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Review

Exploring Biological Risk Factors in Treatment-Resistant Depression

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Abstract

Treatment-resistant depression (TRD) affects 20–30% of patients with major depressive disorder and presents a significant clinical challenge due to its biological diversity. This review highlights standard mechanisms that contribute to treatment resistance beyond traditional monoaminergic models. Evidence supports serotonergic dysregulation, including 5-HT1A autoreceptor dysfunction and "serotonin flooding" as well as dopaminergic deficits linked to anhedonia and an imbalance between glutamate and GABA that impair synaptic plasticity. Changes in neurotrophic signaling, such as reduced BDNF and VEGF activity, complicate recovery by limiting neural repair and regeneration. Chronic inflammation and oxidative stress contribute to neuronal dysfunction, while HPA axis dysregulation may exacerbate depressive symptoms and resistance to antidepressants. Emerging evidence suggests that obesity and gut microbiota imbalance reduce the production of short-chain fatty acids by bacteria and increase intestinal permeability, thereby influencing neuroinflammatory and neurochemical processes in TRD. Neuroimaging studies reveal hyperconnectivity within the default mode network and impaired reward circuits, both of which are associated with persistent symptoms and a poor treatment response. By combining evidence on inflammation, oxidative stress, neuroendocrine disturbances, microbiome changes, and brain connectivity issues, this review develops a comprehensive framework for understanding TRD. It emphasizes the importance of biomarker-based subtyping to guide personalized future treatments.

Keywords: major depressive disorder; treatment-resistant depression; risk factors

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1. Introduction

Major depressive disorder (MDD) is a prevalent and disabling psychiatric condition, characterized by persistent sadness, anhedonia, and cognitive and psychosomatic symptoms that interfere with daily functioning. Beyond its individual impact, MDD contributes substantially to global disability, productivity loss, and suicide rates, underscoring its importance as a public health priority [1].

Treatment-resistant depression (TRD) lacks a universally accepted definition. Still, regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) define it as the failure to achieve response after at least two adequate antidepressant trials with confirmed adherence [2,3]. Using this definition, it is estimated that between 20% and 30% of patients with MDD develop TRD, representing a subgroup with a markedly worse prognosis [4].

Epidemiological studies highlight the distinct clinical profile and burden of TRD compared to treatment-responsive MDD. In a Swedish population-based cohort of over

145,000 patients, 11% of depressive episodes met TRD criteria, with a median age of 42 years, and nearly two-thirds of cases occurred in women. TRD patients showed substantially higher psychiatric comorbidity, threefold more hospitalization days, double the number of outpatient visits, and a 23% increase in all-cause mortality compared to non-TRD cases [5]. Similarly, in the United States, a national study estimated that 30.9% of adults receiving antidepressant treatment met criteria for TRD, equivalent to nearly 2.8 million individuals. Although accounting for less than one-third of treated MDD cases, TRD was responsible for 47.2% of the incremental economic burden, with per-patient annual costs almost three times higher than in treatment-responsive MDD [6]. Further evidence from a retrospective U.S. cohort of more than 800,000 patients showed that TRD cases (n = 139,753) were on average 55–59 years old, predominantly female (70.6%), and presented markedly higher rates of anxiety disorders (53.9%) and substance use disorders (20.8%). Suicide-specific mortality reached 0.14 per 100 person-years in TRD, compared with 0.27 in MDD with suicidal ideation/attempts and 0.04 in treatment-responsive depression, with the highest risks observed among men and younger adults [7].

Taken together, these findings demonstrate that TRD is not merely the absence of response to antidepressants but a clinically distinct phenotype, characterized by female predominance, onset in early or mid-adulthood, elevated psychiatric and medical comorbidity, disproportionate healthcare utilization, and increased suicide risk. Establishing this clinical context is crucial for understanding the biological mechanisms that may explain vulnerability to treatment resistance.

Building on these observations, this review synthesizes current evidence on the most consistent biological risk factors associated with TRD. The discussion is structured along eight thematic domains: neurochemical imbalances, neuroendocrine dysregulation including HPA axis and other endocrinopathies, chronic inflammation and immune mechanisms, oxidative stress, metabolic factors such as obesity and insulin resistance, alterations in brain connectivity, gut microbiota, and psychosocial factors such as chronic stress, childhood adversity, and social isolation. By integrating these domains, the review aims to provide a comprehensive framework for understanding the pathophysiology of TRD and to inform future directions in precision psychiatry.

2. Literature Search and Selection

This review followed a narrative approach. Studies were identified through structured searches in PubMed, Scopus, and Web of Science. The search combined the term “treatment-resistant depression” with the expressions “risk factor”, “predictor”, “biomarker”, “biological”, “mechanism”, and “pathophysiology” in the title or abstract fields, using Boolean operators AND/OR. In PubMed, the search was complemented with the Medical Subject Headings (MeSH) “Depressive Disorder, Treatment-Resistant” to ensure comprehensive retrieval. The PubMed search strategy was, for example: (“treatment-resistant depression”[Title/Abstract]) AND (“biological”[Title/Abstract] OR “mechanism”[Title/Abstract] OR “pathophysiology”[Title/Abstract] OR “risk factor”[Title/Abstract] OR “predictor”[Title/Abstract] OR “biomarker”[Title/Abstract]) OR (“Depressive Disorder, Treatment-Resistant”[MeSH]). Equivalent expressions adapted to the syntax of Scopus and Web of Science were used.

Given the narrative nature of this review, not all retrieved articles were included; instead, priority was given to studies considered most relevant and representative of biological risk factors for TRD. The selection process involved two stages: (1) title and abstract screening to exclude irrelevant records and (2) full-text review of potentially eligible articles. To minimize potential bias, the two reviewers independently evaluated the articles and reached a consensus on which ones to include.

Inclusion criteria required that studies (a) addressed at least one biological risk factor for treatment-resistant depression (TRD), (b) were original research articles, systematic reviews, or meta-analyses, and (c) were published in English. Exclusion criteria were non-peer-reviewed articles, case reports, and conference abstracts.

To ensure thematic completeness, additional targeted searches were conducted using specific terms related to each biological domain (e.g., "inflammation", "oxidative stress", "BDNF", "gut microbiota") in combination with "treatment-resistant depression". These complementary searches enabled the identification of studies that directly addressed the risk factors discussed in subsequent sections.

To ensure both recency and relevance, preference was given to articles published in the last five years. However, older studies were retained when they provided widely cited frameworks or described key mechanistic pathways that shaped subsequent research. Animal studies were included when they offered translational relevance or clarified potential biological mechanisms.

Given the narrative nature of this review, no formal risk-of-bias assessment tool was applied. Nevertheless, emphasis was placed on peer-reviewed articles from journals of recognized quality and impact to reduce potential selection and interpretation bias. Evidence was synthesized thematically across key biological domains (e.g., inflammation, neurotrophic signaling, oxidative stress, neuroendocrine regulation), enabling an integrated perspective across different study designs.

3. Neurochemical Imbalances

3.1. Neurotransmitters

TRD has traditionally been approached from a monoaminergic perspective, focusing on deficits in serotonin, dopamine, and norepinephrine. However, growing evidence suggests that TRD involves a more complex dysfunction of neurotransmitter systems, where multiple interconnected networks contribute to the persistence of the disease. In addition to alterations in the synthesis and release of key neurotransmitters, TRD may be associated with genetic or epigenetic dysfunctions, neuronal damage induced by chronic stress or inflammation, and impairments in receptor function or intracellular signaling pathways. Due to the interconnection of neurotransmitter systems, an imbalance in one can affect others, leading to a global disruption that hinders recovery [4,8]. The following section examines the primary neurotransmitters implicated in TRD and their role in the pathophysiology of the disorder.

3.1.1. Serotonin

Serotonin is a neurotransmitter crucial for regulating mood, sleep, appetite, and pain perception, among other functions. While traditional models of depression emphasize serotonin deficiency, evidence suggests that TRD involves a more complex serotonergic dysfunction [9].

A key hypothesis proposes that TRD is characterized by reduced serotonin availability in projection areas, such as the prefrontal cortex and hippocampus, combined with excessive accumulation in the peri-raphe region. This serotonin overload in the midbrain overactivates 5-HT1A autoreceptors, creating a negative feedback loop that inhibits serotonin release at crucial sites, ultimately exacerbating neurotransmitter dysfunction and contributing to resistance to selective serotonin reuptake inhibitors (SSRIs). This "serotonin flooding" phenomenon may explain why dose escalation of serotonin-targeting antidepressants fails to improve outcomes in TRD. Increasing SSRI or serotonin-norepinephrine reuptake inhibitors (SNRI) doses do not enhance serotonin function at projection sites but rather intensifies inhibitory feedback, further suppressing serotonergic neurotrans-

mission [10]. A meta-analysis by Rink et al. [11] provides evidence consistent with this hypothesis, although it does not conclusively prove the mechanism. Instead, it suggests that higher SNRI doses do not significantly enhance clinical response and may increase adverse effects. This underscores that simply boosting serotonin levels is insufficient in TRD and highlights the need for alternative therapeutic approaches. These findings suggest that TRD results from an imbalance in serotonin distribution and regulation rather than a straightforward depletion.

Further supporting evidence comes from a patient-level mega-analysis by Hieronymus et al. [12], which demonstrated that while low SSRI doses are less effective than standard ones, higher-than-recommended doses offer no additional benefit. Their findings challenge the assumption of a flat dose response curve but also indicate an apparent ceiling effect, beyond which increased dosage does not yield greater therapeutic gains. Although their analysis does not directly examine presynaptic mechanisms or the serotonin flooding hypothesis, it aligns with the broader conclusion that dose escalation is often ineffective in TRD, reinforcing the need to consider alternative targets beyond traditional serotonergic amplification.

Supporting this perspective, a recent in vivo neuroimaging study by Murgaš et al. [13] identified a significant reduction in 5-HT1A receptor binding potential in the dorsal raphe nucleus (−17.45%) and the median raphe nucleus (−18.39%) of patients with TRD compared to healthy controls. In contrast, no significant changes were observed in postsynaptic-rich regions such as the prefrontal cortex, hippocampus, or amygdala. This pattern suggests that serotonergic alterations in TRD may primarily originate from impaired presynaptic regulatory mechanisms in the brainstem. The authors propose that the reduced binding could result from lower receptor expression, neuronal loss, or decreased arborization and cell size, all of which would compromise feedback inhibition mediated by 5-HT1A autoreceptors. These alterations were detected in patients under stable pharmacological treatment and are consistent with findings in unmedicated individuals, supporting the interpretation that they reflect a pathological feature associated with treatment resistance rather than an acute drug effect. Although the study does not explicitly endorse the "serotonin flooding" hypothesis, its results highlight a serotonergic imbalance and suggest that therapeutic strategies aiming to modulate 5-HT1A autoreceptor function or enhance postsynaptic serotonergic signaling may offer a more targeted approach for TRD than simply increasing SSRI or SNRI dosages.

