

Review Article

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Energy Metabolism in Psychiatric Disorders: An Integrated Approach between Family and Community Medicine, Psychiatry, and Psychology

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Abstract

Psychiatric disorders have a multifactorial etiology and have increasingly been associated with metabolic and bioenergetic changes that go beyond traditional models focused exclusively on neurotransmission. The aim of this study was to analyze the relationships between energy metabolism and psychiatric disorders, emphasizing the main biochemical mechanisms involved and their potential diagnostic, prognostic, and therapeutic implications in primary and secondary health care. An integrative literature review was conducted, covering publications from 2021 to 2026, retrieved from the PubMed/MEDLINE, Scopus, Web of Science, PsycINFO, and SciELO databases. Evidence was analyzed primarily related to major depressive disorder, bipolar disorder, and schizophrenia. The results demonstrated that alterations in mitochondrial function, oxidative phosphorylation, ATP production, glucose and lipid metabolism, oxidative stress, neuroinflammation, immunometabolism, and insulin resistance are associated with the disorders under investigation. Mitochondrial dysfunction emerged as a possible transdiagnostic mechanism, interacting with reactive oxygen species, inflammatory processes, and alterations in neuronal plasticity. Metabolomics has shown potential for identifying biomarkers and characterizing biological phenotypes, although its clinical application still depends on further standardization and validation. Strategies targeting energy metabolism-including nutritional interventions, antioxidants, mitochondrial modulators, and metabolic therapies-have shown promising, though still heterogeneous, results. It was concluded that energy metabolism constitutes a relevant component in the contemporary understanding of psychiatric disorders and that its integration into care may facilitate more individualized approaches. The coordination between primary and secondary care has proven to be fundamental for the screening and management of cardiometabolic changes, monitoring the effects of psychotropic medications, and promoting comprehensive mental health care.

Keywords: Energy Metabolism, Mental Disorders, Mitochondria, Oxidative Stress, Neuroinflammation, Psychiatry

1. Introduction

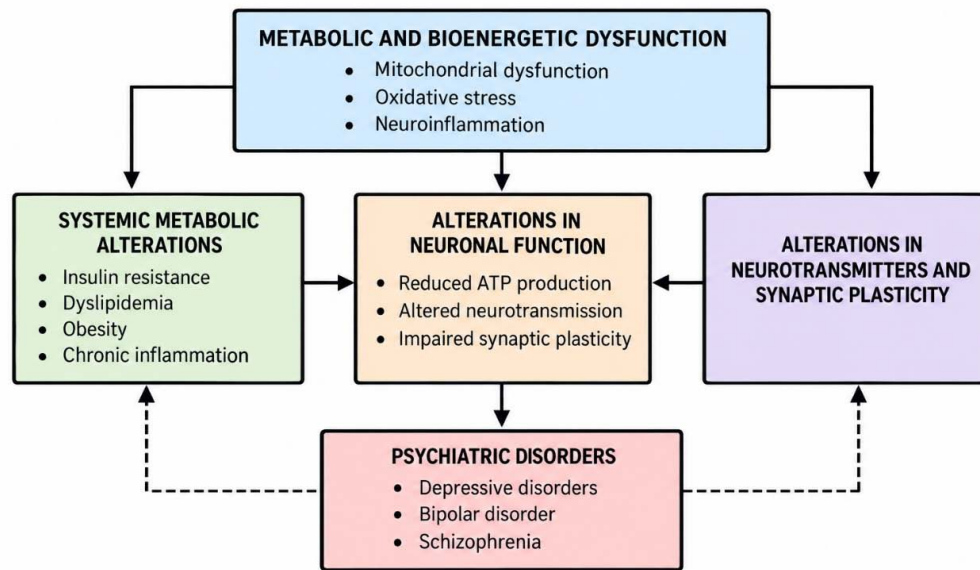
Psychiatric disorders represent a heterogeneous group of clinical conditions associated with changes in mood, cognition, behavior, and overall functioning, often accompanied by systemic repercussions. In recent years, our understanding of their pathophysiology has moved beyond models based exclusively on neurotransmitters, incorporating mechanisms related to cerebral bioenergetics, mitochondrial function, glucose and lipid metabolism, inflammation, oxidative stress, and alterations in metabolic signaling. In this context, energy metabolism has come to occupy a central position in research into the biological basis of depression, bipolar disorder, and schizophrenia [1-3].

The brain has high energy demands and relies on a continuous supply of metabolic substrates to maintain membrane potential, synaptic transmission, neurotransmitter synthesis, neuronal plasticity, and cognitive processes. ATP is generated predominantly through mitochondrial oxidative phosphorylation, although glycolysis, lactate metabolism, the tricarboxylic acid cycle, and

fatty acid oxidation also contribute to the maintenance of energy homeostasis. Alterations in any of these pathways can compromise neuronal activity and modify circuits related to mood, motivation, reward, and cognition [3,4].

Recent evidence has shown that psychiatric disorders may be associated with a complex interplay between alterations in brain energy metabolism, mitochondrial dysfunction, oxidative stress, and neuroinflammatory processes. These mechanisms can impair energy production and utilization, alter neurotransmission and synaptic plasticity, and establish bidirectional relationships with systemic metabolic changes, such as insulin resistance, obesity, dyslipidemia, and inflammation.

In this context, Figure 1 schematically illustrates the integration among the main bioenergetic and metabolic mechanisms potentially related to major depression, bipolar disorder, and schizophrenia [3,5,6].



Source: Prepared by the authors.

