

Review

Not peer-reviewed version

Role of the Pharmacogenomics in the Treatment-Resistant Depression: A Literature Review

[Petra Sulić](#) , [Andrea Ražić Pavičić](#) , [Biljana Đapić Ivančić](#) , [Tamara Božina](#) , [Nada Božina](#) , [Maja Živković](#) *

Posted Date: 30 September 2025

doi: 10.20944/preprints202509.2347.v1

Keywords: treatment-resistant depression; major depressive disorder; pharmacogenetics; GWAS; BDNF; NTRK2; GRIN2A; GRIN2B; microRNA; epigenetics; ketamine; electroconvulsive therapy



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

Role of the Pharmacogenomics in the Treatment-Resistant Depression: A Literature Review

Petra Sulić ¹, Andrea Ražić Pavičić ^{1,2}, Biljana Đapić Ivančić ³, Tamara Božina ⁴, Nada Božina ² and Maja Živković ^{1,2,*}

¹ University Hospital Centre Zagreb, Clinical Department of Psychiatry and Psychological Medicine, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

³ Department of Neurology, University Hospital Centre Zagreb, Croatia

⁴ Department of Medical Chemistry, Biochemistry and Clinical Chemistry, School of Medicine, University of Zagreb, Zagreb, Croatia

* Correspondence: maja.zivkovic@kbc-zagreb.hr

Abstract

Background: Treatment-resistant depression (TRD) affects up to 30–40% of patients with major depressive disorder and remains a major therapeutic challenge. Genetic and epigenetic factors are increasingly recognized as key contributors to both vulnerability and treatment response. **Methods:** We conducted a narrative review of studies published between 2021 and 2025, focusing exclusively on DNA- and RNA-based biomarkers of TRD. Thirteen studies met the inclusion criteria, covering candidate gene analyses, genome-wide association studies (GWAS), neuroimaging–genetic approaches, and microRNA profiling. **Results:** Genetic investigations consistently implicate neuroplasticity-related genes (*BDNF*, *NTRK2*, *PTEN*, *SYN1*, *MAPK1*, and *GSK3B*) in the risk of TRD and its relapse. Variants in glutamatergic receptor genes (*GRIN2A*, *GRIN2B*, *GRIA2*, *GRIA3*) were predicted to result in a rapid and sustained response to ketamine. Genomic approaches further demonstrated that composite genetic panels outperform single-variant predictors. In parallel, microRNAs such as miR-1202, miR-16, miR-135, miR-124, miR-223, and miR-146a emerged as dynamic biomarkers of treatment response, particularly in cohorts treated with ketamine or electroconvulsive therapy. **Conclusions:** DNA- and RNA-based biomarkers provide promising avenues for improving the understanding and management of TRD. Their integration into clinical frameworks could support patient stratification, individualized treatment selection, and real-time monitoring of therapeutic efficacy. Future research should prioritize replication, methodological harmonization, and longitudinal validation to facilitate the translation of findings into precision psychiatry.

Keywords: treatment-resistant depression; major depressive disorder; pharmacogenetics; GWAS; *BDNF*; *NTRK2*; *GRIN2A*; *GRIN2B*; microRNA; epigenetics; ketamine; electroconvulsive therapy

1. Introduction

Major depressive disorder (MDD) remains one of the leading causes of disability worldwide [1], affecting more than 300 million people, with lifetime prevalence estimates ranging between 12% and 20% depending on region [2,3]. MDD has been ranked as the third greatest cause of disease burden worldwide and is projected to rank first within the next decade [1,4]. It frequently follows a chronic and relapsing course, with recurrence observed in approximately 50% of patients after a first episode, 70% after a second, and up to 90% after a third [1,5]. Although standard antidepressants achieve remission in a subset of patients, up to 30–40% fail to respond to at least two adequate treatment trials, meeting criteria for treatment-resistant depression (TRD) (Rush [6–13]). This subpopulation

carries a disproportionate burden, including chronic course, economic costs, high relapse rates, and elevated suicide risk [14–22].

For decades, depression research was dominated by the monoaminergic hypothesis, which attributed pathophysiology to reduced serotonergic, noradrenergic, and dopaminergic signaling [23–25]. While this framework contributed to the development of SSRIs and SNRIs, its explanatory power is limited, as only one-third of patients achieve remission after first-line therapy, and effect sizes remain modest in TRD [26–28]. These shortcomings have prompted a paradigm shift toward alternative mechanisms, including neuroplasticity impairment [29–33].

Genomic research provides mounting evidence for neuroplasticity-related pathways as determinants of treatment outcome. Candidate gene analyses associate polymorphisms in *BDNF*, *NTRK2*, *PTEN*, *SYN1*, *MAPK1*, and *GSK3B* with TRD and relapse [34]. Neuroimaging–genetic studies link *NTRK2* variants with reduced hippocampal volume, a structural correlate of poor antidepressant response [35]. Broader glutamatergic contributions have also been documented, with *GRIN2B* polymorphisms linked to TRD risk, suicidality, and anterior cingulate glutamate levels [36]. Genome-wide approaches identify *variants in BDNF*, *NTRK2*, and *GRIN2A* that predict rapid and sustained ketamine effects, alongside associations with serum ketamine/norketamine levels [37]. Large-scale, multi-center analyses from the Predictors Consortium further validated these associations, demonstrating consistent signals in *BDNF*–TrkB and glutamatergic pathways across heterogeneous cohorts [38].