Although the 5-HT1A autoreceptor remains a compelling therapeutic target due to its central role in serotonergic regulation, clinical attempts to modulate this receptor, such as pindolol augmentation, have generally failed to demonstrate consistent efficacy in TRD, with most randomized controlled trials showing no significant advantage over placebo. This lack of success likely reflects the drug's limited selectivity, partial antagonistic profile, and off-target activity, underscoring the need for more precise strategies to address presynaptic dysregulation [14]. Emerging approaches include biased 5-HT1A ligands that preferentially enhance postsynaptic signaling cascades, allosteric modulators capable of fine-tuning receptor activity without complete blockade, and agents specifically designed to induce autoreceptor desensitization. While these interventions remain largely in preclinical or early translational phases, they represent a biologically grounded extension of the serotonin flooding hypothesis, offering a more refined framework for targeting treatment resistance at its presumed origin.

Genetic and Epigenetic Influence on Serotonergic Function

Genetic variations in serotonin-related genes, particularly *SLC6A4* and *HTR2A*, have been implicated in depression susceptibility and antidepressant response. The 5-HTTLPR

polymorphism in the promoter region of *SLC6A4*, which encodes the serotonin transporter (SERT), has been associated with treatment outcomes. The short (S) allele has been linked to a higher risk of depression and poorer response to SSRIs. In contrast, the long (L) allele is associated with better remission rates, particularly in Caucasian populations [15,16]. Additionally, lower methylation of the *SLC6A4* promoter has been linked to poorer antidepressant response, likely due to increased transporter expression and reduced serotonin availability [17].

The *HTR2A* gene encodes the serotonin 2A receptor, a key target for SSRIs and tricyclic antidepressants (TCAs), involved in mood, anxiety, and cognitive modulation. While its role in depression susceptibility remains uncertain, specific polymorphisms (1438A/G, rs7997012G/A, and 102T/C) have been linked to antidepressant response and tolerability. The 1438A/G polymorphism is associated with higher treatment response rates, while rs7997012G/A correlates with increased remission and 102T/C with a lower risk of adverse effects [18].

Animal and transgenic studies provide stronger mechanistic insights into serotonergic genetics than association studies alone. Knockout and conditional models of *SLC6A4* and 5-HT1A autoreceptors demonstrate that these genes are conserved across species, and their perturbation produces consistent phenotypes such as altered neuroplasticity, anxiety, and depression-like behaviors, and paradoxical responses to SSRIs, that closely parallel human antidepressant resistance [19–21]. Wistar-Kyoto rats resistant to fluoxetine show upregulation of presynaptic 5-HT1A autoreceptors and *IDO1* activity, with pharmacological blockade restoring antidepressant efficacy [19], while inducible deletion of 5-HT1A autoreceptors in mice results in paradoxical anxiogenic effects of SSRIs [20]. Complementary evidence from *SLC6A4* knockout and heterozygous offspring further shows genotype-dependent alterations in affective behavior, stress responsivity, and BDNF-mediated plasticity [21]. Collectively, these findings confirm that serotonergic gene variants produce conserved and reproducible phenotypes across species, underscoring their translational relevance in clarifying the functional consequences of genetic risk factors for treatment-resistant depression.

Despite these findings, genetic influences on serotonergic function remain complex, with inconsistent results across studies. The interplay between genetic, epigenetic, and environmental factors likely determines individual antidepressant response, underscoring the need for further research to refine personalized treatment strategies [22].

3.1.2. Norepinephrine

Norepinephrine plays a crucial role in cognitive functions such as attention, decision-making, and alertness, meaning its dysfunction can contribute to core symptoms of depression like low energy, cognitive impairment, and anhedonia. Antidepressants that enhance norepinephrine signaling, such as SNRIs and TCAs, are key components in TRD treatment. However, evidence suggests that not all TRD patients respond uniformly to these drugs, indicating that norepinephrine dysfunction alone is not the sole underlying mechanism of treatment resistance [11].

From a treatment perspective, these findings emphasize the need for a more personalized approach in TRD management. While norepinephrine-enhancing agents may be particularly beneficial for patients with prominent cognitive symptoms and low energy, they might be ineffective in cases where additional pathophysiological mechanisms, such as glutamatergic or inflammatory dysregulation, are at play. Moreover, given the lack of a clear dose–response relationship in SNRIs [11], treatment strategies should focus on optimizing drug selection rather than relying on dose escalation. In some cases, augmenting norepinephrine-based treatments with dopaminergic or neuroplasticity-enhancing agents (e.g., ketamine or atypical antipsychotics) may provide better outcomes in TRD patients.

3.1.3. Dopamine

Dopamine is central to motivation, pleasure, and emotional regulation, and its dysregulation has been strongly implicated in TRD. Conventional antidepressants, which primarily target serotonin and norepinephrine, often fail to address dopaminergic deficits, leading to persistent symptoms such as anhedonia and apathy. Reduced dopamine signaling in the mesolimbic pathway, especially in the nucleus accumbens and ventral tegmental area, has been linked to diminished reward sensitivity in TRD [23]. Chronic stress and HPA axis hyperactivation may suppress dopaminergic function, exacerbating depressive symptoms [8,23], while alterations in dopamine transporters and receptors (D1, D2, D3) further impair dopaminergic transmission [23]. Supporting this mechanistic framework, an open-label pilot study of high-dose adjunctive pramipexole significantly improved depressive and anhedonic symptoms, reduced peripheral inflammation, and increased reward-related activity in the ventral striatum and nucleus accumbens, providing preliminary clinical evidence of efficacy and target engagement in anhedonic TRD [24]. Building on these findings, dopamine-enhancing strategies, such as triple reuptake inhibitors (TRIs) and agents like ropinirole or bupropion, show promise for patients with prominent motivational deficits. Moreover, recent proposals suggest that dopaminergic augmentation could potentiate and prolong the antidepressant effects of interventions such as esketamine by leveraging NMDA–dopamine interactions within reward circuitry and thereby improving both anhedonia and the durability of treatment response [25]. Novel approaches targeting D1–D2 receptor heterodimers may also offer therapeutic potential [23]. Finally, combining dopaminergic treatments with interventions that enhance neuroplasticity (e.g., BDNF enhancers, ketamine, or anti-inflammatory agents) may yield greater benefits in TRD management [8,23].

Genetic Influence on Dopaminergic Function

The *COMT* (catechol-O-methyltransferase) gene encodes an enzyme involved in the degradation of dopamine, particularly in the prefrontal cortex, a region essential for mood regulation and cognitive function. The Val158Met (rs4680) polymorphism influences enzymatic activity: the Val variant increases COMT activity, resulting in greater dopamine degradation, whereas the Met variant is associated with higher synaptic dopamine levels. Although studies on *COMT* and antidepressant response have shown mixed results, some findings suggest that specific genetic variants may influence treatment outcomes. A meta-analysis found that carriers of the G allele in rs4680 responded better to electroconvulsive therapy (ECT), although further research is needed to confirm these findings [26]. Additionally, polymorphisms in *COMT* (rs4680, rs4818) have been associated with TRD susceptibility, particularly when interacting with variations in *CREB1*, a gene involved in neuroplasticity [27].

Beyond human association studies, transgenic models provide more direct insights into the role of *COMT* variation in dopaminergic regulation. Evidence remains limited, but a key study by Yang et al. [28], using humanized COMT Val/Met mice, it was shown that carriers of the Val allele exhibited a low-effort bias and motivational impairments, consistent with reduced cortical dopamine availability.

These findings suggest that dopaminergic regulation through *COMT* activity may contribute to individual differences in treatment response and TRD risk, reinforcing the importance of personalized approaches in depression management.

3.1.4. Glutamate

Glutamatergic dysfunction is increasingly recognized as a central mechanism in TRD, contributing to persistent symptoms and poor response to conventional treatments. Exces-

sive glutamate activity leads to excitotoxicity, impaired synaptic plasticity, and structural brain changes, particularly in the prefrontal cortex and hippocampus. A key factor is glutamate-induced excitotoxicity, resulting from NMDAR overactivation, which leads to calcium overload, oxidative stress, and neuronal atrophy. These effects are exacerbated by deficient astrocytic glutamate clearance. Chronic stress and HPA axis hyperactivity further exacerbate this imbalance by increasing glutamate release and hindering reuptake, contributing to cortical thinning and synaptic dysfunction [29].

Individual variability in glutamate metabolism, receptor function, and astrocytic regulation may increase vulnerability to TRD, suggesting a complex interaction between excitatory signaling and neurobiological risk factors [30]. Recognizing glutamatergic dysregulation as a core contributor underscores the importance of early identification of at-risk individuals and the development of targeted interventions.

3.1.5. Gamma-Aminobutyric Acid (GABA)

GABAergic dysfunction is increasingly linked to TRD, as the GABA system is vital for maintaining excitatory-inhibitory balance, emotional regulation, and cognitive function [30]. TRD patients show reduced GABA levels in the prefrontal and anterior cingulate cortices, contributing to heightened neural excitability, stress sensitivity, and impaired plasticity, all of which may underline antidepressant resistance [30,31].

Altered GABA-A and GABA-B receptor function may also impair HPA axis regulation, leading to persistent cortisol elevation and disruption of neural networks, further reinforcing symptom chronicity [30]. Neuroimaging studies support these findings. Spurny-Dworak et al. [32] reported cortical GABA deficits in TRD using magnetic resonance spectroscopy, suggesting that monoaminergic treatments may be insufficient when GABAergic transmission is compromised.

Together with glutamatergic hyperactivity, GABA deficits may contribute to the neurobiological rigidity seen in TRD, limiting the brain's capacity to respond to conventional therapies. Understanding these mechanisms is crucial for identifying individuals at high risk and developing interventions that restore the excitatory-inhibitory balance.

Genetic Influence on the GABAergic System

The GABAergic system, in coordination with glutamatergic signaling, plays a crucial role in synaptic plasticity and mood regulation. Recent genetic studies have reinforced its involvement in ketamine's antidepressant efficacy. In addition to its direct modulation of the NMDA receptor, ketamine indirectly enhances GABAergic neurotransmission, resulting in increased inhibitory signaling and a restoration of the excitatory-inhibitory balance in TRD patients. Genome-wide association studies (GWAS) have identified *BDNF* (rs2049048), *NTRK2* (rs10217777), and *GRIN2A* (rs16966731) as key genetic variants associated with ketamine response, reinforcing the interaction between BDNF-TrkB, glutamatergic, and GABAergic systems in treatment mechanisms [33]. These findings suggest that genetic variations affecting both excitatory and inhibitory neurotransmission could influence individual treatment response to ketamine, providing further insight into the molecular underpinnings of TRD.

Further research is needed to explore how genetic modulation of the GABAergic system contributes to TRD pathophysiology and treatment resistance, particularly in response to rapid-acting antidepressants. In line with this, animal models provide mechanistic evidence that complements human GWAS by identifying causal links between genetic alterations in inhibitory signaling and depressive phenotypes. For instance, selective knockdown or deletion of GluN2B-containing NMDA receptors on GABA interneurons was

shown to abolish ketamine's behavioral effects in mice, establishing these interneurons as the initial cellular trigger of ketamine's rapid antidepressant actions [34].