Figure 1: Integration between Metabolic Dysfunction, Bioenergetic Alterations, and Psychiatric Disorders

According to alterations in brain energy metabolism are observed in various models of psychiatric disorders, suggesting that bioenergetic dysfunction is not a phenomenon restricted to a single diagnosis [1]. This transdiagnostic perspective is particularly relevant because mitochondrial alterations, reduced respiratory chain efficiency, inadequate ATP production, and increased generation of reactive oxygen species have been described in conditions such as major depression, bipolar disorder, and schizophrenia. Such alterations may result from both genetic predisposition and chronic exposure to stress, systemic inflammation, hormonal changes, lifestyle factors, and metabolic effects related to pharmacological treatment [7,8].

Mitochondria, in addition to their classic role in energy production, are involved in the regulation of apoptosis, intracellular signaling, calcium homeostasis, amino acid metabolism, and the control of reactive oxygen species production. For this reason, mitochondrial dysfunction has been identified as a possible link between metabolic changes and neuropsychiatric manifestations.

In bipolar disorder, recent studies describe disturbances in oxidative phosphorylation, mitochondrial dynamics, and redox balance, with a potential influence on the recurrence of mood episodes and disease progression [9-12].

Figure 2 provides a schematic representation of the progression from metabolic and bioenergetic dysfunction to cellular and neuronal alterations potentially associated with psychiatric disorders. Mitochondrial dysfunction, impaired oxidative phosphorylation, oxidative stress, neuroinflammation, and disturbances in glucose and lipid metabolism may compromise ATP production, neurotransmission, synaptic plasticity, and neuronal circuits involved in mood, motivation, reward, and cognition. These mechanisms are further influenced by systemic and environmental factors, including insulin resistance, dyslipidemia, obesity, chronic inflammation, hormonal changes, lifestyle factors, and pharmacological treatments, highlighting the complex interplay between metabolic homeostasis and the pathophysiology of major depressive disorder, bipolar disorder, and schizophrenia (Figure 2).

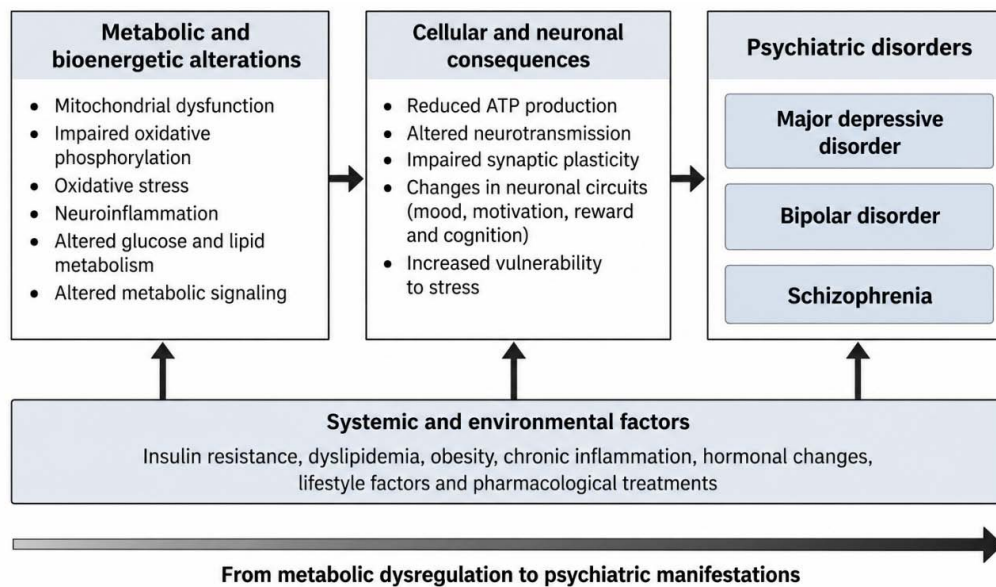


Figure 2: Integration between Metabolic and Bioenergetic Alterations, Cellular and Neuronal Consequences, and Psychiatric Disorders

In schizophrenia, in turn, bioenergetic alterations have been identified in postmortem studies, molecular analyses, metabolomic studies, and investigations of peripheral biomarkers. Highlights evidence of mitochondrial abnormalities in different brain regions, while propose that schizophrenia may involve significant impairment of brain bioenergetics [7,13]. More recently, the interaction between mitochondrial function, inflammation, and cognitive impairment has also come to be considered relevant in explaining some of the neurobiological changes observed in these individuals [14].

Major depression also shows a growing association with metabolic and immunological changes. Highlight that oxidative stress may interact with neuroinflammation, serotonergic metabolism, neurogenesis, and synaptic plasticity [15]. At the same time, metabolomic studies demonstrate alterations in amino acids, lipids, acylcarnitines, and other metabolites linked to energy production and utilization, suggesting that subgroups of individuals with depression may exhibit distinct metabolic phenotypes [16-18].

In this context, the concept of immunometabolism has become particularly important. Immune cells alter their metabolic profile during inflammatory processes, increasing, under certain circumstances, their reliance on glycolysis and altering the consumption of energy substrates. These responses may contribute to systemic and brain- y changes observed in psychiatric disorders. Highlights the potential relationship between glycolytic metabolism, immune activation, and depressive symptoms, while recent studies on immunometabolic depression point to the coexistence of inflammation, insulin resistance, increased adiposity, and lipid abnormalities in certain subgroups of patients [19].

Insulin resistance represents another mechanism of growing interest. Although classically associated with type 2 diabetes mellitus, insulin signaling also plays a role in the central nervous system related to energy metabolism, synaptic plasticity, and cognition.

Alterations in this signaling may contribute to impaired brain metabolism and increased vulnerability to psychiatric manifestations. At the same time, individuals with severe mental disorders have a higher prevalence of obesity, dyslipidemia, insulin resistance, and metabolic syndrome—conditions that may result from the disorder itself, behavioral factors, and the effects of certain psychotropic medications [20-22].

