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Precision medicine for depression: Improving treatment response and remission

Giulio Corrivetti[a,b,1], Francesco Monaco[a,b,1], Annarita Vignapiano[a,b,1], Alessandra Marenna[b,*], Ernesta Panarello[a], Benedetta Di Gruttola[a], Stefania Landi[a], Raffaele Malvone[a], Corrado Vecchi[b], Stefano Leo[b], Pietro Carmellini[c], Luca Steardo Jr[d], Marco Solmi[e,f,g,h,i,j], Riccardo Panella[b,k,l,m], Alessio Fasano[b,n]

[a] *Department of Mental Health, ASL Salerno, Salerno, Italy*
[b] *European Biomedical Research Institute of Salerno (EBRIS), Salerno, Italy*
[c] *Department of Molecular and Developmental Medicine, Division of Psychiatry, University of Siena School of Medicine, Siena, Italy*
[d] *Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy*
[e] *SCIENCES lab, Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada*
[f] *Regional Centre for the Treatment of Eating Disorders and On Track: The Champlain First Episode Psychosis Program, Ottawa Hospital, Ottawa, ON, Canada*
[g] *Department of Mental Health, The Ottawa Hospital, Ottawa, ON, Canada*
[h] *Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program, University of Ottawa, Ottawa, ON, Canada*
[i] *Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany*
[j] *Mental Health Department, The Ottawa Hospital, Ottawa, ON, Canada*
[k] *Center for RNA Medicine, Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark*
[l] *Resalis Therapeutics Srl, Torino, Italy*
[m] *Pharmacology and Toxicology Section, Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy*
[n] *Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Massachusetts General Hospital for Children, Harvard Medical School, Boston, MA, United States*

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ABSTRACT

This review synthesises current knowledge to improve understanding of the pathophysiology of major depressive disorder (MDD) and optimise diagnostic, therapeutic and prognostic approaches. It examines the interplay between genetic, epigenetic, inflammatory, neurotransmitter and gut microbiome factors, together with environmental stressors and different clinical symptom presentations, in shaping MDD presentation and treatment response. Studies have revealed potential biomarkers predictive of treatment response, allowing differentiation of MDD subtypes and facilitating remission monitoring. While studies have identified potential biomarkers predictive of treatment response and enabling MDD subtype differentiation, significant challenges remain in achieving fully optimized therapeutic efficacy and widespread remission. A holistic, data-driven approach is key to addressing the complex aetiology of MDD, ultimately improving outcomes for patients and reducing the substantial burden of this prevalent disorder.

1. Introduction

Major Depressive Disorder (MDD) is the most prevalent mood disorder, characterized by a persistent feeling of sadness, decreased motivation in carrying out daily activities, and a wide range of cognitive, emotional, and physical symptoms that impair daily functioning. MDD is a clinical condition that goes beyond temporary feelings of sadness or low mood and significantly impacts an individual's quality of life. Symptoms of MDD include depressed mood, loss of interest or pleasure in previously enjoyed activities (anhedonia), significant changes in appetite and weight, sleep disturbances (insomnia or hypersomnia), fatigue or loss of energy, difficulty concentrating, feelings of

* Corresponding author.
E-mail address: a.marenna@ebris.eu (A. Marenna).
[1] These authors have contributed equally to this work and share first authorship.

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worthlessness or excessive guilt, and recurrent thoughts of death or suicide (American Psychiatric Association, 2013). The condition can lead to substantial impairment in social, occupational, and other important areas of functioning. The exact cause of MDD is multifactorial, involving a combination of genetic, biological, environmental, and psychological factors (Malhi and Mann, 2018). Neurobiological factors, including imbalances in neurotransmitters such as serotonin, norepinephrine, and dopamine, play a crucial role in the pathophysiology of depression. Additionally, environmental stressors, such as trauma, adverse childhood experiences, and chronic stress, have been linked to the development of MDD (Kupfer et al., 2012). Approximately 280 million people in the world suffer from depression (Institute of Health Metrics and Evaluation, 2023). MDD affects all age groups, with the highest prevalence in adolescents (10–20 %) and young adults (15–20 %) due to hormonal changes, social stress, and life transitions (Hasin et al., 2018). Middle-aged adults (7–10 %) experience depression due to work, family, and health-related stress (Ferrari et al., 2013), while older adults (1–5 %) face underdiagnosed depression linked to chronic illness and social isolation (Blazer, 2020). Late-life depression is more common in institutionalized individuals (up to 15 %) (Blazer, 2020). Understanding these age-related differences helps in targeted prevention and treatment strategies.

Depression is about 50 % more common among women than among men, with studies indicating that women have a lifetime prevalence of MDD nearly twice that of men (Kuehner, 2017). This disparity is attributed to biological factors such as hormonal fluctuations, as well as psychosocial influences like increased exposure to stressors and gender-related societal roles.