Taken together, evidence from both human association studies and animal models underscores that conserved genetic modulation of the GABAergic system is central to vulnerability in TRD and to the efficacy of rapid-acting antidepressants.

3.1.6. Additional Neurotransmitters in TRD

Acetylcholine (ACh) and histamine have been increasingly implicated in TRD. Their interplay with monoaminergic and excitatory-inhibitory systems suggests a broader neurobiological dysregulation contributing to persistent symptoms and poor treatment response.

Acetylcholine, through muscarinic (mAChRs) and nicotinic (nAChRs) receptors, regulate mood, cognition, and stress adaptation. The cholinergic–adrenergic hypothesis of depression proposes that excess cholinergic activity may contribute to TRD, particularly in patients unresponsive to monoaminergic antidepressants. Elevated ACh levels correlate with reduced reward sensitivity and impaired emotional regulation, while nAChRs modulate serotonergic and glutamatergic transmission, potentially affecting stress resilience and neuroplasticity [35]. M1 muscarinic receptors (M1R) in the medial prefrontal cortex (mPFC) regulate inhibitory-excitatory balance, and their dysfunction has been linked to stress vulnerability and synaptic maladaptation [36].

Similarly, histamine, via H1 and H3 receptors, modulates monoaminergic activity and inflammatory responses. Its dysregulation has been associated with neurotransmitter imbalance, metabolic disturbances, and heightened stress sensitivity, all of which may contribute to TRD pathophysiology [35].

The involvement of acetylcholine and histamine in TRD underscores the need for a broader neurobiological perspective, where treatment resistance stems from interconnected neural dysregulations rather than isolated neurotransmitter deficits. Addressing these imbalances may provide key insights into the persistence of symptoms and the limited efficacy of conventional antidepressants.

3.1.7. Clinical and Translational Implications of Neurotransmitters

Neurotransmitter dysregulation in TRD highlights several therapeutic targets, ranging from serotonergic autoreceptors [13] and dopaminergic receptors [37] to glutamatergic and GABAergic modulators [38]. Novel agents such as biased 5-HT1A ligands, dopamine agonists, glutamate receptor modulators, and interventions that restore inhibitory–excitatory balance are promising avenues that extend beyond traditional monoaminergic enhancement [39]. From a preventive perspective, early identification of individuals carrying genetic variants in serotonin transporter (*SLC6A4*), *COMT*, or *GRIN2A*, combined with neuroimaging or biochemical markers of neurotransmitter imbalance, could inform stratified screening programs and guide personalized interventions before resistance develops.

Despite advances in understanding neurotransmitter dysregulation in TRD, translating these insights into clinical practice faces specific challenges. Reliable neurochemical biomarkers capable of stratifying patients or predicting treatment response are still lacking, and current neuroimaging and pharmacogenetic tools remain limited in terms of accessibility and standardization. Moreover, the heterogeneity of neurotransmitter alterations across individuals complicates the selection of targeted interventions [40]. Addressing these challenges will require integrating pharmacogenetic testing, functional imaging, and biomarker-driven clinical trials to clarify which patients are most likely to benefit from therapies modulating serotonergic, dopaminergic, glutamatergic, or GABAergic systems.

3.2. Pharmacokinetics and Antidepressant Metabolism

In the international pharmacogenetic guidelines, for instance, the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), the key enzymes of the cytochrome P450, such as *CYP2C19* and *CYP2D6*, support genotype-informed dose adjustments for specific antidepressants [41,42]. In this context, the Pharmacogenomics Knowledge Base [43] serves as a curated repository summarizing the level of evidence linking gene–drug pairs, their clinical annotations, and the strength of guideline recommendations [44].

The impact of *CYP2C19* polymorphisms on antidepressant response has been observed with drugs like escitalopram and sertraline, where poor metabolizers face an increased risk of treatment changes and self-harm [45]. Similarly, *CYP2D6* poor metabolizers treated with fluoxetine have shown a higher incidence of psychiatric emergencies, suggesting a role in treatment tolerability. However, large-scale studies, such as the Australian Genetics of Depression Study (AGDS), did not find a clear association between *CYP2C19*/*CYP2D6* metabolism profiles and TRD [46].

Additionally, psychological stress may alter *CYP* enzymatic activity through HPA axis activation, potentially modifying antidepressant metabolism and increasing the risk of adverse effects or therapeutic failure [47]. Overall, while *CYP* polymorphisms can influence drug response, their role in TRD appears to be shaped by a complex interplay of genetic factors, comorbidities, and environmental influences [46,48].

Transgenic models provide robust evidence that conserved metabolic genes can influence the response to antidepressants. For example, mice expressing the human *CYP2C19* gene display hippocampal abnormalities and increased anxiety-like behavior, likely due to expression during brain development rather than altered drug metabolism, which may alter neural circuits related to stress reactivity and emotional regulation, paralleling clinical findings in carriers of functional variants [49]. Similarly, *CYP2D6* humanized mice demonstrate that brain-expressed *CYP2D6* is enzymatically active and sufficient to alter drug response [50]. Together, these findings highlight that animal models with conserved pharmacokinetic genes yield clinically relevant insights, reinforcing the complex interplay between genetic variation, metabolism, and antidepressant efficacy.

Clinical and Translational Implications of Pharmacokinetics and Antidepressant Metabolism

The evidence on *CYP2C19* and *CYP2D6* highlights that pharmacogenetic testing can offer practical benefits, particularly by informing drug selection and dosing in patients at risk of poor tolerance or therapeutic failure. Incorporating genotype data into prescribing decisions could prevent avoidable adverse outcomes and help reduce the likelihood of treatment resistance. However, translation to clinical routine remains limited. While international guidelines endorse genotype-informed adjustments, inconsistent findings in large-scale studies and unequal access to testing have slowed implementation. In addition, factors such as comorbidities and stress-related modulation of enzyme activity complicate the direct application of genetic profiles [40]. To move forward, psychiatry will need to complement pharmacogenetic screening with longitudinal clinical monitoring and real-world evidence to determine when, and for whom personalized dosing strategies truly improve outcomes.

3.3. Growth Factors

3.3.1. Brain-Derived Neurotrophic Factor (BDNF)

BDNF is an essential protein for neuroplasticity, neuronal survival, and the formation of new synaptic connections, key functions for the brain's adaptation to stress and recovery from mood disorders. In patients with depression, particularly those with TRD, reduced BDNF levels have been observed in the brain, especially in the hippocampus and prefrontal cortex, which are crucial regions for mood regulation. The decrease in BDNF contributes to reduced neuroplasticity, hindering the formation of new synaptic connections and limiting neuronal recovery capacity [51].

Several studies have found that peripheral BDNF levels are typically lower in patients with MDD compared to healthy controls [52]. Pharmacological treatments, such as SSRIs and ketamine, have been shown to increase BDNF levels, which are often associated with better clinical response. However, these changes do not always correlate with symptom improvement, suggesting that other factors may modulate the relationship between BDNF and treatment response [51,52].

One such factor is inflammation. Elevated levels of interleukin-1 beta (IL-1β), an inflammatory marker, may interfere with the neurotrophic effects of BDNF. Chronic inflammation in TRD patients is thought to reduce the effectiveness of BDNF-regulated neurotrophic pathways, impairing synaptic recovery and neurogenesis [51,53].

Regarding non-pharmacological therapies, the relationship between BDNF and interventions such as repetitive transcranial magnetic stimulation (rTMS) or ECT (electroconvulsive therapy) remains controversial. While some studies have found no significant changes in BDNF levels following ECT [52]. Others have reported that lower baseline BDNF levels are associated with better outcomes after this therapy [54]. These findings suggest that BDNF modulation in response to different therapeutic interventions is complex and may depend on multiple individual factors.

Genetic Influence on BDNF and Treatment Response

Among the key genetic factors influencing neuroplasticity and antidepressant response, the *BDNF* gene has been extensively studied. The rs6265 (*Val66Met*) polymorphism, where valine (Val) is substituted by methionine (Met), has been associated with TRD and antidepressant response. Some studies suggest that the Met allele may contribute to SSRI resistance, while others link it to better outcomes with specific antidepressants [52,54]. Additionally, carriers of the Val allele may respond more favorably to ketamine treatment, supporting its role in rapid-acting antidepressant effects [51].

Beyond Val66Met, other SNPs in neuroplasticity-related genes have been linked to ketamine's therapeutic effects. *BDNF* (rs2049048), *NTRK2* (rs10217777), and *GRIN2A* (rs16966731), genes involved in synaptic plasticity and glutamatergic neurotransmission, have been associated with the rapid and sustained antidepressant response to ketamine in TRD patients [33]. These findings highlight the role of BDNF-TrkB and glutamatergic pathways in ketamine's mechanism of action.

Although Val66Met and other neuroplasticity-related SNPs have been proposed as potential biomarkers for personalized treatment strategies, inconsistencies across studies limit their immediate clinical applicability. Further research is needed to clarify their role in TRD and optimize biomarker-based treatment approaches [52].

In this context, evidence from animal models provides mechanistic support, showing that conserved genetic variation in BDNF and TrkB yields phenotypic effects directly relevant to antidepressant response. Knock-in mice carrying the human *BDNF* Val66Met variant show impaired activity-dependent *BDNF* secretion and fail to respond to ketamine and its metabolite, mirroring clinical findings in human Met carriers [55]. Complemen-

tarily, selective deletion of *BDNF* or TrkB in hippocampal CA3–CA1 synapses abolishes ketamine-induced synaptic potentiation and antidepressant-like effects, demonstrating that postsynaptic BDNF-TrkB signaling is required for ketamine's efficacy [56]. Together, these models highlight the specific role of BDNF-TrkB signaling in mediating ketamine's antidepressant effects, providing mechanistic evidence beyond genetic associations.

3.3.2. Insulin-like Growth Factor 1 (IGF-I)

While most research on neurotrophic factors has focused on BDNF, increasing attention is being given to the study of IGF-I due to its neurotrophic, neuroprotective, and neurogenic effects. Significantly higher IGF-I levels have been reported in patients with depression compared to healthy controls, and those who did not respond to antidepressant treatment exhibited elevated IGF-I levels both at baseline and after six weeks of treatment. This suggests that elevated IGF-I may be linked to a poor response to antidepressant therapy. IGF-I, primarily produced in the liver, plays a crucial role in glucose metabolism and cellular development, as well as in synaptic function and neuronal plasticity within the central nervous system. It is suggested that IGF-I, along with other neurotrophic factors, may contribute to neuroplasticity and treatment response in depression. However, further studies are needed to understand its impact on TRD fully [53].

3.3.3. Vascular Endothelial Growth Factor (VEGF)

VEGF is a key cytokine that promotes angiogenesis, neurogenesis, and synaptic plasticity, playing an essential role in neuronal protection and regeneration [57]. It links the vascular hypothesis of depression with endocrine dysfunction mediated by the mineralocorticoid receptor (MR) and aldosterone [58,59].

