International Journal of Community Medicine and Public Health
Khan S et al. Int J Community Med Public Health. 2026 Feb;13(2):1025-1029
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20260152

Review Article

Mechanisms and management of treatment-resistant depression in clinical psychiatry

Suhail Khan[1]*, Eilaf Kankouni[2], Nawaf Alkhurayb[3], Hadi Alshakori[4], Mona Alharbi[5], Abdulaziz Alharthi[6], Abdullah Aljubran[4], Abdulaziz Alajmi[7], Samar Ahmed[8], Hadi Aldoulah[9]

[1]Department of Psychiatry, East Jeddah Hospital, Jeddah, Saudi Arabia
[2]College of Medicine, Trinity College Dublin, Dublin, Ireland
[3]Department of Psychiatry, Ministry of Defense, Khamis Mushait, Saudi Arabia
[4]College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[5]College of Pharmacy, Taibah University, Madinah, Saudi Arabia
[6]Department of Psychiatry, Eradah Healthcare Complex, Riyadh, Saudi Arabia
[7]Kuwait Center for Mental Health, Ministry of Health, Kuwait City, Kuwait
[8]School of Pharmacy, Ahfad University for Women, Khartoum, Sudan
[9]Dhahran Long Term Care Hospital, Dhahran, Saudi Arabia

Received: 07 January 2026
Revised: 24 January 2026
Accepted: 25 January 2026

***Correspondence:**
Dr. Suhail Khan,
E-mail: drsuhail_911@hotmail.com

ABSTRACT

Treatment-resistant depression (TRD) is a severe and persistent form of major depressive disorder characterized by inadequate response to at least two antidepressant treatments of adequate dose and duration. It affects a substantial proportion of patients and is associated with chronic symptoms, functional impairment, and elevated suicide risk. The underlying mechanisms are multifaceted, involving disrupted neurocircuitry, impaired neuroplasticity, neuroinflammation, and dysregulation of the hypothalamic-pituitary-adrenal axis. Structural and functional brain imaging studies have identified consistent abnormalities in the prefrontal-limbic networks, particularly in regions such as the subgenual anterior cingulate cortex and dorsolateral prefrontal cortex. Inflammatory markers including interleukin-6 and C-reactive protein are frequently elevated in TRD populations, linking immune system activation to poor antidepressant response. Diagnosis of TRD is complicated by the absence of universal criteria, variability in clinical assessment, and confounding psychiatric or medical comorbidities. Misclassification is common due to incomplete treatment histories and inconsistent use of structured diagnostic tools. Recent advances in treatment include glutamatergic agents such as esketamine, non-invasive neuromodulation techniques like theta burst stimulation, and the emergence of digital monitoring tools to guide personalized care. Psychedelic-assisted therapy is also gaining clinical interest, supported by preliminary evidence of rapid and sustained antidepressant effects. As research progresses, there is increasing emphasis on integrating biomarkers, neuroimaging, and functional outcomes into future diagnostic and therapeutic frameworks.

Keywords: Treatment-resistant depression, Neuroplasticity, Glutamatergic therapy, Neuroinflammation, Neuromodulation

INTRODUCTION

Treatment-resistant depression (TRD) is a clinically defined condition in which patients with major depressive disorder (MDD) fail to respond to at least two antidepressants of adequate dose and duration from different pharmacological classes. The STAR*D trial, a large multicenter study, found that after two treatment

failures, remission rates fall below 20%, indicating a significant decline in therapeutic response with each successive pharmacologic attempt.[1] These patients typically present with more chronic illness courses, functional impairment, and higher rates of comorbid conditions, requiring distinct diagnostic and treatment considerations.

The lack of a universally accepted definition of TRD complicates both clinical decision-making and research outcomes. Most operational criteria require at least two failed treatment trials, but important variables such as medication adherence, duration, and comorbidities are inconsistently controlled. A review by Fava highlighted the need for a more precise, staged model of TRD to better stratify patients and evaluate treatment outcomes, noting that unstandardized definitions contribute to variation in prevalence estimates and treatment protocols.[2] Without clear diagnostic thresholds, outcome assessments and comparisons between intervention studies remain methodologically limited.