Suicide, which is the worst outcome of MDD, is committed by more than 700,000 people and places as the fourth leading cause of death in 15–29-year-olds (The Lancet Public Health, 2023). Diagnosis is typically based on clinical assessment using standardized criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (American Psychiatric Association, 2013). Treatment options include psychotherapy (such as cognitive-behavioral therapy), pharmacotherapy (such as selective serotonin reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]), lifestyle modifications, and, in severe cases, neurostimulation techniques like electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) (Kupfer et al., 2012). Early diagnosis and intervention are crucial in managing symptoms and improving overall well-being

MDD represents a global burden. According to a ranking based on disability-adjusted life-years (that measures the loss of the equivalent of one year of full health), MDD went from 19th position in 2016–13 th position in 2019, suggesting that the duration of the disease has also increased in few years (GBD, 2019).

A cause of prolonged disease duration might be due to response to therapy. In fact, approximately 40–50 % of MDD patients do not respond to prescribed antidepressants, which highlight the need for better-targeted therapies (McIntyre et al., 2023). Understanding the neurobiological mechanisms underlying MDD is another critical aspect of ongoing research. Studies have highlighted the role of inflammation, gut microbiota, and genetic predisposition in depression (Felger, 2018).

Neuroimaging research is helping to identify biomarkers that may predict treatment response, allowing for more personalized and effective therapeutic interventions (Williams et al., 2021).

Early diagnosis and prevention are also benefiting from technological advancements. Artificial intelligence and machine learning are being used to detect depression through speech patterns, facial expressions, and genetic markers, enabling earlier interventions and better patient outcomes (Shatte et al., 2019). Additionally, research is shedding light on the differences in MDD prevalence and treatment response based on factors such as gender, age, and socioeconomic status. For example, women are about 50 % more likely to experience depression than men, and studies continue to explore the hormonal and psychosocial factors contributing to this disparity (Kuehner, 2017).

1.1. Research of biomarkers for diagnostics and monitoring of MDD

Accurate diagnosis and effective monitoring of MDD remain challenging due to the subjective nature of clinical assessments and the heterogeneity of the disorder. Research on biomarkers—biological indicators measurable in blood, cerebrospinal fluid, or other bodily substances—offers a promising approach to improving MDD diagnostics and treatment monitoring. MDD also lacks reliable biomarkers that could facilitate diagnosis and monitor the response to the treatment (Paganin et al., 2024). Research efforts have increasingly focused on identifying biomarkers associated with MDD, particularly those linked to inflammation and oxidative stress, such as C-reactive protein and tryptophan catabolites (Paganin et al., 2024).

Elevated levels of pro-inflammatory markers, including interleukin (IL)-6 and C-reactive protein (CRP), have been documented among MDD patients (Nishuty et al., 2019; Osimo et al., 2020). Furthermore, clinical trials suggest that higher inflammation levels may negatively influence responses to standard antidepressants, signaling a potential need for integrating anti-inflammatory treatments for specific patient populations (Yin et al., 2024; Cui et al., 2024).

Proinflammatory cytokines seems to play a role in the re-uptake of serotonin, known to have decreased level already at MDD onset; however, further studies are required to understand whether these molecules have a clinical exploitability (Cui et al., 2024). Biomarkers such as inflammatory markers, neurotrophic factors, and genetic or epigenetic alterations could provide objective measures for detecting MDD, assessing disease severity, and predicting treatment responses. Advancements in this field hold the potential to enhance precision medicine approaches, ultimately leading to better patient outcomes.

1.2. Multiomics approach to major depressive disorder (MDD): unraveling complex biomolecular mechanisms

A multiomics approach to MDD involves the comprehensive analysis of various biological data layers— such as genomics, transcriptomics, proteomics, and metabolomics—to unravel the complex biomolecular mechanisms underlying the disorder.

A multiomics approach refers to the integrated analysis of data from multiple biological layers, or "omics," to gain a comprehensive understanding of a biological system. These layers typically include genomics (the study of genes and their functions), transcriptomics (the study of RNA molecules), proteomics (the study of proteins), and metabolomics (the study of metabolites and metabolic pathways). By combining data from these diverse sources, multiomics allows researchers to investigate the complex interactions between genes, proteins, and metabolites, providing a holistic view of biological processes. This approach is especially valuable in complex diseases like MDD, where multiple molecular alterations contribute to the disorder's pathophysiology. Through multiomics, scientists can identify biomarkers, understand disease mechanisms, and personalize treatments more effectively (Zheng et al., 2023).

