Review Article
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Treatment-Resistant Depression: A Narrative Review of Pathophysiological Mechanisms, Biomarkers, and Novel Therapeutic Frontiers

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ABSTRACT:

Treatment-resistant depression (TRD) represents a major clinical and public health challenge, affecting a substantial proportion of patients with major depressive disorder who fail to achieve remission despite adequate pharmacotherapy. Emerging evidence suggests that TRD is a heterogeneous condition driven by complex interactions among neurobiological, inflammatory, and psychosocial factors. Advances in understanding pathophysiological mechanisms, including neuroinflammation, synaptic dysfunction, and neuroendocrine dysregulation, have facilitated the identification of potential biomarkers and the development of novel therapeutic strategies. This perspective explores current insights into the mechanisms underlying TRD, highlights promising biomarkers for diagnosis and treatment stratification, and discusses emerging therapeutic frontiers such as rapid-acting antidepressants, neuromodulation, and psychedelic-assisted therapy. Integrating these advances into clinical practice may enable a more personalized and effective approach to managing TRD.

INTRODUCTION:

Major depressive disorder (MDD) is among the leading causes of disability worldwide, with approximately 30–40% of patients failing to achieve remission following standard antidepressant interventions (1). This subgroup, commonly referred to as treatment-resistant depression (TRD), is associated with increased functional impairment, recurrent hospitalization, elevated suicide risk, and substantial healthcare burden (2).

Although TRD is often operationally defined as failure to respond to at least two antidepressant trials administered at an adequate dose and duration, important heterogeneity exists across clinical frameworks. The Maudsley Prescribing Guidelines in Psychiatry Maudsley Staging Method incorporates treatment duration, symptom severity, and previous treatment history, whereas the Massachusetts General Hospital (MGH) staging model evaluates cumulative treatment failures. Criteria used for regulatory approval of intranasal esketamine also differ from conventional definitions. Such variability complicates comparisons across studies and may influence biomarker interpretation and treatment outcomes (12,13).

Traditional monoaminergic theories alone have proven insufficient to explain treatment resistance. Contemporary evidence increasingly supports multifactorial models involving neuroinflammation, neuroplasticity deficits, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and abnormalities within neural circuitry regulating emotional processing (3,5,6). This perspective synthesizes current evidence regarding mechanisms underlying TRD, explores emerging biomarkers with potential predictive utility, and discusses novel therapeutic developments that may facilitate a transition toward precision psychiatry.

METHODS

A narrative literature review was conducted using PubMed and other relevant databases to identify studies on the pathophysiology and treatment of TRD. Search terms included "treatment-resistant depression," "neuroinflammation," "biomarkers," "ketamine," "esketamine," "neuromodulation," "psilocybin," and "precision psychiatry." Emphasis was placed on landmark studies, randomized controlled trials, systematic reviews, meta-analyses, and high-impact mechanistic investigations published in peer-reviewed journals. Studies were selected based on relevance, methodological quality, and contribution to understanding biological mechanisms and emerging therapeutic approaches in TRD.

RESULTS

Pathophysiological Mechanisms

Neurotransmitter Dysregulation Beyond Monoamines

While serotonin, norepinephrine, and dopamine remain central to depression models, TRD is increasingly linked to glutamatergic dysfunction and impaired synaptic plasticity. Alterations in NMDA receptor signaling and reduced brain-derived neurotrophic factor (BDNF) levels have been implicated in persistent depressive states (3,4).

Neuroinflammation

Increasing evidence supports chronic low-grade inflammation as a biologically relevant mechanism contributing to TRD. Multiple studies have demonstrated elevated concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), among patients exhibiting poor antidepressant response. These inflammatory mediators may alter monoaminergic transmission, reduce neurogenesis, impair synaptic plasticity, and disrupt glutamatergic signaling pathways (5).

Meta-analytic evidence suggests that patients with TRD exhibit significantly higher peripheral inflammatory markers than treatment-responsive individuals. Inflammatory cytokines can activate indoleamine-2,3-dioxygenase, diverting tryptophan metabolism toward the kynurenine pathway and reducing serotonin availability, while simultaneously generating neurotoxic metabolites. However, substantial heterogeneity exists across studies owing to differences in sample characteristics, antidepressant exposure, and comorbid conditions. Whether inflammation serves as a causal mechanism or a downstream consequence of chronic depressive illness remains debated (6).

HPA Axis Dysregulation

Persistent dysregulation of the HPA axis has emerged as another important contributor to treatment resistance. Chronic stress exposure may result in sustained hypercortisolemia, impaired glucocorticoid receptor sensitivity, and failure of negative feedback mechanisms. Elevated cortisol levels have been associated with hippocampal volume reduction and deficits in emotional regulation (6).