Advances in metabolomics have significantly contributed to our understanding of these relationships. By simultaneously identifying a large number of metabolites, this approach allows for the investigation of biochemical patterns associated with different disorders, clinical stages, and therapeutic responses.

Recent studies have identified metabolic signatures that may be useful in distinguishing between unipolar and bipolar depression, in evaluating patients with a first psychotic episode, and in studying the different phases of bipolar disorder [23-25].

Metabolomics may therefore contribute in the future to precision psychiatry strategies, although its routine clinical application still depends on further standardization and external validation.

Another emerging area is the interaction between the gut microbiota and brain metabolism. Metabolites produced or modulated by the microbiota can influence inflammatory pathways, neurotransmitter production, intestinal barrier integrity, and the availability of energy substrates.

Recent evidence links changes in the microbiota-gut-brain axis to metabolic alterations in individuals with depression and other psychiatric disorders, reinforcing the hypothesis that metabolic balance and system s can exert a significant influence on brain function [26-28].

The incorporation of these mechanisms has also expanded therapeutic possibilities. Strategies aimed at modulating mitochondrial function, reducing oxidative stress, controlling inflammation, and improving metabolic health are being investigated as adjuncts to conventional psychiatric treatment. These include N-acetylcysteine, coenzyme Q10, nutritional interventions, management of insulin resistance, GLP-1 receptor agonists, and dietary approaches capable of modifying the availability of energy substrates [29-31].

Particular attention has been directed toward ketogenic interventions. By modifying cerebral glucose utilization and increasing the availability of ketone bodies as an energy source, the ketogenic diet may exert effects on mitochondrial function, redox balance, cellular signaling, and neurotransmission. Recent reviews and clinical studies have investigated this strategy in depression, bipolar disorder, schizophrenia, and other severe mental disorders, although its use should be considered with caution given the need for adequate clinical and nutritional monitoring [32-36].

This evidence also has implications for the organization of mental health care. In primary care, the follow-up of patients with psychiatric disorders offers an opportunity for the early identification of obesity, hypertension, dyslipidemia, glycemic abnormalities, physical inactivity, and other factors that can exacerbate both cardiometabolic risk and the progression of the psychiatric condition. In secondary care, specialized follow-up allows for the integration of psychopathological assessment, monitoring of the metabolic effects of psychotropic medications, and the use of individualized therapeutic strategies, promoting a collaborative approach among psychiatry, internal medicine, family medicine, nutrition, and other fields.

Thus, understanding psychiatric disorders from a metabolic perspective does not imply replacing traditional neurochemical and psychosocial models, but rather broadening their interpretation by including bioenergetic, immun , and systemic mechanisms. The integration of brain energy metabolism, mitochondrial function, oxidative stress, inflammation, insulin resistance, metabolomics, and new therapeutic interventions can contribute to a more comprehensive view of pathophysiology and support individualized care strategies in primary and secondary care.

Given this scenario, it is important to critically synthesize the current evidence on the relationship between energy metabolism and psychiatric disorders, identifying the main biochemical mechanisms involved and analyzing their potential diagnostic and therapeutic implications. This approach can facilitate both a deeper understanding of the pathophysiology and the development of strategies for prevention, metabolic monitoring, and integrated

treatment of affected individuals.

2. Background

Psychiatric disorders constitute a major public health problem due to their high prevalence, recurrence, associated disability, and impact on the quality of life of individuals and their families.

Although traditional models have emphasized alterations in the monoaminergic, glutamatergic, and dopaminergic systems, contemporary evidence demonstrates that these mechanisms alone do not explain clinical heterogeneity, variability in therapeutic response, and the frequent association between mental disorders and metabolic alterations.

The investigation of brain energy metabolism thus emerges as a complementary approach to understanding the pathophysiology of depression, bipolar disorder, and schizophrenia [1,2,8].

This review is therefore warranted by the need to compile recent evidence on the biochemical mechanisms linking energy metabolism and psychiatric disorders, as well as to assess their diagnostic and therapeutic implications. A synthesis of this information may contribute to broadening the pathophysiological understanding of these conditions and support integrated clinical strategies between primary and secondary care.

3. Objectives

3.1. General Objective

To analyze, based on the scientific literature published between 2021 and 2026, the relationships between energy metabolism and psychiatric disorders, emphasizing the main biochemical mechanisms involved and their potential diagnostic, prognostic, and therapeutic implications in the context of primary and secondary health care.

3.2. Specific Objectives

- i. To describe the main pathways of cerebral energy metabolism involved in maintaining neuronal function and their possible role in the pathophysiology of psychiatric disorders.
- ii. Analyze the role of **mitochondrial dysfunction, alterations in oxidative phosphorylation, and reduced bioenergetic efficiency** in major depression, bipolar disorder, and schizophrenia.
- iii. To investigate the interaction between energy metabolism, **oxidative stress, and neuroinflammation** in psychiatric disorders.
- iv. To examine the influence of alterations in glucose metabolism, insulin resistance, lipid metabolism, and metabolic syndrome on mental health.
- v. To identify metabolomic alterations and potential **metabolic biomarkers** associated with different psychiatric disorders and their respective therapeutic responses.
- vi. To evaluate the possible role of the **microbiota-gut-brain** axis in modulating energy metabolism and the neuroimmune response.
- vii. Examine the metabolic effects associated with the use of psychotropic medications and their implications for clinical management.
- viii. To synthesize recent evidence regarding therapeutic strategies

capable of modifying metabolic pathways, including nutritional interventions, antioxidants, mitochondrial modulators, and emerging metabolic therapies.

ix. To discuss the role of **primary and secondary care** in the identification, prevention, and integrated management of metabolic abnormalities in individuals with psychiatric disorders.

x. Identify gaps in knowledge and future prospects for the development of **metabolic and precision psychiatry**.

