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NEUROBIOLOGICAL BIOMARKERS IN PSYCHIATRY: ADVANCES IN THE DIAGNOSIS AND PROGNOSIS OF MENTAL DISORDERS

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ABSTRACT

Mental disorders show high clinical heterogeneity, symptomatic overlap, and variable prognostic trajectories, which limits diagnostic models based exclusively on clinical criteria. In this context, neurobiological biomarkers have been investigated as complementary tools for diagnosis, prognosis, risk stratification, and prediction of therapeutic response in psychiatry. The aim of this study was to analyze scientific evidence on neurobiological biomarkers applied to mental disorders, with an emphasis on neuroimaging, genomics, electrophysiology, inflammation, metabolomics, and proteomics. This is an integrative literature review developed using a systematized approach, based on studies published in recognized international databases and scientific journals, including PubMed/MEDLINE, PubMed Central, Nature Portfolio, BMC Psychiatry, Molecular Psychiatry, Translational Psychiatry, Biological Psychiatry, and related journals. Twenty studies were included, encompassing systematic reviews, meta-analyses, multicenter studies, genome-wide association studies, and translational investigations.The results demonstrated that genomic and neuroimaging biomarkers show greater methodological robustness, especially through large international consortia, while electrophysiological, inflammatory, metabolomic, and proteomic biomarkers show high translational potential, although they still require greater clinical validation. It was evidenced that no single biomarker has sufficient validity to replace psychiatric clinical assessment, making the development of integrated multimodal panels more promising. It is concluded that neurobiological biomarkers represent a relevant frontier for precision psychiatry, with the potential to enhance understanding of pathophysiology, improve prognostic assessment, and guide individualized therapeutic strategies.

Keywords: Biomarkers; Mental Disorders; Psychiatry; Precision Medicine.

INTRODUCTION

Mental disorders represent one of the greatest contemporary challenges for health systems, both due to the high global burden of disease and the complexity of their etiological, clinical, and therapeutic mechanisms. Conditions such as major depression, bipolar disorder, schizophrenia, anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, and disorders related to substance use involve heterogeneous presentations, variable clinical trajectories, and therapeutic responses often unpredictable. Traditionally, psychiatric diagnosis has been based on clinical assessment, the psychopathological interview, and the application of classificatory criteria based on signs, symptoms, duration, and functional impairment. Although these instruments are indispensable for clinical practice, there are still important limitations related to symptomatic overlap, individual variability, the absence of widely validated objective markers, and the difficulty of predicting clinical course, risk of relapse, and response to treatment [1,2].

In this context, neurobiological biomarkers have received growing attention as tools capable of increasing diagnostic and prognostic accuracy in psychiatry. In general terms, biomarkers can be understood as measurable indicators of normal biological processes, pathological processes, or responses to a therapeutic intervention. In psychiatry, these markers may include parameters obtained through structural and functional neuroimaging, electroencephalography, genetics, epigenetics, proteomics, metabolomics, inflammation, neuroendocrinology, and other integrated approaches. Interest in these resources does not stem from an intention to replace clinical assessment, but rather to complement understanding of mental disorders through objective data that may help with risk stratification, differential diagnosis, the identification of biological subtypes, and the prediction of therapeutic outcomes [1,2].

The emergence of precision psychiatry has strengthened the search for models that go beyond classification that is exclusively syndromic of mental disorders. This perspective considers that different diagnoses

they can share common neurobiological pathways, while patients with the same diagnosis may present distinct pathophysiological mechanisms. Thus, the investigation of biomarkers has contributed to the development of transdiagnostic models, in which dimensions such as synaptic dysfunction, altered brain connectivity, neuroinflammation, vulnerability genetic vulnerability, dysregulation of tryptophan metabolism, and alterations in cortico-limbic circuits can cut across different diagnostic categories [1-3]. This advance is particularly relevant because many psychiatric disorders present overlapping symptoms, such as cognitive changes, anhedonia, impulsivity, anxiety, social withdrawal, sleep disturbances, and functional impairment, making precise clinical delineation difficult in the early stages.

Among the most robust areas of current research, genomic biomarkers stand out. Genome-wide association studies and major international consortia have shown that psychiatric disorders have complex, polygenic, and partially shared genetic architecture. Integrated analysis across multiple disorders revealed genetic overlap among different conditions, reinforcing the the hypothesis that part of psychiatric vulnerability is related to common biological factors, with clinical expression modulated by environment, development, adverse experiences, epigenetic factors, and individual trajectories [3]. In schizophrenia, genomic findings implicate loci related to synaptic biology and neuronal regulation, suggesting that changes in neural communication processes may be involved in the disorder's pathophysiology [8]. In bipolar disorder, studies involving tens of thousands of cases identified variants associated with neuronal and synaptic pathways, contributing to understanding the biological basis of pathological mood [9]. In major depression, genomic meta-analyses identified multiple independent variants and genes related to prefrontal brain regions and synaptic functions, while studies multi-ancestry recent expanded the generalization of the findings to genetically diverse populations [10, 11].