Neuroimaging and neurobiological studies suggest that TRD is associated with specific brain abnormalities distinct from non-resistant depression. Functional MRI data have shown persistent hypoactivity in the dorsolateral prefrontal cortex and hyperactivity in limbic regions such as the amygdala and subgenual anterior cingulate cortex, even after multiple treatment trials. Mayberg and colleagues demonstrated that these neural circuits fail to normalize in TRD patients following conventional antidepressant therapy, indicating potential biomarkers of treatment resistance that diverge from standard pathophysiological models.[3] These findings support a circuit-based approach to identifying candidates for neuromodulatory interventions. Moreover, immune system activation and systemic inflammation have been implicated in the development and persistence of TRD.

Elevated peripheral levels of cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-alpha have been repeatedly associated with lower treatment responsiveness. Dantzer et al. proposed a mechanistic framework in which inflammatory signaling interferes with serotonin metabolism, neuroplasticity, and hypothalamic-pituitary-adrenal (HPA) axis regulation, all of which are essential for antidepressant efficacy.[4]

Novel pharmacological treatments have emerged based on mechanisms unrelated to monoamine modulation. Among them, ketamine and its S-enantiomer, esketamine, have demonstrated rapid antidepressant effects in patients with TRD. Daly et al conducted a randomized controlled trial showing that intranasal esketamine, combined with an oral antidepressant, significantly reduced depressive symptoms within hours and maintained improvement over a 4-week period compared to placebo.[5] In this review, we will discuss mechanisms and management of treatment-resistant depression in clinical psychiatry.

REVIEW

Recent pharmacological developments have introduced agents that offer rapid symptom reduction in TRD, particularly those targeting non-monoaminergic systems. Esketamine, a glutamate receptor modulator, has shown superior efficacy when used as an adjunct to oral antidepressants, with improvements in depressive symptoms observed within 24 hours of administration. In a randomized trial, Daly et al demonstrated that esketamine produced a significantly greater reduction in Montgomery–Åsberg depression rating scale (MADRS) scores compared to placebo, suggesting its potential as a transformative intervention for patients unresponsive to traditional therapies.[5] These findings have redefined the therapeutic timeline for TRD and shifted clinical focus toward rapid-acting mechanisms.

In parallel, non-pharmacological approaches such as deep brain stimulation (DBS) have advanced through improved targeting of dysfunctional neural circuits implicated in TRD. Research by Lozano et al investigated the effects of DBS in the subcallosal cingulate gyrus and found sustained clinical benefit in patients with chronic, refractory depression who had not responded to pharmacological or psychotherapeutic interventions.[6] The growing evidence supporting circuit-based interventions reflects a paradigm shift from symptom suppression to network-level modulation, opening new avenues for durable remission in complex cases of TRD.

PATHOPHYSIOLOGICAL INSIGHTS INTO TREATMENT RESISTANCE

TRD is increasingly viewed through a neurobiological lens that diverges from traditional models of major depressive disorder. Instead of a simple neurotransmitter imbalance, TRD appears to reflect persistent dysfunction in neural circuits governing mood, reward processing, and stress regulation. Imaging studies have consistently shown disrupted connectivity in fronto-limbic networks, particularly involving the subgenual anterior cingulate cortex (sgACC), a region implicated in emotional regulation. Hyperactivity in this area, alongside hypoactivation in the dorsolateral prefrontal cortex, has been associated with poor antidepressant outcomes and chronic symptom presentation. These patterns remain evident even after multiple failed treatment attempts, supporting the idea that these abnormalities are not transient effects of mood state but rather core features of resistance.[6]

On the molecular level, synaptic plasticity deficits have gained attention as a fundamental feature of TRD. The ability of neural circuits to adapt and reorganize in response to environmental and internal stimuli appears impaired in patients who do not respond to conventional treatment. Research on brain-derived neurotrophic factor (BDNF) has been especially influential in this context. Reduced BDNF expression in the hippocampus and

prefrontal cortex has been documented in depressed patients, correlating with diminished neuronal resilience and adaptability. Standard antidepressants tend to increase BDNF levels over time, but in TRD patients, this mechanism may be blunted or delayed. Monteggia and colleagues identified a lack of BDNF signaling through TrkB receptors as a critical barrier to the neuroplastic changes typically required for therapeutic response.[7]