4. Methodology

4.1. Study Design

This study was conducted as an integrative literature review, of a descriptive and analytical nature, with the purpose of gathering, analyzing, and synthesizing recent scientific evidence regarding energy metabolism, the biochemical mechanisms involved, and their possible therapeutic implications in psychiatric disorders.

The review was guided by the following research question: “What are the main alterations in energy metabolism described in psychiatric disorders, and what are their biochemical, clinical, and therapeutic implications for primary and secondary health care?”

An integrative approach was chosen because it allows for the analysis of different research designs, including observational studies, clinical trials, experimental studies, systematic reviews, meta-analyses, and metabolomic studies. This strategy enabled a comprehensive evaluation of the evidence related to cerebral bioenergetics and psychiatric disorders.

4.2. Databases and Search Period

The literature search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, PsycINFO, and SciELO databases, selected for their scope and relevance to the fields of psychiatry, neuroscience, biochemistry, and health sciences.

Studies published between January 2021 and August 2026 were considered, thereby prioritizing contemporary scientific evidence related to energy metabolism and psychiatric disorders.

In addition, the reference lists of the selected studies were examined to identify potentially relevant publications not initially retrieved by the electronic search strategies, provided they fell within the established time frame and met the other eligibility criteria.

4.3. Search Strategy

The search strategy was developed by combining controlled subject headings from Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS), supplemented by free-text terms related to the main thematic components of the review.

The following terms were used, either individually or in various combinations: “Energy Metabolism,” “Brain Energy Metabolism,” “Mitochondria,” “Mitochondrial Dysfunction,” “Oxidative Phosphorylation,” “Oxidative Stress,” “Reactive Oxygen Species,” “Glucose Metabolism,” “Insulin Resistance,” “Metabolomics,” “Neuroinflammation,” “Immunometabolism,”

“Depressive Disorder,” “Major Depressive Disorder,” “Bipolar Disorder,” “Schizophrenia,” “Mental Disorders,” “Metabolic Syndrome,” “Biomarkers,” and “Metabolic Therapy.”

The subject headings were combined using the Boolean operators AND and OR, in accordance with the specific indexing conventions of each database consulted.

As a baseline strategy, a combination similar to the following was used:

("Energy Metabolism" OR "Brain Energy Metabolism" OR "Mitochondrial Dysfunction" OR Mitochondria OR "Oxidative Phosphorylation" OR "Glucose Metabolism" OR Metabolomics OR Immunometabolism) AND ("Mental Disorders" OR "Major Depressive Disorder" OR "Bipolar Disorder" OR Schizophrenia).

Supplementary searches were conducted using terms related to oxidative stress, neuroinflammation, insulin resistance, metabolic syndrome, the gut-brain axis, biomarkers, and metabolic therapies, with the aim of increasing the strategy’s sensitivity and addressing the various established objectives.

4.4. Inclusion Criteria

Studies published between 2021 and 2026, available in Portuguese, English, or Spanish, and published in peer-reviewed scientific journals were included.

Studies involving psychiatric disorders-particularly major depressive disorder, bipolar disorder, and schizophrenia-that investigated aspects related to energy metabolism, mitochondrial function, glycolysis, oxidative phosphorylation, lipid metabolism, glucose metabolism, insulin resistance, oxidative stress, neuroinflammation, immunometabolism, metabolomics, and related biochemical mechanisms.

Also included were studies that evaluated metabolic biomarkers, the metabolic effects of psychotropic medications, and therapeutic strategies targeting bioenergetic pathways, provided they were directly related to the objectives of the review.

4.5. Exclusion Criteria

Publications prior to 2021, editorials, letters to the editor, commentaries, news articles, conference abstracts without full-text publication, and documents lacking sufficient information for analysis were excluded.

Also excluded were studies exclusively related to neurological diseases without an association with psychiatric disorders, studies whose metabolic focus was unrelated to psychiatric manifestations, duplicate publications, and articles that did not address the guiding question or the established objectives.

In cases where different publications used the same population or database, the characteristics of the studies were analyzed to avoid undue duplication of evidence.

4.6. Study Selection Process

The records retrieved from electronic databases were initially organized and screened to identify and remove duplicates. Subsequently, the titles and abstracts were reviewed for a preliminary assessment of thematic relevance.

Studies considered potentially eligible were reviewed in full text. At this stage, compliance with the previously established inclusion and exclusion criteria was verified, as well as the relationship between the presented results and the review's objectives. Upon completion of this process, the studies that constituted the body of evidence used in the qualitative synthesis were selected.

Note for the manuscript: the numbers referring to identified records, removed duplicates, excluded articles, and included studies should be included only if they correspond to the search actually conducted. It is not appropriate to create values retrospectively.

4.7. Data Extraction and Organization

After selection, the studies were analyzed individually, and relevant information was extracted using a standardized instrument developed for this review.

The following data were collected: authors, year of publication, country of origin, study design, characteristics of the population or experimental model, psychiatric disorder investigated, metabolic mechanism evaluated, biomarkers studied, intervention performed when applicable, main results, limitations, and clinical implications.

Subsequently, the evidence was organized according to the main thematic areas identified:

- Axis 1:** Brain bioenergetics and energy metabolism;
- Axis 2:** mitochondrial dysfunction and oxidative phosphorylation;
- Axis 3:** oxidative stress and neuroinflammation;
- Axis 4:** glucose metabolism, insulin resistance, and metabolic syndrome;
- Axis 5:** metabolomics and biomarkers;
- Axis 6:** Metabolic changes in depression, bipolar disorder, and schizophrenia;
- Axis 7:** microbiota, metabolism, and the gut-brain axis;
- Axis 8:** Psychotropic medications and metabolic effects;
- Axis 9:** metabolic therapeutic approaches; and
- Axis 10:** Implications for primary and secondary health care.

