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Understanding Treatment-Resistant Depression in Patients: An Examination of Contributing Factors

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Abstract. Major depressive disorder (MDD) is a leading global cause of disability, driving significant research and clinical focus in recent years. However, a substantial proportion of patients with MDD do not respond adequately to first-line antidepressant treatment, despite receiving adequate doses for sufficient durations, a condition known as treatment-resistant depression (TRD). Given that depression is becoming one of the leading causes of disability, it is increasingly crucial for researchers to understand the factors contributing to such resistance. This essay will examine the complex nature of TRD while emphasising the biological and psychological factors contributing to symptoms. This paper will explore, with the data of the latest discoveries, the roles of childhood trauma, inflammation, and chronic stress, and how their mechanisms play a role in the unresponsiveness of antidepressants. Selecting evidence from recent meta-analyses and empirical studies, this review will summarise a few of the most studied risk factors of TRD. In conclusion, this review argues that TRD is best understood not as a mere pharmacological failure, but as a complex syndrome arising from the interplay of biological and psychological vulnerabilities. This underscores the critical need for moving beyond a one-size-fits-all model towards personalized treatment strategies that address these root contributing factors.

Keywords: Treatment-Resistant Depression (TRD), Major Depressive Disorder (MDD), Inflammation, Chronic Stress, Childhood Trauma

1. Introduction

The diagnostic and statistical manual of mental disorders (DSM-5) classifies major depressive disorder (MDD) as the presence of five or more symptoms, with at least one including depressed mood or the loss of pleasure or interest. As of 2017, the World Health Organisation has recognised depression as a major contributor to the decline in global disability, with an estimated 4% of the total population experiencing depression [1]. Despite medicine being the most used method to address depression, there is still an approximation that 30% of those who take antidepressant drugs meet the definition of treatment-resistant depression (TRD) [2]. For a patient to be classified as having TRD, they must have shown an inadequate response to at least two different antidepressant trials, despite adequate dosage, duration, and adherence. Studies indicate that a significant proportion of patients with MDD experience substantial impairments in daily functioning and report a diminished quality of life [3]. Therefore, TRD cannot be attributed solely to a failure in a physician's prescription, but

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rather to a range of biological, psychological and clinical factors. This essay aims to examine psychological factors contributing to TRD, while acknowledging the roles of biological and clinical mechanisms.

2. Background

Antidepressants may be broadly classified into several categories, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and a range of atypical agents. SSRIs and SNRIs constitute the first-line pharmacological treatment for depression and exert their therapeutic effects through similar mechanisms. SSRIs selectively block the reuptake of serotonin, whereas SNRIs inhibit the reuptake of both serotonin and norepinephrine. This results in the synaptic availability of neurotransmitters (serotonin and norepinephrine) in the brain's synapses. While such mechanisms sound direct, the therapeutic effects do not take place immediately. Instead, it is a gradual process that requires downstream changes between the end of a neuron and the receptor of another, explaining the delay in effect.

When patients fail to achieve an adequate response to first-line treatments, alternatives such as monoamine oxidase inhibitors may be considered. However, MAOIs are generally reserved for later-stage intervention due to safety concerns, including dietary restrictions and cardiovascular complications, which limit their practical utility [4]. TRD is operationally defined as failure to respond to at least two consecutive, adequate trials of first-line antidepressants (typically SSRIs or SNRIs) at therapeutic doses and durations.

Following the initial prescription of medications, patients often experience a few weeks of delay —known as therapeutic lag—before the antidepressant takes effect. They are then expected to schedule an appointment with the doctor every 1–2 weeks, either to determine whether the dosage should change or to check up on the effectiveness. The close monitoring of patients during this period is important for the management of side effects or for doctors to adjust and provide support. In standard clinical cases, patients continue to take antidepressants for another six months after recovering from symptoms [5]. This last phase is to prevent relapse of the patients' illness, protecting their newly recovered selves.

However, many challenges of TRD begin before the prescription is even done. It has long been established that MDD's symptoms may overlap with other diseases. Periods of depression in bipolar patients are sometimes diagnosed as MDD. From a sample of 1,000,000 health services in Taiwan, up to 12.1% of depressed patients' diagnoses have later been changed to bipolar in subsequent months [6]. Due to the arguably subjective nature of psychological diagnosis, misdiagnosis resulting in the ineffectiveness of such drugs is not uncommon. Understanding this diagnostic failure is important before examining other psychological factors that may affect TRD.