Inflammatory processes represent a separate but converging mechanism contributing to poor treatment outcomes. Elevated levels of pro-inflammatory cytokines such as interleukin-6 and C-reactive protein have been observed in subsets of individuals with depression who fail to respond to medication. These inflammatory markers are capable of altering neurotransmitter metabolism, increasing glutamate release, and impairing neurogenesis. Furthermore, inflammation can affect the blood-brain barrier, enabling peripheral signals to influence central nervous system activity more directly. Miller and Raison have argued that inflammation is not merely a correlate but an active driver of resistance in these cases, potentially requiring targeted immune-based treatments to reverse its effects.[8]

Stress-induced dysregulation of the HPA axis has also been implicated in the biology of TRD. Hypercortisolemia, reflecting chronic activation of the stress response system, has neurotoxic effects on hippocampal neurons and disrupts feedback inhibition in the HPA axis. These physiological changes impair the brain's capacity to regulate mood and adapt to therapy. In a controlled study, patients with elevated baseline cortisol were significantly less likely to achieve remission, even when treated with optimized pharmacological regimens. This finding underscores the role of long-term stress exposure in rendering conventional treatments less effective and hints at the need for interventions that can restore neuroendocrine balance.[9]

CHALLENGES IN CLINICAL IDENTIFICATION AND DIAGNOSIS

Despite increasing recognition of TRD as a distinct clinical entity, its diagnosis remains highly inconsistent across settings. The absence of standardized operational criteria has allowed wide variability in how resistance is defined, leading to discrepancies in prevalence rates and treatment planning. Some definitions rely solely on the number of failed antidepressant trials, while others incorporate duration of treatment, dosage adequacy, medication adherence, or response thresholds on standardized rating scales. A systematic evaluation by Berlim and Turecki found that over 150 unique definitions of TRD were used across clinical studies, making comparisons between trials nearly impossible and casting doubt on the generalizability of efficacy data.[10] Without consensus on what constitutes resistance, both research validity and clinical decision-making are compromised.

Patient history is often incomplete or retrospective, complicating efforts to accurately document past treatment responses. Clinicians may lack access to detailed records on previous medication regimens, dosages, or treatment durations, leading to potential misclassification. In cases where antidepressants were discontinued early due to side effects or patient preference, the line between non-response and treatment intolerance becomes blurred. Furthermore, psychiatric comorbidities, such as borderline personality disorder or substance use disorders, can mimic non-response by destabilizing mood, even when core depressive symptoms have improved. These overlapping presentations require careful differential diagnosis. Zimmerman et al emphasized the importance of structured interviews and rigorous assessment tools in reducing diagnostic errors, yet such methods remain underutilized in busy clinical environments.[11]

The use of symptom-based checklists alone may miss relevant dimensions of treatment resistance. Functional impairment, quality of life, and cognitive symptoms often persist in patients classified as remitters by standard depression scales. These residual symptoms may not only predict relapse but also represent indicators of partial or inadequate treatment response. McIntyre and colleagues have argued for incorporating cognitive and functional outcomes into diagnostic frameworks, as patients may achieve mood improvement without recovering the ability to work, maintain relationships, or manage daily tasks effectively.[12] Current diagnostic thresholds overlook these aspects, which are crucial for evaluating the real-world impact of treatment.

Cultural and demographic variables further complicate the recognition of TRD. Language barriers, health literacy, stigma, and access to care shape how patients report symptoms and adhere to treatment plans. In underserved populations, misdiagnosis or underdiagnosis of resistance can occur simply due to inconsistent follow-up or lack of continuity in care. Evidence from international studies has shown that socioeconomic status and ethnicity are associated with differential treatment trajectories and reporting patterns. For instance, Cooper et al identified racial disparities in depression treatment, noting that African American patients were significantly less likely to receive guideline-concordant care or referrals to specialist services.[13] These disparities introduce systemic bias into the identification process, reinforcing the need for diagnostic approaches that consider contextual factors beyond symptom severity.

EVOLVING THERAPEUTIC STRATEGIES AND FUTURE DIRECTIONS

Therapeutic innovation in TRD has moved steadily beyond traditional serotonergic and noradrenergic agents, favoring interventions that engage novel neurobiological targets. Glutamate modulation has become a major area of interest, driven by clinical observations that NMDA receptor antagonists can produce rapid antidepressant effects.