Besides genomics, neuroimaging occupies a central position in the investigation of biomarkers in psychiatry. Multicenter studies coordinated by the ENIGMA consortium have made it possible to assess structural brain changes in

large-scale samples, surpassing the limitations of small studies and increasing the reliability of the findings. In schizophrenia, cortical alterations distributed across multiple brain regions were identified through the analysis of thousands of individuals, suggesting that the disorder involves broad neuroanatomical changes and is not restricted to a single brain area [12]. In major depression, cortical changes in adults and adolescents, as well as white matter disorders, reinforce the involvement of brain circuits associated with emotional regulation, cognition, affective processing, and neural network integration [13, 15]. In bipolar disorder, magnetic resonance imaging analyses indicate cortical abnormalities related to diagnosis, the course of the disease, age, medication use, and the presence of psychotic symptoms [14]. These findings demonstrate that neuroimaging has the potential for characterization

neurobiological, clinical stratification, and prognostic investigation, although its individual diagnostic application still depends on validation, standardization, and integration with other markers [12-16].

The prediction of therapeutic response also constitutes one of the most promising for the use of neurobiological biomarkers. In major depression, for example, structural, functional, and molecular neuroimaging tests have been investigated to identify patterns associated with antidepressant response, recurrence risk, and treatment resistance [16]. This field becomes especially relevant in light of the high variability of response to antidepressants, the delay in identifying effective treatments, and the need to reduce strategies based only on trial and error. Studies on neuroimaging-derived biomarkers have also assessed the rapid antidepressant effects of ketamine, especially in cases of treatment-resistant depression, indicating possible changes in brain networks related to emotional regulation, synaptic plasticity, and functional connectivity [17]. Although promising, these markers still require greater reproducibility and clinical validation before they can be broadly incorporated into psychiatric practice.

Electrophysiological biomarkers, especially those based on electroencephalography, have also gained relevance because they are relatively accessible, noninvasive, and

capable of capturing patterns of brain activity in real time. Recent studies show that EEG-derived markers may contribute to the identification of patterns associated with depression, anxiety, and bipolar disorder, especially when integrated with artificial intelligence and machine learning models [7]. The use of explainable artificial intelligence has been proposed as a strategy to increase the transparency of predictive models, making it possible to understand which characteristics electrophysiological support a given classification or clinical prediction. This aspect is essential so that computational tools can be critically evaluated by healthcare professionals and eventually incorporated into clinical environments in a safe, ethical, and interpretable manner [7].

At the same time, biomarkers Peripheral biomarkers are expanding the scope of research in psychiatry, especially in the areas of inflammation, metabolomics, and proteomics. The inflammatory hypothesis of mental disorders has been supported by evidence linking pro-inflammatory cytokines, immune activation, oxidative stress, and neurochemical changes to conditions such as depression and psychosis [18-20]. In depression, the kynurenine pathway has been particularly investigated for its relationship with tryptophan metabolism, systemic inflammation, and the neurotransmission glutamatergic. Metabolomic studies indicate that kynurenic acid may act as a marker associated with both diagnosis and response to treatment, suggesting a connection between metabolic state, inflammation, and therapeutic outcome [18]. Systematic reviews and meta-analyses reinforce that the kynurenine pathway may represent a relevant axis for the biological subtyping of depression, especially in patients with an inflammatory profile or treatment resistance [19].

In first-episode psychosis, peripheral inflammatory markers have also been associated with the emergence and severity of symptoms, including negative symptoms, which often relate to worse functional prognosis and greater therapeutic difficulty [20]. This finding suggests that early identification of subgroups with an inflammatory profile may contribute to prognostic strategies and, in the future, to interventions adjuvant targeted. Similarly, multicenter programs aimed at clinical risk for psychosis have been seeking

integrate biomarkers from body fluids, genetics, cognition, neuroimaging, electrophysiology, and digital markers, with the aim of predicting conversion to psychosis, symptomatic persistence, and functional outcomes [4]. This multidimensional approach represents an important advance, as it recognizes that no single biomarker is sufficient to explain the complexity of mental disorders.

Proteomics and metabolomics are also consolidating as emerging areas for identifying transdiagnostic biological signatures. Proteomic studies in young adults suggest an association between plasma markers and the general factor of psychopathology, pointing to shared molecular pathways that may reflect the overall burden of symptoms and psychological vulnerability [5]. Reviews of validated metabolomic biomarkers in psychiatric disorders highlight that, although there are promising candidates, challenges still persist related to sample heterogeneity, methodological differences, interference from diet, medication, comorbidities, lifestyle, and the lack of widely accepted clinical cut-off points [6]. Therefore, the clinical utility of these markers depends on longitudinal studies, external validation, and integration with clinical, genomic, and neurofunctional data.

Despite significant advances, the application of biomarkers neurobiological in psychiatry still faces relevant limitations. Among the main challenges are the low specificity of many markers, the overlap between diagnoses, the influence of environmental and pharmacological factors, variability across populations, the need for methodological standardization, and the difficulty of translating group statistical findings into individual clinical decisions [1,2,6]. In addition, many studies still use cross-sectional designs, small samples, or lack independent validation, which limits the generalizability of the results. For this reason, the development of multimodal panels—combining different sources of biological and clinical information—has been considered a more promising alternative than the search for a single, definitive biomarker [1,6,7].