By integrating these diverse datasets, researchers aim to identify novel biomarkers and therapeutic targets, enhancing our understanding of MDD's etiology and progression (Zheng et al., 2023). For instance, the MODOMICS database compiled extensive data on RNA modifications, providing valuable insights into the role of epitranscriptomic changes in MDD (Cappannini et al., 2023). Additionally, studies have utilized multiomics approaches to predict responses to antidepressant treatments, highlighting the potential of these methods in personalizing therapeutic strategies (Fuh et al., 2023). A recent multi-center cohort study has also emphasized the importance of integrating peripheral biomarkers for a more comprehensive diagnostic framework (Zheng et al., 2022). By leveraging multiomics data, researchers can gain a more holistic view of the molecular alterations associated with MDD, paving the way for improved diagnostics and interventions (Zheng et al., 2023).

1.3. The gut microbiota and MDD

Over the last two decades, the gut microbiota—the vast collection of bacteria, archaea, and eukarya residing in the gastrointestinal (GI) tract—has been recognized as playing a crucial role in human health. This complex ecosystem, which co-evolves with its host, supports numerous physiological functions, including energy harvesting, immune regulation, pathogen defense, and maintaining gut barrier integrity, thus preserving overall homeostasis (Thursby, Juge.,2017; Vemuri et al., 2018). However, disturbances in this microbial balance, known as dysbiosis, have been implicated in various conditions, including obesity, inflammatory bowel disease, and metabolic disorders (Zhao et al., 2023). Dysbiosis can affect not only physical health but also mental health, where recent studies have highlighted its emerging association with MDD (Zheng et al., 2016; Liu et al., 2023).

MDD is characterized by various metabolic disturbances that affect both the peripheral and central nervous systems. These metabolic alterations are believed to be driven by disruptions in several key pathways, including amino acid, carbohydrate, glycerophospholipid, and bile acid metabolism. Amino acids, which play a crucial role in neurotransmitter synthesis and brain function, are often imbalanced in individuals with MDD. Alterations in carbohydrate metabolism may contribute to insulin resistance and dysregulated energy homeostasis, which are commonly observed in depressed individuals. Furthermore, changes in glycerophospholipid metabolism can affect membrane fluidity and signaling pathways in the brain, potentially influencing neuronal function and mood regulation. Lastly, bile acid metabolism, which is involved in gut-brain signaling, has been implicated in MDD through its impact on the gut microbiota and inflammation. These interconnected metabolic disturbances offer potential biomarkers for diagnosing and monitoring MDD, as well as novel targets for therapeutic interventions (Fuh et al., 2023).

These disturbances suggest a dysfunctional gut-brain axis as a contributing factor to MDD, implicating the microbiota in neuropsychiatric functioning (Sarkar et al., 2016). Transplantation of fecal microbiota from patients with depression into microbiota-depleted animals has been shown to induce mood-related behaviors in these models (Kelly et al., 2016.; Zheng et al., 2016). Selective serotonin reuptake inhibitors (SSRIs), commonly prescribed antidepressants, not only target serotonergic neurons in the gastrointestinal tract but also exhibit antimicrobial effects that can modify gut microbiota composition. This interaction may partially reverse dysbiosis and decrease gut permeability in MDD patients, suggesting a gut microbiota- related mechanism of action for SSRIs (Macedo et al., 2017). Despite promising preclinical and translational results suggesting the potential of probiotics to positively influence mood, human clinical trials have shown only modest effects, particularly in populations over 65 (Ferrari et al., 2024). Probiotic preparations, primarily consisting of *Bifidobacterium* and *Lactobacillus* strains, may not sufficiently target the specific dysbiosis associated with depression. Further exploration is necessary to identify therapeutic targets within the gut microbiota, aiming to develop enhanced probiotic candidates for effective depression treatments (Wang et al., 2023).

Recent research from the Netherlands Study of Depression and Anxiety (NESDA) cohort has identified an immunometabolic dimension (IMD) of MDD, characterized by atypical symptoms like increased appetite, weight gain, and low energy, significantly associated with elevated inflammatory markers (Lamers et al., 2020; Brydges et al., 2022).

1.4. Aims

This comprehensive review aims to shed light on the intricate and multifaceted landscape of inflammatory and multi-omics biomarkers associated with the various dimensions of MDD. MDD, with its complex clinical and biological presentation, has long challenged traditional diagnostic and therapeutic approaches. By examining the diverse biomarkers, particularly those related to inflammation and multi-omics factors, this review explores how these biological markers are interlinked within complex networks that influence the pathophysiology of MDD. Understanding these networks may allow for the development of improved therapeutic strategies, leading to more personalized and precise treatments.

