REVIEW ARTICLE

CONTENTS

Neuromolecular biomarkers of traumatic stress: Refining diagnostic criteria and personalizing treatment for core biological symptoms in PTSD

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ABSTRACT

Aim: The aim of this review is to assess the role of neuromolecular biomarkers in post-traumatic stress disorder (PTSD) and their usefulness in improving diagnostic accuracy and supporting personalized treatment strategies.

Materials and Methods: A narrative review of studies published between 2015 and 2025 was performed using databases such as PubMed, Scopus, and Web of Science. The analysis included clinical and experimental studies focusing on neuroinflammation, oxidative stress, endoplasmic reticulum stress, and markers of neuronal damage in PTSD. Special attention was given to associations between biomarkers and symptom severity, duration of illness, and treatment outcomes.

Results: PTSD is associated with disturbances in neuroimmune and neuroendocrine pathways. Increased levels of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-18 (IL-18), are frequently observed. Activation of the NLR family pyrin domain containing 3 inflammasome (NLRP3 inflammasome) and elevated oxidative stress markers, such as malondialdehyde (MDA), indicate ongoing inflammatory and oxidative processes. Changes in neuronal injury markers, including ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), suggest neurodegenerative mechanisms. Altered chemokine signaling, particularly fractalkine (chemokine C-X3-C motif ligand 1, CX3CL1), and activation of endoplasmic reticulum stress pathways, such as inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6), are linked to impaired neuronal function and reduced synaptic plasticity. These findings indicate biological heterogeneity within PTSD.

Conclusions: Neuromolecular biomarkers may improve the current symptom-based diagnostic model of PTSD. Their integration with clinical assessment tools may support identification of biologically defined subgroups and enable more targeted treatment.

KEY WORDS: biomarker-based diagnostics, CX3CL1, neuroinflammation, NLRP3 inflammasome, oxidative stress, post-traumatic stress disorder

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is increasingly understood as a disorder with a complex neurobiological basis, rather than only a psychological reaction to trauma. Exposure to traumatic stress induces persistent alterations in central and peripheral systems, including the hypothalamic–pituitary–adrenal axis (HPA axis), the immune system, and neural circuits involved in emotion regulation. Functional and structural changes within the amygdala, hippocampus, and prefrontal cortex are associated with heightened threat processing, impaired memory integration, and reduced top-down control. These alterations contribute to the development and maintenance of core PTSD symptoms such as hyperarousal, intrusive recollections, and avoidance [1].

Current diagnostic frameworks, including the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and the International Classification of Diseases, Eleventh Revision (ICD-11), rely on symptom-based criteria. Although clinically useful, these classifications do not reflect underlying biological mechanisms and do not capture inter-individual variability. Patients presenting with similar symptom profiles may differ in terms of neuroendocrine regulation, inflammatory activity, and neuronal integrity. This limitation reduces diagnostic precision and may contribute to inconsistent treatment outcomes [2].

PTSD demonstrates considerable clinical and biological heterogeneity. Variability in symptom severity, duration of illness, and comorbid conditions indicates the involvement of multiple interacting biological pathways. These include chronic activation of neuroinflammatory processes, increased oxidative stress, dysregulation of the HPA axis, and disturbances in

synaptic plasticity. Such mechanisms may operate differently across individuals, suggesting the presence of biologically distinct subtypes [3, 4].

Integration of biological markers with psychometric assessment may improve the current diagnostic approach. The identification of neuromolecular biomarkers, including cytokines, markers of neuronal injury, and indicators of cellular stress, provides an opportunity to better characterize disease mechanisms.

Integration of biological markers with psychometric assessment may improve the current diagnostic approach and support more precise patient stratification within the framework of precision psychiatry [5].

AIM

The aim of this review is to analyze the role of neuromolecular biomarkers in PTSD in the context of its underlying neurobiological mechanisms. Particular attention is given to biomarkers associated with neuroinflammation, oxidative stress, neuroendocrine regulation, and neuronal injury, which may reflect core pathophysiological processes.

An additional objective of this work is to organize and critically evaluate the available literature regarding the potential diagnostic relevance of these biomarkers. In particular, their associations with symptom severity, duration of illness, and clinical presentation are examined, with consideration of methodological limitations and the lack of full standardization across studies. It is also emphasized that their potential to improve the accuracy of current diagnostic systems, such as DSM-5 and ICD-11, remains preliminary and requires further validation.