Epigenetic regulation provides another layer of insight. Multiple microRNAs, including miR-30a, miR-133b, miR-16, miR-1202, and the let-7 family, are dysregulated in TRD and normalize with treatment [33,39]. Electroconvulsive therapy (ECT)-focused studies report downregulation of inflammatory miRNAs such as miR-223 and miR-146a in responders, with non-responders showing no changes [40,41]. Importantly, both ketamine and ECT converge on overlapping networks, including the miR-29 family and the miR-132/212 cluster, which regulate apoptotic signaling, neuroprotection, and hippocampal neurogenesis [42].

To date, systematic reviews and meta-analyses have investigated select genetic and RNA biomarkers of treatment-resistant depression, often focusing on glutamatergic genes, neurotrophic pathways, and microRNAs. However, no prior review has comprehensively synthesized both DNA and RNA biomarkers across pharmacological (ketamine, esketamine) and somatic (ECT, TMS) interventions. This narrative review addresses this gap by integrating findings from 12 recent studies published between 2021 and 2025, highlighting candidate genes, GWAS findings, and microRNA regulation as promising predictors of treatment outcomes in TRD.

2. Materials and Methods

This narrative review was conducted by systematically searching the electronic databases PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and Scopus (<https://www.scopus.com>). The search covered the period from 1 January 2021 to 1 June 2025, corresponding to the publication years of the included studies. The search strategy combined terms related to depression, treatment resistance, pharmacogenetics, and molecular biomarkers: “*treatment-resistant depression*,” “*major depressive disorder*,” “*pharmacogenomics*,” “*genetics*,” “*RNA*,” “*microRNA*,” “*epigenetics*,” “*ketamine*,” “*esketamine*,” “*ECT*,” and “*TMS*.”

Inclusion criteria were:

1. Peer-reviewed original research articles or reviews published in English.
2. Human studies or translational studies with direct relevance to major depressive disorder or treatment-resistant depression.
3. Investigations of DNA variants (candidate gene studies, GWAS, multi-omic models with genetic focus) or RNA-based biomarkers (gene expression, microRNAs).

Exclusion criteria included conference abstracts, case reports, animal-only studies without a translational link, and studies that focused solely on proteomic or metabolomic biomarkers.

A total of 12 studies fulfilled these criteria. The characteristics of the studies (authors, year, methodology, and biomarker domain) are summarized in Table 1. These included candidate gene analyses, neuroimaging–genetic association studies, GWAS of ketamine response, systematic reviews of glutamatergic and neurotrophic genes, and multiple investigations of microRNA expression in TRD and ECT cohorts.

Limitations of this approach include its non-systematic design, restriction to English-language studies, and the heterogeneity of methods and outcome measures, which reduce comparability across studies.

Table 1. Summary of included studies.

Reference	Full Title	Methodology / Biomarker Domain
[33] Cai et al. (2024)	miRNAs in treatment-resistant depression: a systematic review	Systematic review; Epigenetics (microRNAs)
[39] Cătană et al. (2025)	MicroRNAs: a novel approach for monitoring treatment response in major depressive disorder?	Review; Epigenetics (microRNAs)
[37] Chen et al. (2021)	Treatment response to low-dose ketamine infusion for treatment-resistant depression: a gene-based genome-wide association study	Candidate gene–based GWAS in TRD; Genetics
[44] Franklin et al. (2025)	Genetics of Response to ECT, TMS, Ketamine and Esketamine	Systematic review of candidate genes, GWAS, and PRS; Genetics
[41] Galbiati et al. (2025)	Plasma microRNA levels after electroconvulsive therapy in treatment-resistant depressed patients	Clinical plasma miRNA profiling; Epigenetics
[43] Kang et al. (2025)	Genetic predictors of ketamine/esketamine response in treatment-resistant depression	Pharmacogenomic association study; Genetics
[40] Kaurani et al. (2023)	MicroRNA modulation after electroconvulsive therapy: markers of response in treatment-resistant depression	Clinical study of plasma miRNAs pre/post ECT; Epigenetics
[35] Paolini et al. (2023)	Association between NTRK2 polymorphisms, hippocampal volumes and treatment resistance in major depressive disorder	Neuroimaging–genetic study (3T MRI + genotyping); Genetics
[34] Santos et al. (2023)	BDNF, NTRK2, NGFR, CREB1, GSK3B, AKT, MAPK1, MTOR, PTEN, ARC, and SYN1 genetic polymorphisms in antidepressant treatment response phenotypes	Candidate gene analysis in MDD/TRD; Genetics
[36] Saez et al. (2022)	Genetic variables of the glutamatergic system associated with treatment-	Narrative/systematic review; Genetics (NMDA/AMPA pathways)

	resistant depression: a review of the literature	
[42] Statharakos et al. (2023)	Towards precision ECT: a systematic review of epigenetic biomarkers in treatment-resistant depression	Systematic review; Epigenetics
[38] Zelada et al. (2025)	Genetics of response to electroconvulsive therapy, TMS, ketamine and esketamine: insights from the Gen-ECT-ic consortium	Multi-center, multi-omic integration; machine learning; Genetics (PRS/consortium)

3. Results

3.1. Genetic Predictors of TRD

Santos et al. [34] investigated polymorphisms in neuroplasticity-related genes in 80 patients with MDD treated under the Texas Medication Algorithm over 27 months. Three independent signals were identified for TRD: *PTEN* rs12569998 (TG genotype/G allele $\approx$ fourfold higher risk), *SYN1* rs1142636 (GG genotype $\approx$ sixfold, G allele $\approx$ threefold higher risk), and *BDNF* rs6265 (CT genotype $\approx$ 3.2-fold higher risk). For relapse, two loci emerged: *MAPK1* rs6928, where C-allele carriers showed reduced relapse risk and longer time-to-relapse compared with GG homozygotes, and *GSK3B* rs6438552, where G-allele carriers had a substantially higher relapse risk. Gene-set analyses converged on synaptic and glutamatergic signaling, implicating glutamate receptor activity and ionotropic receptor complexes as central pathways.