This review also underscores the potential of inflammatory markers and other multi-omics data—such as genomic, transcriptomic, proteomic, and metabolomic profiles—to serve as reliable indicators of disease state, response to treatment, and long-term prognosis. In exploring the physiological underpinnings of MDD, limit the critical importance of adopting a holistic approach to treatment. A deeper understanding of the interactions between genetic predispositions, neuroinflammation, neurotransmitter imbalances, and other biological processes is essential for crafting effective, individualized interventions. The integration of multi-omics data allows for a broader, more comprehensive understanding of how various biological systems contribute to the onset and progression of MDD. As such, this review calls for the integration of these diverse biological factors into therapeutic decision-making processes, emphasizing their potential to drive innovative and efficacious treatment paradigms. By combining insights from multiple layers of biological information, we can pave the way for treatments that are not only more targeted but also more effective, ultimately leading to improved outcomes for patients suffering from MDD.

2. Methods

The present review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (PROSPERO: CRD42025631139)

2.1. Search strategy and study eligibility criteria

A systematic search was conducted using two major bibliographic databases: PubMed and APA PsycINFO. Articles published between January 1, 2014, and October 30, 2024, were included. We used the following search terms: (("depression"[MeSH Terms] OR "major depressive disorder"[MeSH Terms] OR "depression"[Title/Abstract] OR "depressive disorder"[Title/Abstract]) AND ("remission"[Title/Abstract] AND ("multi-omics"[Title/Abstract] OR "multiomics"[Title/Abstract] OR "metabolomics"[Title/Abstract] OR "genomics"[Title/Abstract] OR "transcriptomics"[Title/Abstract] OR "proteomics"[Title/Abstract] OR "epigenomics"[Title/Abstract] OR "microbiomics"[Title/Abstract] OR "microbiome"[Title/Abstract] OR "gut microbiota"[Title/Abstract] OR "omics"[Title/Abstract]))) AND ("english"[Language] AND "2014"[Date - Publication]:"2025"[Date - Publication]) AND ("randomized controlled trial"[Publication Type] OR "retrospective cohort study"[Publication Type] OR "cohort study"[Publication Type] OR "open-label study"[Publication Type] OR "expert opinion"[Publication Type] OR "conceptualization"[Title/Abstract]) Studies were chosen based on these

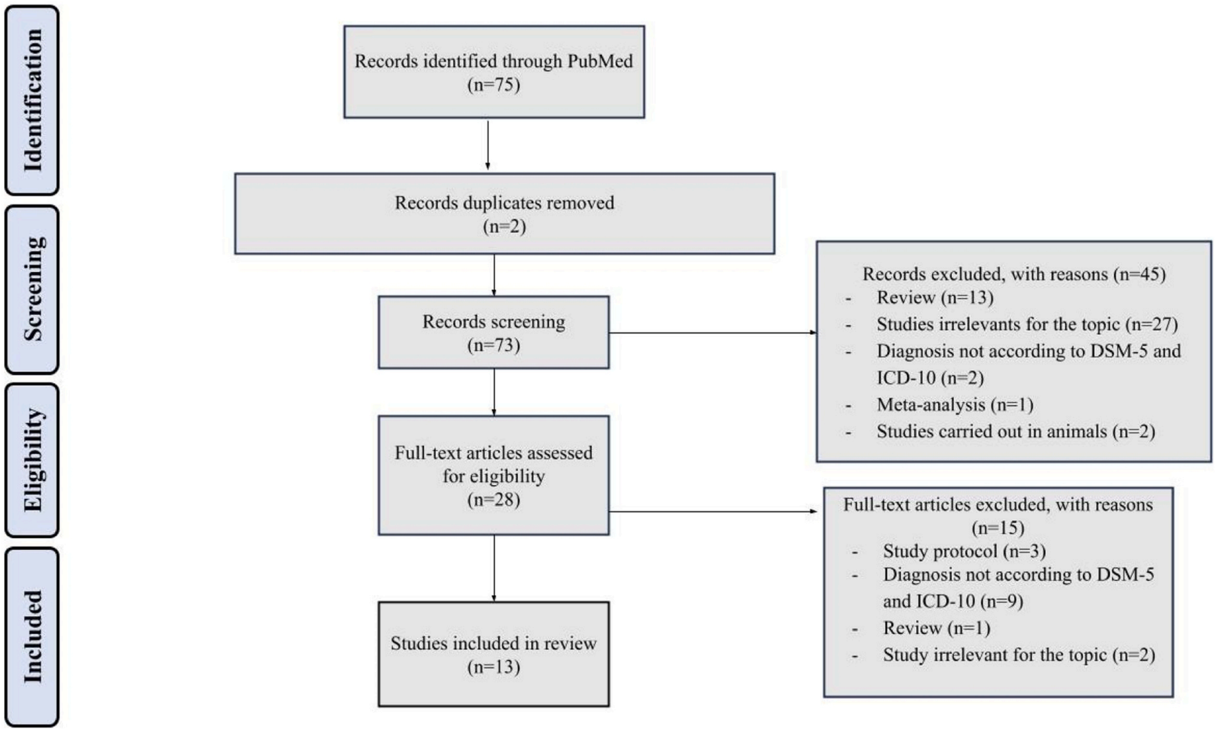

Fig. 1. PRISMA search process.