The review also aims to highlight the possibility of biological heterogeneity within PTSD. Variability in biomarker profiles may suggest the presence of distinct pathophysiological pathways; however, interpretation of these findings should be approached with caution due to inconsistencies in the available data and the need for further research using standardized methodologies.

Furthermore, the review discusses the potential implications of biomarker research for future diagnostic and therapeutic strategies in PTSD. While the identification of specific biological patterns may, in the future, support the development of personalized approaches, this application currently remains largely conceptual and requires further investigation, validation, and methodological standardization [6].

MATERIALS AND METHODS

This narrative review was conducted based on a structured search of the literature published between 2015 and 2025 using the PubMed, Scopus, and Web of Science databases. The search strategy included combinations of keywords related to PTSD, neuroinflammation, oxidative stress, endoplasmic reticulum stress, neurodegeneration, and biomarkers.

Eligible studies included original clinical and experimental research articles as well as relevant review papers published in English. Studies focusing on molecular and cellular mechanisms associated with PTSD were prioritized. Particular emphasis was placed on biomarkers related to neuroinflammatory processes, oxidative imbalance, endoplasmic reticulum stress pathways, and markers of neuronal injury.

Articles were selected based on their relevance to the objectives of the review, including the association of biomarkers with symptom severity, duration of illness, and treatment response. Studies lacking clear relevance to PTSD pathophysiology or biomarker assessment were excluded.

NEUROBIOLOGICAL BASIS OF PTSD

Post-traumatic stress disorder is associated with complex and interacting neurobiological mechanisms involving neuroendocrine regulation, structural and functional brain alterations, neuroimmune activation, oxidative imbalance, and impaired neuroplasticity.

Dysregulation of the HPA axis represents a central component of the stress response disturbance observed in PTSD. Under physiological conditions, activation of this axis begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn induces cortisol release from the adrenal cortex. Cortisol exerts regulatory effects through negative feedback mechanisms acting on both the hypothalamus and the pituitary gland. In PTSD, this regulatory system is altered [7]. Reduced basal cortisol levels and disruption of circadian rhythm are frequently observed. At the same time, increased sensitivity of glucocorticoid receptors enhances negative feedback, which may lead to an attenuated endocrine response despite persistent activation of limbic structures. This dysregulation contributes to abnormal stress reactivity and facilitates maintenance of inflammatory processes.

Structural and functional changes in the brain further contribute to PTSD pathophysiology. The amygdala shows increased activity, which is associated with enhanced threat detection and exaggerated emotional responses. This hyperactivation is linked to symptoms such as hypervigilance and persistent fear. The hippocampus, which is responsible for contextual memory

processing, demonstrates reduced volume and functional impairment. These alterations interfere with proper discrimination between safe and threatening stimuli and contribute to intrusive recollections. The prefrontal cortex, particularly its medial region, exhibits reduced activity, leading to impaired top-down regulation of limbic responses. The imbalance between hyperactive limbic structures and reduced cortical control forms a neurofunctional substrate of PTSD symptoms.

Neuroinflammatory processes play an important role in sustaining these alterations. Chronic stress leads to activation of microglia, the primary immune cells of the central nervous system. Activated microglia release pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-18 (IL-18) [8-10].

The activation of the NLR family pyrin domain containing 3 inflammasome (NLRP3 inflammasome) promotes maturation and release of these cytokines, amplifying inflammatory signaling. Persistent neuroinflammation disrupts synaptic transmission and contributes to neuronal dysfunction. In addition, impaired signaling between neurons and microglia, partly mediated by fractalkine (chemokine C-X3-C motif ligand 1, CX3CL1), alters neuroimmune communication [11, 12].

Oxidative stress and mitochondrial dysfunction represent another critical mechanism. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses. Excess ROS leads to damage of lipids, proteins, and nucleic acids. Malondialdehyde (MDA), a product of lipid peroxidation, reflects membrane damage and neuronal vulnerability. Mitochondria, as the main source of cellular energy, become dysfunctional under chronic stress conditions, leading to increased ROS generation and reduced metabolic efficiency. Antioxidant systems, including glutathione (GSH) and enzymes such as superoxide dismutase (SOD), are often impaired, which further enhances oxidative damage. These processes contribute to neuronal injury and are closely linked to neuroinflammation [13, 14].