Longitudinal studies suggest that abnormal cortisol rhythms and impaired dexamethasone suppression may predict poor antidepressant response. However, findings remain inconsistent, partly because HPA

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abnormalities vary according to illness severity, duration, and psychiatric comorbidity.

Neural Circuit Dysfunction

Functional neuroimaging has shifted the conceptualization of TRD from isolated neurotransmitter abnormalities toward network-level dysfunction. Seminal work by Helen S. Mayberg and colleagues identified the subgenual anterior cingulate cortex as a key node in depression associated with treatment response and symptom modulation (14). Subsequent studies have demonstrated impaired connectivity among the prefrontal cortex, amygdala, hippocampus, and limbic structures in TRD populations. Dunlop et al. further reported that fronto-limbic connectivity patterns may predict differential treatment response, suggesting potential utility for imaging-guided interventions (15). Nevertheless, methodological limitations, including small sample sizes, variable imaging protocols, and heterogeneity in TRD definitions, have hindered the translation of findings into clinically applicable biomarkers (14,15).

Biomarkers in TRD

Inflammatory Biomarkers

C-reactive protein (CRP) and inflammatory cytokines have emerged as promising biomarker candidates. Raison et al. demonstrated that elevated inflammatory profiles may predict response to inflammation-targeted interventions, while Mahableshwarkar et al. reported associations between inflammatory markers and differential antidepressant outcomes (16,17). Higher CRP concentrations in particular have been associated with poorer response to conventional antidepressant therapies and may help identify biologically distinct depressive subtypes.

Neuroimaging Biomarkers

Structural MRI studies consistently demonstrate reduced hippocampal volume and altered connectivity patterns involving fronto-limbic networks. Functional imaging markers may predict response to neuromodulatory interventions, including TMS and DBS; however, reproducibility remains limited (14,15).

Genetic and Epigenetic Markers

Variants involving serotonin transporter genes, BDNF polymorphisms, and stress-response pathways may contribute to susceptibility to treatment resistance. Epigenetic mechanisms, including stress-induced DNA methylation changes, may further influence variability in antidepressant response (8).

Neuroendocrine Biomarkers

Altered cortisol rhythms and dexamethasone suppression abnormalities have demonstrated potential as adjunctive markers; however, their predictive validity remains insufficient for routine clinical implementation (6).

Rapid-Acting Antidepressants

Ketamine has transformed the TRD treatment landscape through rapid antidepressant effects occurring within hours. The landmark randomized trial by Murrough et al. demonstrated significantly greater antidepressant response with ketamine compared with midazolam (9). Subsequently, intranasal esketamine gained regulatory approval following evidence supporting efficacy in TRD populations. Maintenance studies by Daly et al. further demonstrated reduced relapse risk among patients receiving esketamine plus oral antidepressants (9,18).

The landmark randomized trial by Murrough et al. demonstrated significantly greater antidepressant response with ketamine compared with midazolam. More recently, intranasal esketamine gained regulatory approval following trials demonstrating efficacy when combined with oral antidepressants. Maintenance studies further suggest benefit in

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relapse prevention, although concerns remain regarding dissociation, accessibility, and long-term safety.

Neuromodulation Techniques

Repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy remain important interventions for TRD. Meta-analyses support the efficacy of rTMS targeting dorsolateral prefrontal regions, whereas ECT remains among the most effective treatments for severe and refractory depression.

Deep brain stimulation targeting structures, including the subcallosal cingulate, has demonstrated mixed findings. While early studies suggested benefit, larger trials have yielded inconsistent results, highlighting the need for improved patient selection and biomarker-guided targeting.

Psychedelic-Assisted Therapy

Initial investigations involving psilocybin suggested rapid and sustained antidepressant effects among patients with TRD; however, early studies were limited by small sample sizes and lack of controls (11). More recent evidence has substantially expanded the field. The COMP360 phase 2b trial by Goodwin et al. demonstrated clinically meaningful reductions in depressive symptoms among TRD patients receiving psilocybin-assisted therapy (19). Novel therapies such as ketamine, esketamine, and psychedelic-assisted interventions offer exciting opportunities (9,18,19). Additional programs, including USONA studies and emerging investigations involving MDMA-assisted psychotherapy, suggest broader therapeutic potential. Nonetheless, challenges involving expectancy effects, blinding limitations, and long-term safety remain unresolved.

DISCUSSION

TRD represents a multifactorial condition that cannot be adequately addressed by traditional monoaminergic models alone. The integration of neurobiological, immunological, and psychosocial frameworks provides a more comprehensive understanding of its complexity.