inclusion criteria: randomized controlled trial, retrospective study, cross - sectional study, cohort study, open study, expert opinion, concerning conceptualization, diagnosis of Major Depressive Disorder, diagnosis Remission of Major Depressive Disorder according to DSM-5 and ICD-10, utilization of multi omics techniques or metabolomics, genomics, transcriptomics, proteomics,epigenomics, microbiomic techniques. Studies published in English, studies carried out in humans and studies published in journals indexed in Embase or Medline, from 1 January 2014–31 December 2024. The exclusion criteria meta-analysis, review, duplicates, comments, editorials, case reports/case series, theses, study protocol, proceedings, letters, short surveys and notes, studies irrelevant for the topic, unavailable full-text and studies that do not meet inclusion criteria. The study selection process was conducted systematically to ensure rigor and transparency, as illustrated in the PRISMA flow diagram (Fig. 1). A comprehensive search was performed across two major databases: PubMed ($n = 32$) and APA PsycINFO ($n = 43$), yielding a total of 75 records. During the screening phase, titles and abstracts were assessed for relevance based on predefined inclusion criteria. A total of 45 records were excluded at this stage for the following reasons: 1 was a meta-analyses, 13 were review, 27 were studies irrelevant for the topic, 2 were studies carried out in animals and 2 were studies in which the diagnosis was not made according to DSM-5 and ICD-10. Subsequently, full-text articles were assessed for eligibility. Of these,15 articles were excluded. Ultimately, 28 studies met all inclusion criteria and were included in the systematic review. The final selection included 13 studies, comprising randomized controlled trials (RCTs) (Table 2), cohort studies, and open-label feasibility study. A detailed summary of the included studies, including study design, participant characteristics, and intervention details, is presented in Table 1 for further reference (Fig. 1).

A detailed summary of the included studies, including study design, participant characteristics, and intervention details, is presented in Table 1 for further reference.

2.2. Study selection

The selection of studies for this review occurred in a two-stage process. Initially, four independent reviewers assessed the titles and abstracts of all the retrieved papers (AM, SL, BDG, EP). In the subsequent stage, these same reviewers individually examined the full texts of the papers identified in the first phase. Any discrepancies between the four reviewers were resolved by involving a senior researcher.

2.3. Data extraction and data synthesis

Four independent researchers (RM, AM, AV, and SL) carried out data extraction for each included study, utilizing a standardized data extraction sheet in Microsoft Excel. The focus of this extraction encompassed several key subjects, including study design, participant characteristics, diagnosis of MDD or Remission, neuroimaging and AI techniques details derived from the original research. A meta-analysis was not conducted due to significant heterogeneity in study designs, interventions, outcome measures, and durations. Therefore, a narrative synthesis was employed to summarize the findings systematically.

2.4. Quality assessment

Given the heterogeneity of the included studies, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was employed to assess the quality of the evidence. This assessment was conducted by two reviewers (FM, SL) with any disagreements resolved through discussion with an additional reviewer (AV). The GRADE standards categorize the quality of evidence as "high," "moderate," "low," or "very low." A "high-quality" rating suggests that future research is very unlikely to alter the existing evidence and that the true effect closely matches the estimated effect.