The vascular hypothesis suggests that mild cerebrovascular disease (e.g., white matter lesions, neuroimaging hyperintensities) predisposes to depression—particularly in older adults—by impairing cerebral blood flow, disrupting connectivity, and triggering inflammation [59]. In this context, VEGF may function as a compensatory factor that induces angiogenesis, promotes cerebral perfusion, and enhances functional plasticity.

Rapid-acting antidepressants such as ketamine not only enhance activity-dependent BDNF release but also modulate VEGF in the medial prefrontal cortex, both of which are necessary for their synaptic and behavioral effects. BDNF and VEGF synergistically restore plasticity in depression models, although their role as biomarkers in TRD remains unclear [60].

In treatments such as rTMS and ECT, VEGF appears to play a more evident role: In TRD patients treated with rTMS, no significant changes in VEGF were observed, although a slight initial increase was suggested [61]. Conversely, in patients who received ECT, higher VEGF levels were associated with less severe symptoms, suggesting a potential link between VEGF and clinical severity [62].

Regarding aldosterone and MR, recent studies indicate that chronic MR activation in the vasculature, whether by aldosterone or cortisol, induces endothelial dysfunction, vascular inflammation, remodeling, fibrosis, and increased vascular tone, leading to hypoperfusion and white matter lesions, both of which are central to the vascular hypothesis of depression [58,63]. In patients with primary aldosteronism, a higher prevalence of depressive symptoms and structural brain changes (ventricular enlargement, corpus callosum compression) has been reported, which are associated with poorer treatment outcomes [64].

Mineralocorticoid receptor antagonists (MRAs), including spironolactone, eplerenone, and newer agents, have shown potential to improve vascular perfusion, reduce inflammation, and enhance cognition in cardiovascular populations, which could indirectly

benefit brain function [65,66]. Preclinical studies also suggest they may attenuate vascular inflammation and influence VEGF expression.

Overall, while direct evidence for VEGF as a biomarker in TRD is limited, the interplay between neuroplasticity, vascular dysfunction, and endocrine dysregulation points to a possible compensatory role. MRAs, by mitigating vascular damage, could indirectly modulate VEGF, a hypothesis that warrants further biomarker-driven studies in TRD.

Genetic Insights into Angiogenesis and TRD

Recent genome-wide association studies (GWAS) have identified genetic factors linking angiogenesis and vascular function to TRD. Among the key findings, SNPs in *VEGFC* and *PIGF*, two genes involved in VEGF signaling, have been associated with better treatment response to ketamine. These results suggest that angiogenic mechanisms may contribute to the therapeutic effects of ketamine, potentially by modulating neurovascular function and synaptic plasticity [67].

Although these findings offer a new perspective on the vascular component of TRD, further studies are needed to determine whether angiogenesis-related biomarkers can be used to predict treatment response and guide personalized therapeutic strategies in TRD patients.

Animal studies have provided mechanistic evidence for the role of VEGF in depression. Selective deletion of VEGF in the hippocampus reduces neurogenesis and induces depressive-like behaviors, while blockade of VEGF/Flk-1 signaling prevents the antidepressant effects of fluoxetine, desipramine, and even ketamine [68]. These findings indicate that angiogenesis-related pathways are not merely correlated with treatment outcomes but are required for antidepressant efficacy, underscoring the conserved role of VEGF signaling linking vascular plasticity to behavioral improvement in TRD.

3.3.4. Clinical and Translational Implications of Growth Factors

Growth factor dysregulation in TRD presents a range of potential therapeutic opportunities, particularly in targeting the BDNF–TrkB, IGF-I, and VEGF pathways. Pharmacological and neuromodulatory interventions that enhance neurotrophic signaling, such as ketamine, ECT, or rTMS, may act by restoring plasticity through BDNF and VEGF modulation, while mineralocorticoid receptor antagonists could indirectly mitigate vascular dysfunction and influence VEGF activity [60–62]. At the preventive level, peripheral measures of BDNF, IGF-I, or VEGF could be incorporated as early biomarkers to identify patients at risk of treatment resistance or poor clinical response, though their predictive value remains inconsistent. Despite these promising perspectives, critical implementation challenges persist, including variability in peripheral biomarker reliability, the influence of comorbid systemic conditions (e.g., inflammation, metabolic disease) on growth factor levels, and the limited translation of genetic and preclinical findings into clinically actionable strategies [40]. Addressing these gaps will require longitudinal, biomarker-driven studies and clinical trials that integrate neurotrophic and vascular markers into stratified treatment approaches, paving the way toward precision psychiatry in TRD.

3.4. Hypothalamic–Pituitary–Adrenal (HPA) Axis

The HPA axis is a central neuroendocrine system involved in stress regulation, and its dysregulation has been repeatedly implicated in TRD. Under stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), thereby triggering the release of cortisol from the adrenal cortex. Usually, harmful feedback mechanisms suppress cortisol secretion once the stressor is resolved. The traditional "HPA hyperactivity hypothesis" proposes that, in TRD, this feedback is impaired, resulting in sustained hypercortisolemia, which may

exert neurotoxic effects such as hippocampal atrophy, cognitive deficits, and reduced BDNF levels, ultimately compromising neuroplasticity and antidepressant response [69,70].

In addition, excessive cortisol can disrupt monoaminergic signaling, particularly serotonin and dopamine pathways, thereby worsening depressive symptoms and potentially blunting antidepressant efficacy. Although some studies suggest that certain antidepressants, such as SSRIs, may partially normalize cortisol secretion, these findings remain inconsistent and are subject to ongoing debate [69,71].

While hypercortisolism is observed in a subset of TRD patients, others present with normal or even reduced cortisol levels, suggesting heterogeneous HPA axis profiles [72–74]. Clinical exceptions, such as patients with Cushing's syndrome, support the link between sustained cortisol excess and mood disturbances, but also illustrate that depressive symptoms can occur across a wide range of cortisol states [75,76]. Moreover, pharmacological attempts to modulate the HPA axis, such as CRH receptor antagonists (e.g., pexacerfont) and glucocorticoid receptor antagonists (e.g., mifepristone), have yielded inconsistent or largely negative results in mood disorders, including TRD, despite strong preclinical rationale [77,78]. These findings challenge the notion that HPA hyperactivity is a uniform causal mechanism and highlight the need for biomarker-driven stratification before implementing HPA-targeted treatments.

3.4.1. Genetic and Epigenetic Influence on HPA Axis Dysregulation

Genetic variations in *FKBP5* and *NR3C1*, key regulators of the HPA axis, have been linked to TRD susceptibility and treatment response. *FKBP5* encodes a negative regulator of the glucocorticoid receptor (GR), modulating cortisol sensitivity. Increased *FKBP5* expression has been associated with HPA axis dysregulation and treatment resistance, with polymorphisms (rs1360780, rs3800373, rs9470080) influencing depression risk and antidepressant response, though results vary across populations [79–81]. Childhood trauma may further amplify the effects of *FKBP5* variants, increasing stress reactivity and reducing treatment efficacy [80].

Meanwhile, *NR3C1*, encoding the GR, plays a crucial role in HPA axis feedback regulation. Altered *NR3C1* methylation has been observed in TRD, with higher levels linked to poorer ECT response [82]. Early-life stress has been associated with increased NR3C1 expression, and its reduction after psychotherapy correlates with symptom improvement [83].

Animal models provide causal evidence that *FKBP5* directly modulates HPA axis reactivity and stress-related phenotypes. Conditional deletion of *FKBP5* in paraventricular nucleus (PVN) neurons dampens the acute stress response and increases glucocorticoid receptor sensitivity, whereas PVN-specific overexpression induces chronic HPA hyperactivity, with rescue experiments restoring normal function [84]. Complementarily, pharmacological inhibition of FKBP51 with the selective compound SAFit2 promotes hippocampal neurogenesis and confers resilience to chronic psychosocial stress in mice, reducing anxiety and depression-like behaviors [85]. Together, these models demonstrate that conserved *FKBP5-related* mechanisms shape both stress responsivity and treatment outcomes, thereby strengthening the translational relevance of this gene to TRD pathophysiology.

These findings highlight the role of genetic and epigenetic modifications in HPA axis dysregulation, TRD pathophysiology, and treatment variability, underscoring the need for personalized approaches in depression management.

3.4.2. Clinical and Translational Implications of HPA Axis Dysregulation

HPA axis abnormalities in TRD offer several therapeutic opportunities, including modulation of cortisol signaling and pharmacological targeting of CRH or glucocorticoid receptors. Although initial trials with CRH antagonists and glucocorticoid receptor blockers

have yielded disappointing or inconsistent outcomes [77,78], selective compounds, such as FKBP51 inhibitors represent a more promising avenue by addressing molecular regulators of stress reactivity [84]. At the preventive level, assessing cortisol profiles in conjunction with genetic and epigenetic markers in FKBP5 and NR3C1 could help identify patients at a higher risk of stress hypersensitivity and poor treatment response, enabling earlier intervention. Still, essential implementation challenges remain, particularly the heterogeneity of HPA axis alterations across TRD subgroups, the lack of standardized biomarkers for routine clinical use, and the gap between robust preclinical findings and mixed clinical trial results. To overcome these barriers, integrating pharmacogenetics, epigenetic profiling, and longitudinal endocrine monitoring into clinical research will be essential to determine which patients can benefit most from HPA-targeted interventions.

3.5. Other Endocrinopathies Related to TRD

Beyond HPA axis dysfunction, other endocrine disorders have been linked to TRD, as they can complicate depression management and reduce response to conventional antidepressants.

Thyroid dysfunction, particularly hypothyroidism, is associated with depressive symptoms that often persist despite treatment [86,87]. Although thyroid hormone replacement does not seem to improve TRD in these patients significantly [88], assessing thyroid function remains crucial. Hyperthyroidism, though less common, can also contribute to mood disturbances and complicated depression treatment due to metabolic instability [87]. Complementary evidence from animal models supports this link in Wistar-Kyoto rats, a validated TRD model, early psilocybin intervention not only alleviated behavioral despair and cognitive impairment but also reversed stress-induced reductions in thyroid-stimulating hormone (TSH), without affecting corticosterone levels [89]. These findings highlight the translational relevance of thyroid-related endocrine mechanisms in shaping treatment resistance.

Type 2 diabetes mellitus (T2DM) and TRD exhibit a bidirectional relationship mediated by insulin resistance, inflammation, and dysfunction of the HPA axis. Insulin resistance can exacerbate depressive symptoms and reduce antidepressant efficacy [3,8]. While poorly managed T2DM may worsen depression. Research suggests that improving insulin sensitivity, either through pharmacological means or lifestyle modifications, may enhance the antidepressant response.

Parathyroid disorders, particularly primary hyperparathyroidism, can contribute to TRD through hypercalcemia, which affects mood, cognition, and overall well-being. Even subclinical hypercalcemia has been associated with reduced antidepressant response, while parathyroidectomy has been shown to improve psychiatric symptoms and quality of life [90].