This organizational framework made it possible to relate the findings to the specific objectives established for the study.

4.8. Synthesis and Analysis of the Evidence

The extracted data were subjected to narrative synthesis and thematic analysis, taking into account the heterogeneity of the study designs, populations, psychiatric disorders, biomarkers, and interventions identified.

Convergent and divergent findings were compared, allowing for the identification of recurring biochemical mechanisms and possible

relationships between mitochondrial dysfunction, alterations in ATP production, oxidative stress, neuroinflammation, glucose metabolism, insulin resistance, lipid abnormalities, and psychiatric manifestations.

Evidence related to metabolomics and biomarkers was also analyzed, as well as interventions capable of modifying energy metabolism and their possible clinical implications.

When interpreting the results, we distinguished between association and causality, taking care not to attribute a causal nature to metabolic changes identified exclusively in observational or cross-sectional studies.

4.9. Ethical Considerations

Since this is a literature review based exclusively on information from previously published studies, without direct human participation, collection of biological material, or use of individually identifiable data, there was no need to submit it to the Research Ethics Committee.

The principles of scientific integrity, methodological transparency, and proper citation of sources were respected.

5. Results

Analysis of the selected publications revealed that the relationship between energy metabolism and psychiatric disorders has been investigated from various perspectives, ranging from molecular and mitochondrial alterations to systemic repercussions and therapeutic possibilities. In general, the studies pointed to an interaction between mitochondrial dysfunction, alterations in ATP production, oxidative stress, neuroinflammation, carbohydrate and lipid metabolism, insulin resistance, and metabolomic alterations, although the magnitude and direction of these alterations varied depending on the disorder, clinical stage, treatment, and methodology used [1-3].

The findings also demonstrated that these changes were not restricted to a single diagnosis. Major depression, bipolar disorder, and schizophrenia shared different components of bioenergetic impairment, supporting a partially transdiagnostic interpretation of metabolic mechanisms. At the same time, disorder-specific features were identified, along with emerging evidence regarding biomarkers, metabolomics, and metabolism-targeted interventions.

5.1. General Characterization and Overview of the Evidence

The studies analyzed exhibited methodological diversity, including systematic reviews, meta-analyses, observational studies, metabolomic investigations, experimental research, and clinical trials. This heterogeneity made it possible to evaluate energy metabolism from its molecular mechanisms to its clinical and therapeutic implications.

The literature published during the analyzed period showed a progressive increase in interest in so-called metabolic psychiatry, especially following the identification of mitochondrial and

metabolomic alterations in various disorders. Highlighted the role of cerebral energy metabolism in models of depression, bipolar disorder, and schizophrenia [1].

cognition [2,8].

Subsequent studies delved deeper into the investigation of mitochondrial alterations and their possible consequences on neurotransmission, neuronal plasticity, inflammation, and

To organize the main findings and facilitate their relationship to the proposed objectives, Table 1 presents a representative summary of the studies that addressed the key metabolic mechanisms investigated.

Author	Disorder/Axis	Aspect Investigated	Key findings
Kolar et al. (2021) [1]	Transdiagnostic	Brain energy metabolism	Bioenergetic changes have been linked to different models of psychiatric disorders.
Roberts (2021) [7]	Schizophrenia	Mitochondrial function	Postmortem evidence has indicated mitochondrial alterations in brain regions associated with schizophrenia.
Scaini et al. (2021) [9]	Bipolar disorder	Mitochondrial dysfunction	Mitochondrial alterations have been associated with the pathophysiology and progression of bipolar disorder.
Costa et al. (2022) [16]	Major depression	Metabolomics	Metabolic alterations potentially related to the pathophysiology of depression were identified.
Henkel et al. (2022) [13]	Schizophrenia	Cerebral Bioenergetics	The authors identified bioenergetic impairment as a relevant component of the disease.
Liang et al. (2022) [37]	Bipolar disorder	Mitochondrial modulation	Strategies targeting mitochondrial function showed therapeutic potential in bipolar depression.
Büttiker et al. (2023) [2]	Transdiagnostic	Mitochondria and Energy	Dysfunctional mitochondrial processes have been linked to energy imbalance and neuropsychiatric symptoms.
Correia et al. (2023) [15]	Depression	Oxidative stress	Oxidative stress has been shown to interact with neuroinflammation, sero , and neuronal plasticity.
Lam et al. (2023) [11]	Bipolar disorder	Mitochondria	Mitochondrial alterations have been linked to pathophysiology and potential therapeutic targets.
Song et al. (2023) [23]	Schizophrenia	Metabolomics	Metabolic profiles potentially useful as biomarkers were identified.
Rae et al. (2024) [3]	Cerebral Bioenergetics	Energy metabolism	Key mechanisms of brain energy production and utilization were systematized.
Tomasik et al. (2024) [24]	Depression	Biomarkers	Metabolomic signatures have shown potential for distinguishing between bipolar and unipolar depression.
Sethi et al. (2024) [33]	Bipolar Disorder/ Schizophrenia	Metabolic therapy	A ketogenic intervention showed preliminarily favorable metabolic and psychiatric results .
Giménez-Palomo et al. (2024) [24]	Bipolar disorder	Mitochondrial biomarkers	Mitochondrial dysfunction showed a potential association with different disease states.
Singh et al. (2025) [18]	Depression	Metabolomics	Changes in various metabolic pathways have been linked to depressive disorder.
Xia et al. (2025) [38]	Depression	Mitochondrial dysfunction	Mitochondrial mechanisms have been associated with depression and considered potential therapeutic targets.
Wang et al. (2025) [28]	Schizophrenia	Mitochondria/inflammation	The interaction between mitochondrial dysfunction and inflammation has been linked to cognitive impairment.
Miedlich and Lamberti (2025) [22]	Transdiagnostic	Psychotropic Drugs/ Metabolism	Antipsychotics and antidepressants have clinically relevant metabolic effects.