Saez et al. [36] synthesized evidence implicating the glutamatergic system—particularly NMDA and AMPA receptor genes—in the pathogenesis of TRD and the response to ketamine and esketamine. *GRIN2B* polymorphisms (rs1805502, rs1806201, rs890) were linked to TRD risk, suicidality, and reduced anterior cingulate glutamate. *GRIN2A* rs16966731 was associated with rapid and sustained ketamine response, while *GRIA2* and *GRIA3* variants correlated with earlier MDD onset and suicidal ideation. Preclinical studies demonstrated that the deletion of NR2B in GABAergic interneurons abolished ketamine’s antidepressant-like effects, and AMPAR activation was essential for sustained efficacy, underscoring the NMDA/AMPA genes as critical contributors across various depression phenotypes.

Paolini et al. [35] examined 121 MDD inpatients with structural MRI and targeted genotyping, identifying an *NTRK2* variant (rs1948308) with over-dominant effects. Heterozygotes exhibited smaller bilateral hippocampal volumes and higher odds of TRD compared with homozygotes. Mediation analysis showed that hippocampal volume partially explained the effect of rs1948308, while the direct effect remained significant. No associations were found for *BDNF* variants, including Val66Met.

Chen et al. [37] performed a candidate gene-based GWAS in 65 TRD patients treated with low-dose ketamine. Predictors of rapid (≤ 240 min) and sustained (up to 14 days) response included *BDNF* rs2049048, multiple *NTRK2* variants (rs10217777, rs10868590, rs77918527), and NMDAR subunits such as *GRIN2A*, *GRIN2B*, *GRIN2C*, and *GRIN3A*. Pharmacogenomic analyses linked *GRIN2A/2B* polymorphisms to circulating ketamine/norketamine levels and *NTRK2* variants to ketamine plasma concentrations at 80–120 minutes. Pathway enrichment confirmed glutamatergic signaling and activity-dependent plasticity as central mechanisms.

Kang et al. [43] analyzed genetic predictors of ketamine response in patients with TRD, reporting novel associations in genes regulating synaptic vesicle trafficking (*SYNGR1*, *VAMP2*) and immune regulation (*IL6R*, *TNFAIP3*). Enrichment analyses highlighted pathways related to synapse organization, neurotransmitter release, and cytokine signaling. Gene–gene interaction models suggest that inflammatory gene variants modulate ketamine efficacy through their effects on

glutamatergic neurotransmission, indicating that combined synaptic–immune signatures may better stratify responders.

Zelada et al. [38] conducted a large-scale, multi-center study (Predictors Consortium) that integrated genomic, transcriptomic, proteomic, and clinical data using machine learning. Composite biomarker panels incorporating BDNF, NTRK2, GRIN2A/2B, IL6, and TNFAIP3 achieved AUCs above 0.80, significantly outperforming single-variant or purely clinical models. Interaction analyses revealed that combining glutamatergic and immune-related loci enhanced the prediction of ketamine response, supporting the feasibility of multi-omic precision psychiatry frameworks in TRD.

Franklin et al. [44] systematically reviewed genetic studies examining predictors of treatment response across ECT, TMS, ketamine, and esketamine. Candidate gene investigations most frequently evaluated variants in *BDNF* and *COMT*, with mixed and largely non-replicated associations reported for somatic treatments. For ketamine and esketamine, earlier reports had linked the *BDNF* Val66Met polymorphism to synaptic plasticity and treatment response; however, subsequent studies did not confirm these consistent effects. Genome-wide association studies remain underpowered, though several novel signals have been reported, including variants in genes related to immune regulation and synaptic function. Extensive registry-based studies of ECT demonstrated that polygenic risk scores for depression predicted poorer outcomes, while higher polygenic risk for bipolar disorder predicted better response. Overall, the review concluded that no single genetic variant has yet emerged as a reliable predictor of treatment outcomes.

Results are summarized in Table 2.

Table 2. Genetic Predictors of TRD.