Gonadal hormones also play a critical role in depression and TRD. Estrogen fluctuations, particularly during perimenopause, postpartum, and menopause, have been linked to mood disturbances that often resist conventional antidepressants, suggesting that hormonal treatment may be necessary in some instances [91]. Progesterone variations, especially in the luteal phase and postpartum, may also contribute to depressive symptoms [92]. In men, low testosterone levels, particularly in hypogonadism, have been associated with an increased risk of depression and reduced antidepressant response [93]. However, testosterone treatment in women has not shown significant benefits [94].

Postmenopausal women exhibit a distinct endocrine profile marked by declines in estradiol and progesterone that contribute to heightened vulnerability to depression and antidepressant nonresponse. Fluctuating and decreasing estrogen levels during the menopausal transition have been linked to neurochemical instability in serotonergic and dopaminergic systems, neuroinflammation, and reduced neuroprotection, all of which

may increase the risk for treatment resistance [95,96]. Clinical data indicate that standard antidepressants, particularly SSRIs, often show reduced efficacy in postmenopausal women, whereas SNRIs like venlafaxine demonstrate superior outcomes in this population [97]. Importantly, novel glutamatergic approaches appear to bypass some of the estrogen-dependent mechanisms of resistance. In a large clinical cohort, postmenopausal women with TRD achieved response and remission rates to intravenous ketamine comparable to those of premenopausal women, with notable reductions in suicidal ideation [91]. These findings underscore the clinical relevance of the altered hormonal landscape in postmenopausal women as a biological risk context for TRD and highlight the need for tailored therapeutic strategies.

3.5.1. Genetic Links Between Endocrine Dysregulation and TRD

Emerging genetic evidence suggests that endocrine dysfunction may play a role in TRD. Whole-exome sequencing studies have identified rare variants in *ZNF248*, *PRKRA*, *PYHIN1*, *SLC7A8*, and *STK19*, genes involved in transcriptional regulation, immune response, and thyroid hormone transport. These findings highlight the biological heterogeneity of TRD and suggest a potential connection between thyroid dysregulation and treatment resistance [98].

Further research is needed to determine whether thyroid-related genetic variations influence HPA axis function, immune modulation, and antidepressant response, as well as their potential role in biomarker-driven treatment strategies.

3.5.2. Clinical and Translational Implications of Other Endocrinopathies

Endocrine dysfunctions beyond the HPA axis open diverse therapeutic opportunities in TRD. Optimizing thyroid and metabolic control, addressing calcium and parathyroid abnormalities, and considering hormone replacement in select cases may improve outcomes when standard antidepressants fail [99]. Preventive strategies include systematic screening of thyroid, glucose, calcium, and sex hormone levels to detect patients at higher risk of nonresponse. Implementation challenges remain, hormone levels are dynamic, evidence for endocrine-based augmentation is limited, and large randomized trials are lacking. Closer integration of endocrinology into psychiatric care will be key to establishing reliable biomarker-driven approaches in TRD.

4. Chronic Inflammation

4.1. Chronic Inflammation and TRD

Low-grade systemic inflammation has been increasingly associated with the onset, persistence, and treatment resistance of depressive symptoms. Elevated levels of pro-inflammatory markers, such as IL-6, IL-1β, TNF-α, and CRP, are commonly found in individuals with MDD and may disrupt brain function through effects on neurotransmission and neuroplasticity [100].

Cytokines can alter the release and reuptake of serotonin, dopamine, and glutamate, partly by inducing enzymes like indoleamine 2,3-dioxygenase (IDO) that divert tryptophan metabolism toward neurotoxic pathways, reducing serotonin availability [101,102]. Inflammation also activates microglia, promoting neuroinflammation that impairs synaptic function and neuronal integrity, further contributing to antidepressant resistance [103–106].

Moreover, chronic inflammation can dysregulate the HPA axis, elevating cortisol levels and reinforcing stress-related neurobiological disruptions [107]. Patients with high baseline levels of inflammatory markers, especially CRP, IL-6, and TNF-α, often show poor response to SSRIs and tricyclic antidepressants, highlighting their potential as predictive biomarkers for treatment resistance [8,61,74,106,108].

4.1.1. Inflammation-Related Genetic Variants and TRD

Chronic inflammation has been increasingly recognized as a contributor to TRD. Recent GWAS have identified *IL1R1* and *TNFRSF8* polymorphisms, two genes involved in pro-inflammatory signaling that may influence the therapeutic response to ketamine [67].

These findings suggest that the immune-inflammatory response could be a key factor in determining ketamine's efficacy, reinforcing the idea that targeting inflammation may improve treatment outcomes in TRD.

Despite these insights, further functional studies are required to clarify the causal role of inflammation-related genetic variants and their implications for personalized treatment approaches. While GWAS have identified inflammation-related variants such as *IL1R1* and *TNFRSF8*, functional studies in animal models directly testing these human polymorphisms are still lacking. This gap highlights the need for transgenic approaches to establish causal links and translational relevance.

4.1.2. Clinical and Translational Implications of Chronic Inflammation

Inflammation-related abnormalities in TRD highlight promising therapeutic targets, including cytokine inhibitors and interventions modulating IDO activity [109], which may restore neurotransmitter balance and synaptic function in patients with elevated inflammatory markers. From a preventive standpoint, routine assessment of CRP, IL-6, and TNF-α could help identify individuals at greater risk of antidepressant resistance, supporting early stratification and treatment optimization. Significant implementation challenges remain; inflammatory markers are variable across individuals, strongly influenced by comorbid medical conditions, and not yet standardized for clinical use [110]. Translating robust preclinical findings into effective therapies will require biomarker-guided clinical trials designed to test anti-inflammatory interventions in carefully defined subgroups of TRD patients.

5. Obesity and Metabolism

5.1. Obesity

Shared genetic factors have been identified between TRD and metabolic traits, including body composition [111]. The well-established bidirectional link between obesity and depression involves both biological and psychological mechanisms, with chronic low-grade inflammation, driven by visceral fat accumulation, playing a central role. Elevated inflammatory markers such as CRP, TNF-α, and IL-6 are common in obesity, further reinforcing this connection [112,113].

Insulin and leptin resistance, frequent in obesity, also contribute to depressive symptoms and treatment resistance. Insulin resistance has been associated with poor response to SNRIs, while leptin resistance relates to atypical depression symptoms, such as increased appetite and lethargy [112,114,115].

On the other hand, obesity reduces neuroplasticity, particularly affecting the hippocampus, a key region for mood regulation and the response to antidepressant treatments [92]. Moreover, obesity impairs neuroplasticity, particularly in the hippocampus, and disrupts neural circuits involved in mood regulation, such as the reward system and prefrontal cortex [112,116,117].

Obesity also interferes with serotonin and dopamine signaling, key neurotransmitters in emotional regulation. Chronic inflammation may reduce serotonin availability, potentially diminishing the efficacy of SSRIs [115,118]. Both conditions, obesity and depression, share standard mechanisms such as inflammation, gut microbiota alterations, insulin and leptin resistance, and HPA axis dysregulation [119]. These overlapping pathways contribute to worse clinical outcomes and reduced treatment response [112,113,118].

Significantly, a higher genetically predicted body mass index (BMI) has been associated with an increased risk of TRD, especially in women. This relationship appears to be causal and independent of inflammation, suggesting that BMI itself is a direct risk factor for treatment resistance in depression [120]. These findings underscore the importance of considering body weight in the clinical management of TRD.

5.1.1. Genetic Implications of Metabolism in TRD

Recent GWAS have highlighted the role of metabolic regulation and body composition in TRD. Genetic variations associated with obesity, energy homeostasis, and metabolic disorders may contribute to treatment resistance by influencing both neurobiological and inflammatory pathways. Among the most relevant findings, *FTO* and *MCHR1* gene variants have been linked to weight regulation and metabolic balance, suggesting that obesity and type 2 diabetes may increase the risk of TRD through shared biological mechanisms [111,121]. Animal studies demonstrate that *FTO* exerts causal effects on mood regulation and may mediate the metabolic contribution to TRD. Hippocampal *FTO* knockdown or knockout in mice induces depression-like behaviors, while overexpression has antidepressant effects through N6-methyladenosine-dependent regulation of ADRB2 signaling [122]. In contrast, global *FTO* deficiency reduces anxiety and depression-like behaviors via gut microbiota–mediated anti-inflammatory shifts [123]. Similarly, in rodents, chronic stress upregulates *MCHR1* expression in the locus coeruleus, contributing to maladaptive noradrenergic responses and depression-like behaviors [124]. Complementarily, pharmacological blockade of *MCHR1* produces robust antidepressant- and anxiolytic-like effects, reinforcing its role as a promising therapeutic target at the interface of energy balance and mood regulation [125].

Genetic polymorphisms in *TMEM106B* (a lysosomal transmembrane protein) and *ATP2A1* (a calcium pump involved in cellular metabolism) have been linked to specific depression subtypes, particularly those characterized by anxiety and weight gain, suggesting a metabolic contribution to TRD [126]. However, animal studies directly testing these genes in depression models are lacking, which limits the functional validation of these associations.

These genetic insights support the bidirectional relationship between obesity and TRD, where chronic inflammation, insulin resistance, and neuroendocrine dysfunction may contribute to both depressive symptoms and poor antidepressant response. Given this genetic and metabolic interplay, future treatment strategies for TRD should consider personalized interventions that address both metabolic dysregulation and psychiatric symptoms.

5.1.2. Clinical and Translational Implications of Obesity and Metabolism

Metabolic dysregulation and obesity highlight distinct therapeutic opportunities, including insulin-sensitizing drugs [127], leptin pathway modulators [128], and *MCHR1* antagonists [129], which may improve treatment outcomes in patients with TRD and comorbid metabolic conditions. Lifestyle interventions that reduce visceral adiposity and enhance insulin sensitivity could also serve as accessible strategies to improve antidepressant efficacy [127,128]. From a preventive perspective, incorporating metabolic markers such as BMI, insulin resistance, and leptin status into psychiatric evaluations may help identify individuals at greater risk of treatment resistance before standard therapies fail.

Key implementation challenges remain. Metabolic traits interact with inflammation, neuroplasticity, and neuroendocrine pathways, complicating the isolation of obesity-specific mechanisms. Access to metabolic screening and interventions within psychiatric care is still limited, and most genetic associations (e.g., *FTO*, *MCHR1*, *TMEM106B*, *ATP2A1*) require functional validation before they can inform personalized approaches [111,121]. To address these barriers, future research should combine metabolic and psychiatric endpoints in

longitudinal, biomarker-guided trials, paving the way for precision strategies that integrate weight, energy balance, and mental health in TRD management.

6. Alterations in Brain Connectivity

Alterations in brain connectivity are a critical component of TRD. These changes reflect how different brain regions interact with one another, which can impact mood regulation, motivation, cognition, and other emotional processes. Below are some of the networks most associated with TRD (Figure 1).