Source: Prepared by the authors based on the studies included in the review (2021–2025).

Table 1: Summary of the Main Studies Related to Energy Metabolism in Psychiatric Disorders

The summary presented in Table 1 demonstrated that energy dysfunction has been investigated at different biological levels.

While early studies focused primarily on mitochondrial function and oxidative stress, more recent studies have incorporated metabolomics, immunometabolism, the microbiota, and metabolic interventions.

This shift indicated an expansion of the pathophysiological model, in which energy alterations came to be understood as part of a network involving cellular and systemic mechanisms.

5.2. Brain Bioenergetics, Mitochondrial Function, and Oxidative Phosphorylation

Mitochondrial function was one of the most frequently reported findings in the analyzed literature. The evidence indicated alterations in the electron transport chain, oxidative phosphorylation, ATP production, redox balance, and mitochondrial dynamics. As a result, the neuron’s ability to respond adequately to energy demands may be compromised, especially in brain circuits characterized by high synaptic activity [1,2,9].

In bipolar disorder identified mitochondrial dysfunction as a relevant component of the pathophysiology, while highlighted alterations related to energy production, oxidative stress, and mitochondrial dynamics [9,11]. Added that markers related to mitochondrial function may vary depending on the clinical stage of the disease, although methodological heterogeneity still limits their use as established clinical biomarkers [12].

In schizophrenia, demonstrated that postmortem studies provided evidence of mitochondrial alterations in different brain regions [7]. Expanded on this interpretation by describing schizophrenia from the perspective of impaired brain bioenergetics [13]. More recently, linked mitochondrial dysfunction, inflammation, and cognitive alterations, indicating a possible interaction between energy metabolism and the clinical manifestations of the disease [14].

In depression, alterations in mitochondrial function have also been observed.

Compiled evidence linking mitochondrial impairment to the pathophysiology of depression and highlighted various mechanisms potentially involved, including alterations in energy production, increased reactive oxygen species, and impairment of ATP-dependent cellular processes [38].

Table 2 summarizes the main bioenergetic mechanisms identified and their possible psychiatric implications.

Alteration	Biochemical mechanism	Possible Implication
Reduced mitochondrial efficiency	Reduced energy production capacity	Neuronal vulnerability and altered synaptic function
Altered oxidative phosphorylation	Impairment of the respiratory chain	Reduced efficiency in ATP generation
Increased ROS	Imbalance between oxidative production and antioxidant defense	Cellular oxidative damage
Altered mitochondrial dynamics	Imbalance between fusion and fission	Impaired mitochondrial maintenance
Altered calcium homeostasis	Mitochondrial signaling dysfunction	Altered excitability and neurotransmission
Altered glycolytic metabolism	Changes in glucose utilization	Reduced metabolic flexibility
Alterations in the tricarboxylic acid cycle	Changes in metabolic intermediates	Effects on energy and metabolite synthesis
Alteration of acylcarnitines	Alterations in fatty acid transport and oxidation	Potential marker of metabolic dysfunction

Source: Prepared by the authors based on [1-3,7,9,38].

Table 2: Bioenergetic Alterations and Possible Implications for Psychiatric Disorders

The data in Table 2 showed that bioenergetic impairment does not depend on a single pathway. Rather, the studies indicated interconnected changes involving ATP production, oxidative balance, glucose utilization, lipid metabolism, and mitochondrial signaling. Thus, mitochondrial dysfunction emerged as a possible point of convergence among the different mechanisms described in psychiatric disorders.

5.3. Oxidative Stress, Neuroinflammation, and Immunometabolism

The interaction between energy metabolism and the immuno-inflammatory response constituted another recurring theme. Increased production of reactive oxygen species, coupled with reduced antioxidant capacity, can promote protein and lipid oxidation, membrane alterations, and damage to mitochondrial

DNA. At the same time, the activation of inflammatory mechanisms can alter cellular utilization of energy substrates, creating a bidirectional relationship between metabolism and inflammation [15,39].

Linked oxidative stress in depression to mechanisms involving stress response, neuroinflammation, serotonin, neurogenesis, and synaptic plasticity [15]. In turn, highlighted the importance of glycolysis in the functioning of immune cells and its possible relationship with depressive symptoms, reinforcing the concept of immunometabolism [19].

In schizophrenia, the relationship between inflammation and bioenergetics has also been observed. Indicated that the interaction between mitochondrial dysfunction and inflammatory processes

may contribute to cognitive impairment [14]. In bipolar disorder, alterations in the oxidative balance have also been described, including increased ROS production and changes in antioxidant mechanisms [40].

The results thus suggested a possible feedback loop in which mitochondrial dysfunction → increased ROS → inflammatory activation → altered cellular metabolism → further mitochondrial impairment.

However, the predominance of observational and experimental studies has prevented establishing that this sequence occurs uniformly or causally in all individuals.

5.4. Glucose Metabolism, Insulin Resistance, and Systemic Repercussions

The analysis also demonstrated a significant association between psychiatric disorders and alterations in systemic metabolism. Insulin resistance, obesity, dyslipidemia, and metabolic syndrome have been frequently reported, particularly in individuals with severe mental disorders and in those undergoing prolonged use of certain psychotropic medications [20,21].

Insulin resistance was of particular relevance because insulin signaling also plays a role in the central nervous system. Alterations in this pathway can influence cerebral glucose utilization, synaptic plasticity, and cognition. The studies analyzed thus suggested a connection between peripheral metabolism and brain function, although it remains difficult to determine how much of these changes stems directly from the psychiatric disorder and how much is influenced by treatment, diet, physical inactivity, and body composition.

