-blind withdrawal study involving 297 adult TRD patients who achieved remission or response with esketamine treatment revealed that continuing treatment with esketamine nasal spray alongside oral antidepressants significantly delayed relapse compared to antidepressants plus placebo, demonstrating clinically meaningful superiority [16].

In the US, intranasal esketamine is exclusively accessible through a Risk Evaluation and Mitigation Strategy (REMS) program. Under this program, the medication is exclusively dispensed to certified medical facilities catering to specific patients enrolled in a dedicated registry. Patients undergo self-administration of the medication within the facility and receive continuous monitoring by healthcare professionals for a minimum of two hours post-administration. Esketamine is securely stored within the facility and is not permitted to be taken outside. This stringent program is implemented to ensure the safety of patients and prevent any potential misuse or diversion of the medication [13, 17]. The initial dose of intranasal esketamine for TRD on the first day of treatment typically amounts to 56 mg (28 mg in each nostril), with subsequent doses ranging from 56 mg to 84 mg based on individual efficacy and tolerability levels. Treatment sessions are typically conducted twice weekly [17].

A meta-analysis of 24 RCTs (1877 participants) showed that racemic ketamine compared to esketamine demonstrated greater overall response (RAR = 3.01 vs. RAR = 1.38) and remission rates (RAR = 3.70 vs. RAR = 1.47), as well as lower dropouts (RR = 0.76 vs. RR = 1.37) [18].

Common side effects of ketamine in the treatment of depression include dissociation, hallucinations, confusion, elevation of blood pressure and heart rate, nausea, vomiting, and dizziness [19].

Anti-inflammatory agents

Depression is no longer viewed solely through the lens of neurotransmitter imbalances; the immune system's involvement, particularly the inflammatory response, has gained prominence. Mounting evidence suggests a complex interplay between inflammation and depressive disorders. Elevated levels of cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been consistently observed in individuals with depression. These cytokines can trigger neuroinflammation and disrupt neuroregulatory processes, contributing to the development and persistence of depressive symptoms [20].

Anti-inflammatory agents like non-steroidal anti-inflammatory drugs, omega-3 fatty acids, statins, and minocycline have been tried in depression in several RCTs. A meta-analysis of 26 RCTs suggested that anti-

inflammatory agents reduced depressive symptoms [standardized mean difference (SMD) = –0.55, 95% CI: –0.75 to –0.35, I_2 = 71%] compared with placebo. Higher response (RAR = 1.52, 95% CI: 1.30 to 1.79, I_2 = 29%) and remission rates (RAR = 1.79, 95% CI: 1.29 to 2.49, I_2 = 41%) were seen in the group receiving anti-inflammatory agents than in those receiving placebo. Subgroup analysis showed a greater reduction in symptom severity in both the monotherapy and adjunctive treatment groups. Subgroup analysis of non-steroidal anti-inflammatory drugs, omega-3 fatty acids, statins, and minocycline, respectively, disclosed significant antidepressant effects for major depressive disorder [21].

Gamma-aminobutyric acid (GABA) modulators

GABA is the primary inhibitory neurotransmitter in the central nervous system, playing a crucial role in regulating neuronal excitability. In depression, there is evidence to suggest that there may be alterations in the GABAergic system, leading to an imbalance in excitatory and inhibitory neurotransmission [22]. Brexanolone, a neurosteroid and allosteric modulator of GABA-A receptors, has emerged as a potential therapeutic option for depression. Structurally resembling endogenous allopregnanolone, brexanolone primarily enhances GABA-mediated signaling by acting as a positive allosteric modulator of GABA-A receptors [23]. Previous research has implicated GABA in major depressive disorder, with reduced GABA levels correlating with increased depression scores, particularly in women at risk for postpartum depression (PPD) [24].

In March 2019, brexanolone became the first FDA-approved treatment specifically for PPD. Brexanolone is solely given to patients at healthcare facilities with restricted distribution programs, which allow monitoring of IV administration of the medication and ensure adherence to a REMS [25].

A meta-analysis of 3 RCTs involving 156 women with PPD who received brexanolone infusion, and 111 women with PPD on placebo, demonstrated that brexanolone resulted in significantly greater response rates compared to placebo. The response began within 24 hours [risk ratio (RR) = 1.34, 95% CI: 1.03–1.73], peaked at 36 hours (RR = 1.50, 95% CI: 1.06–2.13, P = 0.02)], and persisted until Day 7 (RR = 1.32, 95% CI: 1.01–1.73). Similarly, women with PPD treated with brexanolone experienced significantly higher rates of remission, commencing at 24 hours (RR = 1.86, 95% CI: 1.03–3.34), peaking at 60 hours (RR = 2.20, 95% CI: 1.31–3.70), and lasting until 72 hours (RR = 1.96, 95% CI: 1.41–2.72). The rates of discontinuation due to intolerability and adverse drug reactions were similar between the brexanolone group and the placebo group [26].