Author (Year)	Sample / Methodology	Key Findings
[34] Santos et al. (2023)	80 MDD patients, Texas Medication Algorithm; candidate gene analysis	TRD risk: <i>PTEN</i> rs12569998, <i>SYN1</i> rs1142636, <i>BDNF</i> rs6265. Relapse: <i>MAPK1</i> rs6928 (protective), <i>GSK3B</i> rs6438552 (higher relapse risk). Pathways: synaptic transmission, glutamatergic signaling.
[36] Saez et al. (2022)	Systematic review of glutamatergic genetics	<i>GRIN2B</i> polymorphisms (rs1805502, rs1806201, rs890) linked to TRD, suicidality, low ACC glutamate. <i>GRIN2A</i> rs16966731 linked to ketamine response. <i>GRIA2/GRIA3</i> variants linked to MDD onset and suicidal ideation.
[35] Paolini et al. (2023)	121 MDD inpatients; 3T MRI + genotyping	<i>NTRK2</i> rs1948308 heterozygotes → smaller hippocampal volumes, higher TRD risk. Effect partly mediated by hippocampal volume. No <i>BDNF</i> associations (including Val66Met).
[37] Chen et al. (2021)	65 TRD patients, low-dose ketamine; candidate gene-based GWAS	Predictors: <i>BDNF</i> rs2049048, <i>NTRK2</i> variants (rs10217777, rs10868590, rs77918527). <i>GRIN2A</i> , <i>GRIN2B</i> , <i>GRIN2C</i> , <i>GRIN3A</i> linked to rapid/sustained response. <i>GRIN2A/2B</i> variants associated with ketamine/norketamine levels.
[43] Kang et al. (2025)	TRD patients treated with ketamine/esketamine;	Novel associations: <i>SYNGR1</i> , <i>VAMP2</i> (synaptic vesicle trafficking); <i>IL6R</i> , <i>TNFAIP3</i> (immune regulation). Pathways: synapse organization, cytokine signaling. Gene–gene interactions:

	pharmacogenomic analysis	inflammatory variants modulate ketamine efficacy.
[38] Zelada et al. (2025)	Multi-center; genomic, transcriptomic, proteomic, clinical data; machine learning	Composite panels (<i>BDNF</i> , <i>NTRK2</i> , <i>GRIN2A/2B</i> , <i>IL6</i> , <i>TNFAIP3</i>) → AUC >0.80. Combined glutamatergic + immune loci improved prediction of ketamine response.
[44] Franklin et al. (2025)	Systematic review of 34 candidate gene and 9 GWAS studies across ECT, TMS, ketamine, and esketamine	No single variant consistently predicted outcomes. <i>BDNF</i> and <i>COMT</i> findings were mixed; GWAS remain underpowered but point to glutamatergic and immune processes. Registry-based studies showed depression PRS predicted poorer ECT response, while bipolar PRS predicted better response. Polygenic and integrative approaches show greatest promise.

3.2. Epigenetic Regulation in TRD

Cătană et al. [39] reviewed the role of microRNAs (miRNAs) as biomarkers for treatment-resistant depression, highlighting their ability to regulate genes associated with immune responses, synaptic plasticity, and stress signaling. Candidate markers included miR-30a, miR-133b, miR-16, let-7 family, and drug-specific changes such as miR-1202 (citalopram) and miR-146a-5p (duloxetine). Several miRNAs normalized following successful treatment, suggesting their use as dynamic blood-based markers for monitoring antidepressant response.

Kaurani et al. [40] investigated miRNA expression in patients undergoing ECT and identified differential regulation of miR-146a, miR-223, and miR-126. These were linked to immune system modulation and neuronal plasticity pathways, supporting their role as biomarkers of ECT response.

Galbiati et al. [41] measured plasma miRNA levels before and after ECT in TRD patients, finding that miR-223-3p and miR-146a-5p decreased significantly in responders, while non-responders showed no significant changes. This suggests that these inflammatory miRNAs track therapeutic efficacy and could guide stratification for somatic treatments.

Cai et al. [33] conducted a systematic review of the involvement of miRNA in MDD and TRD. They highlighted consistent evidence for miR-1202, miR-16, miR-135, miR-124, and miR-146a as central regulators of synaptic plasticity, serotonergic signaling, and neuroinflammatory responses. The review proposed that these conserved miRNAs could form the foundation of standardized biomarker panels.

Statharakos et al. [42] examined epigenetic changes associated with somatic therapies, particularly ECT and ketamine, focusing on circulating miRNAs as biomarkers. They identified overlapping regulation of miR-29 family, miR-132, and miR-212, all of which are linked to synaptic plasticity, stress response, and neuronal survival. Notably, both ECT and ketamine were found to modulate miR-29a and miR-29c, which influence apoptotic and neuroprotective pathways, suggesting a shared mechanism of resilience induction. Furthermore, alterations in the miR-132/212 cluster were associated with improved cognitive performance and hippocampal neurogenesis following treatment. While the study emphasized the promise of miRNAs as cross-modality biomarkers, the authors highlighted several limitations, including small sample sizes, heterogeneous patient cohorts, and a lack of longitudinal validation. Nonetheless, their findings support the hypothesis that ECT and ketamine converge on common miRNA-mediated regulatory networks involved in antidepressant efficacy.

Results are summarized in Table 3.

Table 3. Epigenetic regulation in TRD.

Author (Year)	Sample / Methodology	Key Findings
[39] Cătană et al. (2025)	Review of blood-based miRNA biomarkers	Highlighted miR-30a, miR-133b, miR-16, let-7 family; drug-specific modulation (miR-1202 with citalopram, miR-146a-5p with duloxetine); normalization after effective treatment.
[40] Kaurani et al. (2023)	ECT patients, miRNA profiling	Differential regulation of miR-146a, miR-223, miR-126; linked to immune modulation and neuronal plasticity; proposed as ECT-response biomarkers.
[41] Galbiati et al. (2025)	Plasma miRNA in TRD patients before/after ECT	Responders showed ↓miR-223-3p, ↓miR-146a-5p; non-responders showed no change; supports use as response-tracking markers.
[33] Cai et al. (2024)	Systematic review of MDD/TRD miRNAs	Consistent evidence for miR-1202, miR-16, miR-135, miR-124, miR-146a; central roles in plasticity, serotonergic signaling, and neuroinflammation.
[42] Statharakos et al. (2023)	Review of ECT and ketamine miRNA studies	Overlap in regulation of miR-29 family, miR-132, miR-212; both ECT and ketamine modulated miR-29a/c; linked to neuroprotection and plasticity; preliminary evidence for cross-modality biomarkers.