Given this scenario, it is necessary to systematize the evidence available on biomarkers

neurobiological in psychiatry, considering its advances, limitations, diagnostic applications, and prognostic potential. An integrative review makes it possible to bring together findings from different methodological designs, including genomic studies, neuroimaging, electrophysiology, inflammation, metabolomics and proteomics, while also enabling a critical analysis of the scientific maturity of each research axis.

Thus, the present study aims to analyze the scientific evidence regarding neurobiological biomarkers applied to the diagnosis and prognosis of mental disorders, highlighting their contribution to precision psychiatry, their possibilities translational and the main challenges for safe and effective incorporation into clinical practice [1,2,6,7,20].

METHODOLOGY

This is an integrative literature review, developed with a systematic approach, with the purpose of bringing together, analyzing, and synthesizing evidence scientific about neurobiological biomarkers applied to the diagnosis and prognosis of mental disorders. The choice of this design is justified by the breadth of the topic, which involves different methodological approaches, including systematic reviews, meta-analyses, multicenter studies, genomic studies, neuroimaging analyses, metabolomics investigations, proteomics, inflammatory studies, and investigations based on electrophysiology. The integrative review allows for the incorporation of evidence from different fields of biological and translational psychiatry, promoting a critical and comprehensive understanding of the advances, limitations, and clinical possibilities of biomarkers in mental health.

The guiding question that shaped this review was: what are the main scientific evidence scientific about neurobiological biomarkers used in the diagnosis, prognosis, risk stratification and prediction of

therapeutic response in mental disorders? From this question, we sought to identify studies that addressed biomarkers associated with disorders such as major depression, bipolar disorder, schizophrenia, anxiety disorders, obsessive-compulsive disorder,

post-traumatic stress disorder, first-episode psychosis, and psychiatric conditions assessed from a transdiagnostic perspective.

The bibliographic search was conducted in internationally recognized scientific databases, with priority for PubMed/MEDLINE, PubMed Central, Nature Portfolio, BMC Psychiatry, Molecular Psychiatry, Translational Psychiatry, Biological Psychiatry, Nature Genetics, Nature Neuroscience, International Journal of Molecular Sciences, Neuroscience and

Biobehavioral Reviews, Scientific Reports, and Acta Psychiatrica Scandinavica. Studies linked to major international consortia, such as the ENIGMA Consortium, the Psychiatric Genomics Consortium, and the Accelerating Medicines Partnership Schizophrenia Program, were also considered due to their methodological relevance, sample size, and ability to generate more robust and reproducible evidence in translational psychiatry.

Controlled descriptors and free English-language terms were used, combined by Boolean operators, including: **“**psychiatric disorders**”**,**“**mental disorders**”**,**“**biomarkers**”**,**“**neurobiological biomarkers”,

“diagnosis”, “prognosis”, “precision psychiatry”, “neuroimaging”, “EEG”, “genomics”, “polygenic risk score”, “inflammation”, “proteomics”, **“**metabolomics**”**, **“**kynurenine pathway**”**, **“**major depressive disorder**”**, **“**bipolar disorder**”**, **“**schizophrenia**”**, **“**first-episode psychosis**”** and **“**treatment response**”**. The search strategies were adapted according to the specificities of each database, prioritizing studies with the closest adherence to the topic, bibliographic traceability, DOI availability or indexing in recognized databases, and direct contribution to the understanding of biomarkers applied to diagnosis and prognosis in psychiatry.

Studies published in peer-reviewed scientific journals were included, with full text available or bibliographic information sufficient for traceability, addressing neurobiological biomarkers in mental disorders. Primary studies, systematic reviews, meta-analyses, narrative reviews of high relevance, and studies

multicenter, genome-wide association studies, studies of neuroimaging, metabolomic proteomic inflammatory, and electrophysiological studies. The selection prioritized publications with international relevance, methodological rigor, significant samples, participation in scientific consortia, or direct contribution to advancing precision psychiatry.

Studies addressing biomarkers without a direct relationship to mental disorders were excluded, as were publications without adequate traceability, and opinion pieces without sufficient scientific basis sufficient, studies exclusively pre-clinical in animal models, duplicated studies, studies with a very narrow scope without diagnostic or prognostic application, and publications that did not present a clear relationship with neurobiological biomarkers. Studies that addressed only the psychosocial, behavioral, or epidemiological aspects of mental disorders without an association with measurable biological markers were also excluded.

The selection process was carried out in successive stages. Initially, studies were identified through the review of titles and abstracts, considering their alignment with the central theme of the review. Next, potentially eligible articles were evaluated regarding the type of biomarker investigated, the mental disorder addressed, methodological design, publication source, year, scientific relevance, and clinical applicability. After this screening, 20 studies were selected as the most suitable to form the main database of the review, covering different biomarker dimensions neurobiological, including neuroimaging, electrophysiology, genomics, inflammation, metabolomics, and proteomics.