Disturbances in neuroplasticity further exacerbate the condition. Neuroplasticity refers to the ability of the nervous system to adapt through structural and functional changes in synapses. In PTSD, reduced levels of brain-derived neurotrophic factor (BDNF) impair neuronal survival and synaptic formation. Alterations in glutamatergic signaling, particularly involving the N-methyl-D-aspartate receptor (NMDA receptor), lead to excitotoxicity and synaptic dysfunction. Chronic stress also reduces synaptic density and disrupts neural connectivity. These effects are intensified by concurrent inflammatory and oxidative processes.

Together, these mechanisms form an interconnected network of neurobiological alterations that underlie the development and persistence of PTSD [15-17].

These neurobiological mechanisms are reflected in measurable neuromolecular biomarkers, which provide a link between underlying pathophysiology and clinical presentation in PTSD.

NEUROMOLECULAR BIOMARKERS IN PTSD: INFLAMMATION, OXIDATIVE STRESS AND NEURODEGENERATION

Neuromolecular biomarkers provide important insight into the biological mechanisms underlying post-traumatic stress disorder. Evidence indicates that PTSD is associated with persistent activation of inflammatory pathways, increased oxidative stress, and progressive neuronal damage. These processes are closely interconnected and contribute to the development and maintenance of clinical symptoms [18, 19].

Inflammatory markers represent one of the most consistently observed biological alterations in PTSD. Increased levels of pro-inflammatory cytokines, including IL-1β, IL-6 and IL-18, reflect activation of the immune response within both the peripheral and central nervous systems. These cytokines influence neuronal function by modulating synaptic transmission and plasticity. Tumor necrosis factor alpha (tumor necrosis factor alpha, TNF-α) further contributes to inflammatory signaling by affecting blood–brain barrier permeability and promoting microglial activation. Elevated levels of C-reactive protein (CRP) indicate systemic inflammation and are associated with increased risk and severity of PTSD. In contrast, interleukin-10 (IL-10), an anti-inflammatory cytokine, is often reduced, suggesting impaired regulation of the inflammatory response [20-22].

Together, these changes indicate a chronic low-grade inflammatory state. A central component linking inflammation with cellular stress is the NLRP3 inflammasome. This multiprotein complex is activated in response to cellular damage and stress signals. Its activation leads to stimulation of caspase-1 (caspase-1), which converts inactive cytokine precursors into active forms, including IL-1β and IL-18. In PTSD, activation of the NLRP3 inflammasome is associated with chronic stress exposure, mitochondrial dysfunction, and increased production of reactive oxygen species. This pathway amplifies inflammatory signaling and contributes to neuronal injury, making it a potential biomarker of disease activity and a therapeutic target [23-25].

Oxidative stress represents another major mechanism involved in PTSD. It results from an imbalance between the generation of reactive oxygen species ROS and antioxidant defenses. Excessive ROS production leads to damage of cellular components, including lipids, proteins, and nucleic acids. Malondialdehyde,

a product of lipid peroxidation, is widely used as a marker of oxidative damage and reflects disruption of cell membrane integrity. Antioxidant systems are often impaired in PTSD, as indicated by reduced levels of GSH, a key intracellular antioxidant. Enzymes such as superoxide dismutase SOD and catalase, which are responsible for neutralizing reactive oxygen species, may also show altered activity. These disturbances enhance oxidative damage and contribute to neuronal vulnerability [26-28].

Markers of neurodegeneration provide evidence of structural neuronal damage in PTSD. Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) is a neuron-specific protein involved in protein turnover and cellular homeostasis. Increased levels of UCHL1 indicate neuronal injury and disruption of proteostasis. Neuron-specific enolase (NSE), a glycolytic enzyme released during neuronal damage, serves as a marker of neuronal cell loss. Tau protein, which is responsible for stabilizing microtubules in neurons, may undergo pathological changes leading to impaired axonal transport and accumulation of abnormal protein aggregates. Alterations in tau protein levels suggest the presence of neurodegenerative processes [29, 30].

NEUROMOLECULAR BIOMARKERS IN PTSD: NEUROIMMUNE COMMUNICATION, ENDOPLASMIC RETICULUM STRESS, NEUROENDOCRINE AND NEUROTRANSMITTER ALTERATIONS

Neuromolecular biomarkers associated with post-traumatic stress disorder extend beyond classical inflammatory and oxidative pathways and include mechanisms related to neuroimmune communication, cellular stress responses, neuroendocrine regulation, and neurotransmitter systems. These interconnected processes contribute to the complexity and heterogeneity of the disorder.