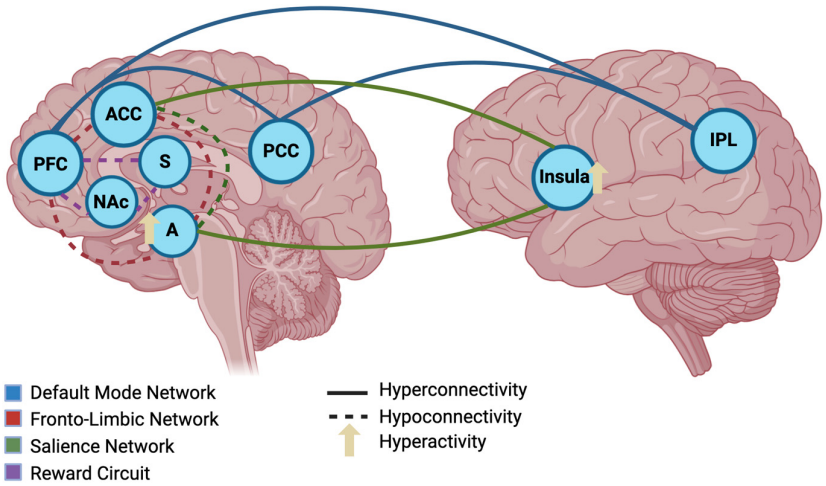


Figure 1. Alterations in Brain Connectivity in TDR. Hyperconnectivity within the Default Mode Network leads to persistent rumination and difficulty deactivating during tasks, interfering with emotional regulation, concentration, and cognitive flexibility. Reduced connectivity within the fronto-limbic network limits emotional regulation and control over negative emotional states, leading to heightened anxiety, fear, and sadness. At the same time, dysfunctions in the anterior cingulate cortex impair the resolution of emotional conflicts and adaptive decision-making. Hyperactivity in the salience network exaggerates threat perception and negative stimuli, impairing the brain's ability to shift between the default mode and central executive networks. This leads to persistent rumination, difficulty focusing on external tasks, and challenges in decision-making and adaptive responses. Dysfunction in the reward circuit leads to persistent anhedonia and reduced treatment response. Abbreviations: A, amygdala; ACC, anterior cingulate cortex; IPL, inferior parietal lobule; NAc, nucleus accumbens; PCC, posterior cingulate cortex; PFC, prefrontal cortex; S, striatum.

6.1. Default Mode Network (DMN)

The DMN is one of the most studied brain networks in the context of depression, including TRD. It includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, inferior parietal cortex, hippocampus, lateral temporal cortex, and retrosplenial cortex. This network is active when the brain is at rest, meaning it is not focused on specific external tasks, and is involved in internal processes such as introspection, self-reflection, and rumination [130,131].

In individuals with depression, particularly those with TRD, hyperconnectivity within the DMN has been observed, manifesting as increased activity and synchronization between the regions that comprise it. This hyperactivity is associated with a greater tendency toward rumination; a repetitive and self-critical thought process focused on adverse past events or future concerns. Rumination is a hallmark symptom of depression and is strongly linked to the severity and chronicity of the disorder. Additionally, in people with TRD, the DMN shows a reduced ability to "deactivate" or disengage during tasks that require external attention. This suggests that even when patients try to focus on an external activity, the DMN remains dominant, interfering with their ability to concentrate and process information effectively. This is particularly problematic in TRD, where traditional

treatments that modulate neurotransmission, such as SSRIs, may not be sufficient to disrupt this cycle of rumination. An overactive DMN can interfere with the ability of brain networks that regulate emotions, such as the fronto-limbic network, making it harder to manage negative emotions and increasing vulnerability to recurrent or chronic depression. The dominance of the DMN at rest may also reduce cognitive flexibility, meaning the brain struggles to shift from a resting state to an active state when concentration or directed attention is required. This rigidity in brain connectivity may be one of the reasons why patients with TRD do not respond well to standard treatments [130,132,133].

In line with these human imaging findings, recent animal and primate studies using causal circuit perturbations provide mechanistic support for the role of DMN hubs in TRD. Within this network, the medial prefrontal cortex and its subregions, including the subcallosal area 25, have emerged as critical nodes whose modulation can causally alter affective behaviors. A systematic review of optogenetic interventions in rodents demonstrated that stimulation of prefrontal, mesolimbic, and habenular circuits can bidirectionally induce or reverse depressive-like behaviors, including social withdrawal, anhedonia, and despair, highlighting the mPFC and its projections as central hubs [134]. More specifically, repeated optogenetic activation of the prelimbic mPFC to nucleus accumbens pathway enhanced the antidepressant efficacy of venlafaxine, indicating that prefrontal–limbic projections downstream of DMN nodes critically shape treatment response [135]. Extending these findings to primates, chemogenetic manipulations in marmosets revealed that hyperactivation of area 25 produced anhedonia via its projections to the nucleus accumbens and anxiety via projections to the amygdala, with ketamine infusion into the nucleus accumbens preventing anhedonia for more than a week [136]. Collectively, these results reinforce the translational relevance of DMN hubs such as the mPFC and area 25 in modulating affective networks and mediating treatment resistance in depression.

6.2. Fronto-Limbic Network

The fronto-limbic network is essential for emotion regulation, reward processing, and decision-making. This network comprises several brain regions that interact to regulate emotional responses and cognitive control. Its key components include the dorsolateral prefrontal cortex, the ventromedial prefrontal cortex, the anterior cingulate cortex (ACC), the amygdala, and the hippocampus. The fronto-limbic network is crucial for integrating emotional and cognitive information. The prefrontal cortex regulates the activity of the amygdala and other limbic structures to control emotional responses and maintain emotional stability. This interaction enables individuals to respond appropriately to emotional stimuli and make decisions that balance reason and emotion [131,137].

In TRD, reduced connectivity between the prefrontal cortex and the amygdala has been observed. This hypoconnectivity means that the prefrontal cortex has less control over the emotional responses generated by the amygdala, which can result in poor emotional regulation and increased vulnerability to negative emotional states. Due to the diminished prefrontal control, the amygdala may become hyperactive in response to harmful stimuli, perpetuating anxiety, fear, and sadness. Additionally, the anterior cingulate cortex, which plays a crucial role in resolving emotional conflicts and making decisions, also exhibits dysfunction in TRD. Altered connectivity in this region may contribute to difficulty overcoming negative thoughts, resolving emotional problems, and making adaptive decisions [138,139].

Recent experimental studies provide causal evidence linking fronto-limbic dysfunction to depression related phenotypes. In rodents, hyperactivity of the basolateral amygdala (BLA)–ACC pathway has been shown to drive depression like behaviors, particularly in the context of chronic pain, while its optogenetic inhibition reverses these deficits, underscoring the pathological role of amygdalo-cingulate connectivity [140]. Complementarily,

dysfunction of the mPFC has been implicated in vulnerability to depressive states, as optogenetic activation of pyramidal neurons in this region restores normal behavior in stress and toxin-induced models [141]. Extending these findings to primates, microstimulation of the subgenual ACC (sgACC) induces a persistent negative decision-making bias accompanied by reduced top-down beta band influence from the dorsolateral PFC, mimicking the impaired emotional regulation seen in human depression [142]. Finally, a recent review highlights how optogenetic and chemogenetic approaches have systematically mapped depression relevant circuits, including PFC, amygdala, hippocampus, and ACC, providing robust translational models that bridge preclinical manipulations with the network-level abnormalities observed in TRD [143].

6.3. Salience Network

The salience network is responsible for detecting and directing attention to the most relevant or essential stimuli in each context, such as signals of danger, potential rewards, or changes in internal states. This network helps coordinate emotional and cognitive responses, allowing the brain to focus on what is most important at any given moment. It plays a crucial role in TRD by mediating how individuals perceive and respond to internal and external stimuli, particularly those related to threat, emotion, and personal relevance. The main components of the salience network are the anterior insula, anterior cingulate cortex, and amygdala [144,145].

In TRD, the anterior insula and amygdala can become hyperactive, leading to an exaggerated perception of threats or negative stimuli. This hyperactivity contributes to an altered emotional state, where negative stimuli are perceived as more salient or relevant than they genuinely are, perpetuating depressive symptoms. The salience network typically coordinates the transition between the DMN and the central executive network, which is activated during tasks requiring attention and cognitive control. In TRD, this coordination can be disrupted, resulting in an inability to properly deactivate the DMN and activate the central executive network when focus is required on external tasks. Due to these alterations in the salience network, patients with TRD may struggle to direct their attention flexibly and appropriately. This can manifest as an inability to shift attention away from negative thoughts or intense emotions, exacerbating rumination and depressive symptoms. The difficulty in identifying and prioritizing relevant stimuli can also impair decision-making and adaptive behavior [133,146,147].

Evidence from nonhuman primates suggests that the salience network functions as an integrated system related to depressive phenotypes. Large-scale single-neuron mapping in macaques has demonstrated that basolateral amygdala neurons project structured motifs to anterior insula and medial cingulate cortices, revealing coordinated salience circuits essential for adaptive emotional and cognitive responses [148]. These findings provide mechanistic support from animal models that alterations in salience network organizations may underlie maladaptive salience attribution, a core feature of TRD.

6.4. Reward Circuit

Dysfunction in the reward circuit has been closely linked to patients' inability to respond to conventional therapies. This circuit includes key brain structures such as the nucleus accumbens (NAc), ventromedial prefrontal cortex (vmPFC), and ventral striatum, all of which are involved in regulating motivation, anhedonia, and reward processing functions that are often impaired in patients with TRD [149].

Recent research has shown that connectivity between the NAc and vmPFC is particularly impaired in TRD, contributing to the persistence of depressive symptoms despite treatment. This impairment in the reward circuit's connectivity has been associated with a

reduced response to treatment, highlighting the importance of this circuit in the pathology of TRD [150,151]. Additionally, chronic inflammation, measured through markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), appears to play a modulatory role in this reward circuit dysfunction. Studies have shown that elevated levels of these inflammatory markers are correlated with reduced connectivity between the ventral striatum and the vmPFC, exacerbating symptoms of anhedonia and contributing to treatment resistance [149].

Deep brain stimulation (DBS) has shown promise in normalizing activity within the reward circuit. By targeting regions such as the ventral anterior limb of the internal capsule (vALIC), DBS has been observed to alter neural activity in the NAc and other associated areas, leading to improved clinical outcomes in patients with TRD. However, the effectiveness of DBS appears to be modulated by the baseline functional state of the reward circuit before treatment. In patients with more severe dysfunction in these areas, a reduced clinical response to DBS has been noted [152].

Evidence from translational studies further supports the causal involvement of the reward circuit in TRD. In rodent models, optogenetic stimulation of the prelimbic PFC-NAc pathway has been shown to overcome resistance to venlafaxine, restoring reward-related behaviors [135]. Complementarily, neuroimaging work in nonhuman primates indicates that microstructural variability within prefrontal–limbic pathways is associated with differences in reward sensitivity, suggesting that structural integrity of these tracts may condition vulnerability to reward circuit dysfunction [153].

In addition to alterations in functional connectivity, patients with TRD exhibit changes in the dynamics of brain networks involved in reward processing and the integration of emotional experience. These changes are more pronounced in individuals with a history of childhood trauma, suggesting that the severity of trauma may moderate the relationship between inflammation and reward circuit dysfunction [149,151]. Childhood adversity as a risk factor for TRD will be discussed later in the section on psychosocial factors.