Data extraction was conducted using a previously structured matrix containing the following variables: author and year of publication, country or consortium responsible, type of study, mental disorder assessed, biomarker investigated, main findings, diagnostic or prognostic application, and level of evidence. This organization enabled a systematic comparison of the studies, identification of areas of convergence and divergence among the findings, and grouping of evidence into thematic axes. The studies were analyzed qualitatively, considering methodological rigor, clinical relevance, consistency of the findings, and the potential for application translational.

The classification of the level of evidence was carried out adapted to the multidisciplinary nature of the review. Studies classified as level I included systematic reviews, meta-analyses, and large multicenter studies or consortia international. Level II was assigned to robust observational studies, genomic studies, cohorts, and translational investigations with relevant samples. Level III included exploratory, cross-sectional, pilot, or initial validation studies. Level IV was assigned to narrative reviews, evidence maps, and methodological articles or study design papers. This classification allowed for a critical interpretation of evidence maturity and differentiated biomarkers already supported by robust data from those still in an exploratory phase.

The synthesis of results was conducted in a narrative and thematic manner, organized into five main axes: genomic biomarkers and polygenic risk; structural and functional neuroimaging biomarkers; electrophysiological EEG-based biomarkers; inflammatory and immunological biomarkers; and metabolomic biomarkers and proteomic. This categorization was defined based on the recurrence of themes in the selected studies and the relevance of these domains to precision psychiatry. The analysis sought to highlight not only positive findings, but also methodological limitations, validation challenges, the heterogeneity of mental disorders, and the difficulty of translating population-level results into individualized clinical decisions.

Because this is an integrative review based exclusively on secondary data available in the scientific literature, without direct involvement of human participants, primary data collection, or access to identifiable individual information, there was no need to submit to the Research Ethics Committee.

Research Ethics.

RESULTS

This integrative review included 20 scientific studies that addressed biomarkers of neurobiological nature applied to diagnosis, prognosis, risk stratification, and prediction of therapeutic response in

mental disorders. The selected studies covered different levels of evidence and included systematic reviews, meta-analyses, multicenter studies, genome-wide association studies, neuroimaging analyses, metabolomic investigations, proteomic,

inflammatory and studies based on electrophysiology. This methodological diversity enabled a broad analysis of recent advances in biological and translational psychiatry, especially in the context of precision psychiatry.

The findings were organized into five main thematic axes: genomic biomarkers and polygenic risk; biomarkers of structural and functional neuroimaging; biomarkers electrophysiology-based based on EEG; inflammatory and immunological biomarkers; and metabolomic biomarkers e proteomics. Organizing by axes made it possible to identify that the most consolidated biomarkers in terms of sample volume and methodological robustness are those derived from large international genomics and neuroimaging consortia, whereas biomarkers peripheral, metabolomic, proteomic, and electrophysiological biomarkers have high translational potential, but still require greater external validation and methodological standardization [1-7].

Table 1 presents a synthesis of the main biomarker axes identified in the included studies, along with the respective disorders assessed, potential clinical applications, and main limitations observed.

Table 1. Synthesis of the neurobiological biomarkers identified in the included studies in the review.

Biomarker axis	Related studies	Disorders assessed	Potential clinical applications	Main limitations
Genomics and polygenic risk	[3,8-11]	Schizophrenia, major depression, bipolar disorder, and transdiagnostic psychiatric disorders	Risk stratification, identification of biological vulnerability, etiological understanding, and support for transdiagnostic models	Low individual specificity, influence of genetic ancestry, need for population validation, and limited clinical applicability in isolation
Structural neuroimaging and	[1, 12-17]	Schizophrenia, major depression, bipolar disorder, and	Neuroanatomical characterization, response prediction	High cost, methodological heterogeneity,

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Biomarker axis	Related studies	Disorders assessed	Potential clinical applications	Main limitations
functional		Treatment-resistant depression	therapy, assessment of recurrence, and identification of brain patterns associated with the clinical course	difficulty in individual application and the absence of universal clinical cutoffs
EEG and electrophysiology	[7]	Depression, anxiety, and bipolar disorder	Screening, therapeutic monitoring, support for diagnosis, and integration with explainable artificial intelligence	Need for External validation, variability of protocols, and the risk of low clinical interpretability without standardization
Inflammation and immunology	[4, 18-20]	Depression, first-episode psychosis, and clinical risk for psychosis	Inflammatory subtyping, prognostic assessment, identification of symptomatic severity, and possible guidance for adjunctive therapeutic direction	Low specificity, influence of comorbidities, medications, lifestyle, and systemic inflammatory states
Metabolomics and proteomics	[5,6, 18, 19]	Major depression, disorders Various psychiatric disorders and transdiagnostic psychopathology	Identification of molecular signatures, monitoring of Therapeutic response, biological subtyping, and personalized psychiatry	Still exploratory studies, the interference of diet and Environment, need for replication and laboratory standardization

On the genomic axis, studies have shown that mental disorders have a complex, polygenic, and partly shared genetic architecture. The integrated analysis of 14 psychiatric disorders highlighted genetic overlap among different diagnostic categories, reinforcing the understanding that psychiatric vulnerability is not restricted to the boundaries of traditional nosological frameworks [3]. This perspective is consistent with findings from large genome-wide association studies that identified loci and genes related to schizophrenia, major depression, and bipolar disorder, many of them associated with synaptic biology, neuronal regulation, and cerebral expression [8-11]. Taken together, these results indicate that genomics has strong potential to deepen our understanding of the etiological basis of mental disorders and support future stratification models risk.