Psychotropic medications represented an additional factor in this interaction. Highlighted metabolic effects associated with antipsychotics and antidepressants, reinforcing the need for cardiometabolic monitoring during treatment [22]. In schizophrenia, this issue has proven particularly relevant due to the association between second-generation antipsychotics, weight gain, and glycemic and metabolic changes.

These findings underscored the need to view metabolic health as an integral part of psychiatric care, rather than merely as an independent comorbidity.

5.5. Metabolomics and Precision Biomarkers

Metabolomics has emerged as one of the areas of greatest recent development. Identified alterations in various metabolites in major depression, while demonstrated the applicability of this approach in investigating the biology of schizophrenia [16,41].

Subsequent studies have expanded the potential for using these profiles as biomarkers. Identified plasma panels potentially associated with the first episode of schizophrenia and with monitoring antipsychotic treatment [23]. In turn, demonstrated the potential of metabolomic signatures in distinguishing between bipolar and unipolar depression [24].

In bipolar disorder, compared metabolic pathways across different clinical phases, indicating that the metabolic profile may undergo changes related to the disease state [25]. Changes in amino acids, lipids, acylcarnitines, and energy pathway intermediates have been found in various studies, although no single, sufficiently validated marker has been identified for routine diagnostic use.

Thus, the results demonstrated that metabolomics holds great potential for precision psychiatry but remains predominantly in the research phase. The heterogeneity of analytical platforms, populations, and sample collection conditions still poses a significant obstacle to direct comparison and the clinical implementation of biomarkers.

5.6. Therapeutic Approaches Targeting Energy Metabolism

In addition to pathophysiological mechanisms, the reviewed literature showed growing interest in interventions capable of modifying energy metabolism. Strategies related to mitochondrial function, xidants, nutritional interventions, and approaches aimed at improving the systemic metabolic profile were investigated.

Analyzed mitochondrial modulators in the treatment of bipolar depression, while investigated evidence regarding N-acetylcysteine [29,38]. Subsequent studies expanded the focus on metabolic interventions capable of simultaneously addressing physical health and psychiatric symptoms.

Among these strategies, ketogenic interventions have received increasing attention. evaluated a dietary intervention in individuals with bipolar disorder and schizophrenia and identified favorable preliminary results regarding metabolic and psychiatric parameters [33]. Subsequent reviews also indicated therapeutic potential, although they highlighted limitations related to the small number of controlled studies, small sample sizes, adherence, and the need for clinical and nutritional follow-up [34-36].

Another emerging perspective involved interventions targeting metabolic complications induced by psychotropic medications. Evaluated GLP-1 receptor agonists in the context of mental health and metabolic disorders associated with psychotropic medications, pointing to an expanding therapeutic field [31].

Strategy	Main Target	Possible application
N-acetylcysteine	Oxidative stress/glutathione	Adjuvant in mood disorders
Mitochondrial modulators	Bioenergetic function	Research primarily on bipolar disorder
Coenzyme Q10	Respiratory chain/antioxidant	Experimental adjunctive strategy

Ketogenic diet	Use of ketone bodies	Depression, bipolar disorder, and schizophrenia
Nutritional interventions	Systemic metabolic health	Prevention and Management of Cardiometabolic Factors
Metformin	Insulin resistance/weight	Metabolic changes related to antipsychotics
GLP-1 agonists	Weight, blood glucose, and metabolic signaling	Metabolic complications associated with psychotropic medications
Physical activity	Systemic and mitochondrial metabolism	Complementary and Preventive Strategies
Metabolic monitoring	Early identification of abnormalities	Applicable to primary and secondary care

Source: Prepared by the authors based on the studies included in the review.

Table 3: Key metabolic Strategies Identified in the Literature

Table 3 demonstrated that therapeutic approaches encompassed both strategies potentially targeting bioenergetic mechanisms and interventions aimed at reducing cardiometabolic risk. However, the strength of the evidence varied among the approaches, making it inappropriate to consider all these strategies as established psychiatric treatments. The results were more consistent in supporting the importance of integrated metabolic management, while several specifically bioenergetic therapies remained experimental.

5.7. Integration of Findings and Implications for Primary and Secondary Care

A joint analysis of the evidence allowed us to develop an integrative model in which genetic, environmental, behavioral, and pharmacological factors can modify systemic and brain metabolism. Changes in glucose utilization, mitochondrial function, and ATP production may interact with oxidative stress and inflammatory mechanisms, affecting neurotransmission, neuronal plasticity, and the functioning of brain circuits.

In this model, the relationship was bidirectional. Psychiatric disorders and their determinants may contribute to metabolic

changes, while obesity, insulin resistance, dyslipidemia, inflammation, and other systemic changes may potentially influence clinical course and therapeutic response. Exposure to psychotropic medications added another component, particularly in patients undergoing prolonged antipsychotic treatment.

In primary care, the findings underscored the importance of periodically assessing weight, body mass index, blood pressure, blood glucose, and lipid profile, along with evaluating dietary habits, physical activity, and other cardiometabolic risk factors. This approach enables the early identification of complications that may remain underdiagnosed when care is focused exclusively on psychiatric manifestations.

In secondary care, the results pointed to the need to integrate psychiatric assessment, the selection and adjustment of pharmacotherapy, monitoring of metabolic adverse effects, and the identification of patients requiring specialized intervention. Coordination between levels of care proved particularly relevant for individuals with severe mental disorders, long-term use of psychotropic medications, and multiple metabolic risk factors.