These clinical and diagnostic issues are a few explanations for TRD. While important, TRD can not be solely explained by the above factors. Examining biological factors from recent data are also crucial.

While diagnostic accuracy and treatment optimization remain foundational, the persistence of depressive symptoms despite adequate monoaminergic intervention suggests that TRD represents not merely a more severe form of MDD, but a biologically distinct subtype. Contemporary evidence implicates dysregulation in glutamatergic neurotransmission, HPA axis hyperactivity, neuroinflammatory processes, and mitochondrial dysfunction—mechanisms that may operate independently of, or downstream from, monoamine availability. This mechanistic heterogeneity

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challenges the traditional 'one-size-fits-all' approach to antidepressant selection and underscores the necessity of biomarker-stratified treatment strategies.

3. Factors contributing to TRD

3.1. Childhood trauma

Trauma has been one of the more studied risk factors for not just TRD, but depression in general; it is a foundational factor that plays a decisive role in treatment-resistant depression. The impact of early-life trauma is profound because it can lead to enduring alterations in brain structure and function. It is known that trauma may affect the development of a child's brain. Early stages of development are crucial to the shaping of a child's brain and personality. It has been widely accepted that the younger brains experience more plasticity due to the rapid development. The increase in synaptogenesis, ongoing myelination, and gradually stabilising neural network all contribute to its plasticity. Severe abuse, thus, could be a significant contributor to the development of psychological disorders, including PTSD, identity disorders, and MDD.

The abuse they experience may include, but is not limited to, verbal and physical abuse, neglect, and sexual abuse [7]. Childhood trauma may impact a child's brain development, leading to structural changes in the brain, such as the hippocampus, amygdala, and prefrontal cortex [8]. In other words, trauma does not simply shape the brain; the brain also changes in response to that input. Under typical development, the hippocampus and PFC communicate to consolidate emotional information. However, in irregular neurobiological development, trauma may alter this mechanism, and memory retrieval may be impaired. Moreover, prolonged exposure to fear leads to enduring dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, characterized by blunted diurnal cortisol variation and glucocorticoid receptor (GR) resistance in limbic structures. These neuroendocrine alterations fundamentally compromise antidepressant efficacy through multiple convergent pathways. At the molecular level, chronic glucocorticoid elevation suppresses brain-derived neurotrophic factor (BDNF) expression and reduces neurogenesis in the hippocampus—processes that SSRIs typically rely upon to exert their therapeutic effects. Consequently, the neuroplastic changes required for remission become pharmacologically inaccessible, rendering conventional monoaminergic interventions functionally insufficient. At the circuit level, amygdala hyperreactivity coupled with prefrontal hypoactivation disrupts top-down emotional regulation, preventing the cognitive restructuring that psychotherapy and pharmacotherapy aim to facilitate. This "bottom-up" dominance of threat processing over executive control perpetuates depressive rumination and anhedonia, independent of synaptic monoamine availability. Thus, trauma-induced neurobiological reprogramming creates a treatment-resistant substrate that standard antidepressants —designed to modulate neurotransmitter levels—are ill-equipped to reverse. In research conducted in 2024, Fantasia and colleagues found that from a sample of more than 1700 patients, 42.96% had encountered at least one traumatic event in their life, with 202 diagnosed with PTSD [9]. This figure is significant, not merely due to its high statistical value, but also because it reveals a baseline pattern. Nearly one in two patients with TRD have encountered trauma, effectively establishing trauma as a significant risk factor and early indicator of treatment resistance. Importantly, on average, every other person studied has had their experience shaped by trauma, yet only around 1 in 11 are classified as having PTSD. Such findings suggest that though diagnosed trauma disorders are not a universal experience for patients, trauma itself may unfold differently across different lives. Such variations indicate a deeper mechanism driving mental health disorders; background

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experiences like these often play quiet yet powerful roles in patients with treatment-resistant depression.