Biomarker-driven approaches hold promise for stratifying patients and guiding personalized treatment. However, challenges remain, including variability in biomarker reliability and limited accessibility in routine clinical practice. Similarly, while novel therapies such as ketamine and psychedelics offer exciting opportunities, concerns regarding long-term safety, accessibility, and ethical considerations must be addressed.

Future research should focus on integrating multimodal biomarkers with clinical phenotyping to develop precision psychiatry frameworks. Collaborative efforts across disciplines will be essential to translate these advances into improved patient outcomes.

Future Directions

Future investigations should move beyond descriptive associations toward mechanism-driven precision psychiatry frameworks. Important priorities include validating multimodal biomarker panels integrating inflammatory markers, neuroimaging signatures, genomic profiles, and digital phenotyping approaches.

Ongoing studies may help address current evidence gaps. The ELEKT-D trial comparing ketamine with ECT, and the continued COMP360 psilocybin investigations, are expected to clarify the comparative efficacy and durability of emerging interventions (18,19). Future work should also focus on standardizing TRD definitions, improving reproducibility across biomarker studies, and identifying predictors of long-term response.

Advances in machine learning may facilitate treatment selection by integrating multidimensional

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clinical and biological datasets. Addressing methodological limitations, including small sample sizes and heterogeneity, will remain essential for translating research findings into routine clinical practice.

CONCLUSION

Treatment-resistant depression represents a heterogeneous and multifactorial disorder extending beyond traditional monoaminergic paradigms. Emerging evidence implicates neuroinflammation, HPA axis dysfunction, impaired neuroplasticity, and circuit-level abnormalities as important contributors to treatment resistance. These findings support a shift toward biologically informed models of depression.

Advances in biomarker research, including inflammatory markers, neuroimaging signatures, and genetic predictors, offer potential pathways toward individualized treatment strategies, although their clinical implementation remains limited by issues of reproducibility and standardization.

Novel interventions such as ketamine, neuromodulation techniques, and psychedelic-assisted therapies have expanded therapeutic possibilities and challenged conventional treatment paradigms. Nevertheless, important questions remain regarding long-term efficacy, safety, and patient selection.

Future progress in TRD management will depend on integrating clinical phenotypes with multimodal biological data within precision psychiatry frameworks. Improved understanding of underlying mechanisms may ultimately enable more personalized and effective treatment approaches for this highly vulnerable population.

AI Use Statement

AI-assisted tools, including ChatGPT (OpenAI), were used exclusively for language refinement and structural editing. No artificial intelligence tools were used for literature searching, evidence synthesis, data analysis, interpretation of findings, or generation of clinical conclusions. All scientific content was reviewed and verified by the authors.

Conflict of Interest

None declared.

Ethical Statement

Not applicable.

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REFERENCES

1. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. American Journal of Psychiatry. 2006 Nov;163(11):1905-17.
2. Berlim MT, Turecki G. Definition, assessment, and staging of treatment—resistant refractory major depression: a review of current concepts and methods. The Canadian Journal of Psychiatry. 2007 Jan;52(1):46-54.
3. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902.
4. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012 Oct 5;338(6103):68-72.
5. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology. 2016 Jan;16(1):22-34.
6. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends in Neurosciences. 2008 Sep 1;31(9):464-8.

https://doi.org/10.63501/54mphj57

7. Klengel T, Binder EB. Epigenetics of stress-related psychiatric disorders and gene× environment interactions. Neuron. 2015 Jun 17;86(6):1343-57.
8. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological Psychiatry. 2013 Aug 15;74(4):250-6.
9. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Archives of General Psychiatry. 2010 May 1;67(5):507-16.
10. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry. 2016 Jul 1;3(7):619-27.
11. Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L, Cleare AJ. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. Journal of Clinical Psychiatry. 2009 Feb 1;70(2):177.
12. Fava M. Diagnosis and definition of treatment-resistant depression. Biological Psychiatry. 2003 Apr 15;53(8):649-59.
13. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. Neuron. 2005 Mar 3;45(5):651-60.
14. Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, Kinkead B, Nemeroff CB, Mayberg HS. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. American Journal of Psychiatry. 2017 Jun 1;174(6):533-45.
15. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013 Jan 1;70(1):31-41.
16. Gasparini A, Callegari C, Lucca G, Bellini A, Caselli I, Ielmini M. Inflammatory biomarker and response to antidepressant in major depressive disorder: a systematic review and meta-analysis. Psychopharmacology Bulletin. 2022 Feb 25;52(1):36.
17. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D, Thase ME. 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;76(9):893-903.
18. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, Bird C, Blom RE, Brennan C, Brusch D, Burke L. Single-dose psilocybin for a treatment-resistant episode of major depression. New England Journal of Medicine. 2022 Nov 3;387(18):1637-48.