Psychedelics

Psychedelics have a long history of use in various cultures for spiritual, religious, and healing purposes. Substances like psilocybin-containing mushrooms have been used ceremonially by indigenous peoples for centuries. Additionally, substances like LSD (lysergic acid diethylamide) were synthesized in the mid-20th century and initially explored for their potential therapeutic benefits before becoming associated with the counterculture movement of the 1960s. In the mid-20th century, researchers began to investigate the therapeutic potential of psychedelics for various mental health conditions, including depression. Early studies suggested that psychedelics could facilitate profound psychological experiences and promote emotional insight, leading to potential therapeutic benefits. However, this research was halted in the 1970s due to regulatory restrictions and cultural backlash [27].

Over the past decade, there has been a resurgence of interest in psychedelics, such as psilocybin, MDMA (3,4-methylenedioxy-*N*-methylamphetamine), and LSD, as potential tools in mental health care, especially in the treatment of depression. Psychedelics exert their effects primarily through the modulation of serotonin receptors, particularly the 5-HT2A receptor. This modulation leads to altered patterns of neural connectivity, increased neuroplasticity, and changes in default mode network (DMN) activity. These neurobiological changes are hypothesized to underlie the therapeutic effects of psychedelics in depression [28].

The efficacy of psychedelic-assisted psychotherapy has been assessed in several clinical trials and observational studies. A systematic review encompassing 14 studies on psychedelic-assisted psychotherapy

involving substances like psilocybin, ayahuasca, or LSD revealed significant short- and long-term reductions in depressive symptoms across all conditions studied when administered with psychological support. In the meta-analysis of 7 RCTs included in this review, symptom reduction was notably observed at three out of four time points: 1-day, 1-week, and 3–5 weeks post-administration, although the evidence was less conclusive at the 6–8 weeks follow-up point. Nonetheless, due to the limited number of studies, poor study designs, and small sample sizes, caution is warranted in interpreting these findings [29].

One critical aspect of psychedelic research is the assessment of safety and tolerability. While psychedelics are generally well-tolerated, it is crucial to acknowledge potential risks, such as acute psychological distress, dependence potential, and exacerbation of pre-existing mental health conditions. Rigorous screening protocols and supportive therapeutic settings are essential to mitigate these risks. Future studies should focus on standardizing treatment protocols, addressing regulatory hurdles, and further elucidating the long-term effects and potential risks [30].

Probiotics, prebiotics, and anti-inflammatory diet

Emerging research in nutritional psychiatry has highlighted the potential influence of gut microbiota on mental health, specifically the bidirectional communication between the gut and the brain, known as the gut-brain axis. Probiotics and prebiotics, pivotal components of this intricate system, have gained attention for their potential role in alleviating depressive symptoms [31].

Probiotics, live microorganisms that confer health benefits to the host when administered in sufficient quantities, exhibit promise in modulating the gut microbiome and subsequently impacting mental health. Numerous studies indicate that specific probiotic strains, including *Lactobacillus* and *Bifidobacterium*, possess anti-inflammatory and neuroprotective effects, potentially ameliorating depressive symptoms. Chronic inflammation, implicated in depression's pathophysiology, may be mitigated by the anti-inflammatory properties of select probiotic strains. Furthermore, probiotics can influence the synthesis and metabolism of neurotransmitters like serotonin and GABA, which play pivotal roles in mood regulation. Alterations in these pathways, linked to mood disorders, are associated with changes in the gut microbiota's production of neurotransmitter precursors [31].

Prebiotics, non-digestible fibers that selectively stimulate beneficial gut bacteria, complement probiotics in maintaining a healthy gut microbiome. Examples include lactulose, inulin, fructo-oligosaccharides, and galactose derivatives. Although research on prebiotics and depression is ongoing, mounting evidence suggests their potential impact on mental health. Prebiotics foster the growth of beneficial bacteria, enhancing microbial diversity. This diversity correlates with the production of short-chain fatty acids (SCFAs), which play a role in neuroinflammation and mood modulation. Additionally, prebiotics may fortify gut barrier function by upregulating tight junction proteins, reducing intestinal permeability. A compromised gut barrier, associated with systemic inflammation, is hypothesized to contribute to mood disorders [31].