Chemokines play a key role in the interaction between neurons and microglial cells. Fractalkine, is primarily expressed by neurons, while its receptor is located on microglia. Under physiological conditions, this signaling pathway maintains microglia in a regulated state and supports synaptic stability. In PTSD, altered CX3CL1 signaling leads to excessive microglial activation, increased production of pro-inflammatory mediators, and disruption of synaptic function. This imbalance contributes to impaired neuronal communication and may enhance neuroinflammatory processes [31].

Endoplasmic reticulum stress represents another important mechanism of cellular dysfunction. The endoplasmic reticulum is responsible for protein folding and cellular homeostasis. Under conditions of chronic stress, accumulation of misfolded proteins activates the unfolded protein response. This response is mediated by three main pathways: inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and protein kinase RNA-like endoplasmic reticulum kinase (PERK). Although initially adaptive, prolonged activation of these pathways may lead to pro-apoptotic signaling. C/EBP homologous protein (CHOP) is a key mediator of this process and promotes cell death when stress persists. These mechanisms are closely linked to neuroinflammation and oxidative stress, further contributing to neuronal damage [32, 33].

Neuroendocrine biomarkers reflect disturbances in the regulation of the stress response. Cortisol, the primary glucocorticoid, often shows reduced basal levels and altered circadian rhythm in PTSD. Adrenocorticotropic hormone secretion may also be dysregulated, indicating impaired signaling within the stress axis. Dehydroepiandrosterone and its sulfated form (DHEA/DHEA-S) exert neuroprotective effects and counterbalance glucocorticoid activity. An imbalance between cortisol and DHEA/DHEA-S may reflect reduced resilience and impaired stress adaptation.

Neurotransmitter systems are also significantly altered in PTSD. Reduced activity of serotonin (5-hydroxytryptamine, 5-HT) is associated with mood disturbances and anxiety. Increased noradrenaline (norepinephrine) activity contributes to hyperarousal and heightened stress responses. Dopamine dysregulation affects reward processing and cognitive function. Alterations in glutamatergic signaling, particularly involving the NMDA receptor, may lead to excitotoxicity and impaired synaptic plasticity. In contrast, reduced gamma-aminobutyric acid (GABA) activity results in diminished inhibitory control over neural circuits [34].

NEUROMOLECULAR BIOMARKERS IN PTSD: NEUROPLASTICITY, APOPTOSIS, EPIGENETIC AND METABOLIC ALTERATIONS

Neuromolecular biomarkers in post-traumatic stress disorder include a wide spectrum of processes reflecting impaired neuroplasticity, activation of apoptotic pathways, epigenetic regulation of gene expression, and systemic metabolic disturbances. These mechanisms are closely interconnected and contribute to both functional and structural alterations in the central nervous system.

Neuroplasticity is essential for adaptive responses to environmental stimuli and involves dynamic changes in synaptic structure and function. In PTSD, impairment of neuroplastic processes is associated with persistent emotional dysregulation and deficits in memory

processing. Brain-derived neurotrophic factor plays a central role in supporting neuronal survival and synaptic formation. Reduced levels of BDNF observed in PTSD are linked to decreased synaptic plasticity and impaired neural adaptation. Insulin-like growth factor 1 (insulin-like growth factor 1, IGF-1) also contributes to neuronal growth, neurogenesis, and cellular repair. Alterations in IGF-1 levels may reflect reduced regenerative capacity and diminished resilience of neural networks. These changes are influenced by chronic stress and interact with inflammatory and neuroendocrine pathways [35].

Apoptotic mechanisms represent another important aspect of neuronal damage in PTSD. Caspase-3 functions as a key executioner enzyme responsible for the final stages of programmed cell death, while caspase-9 is involved in the initiation of the intrinsic mitochondrial apoptotic pathway. Activation of caspase-9 leads to downstream activation of caspase-3, resulting in cellular degradation. Increased activity of these enzymes suggests that chronic stress may induce neuronal loss through mitochondrial-dependent mechanisms. Apoptosis is closely linked to oxidative stress and inflammation, which enhance cellular vulnerability and contribute to cumulative neuronal damage [36, 37].