Study	Randomization bias	Deviation from planned intervention	Missing outcome data	Outcome measurement bias	Selective reporting	Overall judgment
Thase et al. (2019)	Low risk. Randomization was performed appropriately, and blinding was maintained until week 8.	Low risk. No significant deviations were reported; blinding minimized potential bias.	Low risk. Minimal attrition with no substantial missing data affecting results.	Low risk. Outcomes were assessed using validated scales (HDRS-17) by blinded evaluators.	Low risk. Predefined outcomes were reported comprehensively without evidence of selective reporting.	Low risk of bias
Van Assche et al. (2023)	Low risk. Randomization was appropriately conducted for all 112 participants.	Low risk. No significant deviations from the cognitive intervention were reported.	Moderate risk. 84 out of 112 participants completed the study, and 73 provided full DNA methylation data. Missing data were handled appropriately, but some risk remains.	Low risk. Outcomes were assessed using validated scales (MADRS) and standardized DNA methylation techniques.	Low risk. Predefined outcomes were fully reported without evidence of selective reporting.	Low risk of bias
Bhattacharyya et al. (2019)	Not applicable. Subset analysis from the PReDICT study; no randomization details specified.	Low risk. CBT was delivered as per protocol with no deviations.	Moderate risk. Data completeness for the subset is unclear, posing some bias risk.	Low risk. HAM-D17 was used, ensuring objective outcome measurement.	Low risk. Predefined outcomes were fully reported	Moderate risk of bias
Dunlop et al. (2019)	Low risk. Randomized, patient- and rater-blinded trial with appropriate methods.	Low risk. Interventions were delivered as per protocol	Low risk. Comprehensive data collection for 1541 patients with intent-to-treat analysis	Low risk. Outcomes measured using validated tools (HAM-D17, HAM-D6)	Low risk. Predefined outcomes fully reported without bias	Low risk of bias
Gadad et al. (2018)	Low risk. The study was a randomized, double-blind, placebo-controlled trial	Low risk. Interventions were administered according to the study protocol without significant deviations	Low risk. Data collection was comprehensive, with minimal attrition reported	Low risk. Outcomes were assessed using validated instruments, ensuring objective measurements	Low risk. Predefined outcomes were reported transparently, with no evidence of selective reporting	Low risk of bias
Gadad et al. (2018)	Low risk. Participants were randomized appropriately in the CO-MED trial	Low risk. Interventions were administered as per protocol without significant deviations	Low risk. Comprehensive data collection with minimal attrition reported	Low risk. Outcomes were assessed using validated instruments, ensuring objective measurements	Low risk. The study reported all predefined outcomes transparently, with no evidence of selective reporting	Low risk of bias
Lee et al. (2022)	Not applicable. Secondary analysis without detailed randomization for the subset.	Low risk. Protocol for levomilnacipran or placebo was followed.	Moderate risk. Small sample size (17 subjects) raises robustness concerns.	Low risk. Validated tools (HAM-D) were used	Low risk. Predefined outcomes were fully reported	Moderate risk of bias
Brydges et al. (2022)	Moderate risk. Secondary analysis based on data from a randomized controlled trial	Low risk. Original interventions followed the protocol	Moderate risk. Limited details on data handling, though results appear robust	Low risk. Outcomes assessed using validated tools	Low risk. Predefined outcomes transparently reported	Moderate risk of bias
Greden et al. (2019)	Low risk. Patient- and rater-blinded randomized controlled trial	Low risk. Interventions followed the protocol	Low risk. Comprehensive data collection for 1167 patients	Low risk. Validated tools (HAM-D17) were used	Low risk. Predefined outcomes were fully reported	Low risk of bias
Kopczak et al. (2014)	Low risk. The study was a randomized, double-blind, placebo-controlled trial.	Low risk. Interventions were administered according to the study protocol without significant deviations	Low risk. Data collection was comprehensive, with minimal attrition reported	Low risk. Outcomes were assessed using validated instruments, ensuring objective measurements	Low risk. Predefined outcomes were reported transparently, with no evidence of selective reporting	Low risk of bias

Note: HDRS-17: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; CBT: Cognitive Behavioral Therapy; HAM-D6/HAM-D17: Hamilton Depression Rating Scale; HAM-D: Hamilton Depression Rating Scale

3. Results

The multifaceted nature of MDD necessitates a sophisticated approach to treatment, moving beyond generalized strategies toward personalized interventions that facilitate remission. Several key elements support this advanced approach: 1) integrating genomic, transcriptomic, proteomic, metabolomic, and metagenomic data to reveal complex biological interactions; 2) developing and validating biomarkers for earlier diagnosis, predicting treatment response, and monitoring efficacy; 3) tailoring treatment strategies to individual patient characteristics; 4) investigating key genes and pathways (including neurotransmitter systems, inflammation, and the gut-brain axis) to identify novel therapeutic targets; 5) the use of validated clinical rating scales (e.g., HAM-D, QIDS-SR) coupled with objective biological measures provides a reliable means for tracking symptom improvement, determining response rates, and assessing the likelihood of achieving remission (sustained absence of significant symptoms).

3.1. Gut microbiota as a predictor of antidepressant treatment response in major depressive disorder

Lee et al. (2022) explore the complex relationship between gut microbiota composition and antidepressant treatment response in geriatric depression, a population often characterized by treatment resistance and high rates of relapse. The research, framed as a secondary analysis of a previously conducted 12-week randomized, placebo-controlled clinical trial investigating the efficacy of levomilnacipran (LVM) in geriatric depression, focuses on identifying baseline gut

Table 1
Overview of included studies.