In a case-control study by Mason et al. [32] microbiota characterization in participants with major depression comorbid with anxiety revealed a significant correlation between anhedonia scores and gut *clostridiales*. Despite a small sample size (60 participants) and predominantly female (82%) inclusion, the study demonstrated that altered clostridial populations were associated with depression. Specifically, the absence of *Clostridia* correlated with depression, while reduced *Bacteroides* levels were linked to anxiety [32].

In a 12-week, randomized, double-blind, placebo-controlled multicenter trial, Kim et al. [33] investigated the impact of probiotics on cognition and mood in healthy older adults (age > 65). Participants received either *Bifidobacterium* bifidum or longum. Gut microbiota analysis via 16s RNA sequencing revealed reduced inflammation-causing bacteria, improved mental flexibility, lower stress scores, and significantly increased serum brain-derived natriuretic peptide (BDNF) levels [33].

In an RCT, Schaub et al. [34] investigated probiotic supplementation's effects on depressive symptoms in major depressive disorder patients. Participants received a multi-strain probiotic or placebo for 31 days.

Results revealed decreased HAM-D (Hamilton Depression Rating Scale) scores, maintained microbial diversity, increased *Lactobacillus* abundance, and reduced putamen activation in response to neutral faces. Caution is warranted due to the study's small sample size [34].

Some studies have investigated the potential of an anti-inflammatory diet as an intervention for major depression. Diets abundant in whole grains, choline (found in eggs, broccoli, and cauliflower), and betaine possess anti-inflammatory properties [35]. A meta-analysis involving 11 studies revealed a notable association between a pro-inflammatory diet and an elevated risk of depression diagnosis or symptoms compared to those adhering to an anti-inflammatory diet [odds ratio (OR): 1.40, 95% CI: 1.21–1.62, $P < 0.001$] [36]. Similarly, some small RCTs have shown significant antidepressant effects of curcumin, a principal curcuminoid found in turmeric (*Curcuma longa*) when added to standard care [37].

Electrophysiological/Magnetic stimulation techniques

Ketamine-assisted electroconvulsive therapy

ECT has long been used for the treatment of depression and is considered the gold-standard treatment for depression [8]. It has been proven to be more effective than antidepressant medications and is reserved for TRD, suicidality, and catatonia [38]. In recent years, the combination of ketamine with ECT has emerged as an innovative approach in the treatment of depression, addressing the need for more effective and rapidly acting interventions. When administered in conjunction with ECT, ketamine may enhance the overall therapeutic outcomes. The synergy between these two modalities is thought to arise from ketamine's ability to modulate glutamatergic neurotransmission and induce neuroplastic changes, potentially augmenting the neurobiological mechanisms activated by ECT.

The studies on ketamine augmentation of ECT have yielded mixed results [39]. A meta-analysis of 16 RCTs showed that though ketamine augmentation did not improve response or remission rates or depressive symptom scores at the end of ECT, the depressive scores were lower in the initial ECT sessions, indicating a quicker onset of action. However, it also resulted in increased adverse events, especially related to cardiovascular and psychiatric systems, during the whole ECT course [40]. Hence, ketamine-assisted ECT might be helpful in cases where rapid antidepressant effects are desired (e.g., suicidality).

Repetitive transcranial magnetic stimulation (rTMS)

rTMS has emerged as a promising non-invasive neuromodulation technique for the treatment of depression in adults. rTMS operates on the principle of electromagnetic induction, targeting specific brain regions implicated in mood regulation. The magnetic fields generated during rTMS penetrate the skull and modulate neuronal activity, leading to changes in synaptic plasticity, neurotransmitter release, and connectivity within neural circuits associated with mood regulation, such as the dorsolateral prefrontal cortex (DLPFC). Studies suggest that rTMS may influence neurotransmitter levels, particularly serotonin, dopamine, and norepinephrine, which play crucial roles in mood regulation. The precise neurobiological mechanisms underlying rTMS's antidepressant effects are still under investigation, but evidence supports its ability to induce neuroplastic changes in the brain [41].

In 2008, the US FDA granted approval for rTMS as a treatment for TRD in adults [42]. Typically, for the acute treatment of unipolar major depression, rTMS involves daily stimulation of the left dorsal lateral prefrontal cortex over a period of four to six weeks, administered from Monday to Friday. Following successful acute treatment, maintenance sessions can be gradually reduced. Common types of stimulation used in rTMS include surface cortical stimulation (high frequency or low frequency), theta burst stimulation, and deep stimulation [43].