In schizophrenia, genomic findings reinforced the involvement ofbgenes associated with synaptic communication and neuronal development [8]. In bipolar disorder, genetic variants identif- ied on a large scale helped to improve the understanding of biological pathways re- lated to synaptic signaling and mood regulation [9]. In major depression, ge- nomic studies identified multiple indep- endent variants and highlighted the impo- rtance of prefrontal regions, neural netw- orks, and greater ancestral diversity in genetic analyses [10, 11]. Despite these advances, the results also indicate that polygenic risk scores still have important limitations for individual clinical use, especially because they depend on valid- ation in different populations and because they lack sufficient diagnostic specificity when used in isolation.

In the neuroimaging axis, the included studies showed structural and functional changes associated with severe mental dis- orders. Multicenter analyses from the EN- IGMA consortium demonstrated widespr- ead cortical alterations in individuals with schizophrenia, including differences in cor- tical thickness and in the cortical surface area, suggesting that the disorder involves distributed neuroanatomical patterns across multiple brain regions [12]. In major depression, cortical alterations were observed in adults and adolescents, in addition to white matter disturbances in international cohorts, indicating involvement of circuits related to emotional regulation, cognition, connectivity, and neural network integration [13,15]. In bipolar disorder, analysis of thousands of participants identified cortical abnormalities related to diagnosis and modulated by factors such as age, medication, presence of psychosis, and clinical characteristics of the course of the illness [14].

Neuroimaging biomarkers have also been investigated in the context of therapeutic response and recurrence of major depression. Reviews on structural, functional, and molecular neuroimaging indicated that certain brain patterns may be associated with antidepressant response, recurrence, and treatment resistance [16]. In treatment-resistant depression, studies on the antidepressant effects of ketamine suggested that neuroimaging-derived biomarkers may help identify alterations in brain networks

related to synaptic plasticity, functional connectivity, and emotional regulation [17]. These findings suggest important prognostic potential for neuroimaging, especially when applied to predicting therapeutic response. However, heterogeneity among protocols, the high cost of exams, the need for large samples, and the difficulty of extrapolating group results to individual decisions still limit its routine incorporation into clinical practice.

On the electrophysiological axis, EEG-based studies have demonstrated potential for identifying patterns associated with depression, anxiety, and bipolar disorder [7]. The systematic review on biomarkers

derived from EEG highlighted the growth of explainable artificial intelligence-based models, which seek to increase the transparency and interpretability of the algorithms used in clinical classification or prediction. This approach is relevant because electroencephalography is a non-invasive, relatively accessible method capable of capturing temporal changes in brain activity with high resolution. The results indicate that electrophysiological biomarkers may in the future contribute to screening,

therapeutic monitoring and diagnostic support, mainly when combined with clinical and computational data. However, there is still a need to standardize protocols, externally validate the models, and define clinically interpretable parameters.

On the inflammatory and immunological axis, the analyzed studies indicated an association between peripheral inflammatory markers and disorders such as depression and first-episode psychosis [18-20]. The kynurenine pathway showed special relevance in depression, due to its relationship with tryptophan metabolism, inflammatory inflammatory,

processes, glutamatergic neurotransmission, and therapeutic response [18, 19]. In the metabolomic study, Erabi et al. identified kynurenic acid as a potential biomarker associated with both diagnosis and treatment response in major depression, suggesting that metabolic changes may reflect specific biological subtypes of the disease [18]. A systematic review and meta-analysis on the kynurenine pathway reinforced that this metabolic-inflammatory axis may contribute to understanding depression, especially in patient subgroups with a higher inflammatory burden [19].

In first-episode psychosis, evidence indicated that peripheral inflammatory markers may be related to the emergence of negative symptoms, the clinical dimension associated with worse functioning, and greater therapeutic difficulty [20]. In addition, the Accelerating Medicines Partnership Schizophrenia Program was identified as a relevant initiative to investigate biomarkers in bodily fluids, neuroimaging, cognition, electrophysiology, genetics, and digital markers in individuals at clinical risk for psychosis [4]. This multimodal integration shows a growing trend of moving away from the search for isolated biomarkers and toward combined panels capable of improving the prediction of conversion to psychosis, symptomatic persistence, and functional outcomes.

Metabolomics and proteomics have emerged as promising fields for the identification of molecular signatures in mental disorders. The review on validated metabolomic

biomarkers showed that different metabolites have been investigated in psychiatric disorders, but their clinical application still depends on greater reproducibility, standardization

of laboratory procedures and control of variables

external factors, such as diet, medication use, comorbidities, and lifestyle [6]. In the field of proteomics, a study conducted in young adults identified plasma proteins associated with the general factor of psychopathology, with particular emphasis on pathways related to epidermal growth factor receptor signaling [5]. This finding suggests that peripheral protein markers may reflect transdiagnostic vulnerability or overall symptom burden, although longitudinal studies and validation in larger clinical populations are still needed.