Dimension	Primary Care	Secondary Care
Screening	Weight, BMI, blood pressure, blood glucose, lipids, and lifestyle habits	Metabolic assessment associated with psychiatric diagnosis
Prevention	Diet, physical activity, and risk factor reduction	Therapeutic decision-making considering metabolic risk
Psychotropic medications	Monitoring of metabolic effects	Adjustment and substitution when clinically indicated
Metabolic syndrome	Identification and initial management	Shared management in complex cases
Biomarkers	Application still limited	Future potential for stratification
Metabolic therapies	Lifestyle interventions	Individualized evaluation of adjuvant strategies
Continuity of care	Longitudinal follow-up	Specialized support and referral back

Source: Prepared by the authors based on the synthesis of evidence from this review.

Table 4: Proposal for Integrating Energy Metabolism into Mental Health Care

Table 4 summarizes one of the main practical implications of the review: the metabolic approach to psychiatric disorders should not be understood exclusively as the application of new experimental therapies. Its most immediate application lies in the integration of mental health and metabolic health, including screening, prevention, monitoring, and treatment of cardiometabolic abnormalities throughout the course of care.

Taken together, the results revealed three complementary levels. At the molecular level, mitochondrial dysfunction, bioenergetic alterations, oxidative stress, and immunometabolism stood out.

At the clinical level, associations were observed with insulin resistance, metabolic syndrome, metabolomic changes, and the effects of psychotropic medications. At the therapeutic and care level, metabolic interventions and the need for integration between primary and secondary care emerged. These findings provided the basis for a critical discussion of the consistency of the evidence, the causal relationships that have not yet been established, and the future prospects of metabolic psychiatry.

6. Discussion

The findings of this review demonstrated that energy metabolism plays a significant role in the contemporary understanding of psychiatric disorders. The analyzed evidence indicated that major depression, bipolar disorder, and schizophrenia share alterations related to mitochondrial function, ATP production, oxidative stress, and energy substrate utilization. These results reinforce the existence of partially transdiagnostic bioenergetic mechanisms, although they do not allow metabolic dysfunction to be considered the sole cause of these conditions [1-3].

Mitochondrial dysfunction emerged as one of the most consistent mechanisms. Highlighted mitochondrial alterations in bipolar disorder, while identified similar evidence in schizophrenia [7,9,11,13]. In depression, alterations in energy efficiency, redox balance, and mitochondrial activity have also been described, indicating that reduced bioenergetic capacity may influence neurotransmission, synaptic plasticity, and neuronal function [38].

Another important aspect was the interaction between mitochondrial dysfunction, oxidative stress, and neuroinflammation. Increased levels of reactive oxygen species may contribute to cellular damage and inflammatory activation, while inflammatory mediators may alter glucose utilization and mitochondrial activity. This process may establish a feedback loop capable of contributing to the maintenance of neurobiological changes associated with psychiatric symptoms [14,15,19].

Systemic metabolic changes have also been shown to have clinical relevance. Obesity, insulin resistance, dyslipidemia, and metabolic syndrome have frequently been associated with severe mental disorders, particularly in individuals treated with certain psychotropic medications.

This relationship likely results from the interaction between characteristics of the disorder itself, behavioral factors, and pharmacological effects, highlighting the need to simultaneously consider both mental and cardiometabolic health [20-22].

Metabolomics has proven particularly promising for identifying biological phenotypes. Recent studies have identified alterations in lipids, amino acids, acylcarnitines, and other metabolites, including those with the potential to differentiate between unipolar and bipolar depression and characterize alterations in schizophrenia [16,23,24].

However, differences among analytical platforms, populations, and collection methods still make it difficult to define biomarkers that are sufficiently validated for routine clinical application.

In the therapeutic field, strategies targeting energy metabolism represent an emerging area. Mitochondrial modulators, antioxidants, nutritional interventions, and ketogenic therapies have shown preliminary results of interest [33,35,37]. However, these interventions should not be interpreted as substitutes for established psychiatric treatments, since much of the evidence still comes from small, heterogeneous, or exploratory studies. From a care perspective, the results reinforced the need for integration between primary and secondary care.

Screening for obesity, hypertension, glycemic abnormalities, dyslipidemia, and other cardiometabolic factors can be incorporated into longitudinal follow-up, while specialized care can assess the relationship between psychopharmacological treatment, psychiatric progression, and metabolic consequences.

Thus, the metabolic perspective can contribute to a more comprehensive model of care, without reducing the complexity of psychiatric disorders exclusively to biochemical changes.

Finally, the main limitation of the available evidence was the high methodological heterogeneity. Different disorders, clinical stages, treatments, biomarkers, and laboratory techniques were evaluated, making direct comparisons difficult.

The presence of metabolic alterations does not necessarily establish causality. Longitudinal studies and larger clinical trials are needed to determine whether specific modulation of bioenergetic pathways can effectively alter the course of psychiatric disorders.

7. Conclusions

This review demonstrated that alterations in energy metabolism are associated with various psychiatric disorders, notably , mitochondrial dysfunction, bioenergetic impairment, oxidative stress, neuroinflammation, alterations in carbohydrate and lipid metabolism, insulin resistance, and metabolomic changes.

Major depression, bipolar disorder, and schizophrenia share some common metabolic mechanisms, suggesting that cerebral bioenergetics may represent an important transdiagnostic

component. However, the available evidence does not yet allow these alterations to be established as isolated causes of psychiatric disorders.

Metabolomics and metabolic biomarkers have demonstrated potential to contribute in the future to diagnosis, clinical stratification, and precision psychiatry. Similarly, interventions targeting mitochondrial function and metabolism represent promising therapeutic approaches, but they still require further validation before their widespread clinical application.

It was also concluded that integration between primary and secondary care is essential for the follow-up of these patients, especially for the early identification and management of cardiometabolic abnormalities and adverse effects of psychotropic medications. Thus, incorporating the metabolic dimension into mental health care can promote a more integrated, individualized, and preventive approach to psychiatric disorders [42-60].

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