Epigenetic mechanisms provide an additional layer of regulation by modifying gene expression without altering DNA sequence. DNA methylation, particularly in genes related to stress regulation such as the glucocorticoid receptor gene (NR3C1), can influence sensitivity to cortisol and alter HPA axis function. FK506 binding protein 5 (FKBP5) is another critical regulator of glucocorticoid receptor activity, and its genetic and epigenetic modifications have been associated with altered stress responses and increased susceptibility to PTSD. MicroRNAs, including microRNA-124 and microRNA-146a, regulate gene expression at the post-transcriptional level and are involved in controlling inflammatory and neuronal processes. Alterations in microRNA expression contribute to dysregulation of neuroimmune signaling and synaptic function [38, 39].

Metabolic biomarkers reflect systemic alterations associated with PTSD and link central nervous system dysfunction with peripheral physiology. The kynurenine pathway, responsible for tryptophan metabolism, is activated under inflammatory conditions and leads to the production of neuroactive metabolites. Quinolinic acid, one of these metabolites, has neurotoxic properties and can enhance excitotoxicity through activation of the N-methyl-D-aspartate receptor. Disturbances in lipid metabolism may affect membrane integrity and inflammatory signaling, while alterations in glucose metabolism can impair neuronal energy supply. Chronic stress may promote insulin resistance and disrupt metabolic homeostasis, further contributing to cognitive and emotional dysfunction.

Taken together, these biomarker groups suggest that PTSD involves interacting inflammatory, oxidative, neuroendocrine, neuroplastic, and metabolic mechanisms that may contribute to symptom persistence and clinical heterogeneity.

The main groups of neuromolecular biomarkers involved in PTSD, along with their underlying mechanisms and functional significance, are summarized in Table 1.

DIAGNOSTIC IMPLICATIONS

Neuromolecular biomarkers provide important information regarding the biological basis of post-traumatic stress disorder and may enhance current diagnostic approaches. One of the key aspects is their association with symptom severity. Increased levels of pro-inflammatory cytokines, oxidative stress markers, and indicators of neuronal injury have been linked to more severe clinical manifestations, including heightened anxiety, intrusive symptoms, and impaired cognitive function. Similarly, alterations in neuroendocrine markers, such as cortisol and ACTH, may reflect dysregulated stress responses corresponding to symptom intensity [40].

Biomarkers are also related to the duration of PTSD. Chronic forms of the disorder are often characterized by sustained activation of inflammatory pathways, persistent oxidative imbalance, and progressive neuronal damage. In contrast, early stages may involve more dynamic and potentially reversible changes. This suggests that biomarker profiles may differ depending on the stage of the disorder and could be used to monitor disease progression [2, 12, 18].

The variability in biomarker expression supports the concept of biologically distinct subtypes of PTSD. Differences in inflammatory activity, neuroendocrine regulation, and neuroplasticity may define subgroups of patients with specific pathophysiological mechanisms. Identification of such subtypes may improve classification systems and facilitate more precise clinical characterization.

Integration of biomarker data with psychometric tools represents an important step toward improving diagnostic accuracy. Instruments such as the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and the PTSD Checklist for DSM-5 (PCL-5) provide standardized assessment of symptom severity. Combining these tools with biological measures may allow for a more comprehensive evaluation that reflects both clinical presentation and underlying biological processes [21, 25, 34].

Table 1. Neuromolecular biomarkers in PTSD: mechanisms and functional significance

Biomarker group	Example biomarkers	Mechanism	Functional significance in PTSD
Inflammatory markers	IL-1β, IL-6, IL-18, TNF-α, CRP	Activation of immune response, cytokine signaling	Chronic inflammation, synaptic dysfunction
Inflammasome	NLRP3 inflammasome	Caspase-1 activation, cytokine maturation	Amplification of neuroinflammation
Oxidative stress	ROS, MDA, GSH, SOD	Redox imbalance, lipid peroxidation	Cellular damage, neuronal vulnerability
Neurodegeneration	UCHL1, NSE, tau protein	Protein degradation dysfunction, neuronal injury	Neurodegenerative changes
Chemokines	CX3CL1	Neuron–microglia signaling	Dysregulated neuroimmune communication
Endoplasmic reticulum stress	IRE1, ATF6, PERK, CHOP	Unfolded protein response, apoptosis	Cellular stress, neuronal death
Neuroendocrine markers	Cortisol, ACTH, DHEA/DHEA-S	Stress axis dysregulation	Altered stress response
Neurotransmitters	Serotonin, dopamine, glutamate, GABA	Neurotransmission imbalance	Emotional and cognitive symptoms
Neuroplasticity markers	BDNF, IGF-1	Synaptic remodeling, neurogenesis	Impaired adaptation and memory
Apoptosis markers	Caspase-3, caspase-9	Programmed cell death	Neuronal loss
Epigenetic markers	NR3C1, FKBP5, microRNA	Gene expression regulation	Stress sensitivity, vulnerability
Metabolic markers	Kynurenine pathway, lipids, glucose	Metabolic dysregulation	Neurotoxicity, systemic effects