Author	Year and Country	Period	Study design	Study sample	Measures	Outcomes	GRADE Assessment of Articles	Comments
Van Assche et al.	2023, Germany and Australia	8 weeks	RCT with longitudinal epigenomic analysis	N = 112 adults with MDD; mean age 45 years; 68 % female at baseline; final sample N = 84 after 8 weeks	MADRS	DNA methylation changes associated with treatment response and remission; significant pathways linked to neurotransmissi on, telomeres, sodium transport, phosphatase regulation, and synaptic functioning	High	Study highlights the potential of DNA methylation as an early biomarker for treatment response and remission in MDD, though genome-wide significance was not achieved.
Bhattacharyya et al.	2019, US	12 weeks	Pilot study with targeted metabolomic profiling	N = 26 MDDoutpatients; treatment- naïve; mean age 37.4 years; 61.5 % female	HAMD-17	Three metabolomic modules associated with symptom change; significant metabolites included BCAAs, acylcarnitines, methionine sulfoxide, and phosphatidylcho lines	High	Study demonstrates potential metabolomic markers for CBT response in MDD, but findings need replication due to small sample size.
Brydges et al.	2022, US	12 weeks	Observational study with metabolomic and inflammatory profiling	N = 158 adults; treatment- naïve patients with MDD; enrolled in the PReDICTstudy; mean age 39 years; 64.6 % female	HAM-D-24; HAM-A; QUIDS-SR; IDS-SR	The study identified distinct metabolomic and inflammatory signatures associated with three MDD dimensions (immunometabo lic, melancholia, anxious distress). These findings highlight the heterogeneity of MDD and its symptom- specific biochemical underpinnings	High	Robust design with valuable replication of prior findings
Chen et al.	2021, China	2 weeks	Cross- sectional study with gut microbiota analysis	N = 108 women; 62 diagnosed with MDD and 46 healthy controls	HAMD-17; HAM-A; PANSS; GAF	The study explores gut microbiota composition and functional capacity in women with MDD. Key findings include significant differences in microbiota diversity and specific bacterial taxa between MDD patients and healthy controls, supporting gut microbiota as a potential non-invasive diagnostic tool for depression	Moderate	Strong methodology; causal links need longitudinal validation
Choi et al.	2021, South Korea	-	Cross- sectional proteomic study	N = 129 adults; 69 patients with MDD and 60 in remission; samples collected in discovery and validation phases	HAMD	The study identifies prothrombin as a novel biomarker for differentiating depressive states from remission in MDD. The biomarker's role is linked to platelet activation and thrombin- mediated pathways, supporting its potential for diagnostic and prognostic use	Moderate	Strong proteomic approach; requires larger cohorts for validation
Dunlop et al.	2019, US	24 weeks	RCT (GUIDED study) with post hoc analysis	N = 1541 adults with MDD; mean age not specified; gender	QIDS-SR16	HAM-D6 showed significant improvement in	High	Study supports HAM-D6 as a more sensitive measure for

(continued on next page)

Table 1 (*continued*)

Author	Year and Country	Period	Study design	Study sample	Measures	Outcomes	GRADE Assessment of Articles	Comments
				distribution not specified; final N = 1298 at week 8 compared to TAU; HAM-D17was lesssensitive		symptom reduction (Δ=4.4 %, p = 0.023), response rate (Δ=7.0 %, p = 0.004), and remission (Δ=4.6 %, p = 0.031)		pharmacogenomics-guided MDD treatment; robust design but limited by post hoc nature and lack of genome-wide significance.
Gadad et al.	2018, USA	12 weeks	Single-blind, RCT analyzing inflammatory biomarkers in the CO-MED study	N = 102 adults; diagnosed with MDD; plasma samples collected at baseline and after 12 weeks of treatment	QUIDS-SR; QUIDS-C; IDS-C; FIBSER	The study identified changes in inflammatory markers over 12 weeks of antidepressant treatment. Increased levels of Eotaxin−1 correlated with remission, while decreased levels of IFN-γ were associated with non-remission. These biomarkers highlight the interplay between inflammation and antidepressant efficacy	Moderate	Strong biomarker focus; limited by small sample size and lack of longitudinal analysis
Gadad et al.	2018, USA	7 months	Single-blind, RCT with GWAS	N = 459 adults; MDD; provided DNA samples for genetic analysis; divided into monotherapy (n = 155) and combination therapy groups (n = 304)	MINI international Neurpsychiatric Interview	The study identified novel SNPs in the ALX4 gene associated with early antidepressant response to escitalopram monotherapy. Haplotype analysis revealed regulatory variants impacting treatment outcomes, supporting the role of ALX4 in Antidepressant responsiveness	Moderate	Promising findings; requires validation in larger and ethnically diverse cohorts
Greden et al.	2019, USA	24 weeks	Patient- and rater-blinded, randomized controlled trial	N = 1541 adults; diagnosed with MDD; randomized into treatment as usual (n = 717) or pharmacogen omics-guided care (n = 681)	QUIDS- SR16; QUID S-C16; HAMD-17	The study evaluated pharmacogenom ic testing to guide antidepressant treatment. While overall symptom improvement (HAM-D17) was not significant, the guided-care group showed higher response (26.0 % vs. 19.9 %) and remission rates (15.3 % vs. 10.1 %) compared to treatment as usual	High	Large sample and robust methodology; limited by reliance on a single pharmacogenomic platform
Hung et al.	2021, China	-	Cross- sectional metabolomics study using 1H-NMR spectroscopy	N = 119 adults; 47 patients with MDD in full remission and 72 HCs; matched by age and gender	HAM-D	The study identified eight plasma metabolites that differed significantly between MDD patients in remission and HCs. A machine learning model based on these metabolites achieved high predictive accuracy (0.846), sensitivity, and specificity for distinguishing MDD patients from HCs,	Moderate	Promising findings; requires validation in larger and diverse populations