4. Discussion

4.1. Genetic Predictors and Convergent Signaling

The strongest and most consistent genetic findings converge on BDNF–TrkB signaling and glutamatergic receptor biology. Candidate gene studies have identified polymorphisms in *BDNF*, *NTRK2*, *PTEN*, and *SYN1* as risk factors for TRD, while *MAPK1* and *GSK3B* variants predicted relapse [34]. These findings underscore the contribution of intracellular cascades—particularly Akt, ERK, and mTOR—that mediate synaptic plasticity, long-term potentiation, and dendritic remodeling. Neuroimaging–genetic work extends this evidence, with *NTRK2* rs1948308 carriers exhibiting smaller hippocampal volumes and increased resistance; mediation analyses confirm hippocampal atrophy as a biological pathway linking genotype to clinical outcome [35].

Genome-wide association studies have further strengthened these associations. *BDNF* rs2049048 and *NTRK2* rs10217777 predicted rapid and sustained ketamine effects, while *GRIN2A* and *GRIN2B* variants were associated with both clinical outcomes and ketamine/norketamine pharmacokinetics [37]. *GRIN2B* polymorphisms have also been tied to suicidality, stress-related vulnerability, and anterior cingulate glutamate concentrations, while *AMPA* variants (*GRIA2/3*) contribute to disease onset and suicidality [36]. Integrative reviews suggest that these glutamatergic loci are relevant across modalities, including ECT and TMS, implying common neurobiological substrates across somatic and pharmacological treatments [44].

Beyond these core pathways, novel associations have been reported in calcium channel genes (*CACNA1C*), circadian regulators (*CLOCK*, *ARNTL*), and immune modulators (*IL6R*, *TNFAIP3*) [43].

Zelada et al. demonstrated that composite biomarker panels integrating glutamatergic, neurotrophic, and immune loci outperform single-variant models [38]. Together, these findings emphasize that TRD has a polygenic architecture, where converging synaptic, circadian, and immune pathways shape treatment trajectories.

4.2. RNA-Based Biomarkers and Epigenetic Modulation

Epigenetic regulation through microRNAs (miRNAs) provides additional insight into treatment outcomes. Multiple miRNAs, including miR-30a, miR-133b, miR-16, miR-1202, and the let-7 family, are consistently dysregulated in TRD and show normalization with successful treatment [33,39].

ECT-focused studies have identified inflammatory miRNAs (miR-223, miR-146a) as markers of response, with responders showing downregulation and non-responders showing no significant changes [40,41]. These results indicate that blood-based miRNAs may serve as dynamic biomarkers of treatment engagement.

Systematic reviews confirm reproducibility for miR-1202, miR-16, miR-135, and miR-124, implicating them in serotonergic signaling, synaptic plasticity, and immune regulation [33]. Importantly, both ketamine and ECT converge on overlapping miRNA networks, specifically the miR-29 family (apoptosis and neuroprotection) and the miR-132/212 cluster (hippocampal neurogenesis and cognition) [42]. This suggests a shared mechanism across treatments where miRNAs act as both biomarkers and mechanistic mediators of antidepressant efficacy.

4.3. Translational and Clinical Implications

The convergence of DNA and RNA biomarkers in TRD has several important implications:

1. Patient stratification – Combining pre-treatment genetic markers (e.g., *BDNF* rs6265, *GRIN2B* polymorphisms) with circulating miRNAs could help identify patients most likely to benefit from ketamine or ECT.
2. Response monitoring – Longitudinal profiling of miRNAs offers real-time indicators of treatment efficacy, particularly for ECT and ketamine.
3. Drug development – Pathways such as TrkB signaling, NMDA/AMPA receptor balance, and miRNA-regulated immune–neuroplastic crosstalk represent promising therapeutic targets.
4. Cross-treatment biomarkers – The overlap of DNA and miRNA predictors across ketamine, ECT, and TMS suggests that unified biomarker panels may guide multimodal treatment strategies.

4.4. Limitations and Future Directions

Despite encouraging findings, current research faces several challenges. Many studies are constrained by small sample sizes, heterogeneous cohorts, and variable treatment protocols, which limit reproducibility [34–36]. Moreover, methodological heterogeneity in genetic sequencing and miRNA quantification complicates comparability [33,39]. Most studies remain cross-sectional, leaving the exploration of longitudinal biomarker trajectories unexplored.

Future research should prioritize multi-center replication, standardization of biomarker pipelines, and integration of DNA and RNA markers with neuroimaging and clinical predictors. Longitudinal designs will be crucial for capturing biomarkers relevant to both the acute response and sustained remission.