Understanding the interaction between inflammation, trauma, and reward circuit connectivity is essential for developing more effective and personalized therapeutic strategies for TRD.

6.5. Clinical and Translational Implications of Brain Connectivity Alterations

Connectivity abnormalities across DMN, fronto-limbic, salience, and reward networks provide convergent therapeutic opportunities, such as neuromodulation strategies (rTMS, DBS) [142,152] and circuit-targeted pharmacological approaches that aim to restore network balance rather than acting solely on neurotransmitter levels [135]. From a preventive perspective, functional imaging and electrophysiological measures could help identify patients at higher risk of TRD by detecting early disruptions in network dynamics, allowing earlier and more targeted interventions. However, significant implementation challenges remain, including the lack of standardization of biomarkers of connectivity, cross-species translation is still limited despite promising optogenetic and chemogenetic evidence, and neuromodulation trials show heterogeneous responses [130,134,142]. Bridging these gaps will require biomarker-driven stratification, integration of neuroimaging with clinical phenotyping, and longitudinal studies to validate network-based targets for precision interventions in TRD.

7. Gut Microbiota

The gut–brain–microbiota axis is increasingly recognized as a modulator of depression and treatment resistance through interconnected effects on immune signaling, HPA axis regulation, and neurotransmission [154,155].

Intestinal microorganisms produce bioactive metabolites, such as short-chain fatty acids (SCFAs), including butyrate, which can cross the blood–brain barrier and influence brain function. Butyrates have been linked to the regulation of serotonin synthesis in the gut, where approximately 95% of the body's serotonin is produced [156,157]. Convergent evidence from animal and human studies indicates that SCFAs, particularly butyrate, also promote neuroplasticity and exert antidepressant-like effects, reinforcing their potential as mechanistic mediators across species [156].

Gut dysbiosis, characterized by reduced SCFA-producing bacteria (e.g., Faecalibacterium) and increased pro-inflammatory species (e.g., Desulfovibrio), has been associated with elevated intestinal permeability ("leaky gut"), facilitating the translocation of bacterial products such as lipopolysaccharides (LPS) into the systemic circulation. This can trigger chronic low-grade inflammation and exacerbate mood symptoms [158–160]. Reduced microbial diversity has also been reported in some TRD cohorts and may relate to greater symptom severity and poorer treatment outcomes, although findings are not entirely consistent across studies [119,161]. Preclinical work supports this link: fecal microbiota transplantation from depressed patients into rodents induces depressive-like behaviors and neuroinflammatory changes, providing causal evidence of dysbiosis-related mood alterations. Nevertheless, some studies report more modest or inconsistent effects depending on host strain, donor variability, or experimental conditions, which may explain discordant results [162,163].

Communication between the gut and brain occurs via multiple pathways, including immune mediators, microbial metabolites, and neural routes such as the vagus nerve. Preclinical studies indicate that vagal integrity is required for microbiota-induced behavioral effects [162], and vagus nerve stimulation may partly exert its benefit through modulation of inflammatory and microbial pathways [164,165]. Consistently, rodent studies show that vagal integrity is essential for microbiota-induced behavioral effects, highlighting a conserved vagal–immune route across species [162,163].

Distinct microbial profiles have been observed in some TRD patients compared to responders, suggesting a potential role for microbiota composition in treatment efficacy [166,167]. Baseline microbiota profiles also appear to differentiate responders from non-responders in animal models, underscoring the translational relevance of microbial signatures in predicting treatment outcomes [161,168].

Antidepressants themselves interact with gut microorganisms. In experimental models, fluoxetine and amitriptyline reshape microbial composition in stressed rats, producing behavioral changes that parallel clinical findings of bidirectional microbiota–drug interactions [169,170]. This supports the idea that therapeutic response is not only pharmacologically mediated but also shaped by host–microbiome dynamics.

Moreover, dysbiosis has been linked to changes in hippocampal protein phosphorylation and lysine acetylation, processes involved in neuroplasticity and antidepressant response [171,172]. Specific metabolites, such as N-ε-acetyl-lysine associated with the abundance of Odoribacter, have been proposed as candidate biomarkers of treatment response, as increased levels during therapy have correlated with symptom improvement in some studies [154].

Altogether, current evidence supports a multifaceted interaction between the gut microbiota and the pathophysiology of TRD. Importantly, both human and animal data point toward largely concordant mechanisms, although inconsistencies highlight the influence of methodological differences. Future research should address whether microbiota-targeted interventions (e.g., probiotics, dietary modulation) can reliably enhance treatment outcomes in well-characterized TRD populations.

Clinical and Translational Implications of Gut Microbiota

Gut microbiota alterations in TRD reveal multiple therapeutic opportunities, including probiotics, prebiotics, fecal microbiota transplantation, and dietary interventions aimed at restoring microbial diversity and enhancing SCFA production [173–175]. Modulation of vagal signaling may also represent a promising avenue, given its role in mediating microbiota–brain interactions [162]. From a preventive perspective, microbial and metabolite profiles, such as SCFA levels or N-ε-acetyl-lysine, could serve as biomarkers to identify patients at higher risk of nonresponse and guide early dietary or microbiome-targeted interventions.

However, microbiota studies in TRD show heterogeneity due to host factors, methodological variability, and donor–recipient mismatches in transplantation models [161–163]. Moreover, most clinical trials of microbiota-targeted therapies are still preliminary, with inconsistent efficacy [166–168]. Bridging these gaps will require standardized microbiome profiling, integration of microbial biomarkers into psychiatric assessment, and longitudinal, placebo-controlled trials to test the efficacy of microbiota-based interventions in TRD.

8. Oxidative Stress

Oxidative stress is a biological process resulting from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them through antioxidants. This imbalance can cause cellular damage, including to neurons, and has been implicated in the pathogenesis of various neuropsychiatric disorders, including TRD. ROS are highly reactive molecules that include free radicals such as superoxide (O2•−), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•). These species are primarily produced as byproducts of cellular metabolism, especially in the mitochondria. On the other hand, antioxidants are compounds that neutralize ROS, preventing cellular damage. Endogenous antioxidants include enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), as well as molecules like glutathione, vitamin E, and vitamin C [176].

The brain is particularly susceptible to oxidative stress due to its high oxygen consumption, its rich composition of polyunsaturated fatty acids (which are vulnerable to lipid peroxidation), and its abundance of iron, which catalyzes the formation of ROS. Oxidative stress can damage cell membranes, destabilize mitochondria, and disrupt synaptic signaling, contributing to neuronal dysfunction and cell death in key brain areas such as the prefrontal cortex and hippocampus, both of which are essential for mood regulation [177].

There is a bidirectional relationship between chronic inflammation and oxidative stress. Pro-inflammatory cytokines, which are common in people with depression, can induce the production of ROS, exacerbating oxidative stress [178]. Additionally, in TRD, mitochondrial dysfunction, exacerbated by oxidative stress, can lead to a decrease in ATP production and an increase in ROS generation. This creates a vicious cycle that perpetuates neuronal damage, brain dysfunction, and the persistence of depressive symptoms. Chronic oxidative stress also negatively impacts neuroplasticity, and since many antidepressant treatments rely on enhancing this process, the reduction in neuroplasticity may contribute to treatment resistance [179–181].

Among the biomarkers studied in relation to TRD is malondialdehyde (MDA), a marker of lipid peroxidation. Elevated levels of MDA have been found in individuals with depression, particularly those with TRD, indicating increased oxidative damage to cell membranes [179,182,183]. Some studies have also shown that patients with TRD often have altered levels of antioxidants such as glutathione and antioxidant enzymes (like SOD and CAT), suggesting a reduced capacity to neutralize ROS. However, these studies are limited in number, have methodological constraints, and their results remain controversial [184].

Clinical and Translational Implications of Oxidative Stress

Oxidative stress in TRD offers potential therapeutic targets, including antioxidant strategies (e.g., N-acetylcysteine) and agents that enhance endogenous antioxidant enzyme activity [185,186]. Modulating mitochondrial function to reduce ROS production may also restore neuroplasticity and improve antidepressant efficacy [187]. From a preventive perspective, biomarkers such as MDA, glutathione, and antioxidant enzyme levels could serve as indicators of patients at greater risk of treatment resistance, enabling early monitoring and stratified interventions.

Oxidative stress biomarkers lack specificity, vary across populations, and are influenced by diet, lifestyle, and comorbid conditions, limiting their immediate use in clinical decision-making. Moreover, while preclinical models support a causal role of oxidative stress in TRD, clinical trials with antioxidant therapies have produced inconsistent results. Future progress will depend on biomarker-guided studies that integrate oxidative stress profiling with other biological domains (e.g., inflammation, metabolism) to test precision interventions targeting redox imbalance in TRD.

9. Psychosocial Factors

9.1. Chronic Stress

Beyond its direct effects on HPA axis dysregulation and glucocorticoid resistance, sustained stress is often embedded in adverse life experiences such as early trauma, persistent socioeconomic adversity, or lack of social support that amplify immune–inflammatory activation and impair neuroplasticity. Clinical and translational data indicate that patients exposed to prolonged psychosocial stress show elevated inflammatory markers and reduced treatment responsiveness, highlighting the interplay between environmental stressors and biological cascades that sustain treatment resistance [74,188].

Animal models, particularly chronic mild stress paradigms, mirror this complexity by showing that a subset of stressed subjects remains non-responsive to antidepressants, paralleling TRD heterogeneity in humans [188]. Recent longitudinal studies suggest that protective psychosocial factors, such as strong social support, may buffer these biological effects, attenuate inflammation, and improve treatment outcomes [189,190]. These findings underscore that addressing chronic stress in TRD requires strategies that integrate pharmacological and psychosocial interventions to enhance resilience and recovery.

9.2. Childhood Adversity

Exposure to adverse childhood experiences (ACEs) is strongly associated with a higher risk of severe and treatment-resistant depression in adulthood. Physical, sexual, and emotional abuse, as well as neglect, not only increase the likelihood of developing chronic forms of depression but also reduce responsiveness to standard antidepressant treatments. Recent findings indicate that cumulative exposure to multiple ACEs is linked to greater symptom severity, increased suicide attempts, and higher psychiatric hospitalization rates among TRD patients. Specific subtypes, such as sexual abuse and physical violence, appear to be particularly robust predictors of poor treatment outcomes [191].

Childhood trauma, especially physical neglect, has also been identified as a major driver of suicidal behavior in TRD populations, reinforcing the long-term consequences of early adversity on treatment refractoriness [192]. Beyond symptom severity, ACEs often lead to dysfunctional cognitive styles, including rumination and excessive self-criticism, which perpetuate negative thinking cycles and hinder the efficacy of conventional therapies [193,194].

Moreover, childhood adversity increases the risk of psychiatric comorbidities such as anxiety disorders [195,196], post-traumatic stress disorder [197], personality

disorders [198,199], and substance use disorders [200], which further complicates clinical management. These complications often translate into interpersonal difficulties, mistrust, and social isolation, thereby reducing access to effective support networks and exacerbating the challenges of treating TRD.