Source: Compiled by the authors of this study

Table 2. Clinical implications of neuromolecular biomarkers in PTSD

Clinical domain	Biomarker relevance	Potential application
Symptom severity	Cytokines, cortisol, oxidative markers	Correlation with clinical intensity
Disease duration	Inflammation, neurodegeneration markers	Monitoring progression
Biological subtypes	Multi-pathway biomarker profiles	Stratification of patients
Early detection	Neuroendocrine, inflammatory markers	Identification of at-risk individuals
Treatment selection	Neurotransmitters, inflammation, oxidative stress	Targeted therapy
Treatment response	BDNF, cytokines, cortisol	Monitoring effectiveness
Precision psychiatry	Integrated biomarker panels	Personalized treatment planning

Source: Compiled by the authors of this study

Neuromolecular biomarkers also have potential in early detection of PTSD. Changes in inflammatory, neuroendocrine, and metabolic markers may occur before the full development of clinical symptoms. Early identification of individuals at risk could enable timely intervention and reduce the likelihood of chronic disease progression.

PERSONALIZED TREATMENT APPROACHES

The growing understanding of neuromolecular mechanisms underlying post-traumatic stress disorder has created the basis for more targeted and individualized therapeutic strategies. Personalized treatment approaches aim to address specific biological disturbances, including inflammation, oxidative stress, neuroendocrine dysregulation, neurotransmitter imbalance, and impaired neuroplasticity. Such strategies move beyond symptom-based treatment and focus on underlying pathophysiological processes [18, 22, 26].

Anti-inflammatory therapies represent a promising direction, given the consistent evidence of chronic low-grade inflammation in PTSD. Modulation of inflammatory pathways may involve pharmacological agents targeting cytokine signaling, as well as interventions that reduce microglial activation. By decreasing levels of pro-inflammatory mediators, such approaches may improve neuronal function and reduce symptom severity.

Targeting pathways associated with the NLR family pyrin domain containing 3 inflammasome may further limit the amplification of inflammatory responses.

Oxidative stress is closely linked to inflammation and neuronal damage, making antioxidant therapies another important component of treatment. Strategies aimed at restoring redox balance include the use of compounds that enhance antioxidant capacity, such as glutathione precursors or agents supporting mitochondrial function. Reduction of reactive oxygen species may protect cellular structures, improve neuronal viability, and support functional recovery [16, 23, 34].

Modulation of the hypothalamic–pituitary–adrenal axis is also of therapeutic interest. Interventions targeting cortisol regulation and glucocorticoid receptor sensitivity may help normalize stress responses. Balancing the interaction between cortisol and dehydroepiandrosterone may further improve resilience to stress and reduce maladaptive physiological responses.

Therapies targeting neurotransmitter systems remain a central component of PTSD treatment. Modulation of serotonergic, noradrenergic, and dopaminergic pathways may improve mood regulation, reduce hyperarousal, and enhance cognitive function. Additionally, targeting glutamatergic signaling, particularly through the N-methyl-D-aspartate receptor, may influence synaptic plasticity and facilitate extinction of traumatic memories. Enhancing gamma-aminobutyric acid activity may further support inhibitory control within neural circuits [17, 19, 24, 34].

Neuroprotective strategies and interventions supporting neuroplasticity are increasingly recognized as essential. Enhancing levels of brain-derived neurotrophic factor and other growth factors may promote synaptic remodeling and neuronal survival. Such approaches may improve cognitive flexibility and facilitate adaptive processing of traumatic experiences. Interventions that support neurogenesis and synaptic connectivity may contribute to long-term recovery.

The integration of biomarker profiles with clinical phenotypes represents a core principle of precision psychiatry, enabling the identification of biologically distinct subgroups of PTSD. This approach may facilitate the selection of targeted interventions based on dominant pathophysiological mechanisms, such as inflammation-driven, neuroendocrine-dysregulated, or neuroplasticity-impaired subtypes.