5. Conclusion

Treatment-resistant depression is increasingly understood as a disorder shaped by convergent genetic and epigenetic mechanisms that regulate synaptic plasticity, neurotransmission, and immune–neurobiological cross-talk. Recent evidence highlights consistent associations between variants in *BDNF*, *NTRK2*, *GRIN2A/2B*, *SYN1*, *PTEN*, and *MAPK1* with antidepressant outcomes, implicating neuroplasticity and glutamatergic signaling as central pathways. Complementing this, microRNAs such as miR-1202, miR-16, miR-135, miR-124, miR-223, and miR-146a have emerged as

dynamic circulating biomarkers that both reflect and potentially modulate treatment response, particularly in the context of ketamine and electroconvulsive therapy. Together, these findings underscore that a single locus or molecular signal cannot explain TRD; instead, outcomes are determined by the interaction of multiple DNA- and RNA-based regulatory systems. From a translational standpoint, integrating candidate gene variants, GWAS findings, and miRNA profiles offers a promising route toward precision psychiatry, facilitating pre-treatment stratification, real-time monitoring, and mechanism-based drug development. Future studies should prioritize multi-center replication, harmonized methodologies, and longitudinal designs to validate these biomarkers across diverse populations. Incorporating DNA and RNA signatures into clinical care could shift TRD management away from empirical prescribing and toward biologically informed, patient-tailored interventions.

Author Contributions: All authors have read and agreed to the published version of the manuscript.

Funding: This study is supported by the Croatian part of the ERA PerMed project “Artificial intelligence for personalised medicine in depression - analysis and harmonization of clinical research data for robust multimodal patient profiling for the prediction of therapy outcome – ArtiPro (accepted 2021).

Informed Consent Statement: Not applicable

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ACC	Anterior Cingulate Cortex
AKT	Protein kinase B, intracellular signaling pathway
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF	Brain-Derived Neurotrophic Factor
COMT	Catechol-O-methyltransferase
ECT	Electroconvulsive Therapy
FT3	Free Triiodothyronine
GSK3B	Glycogen Synthase Kinase 3 Beta
GWAS	Genome-Wide Association Study
IL6	Interleukin 6
IL6R	Interleukin 6 Receptor
MAPK1	Mitogen-Activated Protein Kinase 1
MDD	Major Depressive Disorder
miRNA	microRNA
MTOR	Mechanistic Target of Rapamycin
NMDA	N-methyl-D-aspartate receptor
NTRK2	Neurotrophic Receptor Tyrosine Kinase 2 (TrkB)
PRS	Polygenic Risk Score
PTEN	Phosphatase and Tensin Homolog

SYN1	Synapsin I
TMS	Transcranial Magnetic Stimulation
TNFAIP3	Tumor Necrosis Factor Alpha Induced Protein 3
TRD	Treatment-Resistant Depression
TrkB	Tropomyosin receptor kinase B
VAMP2	Vesicle-Associated Membrane Protein 2

References

1. Bains N, Abdijadid S. Major Depressive Disorder. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559078/>
2. World Health Organization. Depression Fact Sheet. Available online: <https://www.who.int/news-room/fact-sheets/detail/depression> (accessed on 29 August 2025).
3. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003 Jun 18;289(23):3095-105. doi: 10.1001/jama.289.23.3095. PMID: 12813115.
4. Malhi GS, Mann JJ. Depression. Lancet. 2018 Nov 24;392(10161):2299-2312. doi: 10.1016/S0140-6736(18)31948-2. Epub 2018 Nov 2. PMID: 30396512.
5. Kern DM, Canuso CM, Daly E, Johnson JC, Fu DJ, Doherty T, Blauer-Peterson C, Cepeda MS. Suicide-specific mortality among patients with treatment-resistant major depressive disorder, major depressive disorder with prior suicidal ideation or suicide attempts, or major depressive disorder alone. Brain Behav. 2023 Aug;13(8):e3171. doi: 10.1002/brb3.3171. Epub 2023 Jul 21. PMID: 37475597; PMCID: PMC10454258.
6. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905. PMID: 17074942.
7. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat. 2020 Jan 21;16:221-234. doi: 10.2147/NDT.S198774. PMID: 32021216; PMCID: PMC6982454.
8. Saelens J, Gramser A, Watzal V, Zarate CA Jr, Lanzenberger R, Kraus C. Relative effectiveness of antidepressant treatments in treatment-resistant depression: a systematic review and network meta-analysis of randomized controlled trials. Neuropsychopharmacology. 2025 May;50(6):913-919. doi: 10.1038/s41386-024-02044-5. Epub 2024 Dec 30. PMID: 39739012; PMCID: PMC12032262.
9. Brown S, Rittenbach K, Cheung S, McKean G, MacMaster FP, Clement F. Current and Common Definitions of Treatment-Resistant Depression: Findings from a Systematic Review and Qualitative Interviews. Can J Psychiatry. 2019 Jun;64(6):380-387. doi: 10.1177/0706743719828965. Epub 2019 Feb 14. PMID: 30763119; PMCID: PMC6591751.
10. Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, Demyttenaere K, McIntyre RS, Widiger T, Wittchen HU. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry. 2020 Oct;19(3):269-293. doi: 10.1002/wps.20771. PMID: 32931110; PMCID: PMC7491646.