Numerous clinical trials have investigated the efficacy of rTMS in various populations of depressed individuals [44–47]. Meta-analyses and systematic reviews consistently report significant antidepressant effects of rTMS compared to sham stimulation, with response rates and remission rates exceeding those of placebo in several studies. A meta-analysis combining data from 23 RCTs comparing rTMS with sham treatment demonstrated a statistically significant improvement in depression scores with rTMS [weighted

mean difference (WMD) 2.31, 95% CI: 1.19–3.43; $P < 0.001$)]. The risk ratios for remission and response were 2.20 (95% CI: 1.44–3.38, $P = 0.001$) and 1.72 (95% CI: 1.13–2.62, $P = 0.01$), respectively, indicating a favorable outcome for rTMS in both measures. This meta-analysis also evaluated six RCTs comparing rTMS with ECT, revealing a statistically and clinically significant distinction between the two treatments, favoring ECT (WMD 5.97, 95% CI: 0.94–11.0, $P = 0.02$). The risk ratios for remission and response were 1.44 (95% CI: 0.64–3.23, $P = 0.38$) and 1.72 (95% CI: 0.95–3.11, $P = 0.07$), respectively, indicating a preference for ECT in both outcomes [48].

It has also been found to be effective and safe in the treatment of depression in the elderly. A meta-analysis of 14 RCTs involving patients aged 50 years and above revealed that active rTMS was more effective than sham treatment in reducing severity (SMD = 0.36; 95% CI: 0.13–0.60), as well as increasing response rates (OR = 3.26; 95% CI: 2.11–5.04) and achieving remission (OR = 4.63; 95% CI: 2.24–9.55) [49].

The effectiveness of rTMS in treating adolescent depression remains uncertain due to the scarcity of available studies. A systematic review and meta-analysis of rTMS in adolescents, encompassing 2 RCTs and 8 uncontrolled studies, suggested that rTMS could potentially be more beneficial for younger individuals and those with more severe depression. Moreover, the study hinted at the possibility of increased efficacy with specific treatment settings, such as a higher number of TMS sessions, longer treatment durations, and unilateral rather than bilateral stimulation [50]. However, it's important to approach these findings cautiously due to the methodological constraints of the studies included in the analysis. Though rTMS is not yet approved by the FDA for adolescent depression, the FDA recently cleared NeuroStar advanced therapy TMS for use as an adjunct for the treatment of major depressive disorder in adolescent patients aged 15–21. This was based on an analysis of real-world data collected through NeuroStar's proprietary TrakStar® platform [51].

rTMS is generally considered safe and is associated with mild and transient adverse effects, such as scalp discomfort, headache, and, rarely, seizures. The overall safety profile of rTMS supports its use as a well-tolerated intervention for depression [52]. Ongoing research focuses on ways to tailor rTMS protocols to individual patients, its synergistic effects when combined with other interventions, and its long-term effects beyond the acute treatment phases.

Magnetic seizure therapy (MST)

MST, a non-invasive brain stimulation technique, involves the application of magnetic pulses to induce controlled seizures. Unlike ECT which causes widespread stimulation of cortical and subcortical brain regions, MST specifically targets key brain regions implicated in depression, such as the DLPFC. Magnetic pulses generate a seizure with fewer cognitive side effects than traditional ECT, making MST an attractive option for patients who may be intolerant to ECT [53].

A systematic review of 8 studies, including 4 comparative RCTs with ECT, of MST in TRD reported significant antidepressant effects, with remission rates ranging from 30% to 40%, compared to the 50%–70% remission rates with ECT. The precise mechanisms through which MST exerts its antidepressant effects are not fully understood. However, it is believed that the controlled induction of seizures triggers neurobiological changes, including alterations in neurotransmitter release, synaptic plasticity, and neurotrophic factors. These changes may contribute to the observed improvements in mood and reduction of depressive symptoms [54]. Ongoing research is focused on optimizing the parameters of MST to further enhance its safety profile and refine its application in diverse patient populations.

Transcranial direct current stimulation (tDCS)

tDCS involves the application of a low electrical current (1 to 2 milliamps applied for a duration of 20 to 30 minutes per session) to the scalp through electrodes, modulating neuronal activity. The anode and cathode electrodes alter the resting membrane potential beneath the electrode sites, influencing cortical excitability and synaptic plasticity. Depression is associated with dysfunction in several brain networks, including the DMN, salience network, and executive control network. tDCS can modulate the activity and connectivity of these networks, restoring aberrant patterns of neural activation observed in depressed individuals. For

example, stimulation of the DLPFC, a key node in the executive control network, may enhance cognitive control processes and regulate emotional reactivity [55].