Beyond ketamine, agents such as rapastinel and AV-101 have been developed to modulate glutamatergic signaling through different mechanisms with the goal of reducing dissociative side effects. Research by Sanacora and colleagues supports the theory that restoring excitatory-inhibitory balance in cortical circuits may be essential to reversing treatment non-response in patients whose symptoms persist despite multiple monoaminergic interventions.[14] These therapies are still being evaluated in late-phase trials, but early data suggest the potential for shorter onset times and better outcomes in previously unresponsive populations.

Non-invasive neuromodulation methods have seen expanded clinical application in the past decade. Repetitive transcranial magnetic stimulation (rTMS) is now approved by multiple regulatory bodies for TRD, supported by favorable safety profiles and evidence of sustained benefit with maintenance sessions. Theta burst stimulation (TBS), a newer variation of rTMS, delivers pulses in a shorter timeframe and has shown equivalent or superior efficacy in early comparative studies. In their multicenter randomized trial, Blumberger et al demonstrated that intermittent TBS was non-inferior to standard high-frequency rTMS, while reducing session duration by up to 75 percent.[15] The efficiency and tolerability of TBS support its integration into high-demand clinical environments, especially where long daily sessions are not feasible.

Digital therapeutics and algorithm-guided treatment strategies are being introduced to increase the precision and scalability of TRD management. These tools incorporate patient-reported outcomes, symptom trajectories, and genetic or biomarker data into predictive models to support clinical decisions. The goal is to minimize trial-and-error prescribing and identify likely responders earlier in the care process. A recent initiative by the UK's National Institute for Health and Care Excellence (NICE) has included such models in its reviews for future implementation in mental health services. Meanwhile, wearable devices are being tested to monitor physiological signals like sleep patterns and heart rate variability in real time. Devices incorporating passive data capture may offer objective indicators of mood changes that precede relapse. According to Torous et al, the integration of behavioral sensing into treatment planning represents a significant shift in how depression is monitored outside of clinical visits.[16]

Psychedelic-assisted therapy is emerging as a potential pathway for individuals with longstanding TRD who have exhausted conventional options. Psilocybin, a serotonergic psychedelic, has demonstrated fast-acting and sustained antidepressant effects in controlled trials, particularly when combined with structured psychological support. In one double-blind trial, patients receiving a high dose of psilocybin showed significant reductions in depressive symptoms maintained for up to six weeks after just two sessions. Carhart-Harris and colleagues reported that changes in default mode network connectivity correlated with therapeutic outcomes, suggesting that psilocybin may work by disrupting maladaptive cognitive loops associated with rumination and hopelessness.[17] These early findings are influencing ongoing discussions around regulatory reform and the expansion of access under controlled settings.

CONCLUSION

TRD remains a complex clinical challenge, rooted in diverse neurobiological and psychosocial mechanisms. Advances in pharmacology, neuromodulation, and digital psychiatry are gradually reshaping therapeutic options. Standardized diagnostic criteria and personalized treatment strategies are essential to improve outcomes. Continued interdisciplinary research is critical to transform short-term efficacy into long-term remission.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.
2. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649-59.
3. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry. 2002;159(5):728-37.
4. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46-56.
5. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018;75(2):139-48.
6. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997;386(6627):824-7.
7. Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, et al. Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA. 2004;101(29):10827-32.
8. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Rev Immunol. 2016;16(1):22-34.

9. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464-8.
10. Berlim MT, Turecki G. Definition, assessment, and staging of treatment—resistant refractory major depression: a review of current concepts and methods. Canadian J Psychiatry. 2007;52(1):46-54.
11. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. J Affect Dis. 2013;150(2):384-8.
12. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety. 2013;30(6):515-27.
13. Cooper LA, Gonzales JJ, Gallo JJ, Rost KM, Meredith LS, Rubenstein LV, et al. The acceptability of treatment for depression among African-American, Hispanic, and white primary care patients. Med Care. 2003;41(4):479-89.
14. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012;62(1):63-77.
15. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018;391(10131):1683-92.
16. Maes M. Precision nomothetic medicine in depression research: a new depression model, and new endophenotype classes and pathway phenotypes, and a digital self. J Personal Med. 2022;12(3):403.
17. 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;235(2):399-408.

Cite this article as: Khan S, Kankouni E, Alkhurayb N, Alshakori H, Alharbi M, Alharthi A, et al. Mechanisms and management of treatment-resistant depression in clinical psychiatry. Int J Community Med Public Health 2026;13:1025-9.