Overall, the results show that neurobiological biomarkers have greater potential when interpreted in an integrated, multimodal way. The analysis of the included studies demonstrated that no single biomarker showed sufficient robustness to replace clinical assessment or establish a definitive psychiatric diagnosis. However, multiple categories of biomarkers have demonstrated potential usefulness for complementing diagnosis, improving prognostic assessment, identifying biological subgroups, predicting therapeutic response, and guiding future strategies for personalized medicine in mental health [1,2,6,7]. This finding

reinforces the need for integrative models that combine clinical, neurobiological, genetic, inflammatory, metabolic, proteomic, electrophysiological, and psychosocial data.

The distribution of the studies also indicates that there is a significant difference between scientific maturity and clinical applicability. Genomic and neuroimaging biomarkers show greater methodological robustness, especially due to the presence of large international consortia and substantial samples [3,8-15]. In in return, biomarkers metabolomic, proteomic, inflammatory and Electrophysiological studies present great translational potential, but they are still in the consolidation phase, requiring replication, external validation, and technical standardization [5-7, 18-20]. Thus, the results suggest that precision psychiatry depends less on identifying a single biomarker and more on building combined models capable of translating multiple biological dimensions into clinically useful information.

translational applicability.

Therefore, the studies included in this review indicate that neurobiological biomarkers represent one of the main frontiers of contemporary psychiatry. Their most promising applications focus on risk stratification, predicting therapeutic response, identifying clinical trajectories, differentiating biological subgroups, and understanding the pathophysiological mechanisms of mental disorders. However, the clinical implementation of these

biomarkers still require caution, as limitations related to specificity, individual predictive validity, diagnostic heterogeneity, population variability, the influence of environmental factors, and the absence of standardized protocols persist. Thus, the results support that the future incorporation of biomarkers in psychiatry should occur in a complementary manner to clinical assessment, preferably through validated, precision-oriented multimodal panels that address

DISCUSSION

The findings of this integrative review demonstrate that neurobiological biomarkers are assuming an increasingly relevant role in contemporary psychiatry, especially in light of the limitations of the diagnostic model based exclusively on symptoms. The literature analyzed indicates that mental disorders cannot be understood only as isolated clinical categories, but as complex conditions, multifactorial and biologically heterogeneous, in which genetic, neuroanatomical, electrophysiological, inflammatory, metabolic, and proteomic factors interact with environmental, psychosocial, and developmental variables [1,2]. This understanding strengthens the transition from a predominantly descriptive psychiatry to a precision psychiatry, guided by the integration between clinical assessment and objective markers.

One of the central points identified was the growing relevance of transdiagnostic models. The genetic overlap observed between different psychiatric disorders reinforces that traditional diagnostic categories, although useful for clinical practice, do not always reflect rigid biological boundaries [3]. This finding is particularly important because symptoms such as cognitive changes, anhedonia, anxiety, impulsivity, social withdrawal, emotional instability, and functional impairment can occur in multiple disorders, making differential diagnosis difficult in the early stages. Thus, genomic, neurofunctional, and peripheral biomarkers may help to identify shared biological dimensions, favoring more individualized approaches that are less dependent on isolated syndromic classifications [1-3].

In the field of genomics, the studies analyzed show that schizophrenia, bipolar disorder, and major depression have complex polygenic architecture, with multiple small-effect variants distributed across the genome [8-11]. In schizophrenia, identifying loci associated with synaptic biology reinforces the role of neuronal processes and communication between brain networks in the disorder's pathophysiology [8]. In bipolar disorder, genomic findings also indicate involvement of pathways related to synaptic signaling and neuronal regulation, suggesting that molecular changes may contribute to mood instability and to vulnerability to the disease's episodic course [9]. In major depression, the identification of variants associated with

prefrontal regions and synaptic functions expand the understanding of the mechanisms related to emotional regulation, cognition, and the stress response [10, 11].

Despite these advances, the clinical application of genomic biomarkers remains limited. Polygenic risk scores have promising value for population-level investigation and stratifying vulnerability, but their individual accuracy is still insufficient for isolated clinical diagnosis. In addition, many genomic studies have historically been conducted in populations of European ancestry, which reduces the generalizability of results to diverse population groups. In this sense, multi-ancestry studies represent an important advance, because they expand the external validity of findings and reduce applicability biases in under-represented populations [11]. For psychiatric practice, this means that genomics should be understood as a tool to support understanding of etiology and risk, and not as an autonomous diagnostic instrument.

Neuroimaging also stood out as one of the most established fields in terms of methodological robustness, especially due to the contribution of large international consortia such as ENIGMA. The findings of cortical alterations in schizophrenia, major depression, and bipolar disorder show that different mental disorders have detectable neuroanatomical signatures at the population level [12-14]. These alterations involve cortical thickness, cortical surface area, white matter integrity, and patterns of brain connectivity, suggesting that psychiatric disorders are associated with changes in brain circuits related to cognition, affect, emotional processing, and functional integration [12-15].