Several clinical trials have explored the efficacy of tDCS in treating depression. A meta-analysis pooling individual patient data from nine randomized, sham-controlled trials revealed that tDCS significantly outperformed sham treatment in terms of response rates [30.9% vs. 18.9% respectively; OR = 1.96, 95% CI: 1.30–2.95, numbers needed to treat (NNT) = 9] and remission rates (19.9% vs. 11.7%, OR = 1.94, 95% CI: 1.19–3.16, NNT = 13) [56]. However, the variability in protocols, electrode placements, and participant characteristics necessitate further research to establish standardized procedures and optimize treatment parameters.

One advantage of tDCS is its favorable safety profile. Reported side effects are generally mild and transient, including tingling sensations, itching, or mild discomfort at the electrode sites. The non-invasive nature of tDCS makes it an attractive option for individuals who may be hesitant to pursue more invasive treatments [57].

Deep brain stimulation (DBS)

Originally developed for movement disorders like Parkinson's disease, DBS involves the neurosurgical implantation of electrodes into specific brain regions to modulate neural activity. DBS for depression typically targets the subgenual cingulate cortex (SGC), a region implicated in mood regulation. Some studies have also explored other target areas like ventral capsule/ventral striatum (VC/VS), nucleus accumbens, and medial forebrain bundle (MFB). The electrodes implanted in this area deliver electrical impulses, modulating the neural circuits associated with depression. The exact mechanisms underlying the antidepressant effects of DBS are not fully understood, but research suggests that it may influence neurotransmitter systems, neural connectivity, and neuroplasticity [58].

Several clinical studies have explored the efficacy of DBS in alleviating symptoms of TRD. A systematic review and meta-analysis focusing on DBS for TRD, encompassing 2 RCTs and 8 open-label trials, revealed that patients receiving active treatment, as opposed to sham, experienced significantly higher response rates (OR = 5.50; 95% CI: = 2.79 to 10.85; $P < 0.0001$) and reductions in mean depression scores (SMD = –0.42; 95% CI: –0.72 to –0.12; $P = 0.006$). Nonetheless, the effect was somewhat diminished in certain subgroup and sensitivity analyses, indicating limited efficacy in sham-controlled RCTs [59]. The effectiveness of DBS in TRD highlights its potential as a therapeutic option for individuals who have not responded adequately to conventional treatments. However, the variability in individual responses and the need for further long-term studies necessitate a cautious interpretation of these findings.

While DBS shows promise, there are notable challenges and ethical considerations associated with its use in treating depression. Surgical risks, potential side effects, and the need for continuous monitoring are critical aspects that require careful consideration. Additionally, ethical concerns arise regarding patient autonomy, informed consent, and the potential for unintended consequences on personality and cognition [60]. Striking a balance between the potential benefits and risks is crucial for the responsible implementation of DBS in the treatment of depression. Hence, it remains an investigational treatment for depression.

Vagal nerve stimulation (VNS)

VNS, initially used for the treatment of pharmacoresistant epilepsy since 1997, was approved by the US FDA for TRD in July 2005. It operates on the premise that the vagus nerve, a key component of the autonomic nervous system, plays a crucial role in regulating mood and emotional states. The stimulation is typically delivered via a surgically implanted device that intermittently activates the vagus nerve in the neck, influencing various neurotransmitter systems, including serotonin and norepinephrine. It does so by activating the nucleus tractus solitarius, which in turn can modulate multiple regions of the brain via its neuronal connections to anatomically distributed subcortical and cortical regions of the brain [61].

A meta-analysis of open-label studies (7 studies, $N = 426$) found a response rate of 31.8% [62]. However, only 1 RCT ($N = 235$) has evaluated the efficacy of VNS versus a sham-control condition, with no significant differences in efficacy between the conditions at 12 weeks [63]. Long-term follow-up studies have also demonstrated sustained benefits, emphasizing the enduring impact of VNS on depressive disorders [64]. Recently, a non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) method has been developed to overcome the surgical risk and high procedural cost concerns with traditional VNS. A meta-analysis of 12 RCTs, mostly originating from China, shows low-quality evidence for the efficacy of taVNS compared to sham-taVNS and comparable response rates compared to antidepressants and that taVNS combined with antidepressants had comparable efficacy to antidepressants with fewer side effects [65].