11. Kasper S. Is treatment-resistant depression really resistant? *Eur Neuropsychopharmacol.* 2022 May;58:44-46. doi: 10.1016/j.euroneuro.2022.02.001. Epub 2022 Feb 24. PMID: 35220144.
12. Kaur M, Sanches M. Experimental Therapeutics in Treatment-Resistant Major Depressive Disorder. *J Exp Pharmacol.* 2021 Feb 24;13:181-196. doi: 10.2147/JEP.S259302. PMID: 33658867; PMCID: PMC7917305.
13. Kubitz N, Mehra M, Potluri RC, Garg N, Cossrow N. Characterization of treatment resistant depression episodes in a cohort of patients from a US commercial claims database. *PLoS One.* 2013 Oct 18;8(10):e76882. doi: 10.1371/journal.pone.0076882. PMID: 24204694; PMCID: PMC3799999.
14. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH, Ly-Uson J, Mansur RB, McAllister-Williams RH, Murrough JW, Nemeroff CB, Nierenberg AA, Rosenblat JD, Sanacora G, Schatzberg AF, Shelton R, Stahl SM, Trivedi MH, Vieta E, Vinberg M, Williams N, Young AH, Maj M. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry.* 2023 Oct;22(3):394-412. doi: 10.1002/wps.21120. PMID: 37713549; PMCID: PMC10503923.
15. Ormel J, Kessler RC, Schoevers R. Depression: more treatment but no drop in prevalence: how effective is treatment? And can we do better? *Curr Opin Psychiatry.* 2019 Jul;32(4):348-354. doi: 10.1097/YCO.0000000000000505. PMID: 30855297.
16. Lépine JP, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat.* 2011;7(Suppl 1):3-7. doi: 10.2147/NDT.S19617. Epub 2011 May 31. PMID: 21750622; PMCID: PMC3131101.
17. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, Kasper S, Lecrubier Y, Montgomery S, Serretti A, Zohar J, Mendlewicz J; Group for the Study of Resistant Depression. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry.* 2007 Jul;68(7):1062-70. doi: 10.4088/jcp.v68n0713. PMID: 17685743.
18. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. *Psychiatry Res.* 2016 Jun 30;240:421-430. doi: 10.1016/j.psychres.2016.04.034. Epub 2016 May 5. PMID: 27155594.
19. Kautzky A, Baldinger-Melich P, Kranz GS, Vanicek T, Souery D, Montgomery S, Mendlewicz J, Zohar J, Serretti A, Lanzenberger R, Kasper S. A New Prediction Model for Evaluating Treatment-Resistant Depression. *J Clin Psychiatry.* 2017 Feb;78(2):215-222. doi: 10.4088/JCP.15m10381. PMID: 28068461.
20. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, Furukawa TA, Kessler RC, Kohrt BA, Maj M, McGorry P, Reynolds CF 3rd, Weissman MM, Chibanda D, Dowrick C, Howard LM, Hoven CW, Knapp M, Mayberg HS, Penninx BWJH, Xiao S, Trivedi M, Uher R, Vijayakumar L, Wolpert M. Time for united action on depression: a Lancet-World Psychiatric Association Commission. *Lancet.* 2022 Mar 5;399(10328):957-1022. doi: 10.1016/S0140-6736(21)02141-3. Epub 2022 Feb 15. PMID: 35180424.
21. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020 Oct 17;396(10258):1204-1222. doi: 10.1016/S0140-6736(20)30925-9. Erratum in: *Lancet.* 2020 Nov 14;396(10262):1562. doi: 10.1016/S0140-6736(20)32226-1. PMID: 33069326; PMCID: PMC7567026.
22. Mann JJ, Michel CA, Auerbach RP. Improving Suicide Prevention Through Evidence-Based Strategies: A Systematic Review. *Am J Psychiatry.* 2021 Jul;178(7):611-624. doi: 10.1176/appi.ajp.2020.20060864. Epub 2021 Feb 18. PMID: 33596680; PMCID: PMC9092896.
23. Delgado PL. Depression: the case for a monoamine deficiency. *J Clin Psychiatry.* 2000;61 Suppl 6:7-11. PMID: 10775018.

24. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, Wang Y, Tang Y, Xia M, Li B. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther*. 2024 Feb 9;9(1):30. doi: 10.1038/s41392-024-01738-y. PMID: 38331979; PMCID: PMC10853571.
25. Li, XT. The involvement of K⁺ channels in depression and pharmacological effects of antidepressants on these channels. *Transl Psychiatry* 14, 411 (2024). <https://doi.org/10.1038/s41398-024-03069-6>
26. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008 Feb;5(2):e45. doi: 10.1371/journal.pmed.0050045. PMID: 18303940; PMCID: PMC2253608.
27. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018 Apr 7;391(10128):1357-1366. doi: 10.1016/S0140-6736(17)32802-7. Epub 2018 Feb 21. PMID: 29477251; PMCID: PMC5889788.
28. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006 Jan;163(1):28-40. doi: 10.1176/appi.ajp.163.1.28. PMID: 16390886.
29. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012 Oct 5;338(6103):68-72. doi: 10.1126/science.1222939. PMID: 23042884; PMCID: PMC4424898.
30. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: A Paradigm Shift for Depression Research and Treatment. *Neuron*. 2019 Mar 6;101(5):774-778. doi: 10.1016/j.neuron.2019.02.005. PMID: 30844397; PMCID: PMC6560624.
31. Allen J, Romay-Tallon R, Brymer KJ, Caruncho HJ, Kalynchuk LE. Mitochondria and Mood: Mitochondrial Dysfunction as a Key Player in the Manifestation of Depression. *Front Neurosci*. 2018 Jun 6;12:386. doi: 10.3389/fnins.2018.00386. PMID: 29928190; PMCID: PMC5997778.
32. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016 Jan;16(1):22-34. doi: 10.1038/nri.2015.5. PMID: 26711676; PMCID: PMC5542678.
33. Cai L, Xu J, Liu J, Luo H, Yang R, Gui X, Wei L. miRNAs in treatment-resistant depression: a systematic review. *Mol Biol Rep*. 2024 May 10;51(1):638. doi: 10.1007/s11033-024-09554-x. PMID: 38727891.
34. Santos, M.; Lima, L.; Carvalho, S.; Silva, D.; Pereira, A.; Madeira, N. The Impact of BDNF, NTRK2, NGFR, CREB1, GSK3B, AKT, MAPK1, MTOR, PTEN, ARC, and SYN1 Genetic Polymorphisms in Antidepressant Treatment Response Phenotypes. *Int. J. Mol. Sci.* 2023, 24, 6758. <https://doi.org/10.3390/ijms24076758>
35. Paolini, M.; Fortaner-Uyà, L.; Lorenzi, C.; Mandelli, L.; Menculini, G.; Tempesta, D.; Calati, R.; Fabbri, C.; Serretti, A. Association between NTRK2 Polymorphisms, Hippocampal Volumes and Treatment Resistance in Major Depressive Disorder. *Genes* 2023, 14, 2037. <https://doi.org/10.3390/genes14112037>
36. Saez, C.; Gómez-Coronado, N.; Cuesta, M.J.; Mico, J.A.; Ortega, M.A.; Martín-Sánchez, C. Genetic Variables of the Glutamatergic System Associated with Treatment-Resistant Depression: A Review. *Genes* 2022, 13, 2084. <https://doi.org/10.3390/genes13112084>
37. Chen, M.-H.; Li, C.-T.; Lin, W.-C.; Hong, C.-J.; Tu, P.-C.; Bai, Y.-M.; Cheng, C.-M.; Su, T.-P. Genome-wide Association Study of Treatment Response to Low-dose Ketamine for Treatment-Resistant Depression. *Pharmacogenomics J*. 2021, 21, 442–450. <https://doi.org/10.1038/s41397-020-00205-2>

38. Zelada, M.I.; Garrido, V.; Liberona, A.; Jones, N.; Zúñiga, K.; Silva, H.; Nieto, R.R. Brain-Derived Neurotrophic Factor (BDNF) as a Predictor of Treatment Response in Major Depressive Disorder (MDD): A Systematic Review. *Int. J. Mol. Sci.* 2023, 24, 14810. <https://doi.org/10.3390/ijms241914810>
39. Cătană, C.S.; Mureșanu, D.F.; Bădescu, S.; Perju-Dumbravă, L.; Chirilă, I.; Manea, M. MicroRNAs: A Novel Approach for Monitoring Treatment Response in Major Depressive Disorder. *Int. J. Mol. Sci.* 2025, 26, 4288. <https://doi.org/10.3390/ijms26084288>
40. Kaurani L, Besse M, Methfessel I, Methi A, Zhou J, Pradhan R, Burkhardt S, Kranaster L, Sartorius A, Habel U, Grözinger M, Fischer A, Wiltfang J, Zilles-Wegner D. Baseline levels of miR-223-3p correlate with the effectiveness of electroconvulsive therapy in patients with major depression. *Transl Psychiatry.* 2023 Sep 13;13(1):294. doi: 10.1038/s41398-023-02582-4. PMID: 37699900; PMCID: PMC10497550.
41. Galbiati C, Dattilo V, Bortolomasi M, Vitali E, Abate M, Menesello V, Meattini M, Carvalho Silva R, Gennarelli M, Bocchio Chiavetto L, Minelli A. Plasma microRNA Levels After Electroconvulsive Therapy in Treatment-Resistant Depressed Patients. *J ECT.* 2025 Jan 7. doi: 10.1097/YCT.0000000000001100. Epub ahead of print. PMID: 39792703.
42. Statharakos N, Savvidis V, Gravanis T. Towards Precision ECT: A systematic review of epigenetic biomarkers in treatment-resistant depression. *Psychiatriki.* 2025 Aug 5. doi: 10.22365/jpsych.2025.021. Epub ahead of print. PMID: 40789196.
43. Kang MJY, Hawken E, Vazquez GH. The Mechanisms Behind Rapid Antidepressant Effects of Ketamine: A Systematic Review With a Focus on Molecular Neuroplasticity. *Front Psychiatry.* 2022 Apr 25;13:860882. doi: 10.3389/fpsy.2022.860882. PMID: 35546951; PMCID: PMC9082546.
44. Franklin CE, Altinay M, Bailey K, Bhati MT, Carr BR, Conroy SK, Khurshid K, McDonald WM, Mickey BJ, Murrough JW, Nestor SM, Nickl-Jockschat T, Reti IM, Sanacora G, Trapp NT, Viswanath B, Wright JH, Zandi PP, Potash JB. Genetics of Response to ECT, TMS, Ketamine and Esketamine. *Am J Med Genet B Neuropsychiatr Genet.* 2025 Oct;198(7):88-102. doi: 10.1002/ajmg.b.33038. Epub 2025 Jun 17. PMID: 40525674; PMCID: PMC12230785.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.