The concept of precision psychiatry integrates these approaches by tailoring treatment to individual biological profiles. Biomarker-based stratification may enable the identification of dominant pathological mechanisms in each patient, allowing for the selection of targeted interventions. This approach has the potential to improve treatment effectiveness, reduce variability in outcomes, and support more efficient management of PTSD [11, 18, 33, 38, 40].

Overall, personalized treatment strategies based on neuromolecular biomarkers represent a promising direction in the management of PTSD, linking advances in neurobiology with clinical practice.

FUTURE DIRECTIONS

Future research on neuromolecular biomarkers in post-traumatic stress disorder should focus on several key areas that may improve understanding of disease mechanisms and support translation into clinical practice. One of the most important directions involves longitudinal studies. Most available data are derived from cross-sectional designs, which limit the ability to determine causal relationships and temporal dynamics. Longitudinal studies would allow for the assessment of biomarker changes over time, including the transition from acute stress responses to chronic PTSD. Such approaches may help identify early biological predictors of disease onset, progression, and remission, as well as factors associated with treatment response [15, 23].

Another critical area is the validation of biomarker panels. Single biomarkers often lack sufficient specificity and sensitivity to serve as reliable diagnostic tools. Therefore, combining multiple biomarkers representing different biological pathways, such as inflammation, oxidative stress, neuroendocrine regulation, and neuroplasticity, may provide a more accurate representation of the disorder. Standardization of measurement methods, population characteristics, and analytical approaches is necessary to ensure reproducibility and comparability across studies. Large-scale, multicenter investigations are particularly important for establishing clinically relevant biomarker profiles [18, 37].

Integration of multi-omics approaches represents a further step toward a comprehensive understanding of PTSD. Combining data from genomics, epigenomics, transcriptomics, proteomics, and metabolomics may reveal complex interactions between biological systems and identify key regulatory networks involved in stress responses. Such integrative analyses may also facilitate the identification of novel therapeutic targets and improve the ability to classify biologically distinct subtypes of PTSD [12, 22, 36].

Translation of biomarker research into clinical practice remains a major challenge. For biomarkers to be clinically useful, they must be accessible, cost-effective, and easy to interpret. Development of standardized protocols for biomarker assessment, including sample collection, processing, and analysis, is essential. In addition, clinical guidelines are needed to define how

biomarker data should be integrated with existing diagnostic tools.

The development of biomarker-based diagnostic systems may ultimately improve the current symptom-based classification of PTSD. Such systems could support early identification of individuals at risk, enable more precise diagnosis, and guide personalized treatment strategies. Continued research integrating biological and clinical data will be necessary to achieve these goals and to fully implement biomarker-driven approaches in psychiatry [11, 18, 22, 36].

The clinical relevance of neuromolecular biomarkers in PTSD extends beyond pathophysiological insight and includes their potential application in diagnosis, patient stratification, and personalized treatment planning, as summarized in Table 2.

LIMITATIONS

Several limitations should be considered. Most studies on neuromolecular biomarkers in PTSD are cross-sectional, limiting causal interpretation. There is also significant variability in measurement methods, sample types, and study populations, which reduces comparability. In addition, many biomarkers lack standardized thresholds, limiting their current clinical applicability. Finally, comorbid conditions may influence biomarker levels and complicate interpretation.

CONCLUSIONS

Post-traumatic stress disorder should be understood as a biologically complex and multidimensional condition involving interactions between neuroendocrine, immune, metabolic, and neurodegenerative mechanisms. The evidence presented in this review indicates that processes such as neuroinflammation, oxidative stress, dysregulation of the HPA axis, impaired neuroplasticity, and cellular damage collectively contribute to the development and persistence of PTSD symptoms. These findings support the view that PTSD extends beyond a purely psychological framework and involves measurable biological alterations.

Neuromolecular biomarkers may complement symptom-based diagnostic systems by providing objective information on underlying biological processes and, in the future, may help identify clinically relevant biological subgroups of PTSD. Their clinical application, however, still requires further validation and standardization.

Despite these promising perspectives, further translational research is required. Future studies should focus on validating biomarker panels, standardizing measurement methods, and establishing their clinical utility. Bridging the gap between experimental findings and clinical application remains a critical step in advancing biomarker-based approaches in psychiatry. Future advances in biomarker standardization and multi-modal integration may enable the transition from symptom-based classification toward biologically informed diagnostic systems in PTSD.

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CONFLICT OF INTEREST
The Author declares no conflict of interest

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