VNS has generally been well-tolerated in clinical settings, with adverse effects typically limited to hoarseness and coughing during stimulation [66]. The safety profile of VNS positions it as a viable option for individuals who may not tolerate or respond to other interventions. Ongoing research is focused on refining stimulation parameters to enhance efficacy while minimizing side effects.

Conclusions

Table 1 summarizes the evidence base and FDA approval status for the above-discussed novel depression treatments. Innovative therapies targeting glutamatergic modulation, GABA modulation, anti-inflammatory pathways, interactions within the gut-brain axis, brain stimulation techniques, and psychedelic-assisted therapy offer promising avenues for addressing the multifaceted nature of depression. Of these approaches, intranasal esketamine has garnered significant attention within the realm of pharmacotherapy, while the utilization of ketamine infusion remains primarily within specialized clinical settings, primarily for cases of TRD. Nevertheless, the widespread adoption of these agents is constrained by their limited application scope.

Table 1. Evidence base and FDA approval for novel treatments of depression

Treatment modalities	Major depressive disorder	Treatment-resistant depression	Pediatric depression	Geriatric depression	Disadvantages	FDA approval
Intravenous ketamine	+	+	+/-	+/-	Limited availability	No
Esketamine	-	+	-	-	Limited indications	Yes[a]
Anti-inflammatory agents	+	-	-	-	Limited evidence base	No
Brexanolone	-	-	-	-	Only approved for PPD, intravenous use only	Yes[c]
Psychedelic-assisted psychotherapy	+/-	+/-	-	-	Regulatory constraints, limited evidence base	
Probiotics/prebiotics	+/-	-	-	-	Limited evidence base	No
Anti-inflammatory diet	+/-	-	-	-	Limited evidence base	No
Ketamine-assisted ECT	+	-	-	-	Conflicting evidence of efficacy	No
rTMS	+	+	+/-	+	Limited availability	Yes[a,b]
MST	-	+	-	-	Limited availability and indications; poorly defined treatment parameters	No
tDCS	+	-	-	-	Limited availability; poorly defined treatment parameters	No*
DBS	-	+	-	-	Invasive, poor acceptability, limited indications	No
VNS	-	+	-	-	Invasive, poor acceptability, limited indications	Yes[a]

+: Evidence present; -: no evidence; +/-: limited evidence; [a] approved in adult TRD; [b] cleared in adolescent MDD; [c] approved in Postpartum depression (PPD); * approved for clinical trials. ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation; MST: magnetic seizure therapy; tDCS: transcranial direct current stimulation; DBS: deep brain stimulation; VNS: vagal nerve stimulation

The use of anti-inflammatory agents and probiotics lacks substantial evidence to support their broad recommendation. Similarly, regulatory constraints and a limited evidence base have confined psychedelics to adjunct roles in psychotherapy settings. In the domain of brain stimulation, non-invasive techniques like rTMS present as the most well-supported and accessible options, while invasive methods such as VNS and DBS encounter comparatively less acceptance.

Concerning pharmacological interventions, augmenting ECT with ketamine yields conflicting evidence, necessitating further investigation into its dose-dependent effects. Future research endeavors should prioritize elucidating the mechanisms underlying these innovative treatments, refining treatment protocols, and ensuring their safety and efficacy across diverse patient cohorts.

The concept of personalized treatment strategies holds significant promise, underscoring the importance of ongoing innovation to advance depression management and enhance therapeutic outcomes. Continual investigation and refinement of these novel treatments stand to reshape the landscape of mental healthcare, offering hope for more effective interventions in the future.

Abbreviations

DBS: deep brain stimulation

DLPFC: dorsolateral prefrontal cortex

ECT: electroconvulsive therapy

FDA: Food and Drug Administration

GABA: gamma-aminobutyric acid

LSD: lysergic acid diethylamide

MST: magnetic seizure therapy

OR: odds ratio

PPD: postpartum depression

RAR: rate ratios

RCTs: randomized control trials

RR: risk ratio

rTMS: repetitive transcranial magnetic stimulation

taVNS: transcutaneous auricular vagus nerve stimulation

tDCS: transcranial direct current stimulation

TRD: treatment-resistant depression

VNS: vagal nerve stimulation

Declarations

Author contributions

AJ: Conceptualization, Investigation, Writing—original draft, Writing—review & editing

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The author declares that he has no conflicts of interest.

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Consent to participate

Not applicable.

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