However, the clinical interpretation of these findings requires caution. Although neuroimaging studies reveal statistically significant differences between clinical groups and controls, these alterations do not always have sufficient specificity to distinguish individuals at the diagnostic level. In addition, factors such as age, sex, medication use, duration of illness, comorbidities, symptomatic severity, and episode history may influence imaging results [12-15]. Thus, neuroimaging currently has greater utility as a tool for

translational research and characterization

more than as an isolated diagnostic method in routine clinical practice. Its most promising clinical potential seems to lie in predicting therapeutic response, recurrence, and stratifying subgroups, especially in conditions such as treatment-resistant depression [16, 17].

Predicting therapeutic response is one of the areas with the greatest impact for biomarkers in psychiatry. Clinical practice still often relies on trial-and-error strategies, particularly in the treatment of major depression, in which many patients do not respond adequately to the first treatment regimen. In this context, biomarkers derived from neuroimaging, metabolomics, and electrophysiology can help anticipate which patients are more likely to respond to certain treatments [16-18]. Studies on ketamine in treatment-resistant depression, for example, indicate that changes in brain networks associated with synaptic plasticity and emotional regulation may be related to the rapid antidepressant effects of this treatment [17]. Even so, the heterogeneity of the protocols and the small number of studies with external validation limit its immediate clinical application.

Electrophysiological biomarkers based on EEG present relevant advantages, such as lower cost, wide availability, a non-invasive nature, and high temporal resolution. The review on EEG in depression, anxiety, and bipolar disorder showed that electrophysiological patterns can be used in predictive models, especially when integrated with explainable artificial intelligence techniques [7]. This integration is relevant because artificial intelligence can identify complex patterns not evident in conventional analyses.

However, the clinical applicability of these models depends on algorithm transparency, validation in independent samples, and the definition of interpretable parameters for healthcare professionals. Without these requirements, there is a risk that models that appear accurate in experimental settings may not remain reliable in real clinical contexts [7].

Another important axis discussed in the literature is inflammation. Growing evidence indicates that subgroups of patients with depression and psychosis show inflammatory changes

peripheral, suggesting that immunological processes may contribute to psychiatric manifestations in certain clinical profiles [18-20]. In major depression, the kynurenine pathway represents an important link between inflammation, tryptophan metabolism, glutamatergic neurotransmission, and affective symptoms [18, 19]. A reduction or alteration of metabolites from this pathway may reflect changes in neurochemical balance and response to treatment, indicating potential for biological subtyping of patients with depression—especially those with systemic inflammation or treatment resistance [18, 19].

In first-episode psychosis, the association between inflammatory biomarkers and negative symptoms deserves emphasis, since these symptoms are related to worse social functioning, greater cognitive impairment, and lower therapeutic response [20]. Identifying inflammatory profiles in the early stages of psychosis can contribute to more refined prognostic models, allowing clinicians to recognize patients at higher risk of an unfavorable course. In addition, multicenter programs such as the Accelerating Medicines Partnership Schizophrenia Program indicate a relevant methodological trend: the integration of biomarkers in bodily fluids, neuroimaging, genetics, electrophysiology, cognition, and digital markers to predict conversion to psychosis and functional outcomes [4]. This multidimensional approach seems more suited to the complexity of psychiatric disorders than the search for a single universal marker.

Metabolomics and proteomics broaden this perspective by enabling the identification of molecular signatures associated with psychopathology. Proteomic studies suggest that plasma proteins may be related to the general factor of psychopathology, indicating that some peripheral changes may reflect transdiagnostic vulnerability or the overall burden of symptoms [5]. Similarly, reviews on metabolomics point to candidate metabolites in different psychiatric disorders, although there are still important validation challenges [6]. These challenges include dietary variations, medication use, clinical comorbidities, differences in laboratory processing, the cross-sectional design of studies, and the absence of standardized clinical cut-off points. Therefore, although these markers are promising, their clinical use still depends on replication in cohorts

independent and uniform laboratory protocols.

A transversal aspect across the studies analyzed is that no isolated biomarker showed sufficient robustness to replace clinical assessment in psychiatry. This point is fundamental to avoid reductionist interpretations. Biomarkers should be understood as complementary resources, capable of strengthening clinical reasoning, expanding understanding of pathophysiology, and supporting decisions in specific scenarios, such as complex differential diagnosis, risk of conversion to psychosis, treatment-resistant depression, recurrence, therapeutic response, and biological subtyping [1,2,4,6]. Precision psychiatry, therefore, should not be interpreted as abandoning clinical practice, but as expanding it through objective and integrated data.

The main trend identified in this review is the construction of multimodal panels. Rather than relying on a single marker, future models tend to combine clinical, neuropsychological, genomic,

neuroimaging, EEG, inflammation, metabolomics, proteomics, and digital markers. This combination can increase predictive accuracy and reduce limitations of each marker and enable a more integrated understanding of the patient. However, for these panels to be clinically useful, standardized protocols will need to be established, multicenter validation, reproducibility across populations, cost-effectiveness assessment, and ethical criteria for the use of biological and computational data [1,4,6,7].