Together, these findings emphasize that both the severity and type of childhood adversity must be carefully considered when assessing risk, prognosis, and treatment planning in TRD patients.

9.3. Social Isolation

Defined as the objective lack of social relationships and interactions, social isolation has been increasingly recognized as a factor that worsens the course of depression and may contribute to treatment resistance. While depressive symptoms often lead to withdrawal, sustained isolation amplifies stress responses, reduces the buffering effect of social support, and exacerbates biological processes linked to TRD. Longitudinal and Mendelian randomization studies indicate a bidirectional relationship between social isolation and depression, showing that isolation predicts subsequent depressive symptoms, while depression itself also increases the likelihood of isolation [201].

Preclinical evidence reinforces this link; solitary housing in rodent models induces behavioral patterns consistent with depressive phenotypes and attenuates the response to antidepressant treatments, supporting the role of social disconnection in maintaining resistance [202].

Taken together, these findings suggest that social isolation should be considered not only as a consequence of chronic depression but also as an active factor that perpetuates treatment resistance.

9.4. Clinical and Translational Implications of Psychosocial Factors

Psychosocial adversity provides critical therapeutic targets, including interventions that reduce stress reactivity, such as mindfulness-based cognitive therapy (MBCT), which has shown beneficial effects even when delivered online as an adjunctive treatment for TRD [203]. Trauma-focused psychotherapies are particularly relevant for individuals with childhood adversity, while programs that strengthen social connectedness, such as structured "Community Navigator" interventions, have demonstrated potential to reduce loneliness and improve outcomes in patients with TRD [204]. From a preventive perspective, early identification of at-risk individuals (ACEs, chronic stress exposure, or limited social networks) could guide targeted interventions that integrate psychosocial and biological approaches before resistance consolidates.

Implementation challenges include the heterogeneity of psychosocial stressors, their frequent overlap with comorbid psychiatric disorders, and the limited integration of psychosocial screening into routine psychiatric care. Moreover, translating protective factors, such as social support, into scalable interventions remains a complex task. Bridging these gaps will require longitudinal studies, culturally adapted interventions, and multidisciplinary strategies that embed psychosocial assessment into precision models of TRD care.

Figure 2 exemplifies the proposed interplay among key biological domains implicated in treatment resistant depression.

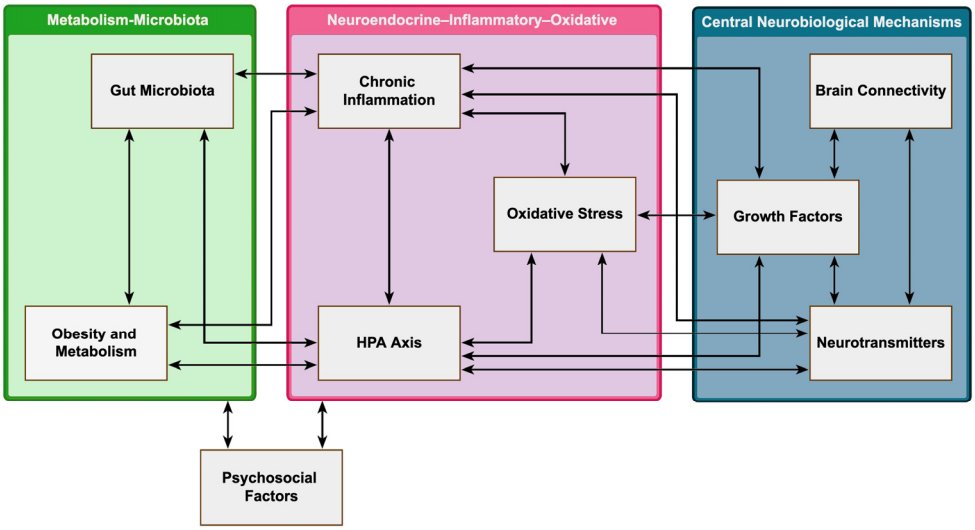


Figure 2. Proposed interplay among key biological domains implicated in TRD. The Metabolism–Microbiota block illustrates potential interactions by which obesity, metabolic alterations, and gut dysbiosis may converge with psychosocial stressors to influence systemic physiology. The Neuroendocrine–Inflammatory–Oxidative block highlights chronic low-grade inflammation, oxidative stress, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation as frequent convergent mechanisms mediating stress vulnerability. The Central Neurobiological Mechanisms block represents brain-level consequences, including altered neurotransmission, impaired growth factor signaling, and disrupted connectivity. Arrows denote predominantly bidirectional and cross-domain relationships reported in the literature, underscoring the integrated yet heterogeneous nature of these processes in shaping treatment resistance.

10. Animal Models and Non-Clinical Studies in TRD

Preclinical and animal models have provided valuable insights into the mechanisms underlying TRD, complementing findings from clinical research. Transgenic and knock-in/knock-out approaches have shown that genetic variants associated with TRD in humans, such as those in *SLC6A4*, *BDNF*, and *FKBP5*, produce conserved phenotypes in rodents, including impaired stress responsivity and reduced antidepressant efficacy [19–21,55,84]. Optogenetic and chemogenetic studies have further demonstrated causal involvement of fronto-limbic, salience, and reward circuits in depressive-like behaviors and anhedonia, while functional imaging in nonhuman primates has revealed alterations in homologous networks relevant to TRD [134–136]. Moreover, fecal microbiota transplantation from depressed patients to rodents induces depressive-like behavior and neuroinflammatory changes, largely concordant with clinical observations [162,163]. Together, these models provide mechanistic evidence that strengthens causal inference and highlights potential therapeutic targets, thereby enriching the translational perspective on TRD.

11. Limitations and Future Directions

The complexity of TRD stems from its biological and clinical heterogeneity, methodological inconsistencies across studies, and the lack of standardized biomarkers, which collectively hinder the identification of robust predictors and the development of effective, individualized interventions. A critical limitation remains the absence of a universally accepted definition of TRD, which reduces comparability and reproducibility across research studies. Many studies are further constrained by small sample sizes, limited follow-up periods, and low statistical power, particularly in genetic, neuroimaging, and microbiome research.

Despite the identification of multiple biological associations, clinically validated biomarkers remain elusive. Most evidence is correlational, and causal mechanisms have yet to be firmly established, underscoring the need for longitudinal, multimodal, and mechanistic studies. Limited population diversity also restricts the generalizability of findings, as most cohorts overrepresent high-income, Western populations.

Integrating machine learning models with multimodal datasets presents a promising approach to defining biologically distinct TRD subtypes, predicting treatment trajectories, and informing therapeutic decision-making. In parallel, the evaluation of emerging interventions such as rapid-acting antidepressants, anti-inflammatory agents, metabolic modulators, and microbiome-based therapies should be embedded within these personalized designs to identify which subgroups derive the most significant benefit.

While most of the available evidence remains correlational, moving beyond associations will require study designs capable of causal inference. Longitudinal cohort studies are needed to clarify temporal relationships between biological alterations and the emergence of treatment resistance. Randomized controlled trials targeting specific biomarkers (e.g., inflammatory cytokines, BDNF, or metabolic markers) would directly test whether modifying these pathways improves treatment outcomes. Mechanistic experimental approaches, integrating pharmacological interventions with neuroimaging or biomarker assessments, can provide further causal evidence. Finally, multi-omics longitudinal frameworks may disentangle the complex interplay among genetic, epigenetic, proteomic, and microbiome factors in TRD. Together, these strategies will be essential for establishing causal mechanisms and guiding the development of biomarker-based precision interventions.

Ultimately, the field will advance by moving beyond "one-size-fits-all" paradigms toward prospectively validated, biomarker-driven treatment algorithms, supported by rigorous, adaptive, and patient-centered study designs.

12. Conclusions

TRD is a complex and multifactorial disorder in which multiple biological systems interact dynamically, contributing to variability in therapeutic response. While polymorphisms in genes are related to neurotransmission (*SLC6A4*, *HTR2A*, *BDNF*), drug metabolism (*CYP2D6*, *CYP2C19*), and HPA axis regulation (*FKBP5*, *NR3C1*) may increase vulnerability, their influence is not uniform and is modulated by epigenetic and environmental factors such as chronic stress and inflammation. Evidence indicates that not all TRD patients share the same biological profiles, underscoring the need for precise subtyping.

Persistent alterations in serotonergic, dopaminergic, and glutamatergic neurotransmission, together with inflammatory processes and oxidative stress, may converge to reduce neuroplasticity and produce functional changes in neural networks such as the DMN, the fronto-limbic network, and the reward circuit. Additional factors, including gut dysbiosis and microvascular dysfunction, add further layers of complexity to the clinical picture. However, most of the biomarkers described remain correlational and lack robust clinical validation, limiting their direct applicability.

Advancing toward personalized strategies will require integrating genetic, epigenetic, inflammatory, neuroendocrine, microbiome, and neuroimaging data into prospectively validated predictive models. Longitudinal, multimodal studies with diverse samples will be essential for identifying biological TRD subtypes and linking them to specific interventions, including rapid-acting antidepressants, anti-inflammatory modulators, metabolic strategies, and microbiome-targeted therapies. As this field is still emerging, the available evidence remains limited and continues to evolve, underscoring the importance of ongoing research to capture the full spectrum of relevant findings. Only through this integrative and stratified

approach will it be possible to optimize treatment selection and improve response rates in this difficult-to-treat population.

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Abbreviations

The following abbreviations are used in this manuscript:

ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
AGDS	Australian Genetics of Depression Study
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CAT	Catalase
COMT	Catechol-O-methyltransferase
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
DBS	Deep brain stimulation
DPWG	Dutch Pharmacogenetics Working Group
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GPX	Glutathione peroxidase
GR	Glucocorticoid receptor
GWAS	Genome-wide association studies
HPA	Hypothalamic–pituitary–adrenal
IDO	Indoleamine 2,3-dioxygenase
IGF-I	Insulin-like Growth Factor 1
IL	Interleukin
LPS	Lipopolysaccharides
MDA	Malondialdehyde
MDD	Major depressive disorder
Met	Methionine
mPFC	Medial prefrontal cortex
MR	Mineralocorticoid receptor
MRAs	Mineralocorticoid receptor antagonists
NAc	Nucleus accumbens
PCC	Posterior cingulate cortex

ROS	Reactive oxygen species
rTMS	Repetitive transcranial magnetic stimulation
SCFAs	Short-chain fatty acids
SERT	Serotonin transporter
SNRI	Serotonin-norepinephrine reuptake inhibitors
SOD	Superoxide dismutase
SSRI	Serotonin reuptake inhibitors
T2DM	Type 2 diabetes mellitus
TCAs	Tricyclic antidepressants
TNF	Tumor Necrosis Factor
TRD	Treatment-resistant depression
TRIs	Triple reuptake inhibitors
Val	Valine
vALIC	Ventral anterior limb of the internal capsule
VEGF	Vascular Endothelial Growth Factor
vmPFC	Ventromedial prefrontal cortex

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