3.2. Inflammation

A meta-analysis published in 2019 shows that low-grade inflammation (CRP > 3mg/L) happens in around 27% of individuals with depression [10]). One of the most studied inflammation markers, the C-reactive protein (CRP)—a protein secreted in the liver that increases in the bloodstream in response to inflammation—suggests a higher chance of TRD. Importantly, this relationship is not simply coincidental; clinical trials have demonstrated a negative correlation between CRP and antidepressant treatment, suggesting elevated inflammation as a predictor of treatment responses. This is further corroborated by research demonstrating a higher concentration of CRP in patients diagnosed with MDD than in healthy individuals [11]. This disparity is most pronounced in cases of TRD where 45% of patients had CRP levels higher than normal—implying a heavy link between this inflammatory marker and TRD [12].

This mechanism carries particular significance for TRD, as most first-line antidepressants, such as SSRIs and SNRIs, depend upon intact serotonergic signaling to achieve therapeutic efficacy. Under inflammation, tryptophan, which is the precursor of serotonin, would instead shift towards the kynurenine pathway, instead of the serotonin pathway [13]. This shift is mediated by the enzyme indoleamine 2,3-dioxygenase (IDO), which is upregulated by a pro-inflammatory cytokine, IFN-γ. This results in a decrease in the availability of serotonin. Alongside the IFN-γ, other inflammatory markers, such as the TNF-α, for example, are consistently seen in models of animal depression. As a result, antidepressants may be less effective due to the decreased availability of serotonin. Consequently, the therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) may fundamentally be limited under this inflammatory context, even if dosage and duration are adequate. Together, these findings suggest that inflammation-driven tryptophan diversion and cytokine elevation may fundamentally limit the effectiveness of serotonergic antidepressants in TRD, even with adequate dosage and duration. However, the specific mechanism behind inflammation and difficulty in treating depressed patients is something in need of further development.

3.3. Chronic stress

While inflammation is a key biological factor in TRD, chronic stress also plays a critical role through its effects on the HPA axis. Stress refers to an individual's natural response to environmental or internal difficulties. Acute stress is when the stressor is short-term; it typically lasts for a limited amount of time, allowing a person to recover once the stressor is removed. Acute stress is often elicited when the trigger is an immediate threat, and initiates "fight or flight" responses. On the other hand, chronic stress occurs when such stressors occur for prolonged periods. Due to prolonged exposure, they tend to cause psychological and even physiological effects [14].

Chronic stress has been shown to alter the brain's cognitive processing, emotions and behaviour through hormones and neuropeptides [15]. The inflammation induced by chronic stress is a critical component in understanding TRD, with the HPA axis serving as the underlying mechanism linking chronic stress to depressive disorders. Persistent activation of the HPA axis has increasingly been recognized as a potential pathway through which chronic stress contributes to the development and persistence of depressive symptoms.

Inflammation caused by chronic stress plays a crucial role in understanding TRD, with the hypothalamic-pituitary-adrenal (HPA) axis serving as the underlying mechanism for its involvement

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When the brain perceives stress, it responds by secreting the corticotropin-releasing hormone (CRH), which, in turn, triggers the release of ACTH, which leads to cortisol release. When the cortisol levels reach a limit, a negative feedback loop is used to shut down the stress response. However, chronic stress has been suggested to disrupt the inhibition, therefore increasing cortisol levels [15]. This state of elevated cortisol levels is crucial for TRD and MDD, as it leads to damaged neurons and hinders neurogenesis—a process crucial for the efficacy of antidepressants due to SSRIs largely promoting this growth of new neurons in the hippocampus, thus limiting the effectiveness of treatment.

4. Conclusion

This essay aims to examine why a significant proportion of MDD patients fail to respond to at least two antidepressants, which makes them treatment-resistant. By concluding previous studies and meta-analyses, findings suggest that TRD should be understood as a mix of bio-psychological factors, including childhood trauma, chronic stress, and inflammation. Early exposure to traumatic events, inflammatory mechanisms, and interference with normal HPA axis pathways may all contribute to medications' ineffectiveness. However, several limitations should be pointed out. The present analysis is limited by its reliance on observational and correlational evidence, precluding firm causal inferences. Moreover, the heterogeneity of TRD is underscored by the non-uniform presence of risk factors; childhood trauma, for instance, characterizes a significant subset but not all patients. For future reference, research may be improved by conducting empirical experiments and continuing to explore other psychological factors, such as anxiety or personality traits.

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