From an ethical standpoint, incorporating biomarkers in psychiatry requires special attention. Genetic, neurobiological, and predictive information can affect identity, autonomy, privacy, stigma, and access to care. A risk biomarker, for example, should not be interpreted as an inevitable clinical destiny, but as a probabilistic indicator embedded in a biopsychosocial context. In addition, artificial intelligence algorithms applied to neuroimaging, EEG, or multimodal data must be transparent, auditable, and free of biases that could harm specific population groups. Thus, technological innovation must go hand in hand with ethical responsibility, equity, and patient protection.

The heterogeneity of mental disorders remains one of the

major barriers to validating biomarkers. Patients with the same diagnosis may show very different clinical trajectories, different comorbidities, varying levels of functionality, divergent therapeutic responses, and heterogeneous biological profiles. This variability reduces the specificity of biomarkers and makes it difficult to establish universal cutoff points. Therefore, biomarkers may be more useful when applied to identifying biological subtypes, clinical dimensions, or prognostic trajectories, and not necessarily to categorical diagnostic confirmation. This shift in focus can make the use of biomarkers more realistic and clinically relevant.

The limitations of this review should also be acknowledged. Because this is an integrative review, studies with different methodological designs, levels of evidence, and scientific objectives were included, which expands the scope of the analysis but also increases the heterogeneity of the synthesis. In addition, some emerging fields, such as metabolomics, proteomics, and AI-based EEG, still have more exploratory evidence when compared to the large genomic and neuroimaging. Another limitation refers to the absence of its own quantitative meta-analysis, since the aim of the study was to critically synthesize the available literature and not to calculate combined effect measures.

Despite these limitations, the review provides a relevant contribution by bringing together, in a single analysis, different categories of biomarkers used for the diagnosis and prognosis of mental disorders. The results reinforce that psychiatry is moving toward a more integrated model, in which biological data can help to understand patients' clinical complexity and guide more individualized therapeutic strategies. The main scientific contribution of this study is to show that neurobiological biomarkers should not be assessed in isolation, but as part of a translational ecosystem that connects neuroscience, clinical practice, genetics, technology, immunology, metabolism, and mental health.

Thus, neurobiological biomarkers represent a promising frontier, but one that is still being consolidated. Current evidence supports their potential for risk stratification, biological subtyping, prediction of therapeutic response, and assessment

prognostic, especially when used in multimodal models. However, its clinical incorporation requires rigorous validation, international standardization, longitudinal studies, population diversity, and ethical integration with psychiatric practice. Thus, the future of precision psychiatry will depend on the ability to transform complex neurobiological findings into clinically interpretable, accessible, safe, and effectively useful tools for mental health care.

CONCLUSION

Neurobiological biomarkers represent one of the main frontiers of contemporary psychiatry, especially because they offer possibilities to broaden the diagnostic, prognostic, and therapeutic understanding of mental disorders. This integrative review showed that different categories of biomarkers, including genomic markers, neuroimaging, electrophysiology, inflammation, metabolomics and proteomics are being progressively investigated as complementary tools to traditional clinical assessment. These advances indicate an important transition from a psychiatry essentially based on symptoms to a more integrative, objective, and precision-medicine-oriented model [1,2].

The studies analyzed show that genomic and neuroimaging biomarkers have greater robustness methodological, mainly due to the participation of large international consortia, such as ENIGMA and the Psychiatric Genomics Consortium. These studies showed brain structural changes, genetic overlap between psychiatric disorders, and involvement of synaptic, neuronal, and cortical pathways in conditions such as schizophrenia, major depression, and bipolar disorder [3,8-15]. Such findings contribute to understanding the neurobiological basis of mental disorders and reinforce the need for transdiagnostic models, capable of recognizing shared biological mechanisms across different clinical categories.

Also, electrophysiological biomarkers, inflammatory, metabolomic and proteomic studies have shown high translational potential, especially for biological subtyping, clinical monitoring,

risk stratification and prediction of therapeutic response [5-7, 18-20]. The kynurenine pathway, peripheral inflammatory markers, plasma proteomic signatures, and patterns derived from EEG emerge as promising areas for building more individualized care models in mental health. However, these markers still depend on greater methodological standardization, replication in different populations, external validation, and the definition of clinically applicable cutoff points.

The analysis of the studies also showed that no isolated biomarker, to date, has sufficient validity to replace clinical assessment in psychiatry. The complexity of mental disorders requires a multimodal approach, in which biological data are interpreted together with clinical history, psychopathological examination, functioning, psychosocial context, comorbidities, medication use, and the patient's individual trajectory. Thus, biomarkers should be understood as complementary tools, capable of strengthening clinical reasoning and not replacing listening, diagnostic assessment, and longitudinal follow-up.

It follows that the future incorporation of neurobiological biomarkers into psychiatric practice will depend on the consolidation of integrated panels, combining genomics, neuroimaging, EEG, inflammation, metabolomics, proteomics, clinical data, and possibly tools for explainable artificial intelligence. For this translational process to occur safely and effectively, longitudinal studies will be needed, multicenter, methodologically standardized and representative of diverse populations. Thus, neurobiological biomarkers should not be seen as a definitive and isolated solution to the diagnostic challenges of psychiatry, but as strategic components of a new scientific stage, aimed at precision, personalization therapeutics, for early identification of risk and improved clinical outcomes in mental health.

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