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Table 1 (*continued*)

Author	Year and Country	Period	Study design	Study sample	Measures	Outcomes	GRADE Assessment of Articles	Comments
						highlighting persistent metabolic alterations even in full remission		
Israel-Elgali et al.	2021, Israel	-	Randomized, observational study analyzing blood transcriptional changes	N = 78 adults; 47 with TRD and 31 healthy controls; TRD patients treated with ECT (n = 17), pharmacother apy (TAU, n = 16), or ketamine (n = 14)	HAM-D; HAM-A; QUIDS-SR	The study identified FKBP5, ITGA2B, and miR−24–3p as potential biomarkers of ECT response in TRD. Gene expression changes were most pronounced in ECT responders, with elevated FKBP5 and reduced ITGA2B linked to treatment success	Moderate	Small sample size; promising biomarkers for future studies
Kopzak et al.	2014, Germany	6 weeks	Observational cohort study measuring IGF-I and cortisol levels in serum	N = 170 adults; 78 patients with MDD and 92 HCs; patients were further categorized as remitters (n = 39) and non- remitters (n = 39) based on 6-week antidepressan t treatment response	HAM-D-21	The study revealed elevated IGF-I levels in MDD patients compared to HCs. Non- remitters exhibited significantly higher IGF-I levels at admission and a trend for persistently higher levels after treatment. Changes in IGF-I levels correlated with cortisol changes among remitters, indicating a potential biomarker for antidepressant response	Moderate	Strong endocrinological focus; limited by small sample size in subgroup analyses
Lee et al.	2022, USA	12 weeks	Prospective pilot study with microbiome analysis using 16S-rRNA sequencing	N = 12 adults; aged ≥ 60 years; diagnosed with GD; received either levomilnacipr an (n = 4) or placebo (n = 8)	LVM; HAM-D-24	The study identified baseline gut microbiota differences predictive of antidepressant treatment response in GD. A random forest classifier using nine genera achieved high accuracy (AUC = 0.857) in predicting remission. Significant taxa changes were observed in remitters post- treatment, highlighting gut microbiota as a potential biomarker for treatment response	Moderate	Innovative microbiome approach; limited by small sample size
Lee et al.	2024, Korea	-	Cross- sectional proteomic study comparing serum protein levels	N = 206 adults; divided into control (n = 85), NT-MDD, n = 61, and DT-MDD, n = 60 groups	HAM-D	The study identified eight serum proteins (e.g., Apolipoprotein A-I, Complement C5) as biomarkers for monitoring antidepressant effectiveness. Drug-treated MDD patients exhibited protein expression levels approaching those of healthy controls, suggesting these biomarkers reflect treatment response	Moderate	Valuable biomarker discovery; requires further validation across larger and more diverse cohorts

(continued on next page)

Table 1 (*continued*)

Author	Year and Country	Period	Study design	Study sample	Measures	Outcomes	GRADE Assessment of Articles	Comments
Thase et al.	2019, USA	24 weeks	Post-hoc analysis of a RCT evaluating pharmacogen omic-guided care vs. TAU	N = 912 adults; diagnosed with MDD; all taking medications with predicted gene-drug interactions	HDRS-17	Patients receiving pharmacogenom ic-guided care experienced significant improvements in symptom reduction (27.1 % vs. 22.1 %), response rates (27.0 % vs. 19.0 %), and remission rates (18.2 % vs. 10.7 %) compared to TAU at 8 weeks. Benefits were more pronounced among those who switched medications	High	Robust design; demonstrates clinical utility of pharmacogenomic testing
Wang et al.	2023, China	12 weeks	Longitudinal multi-omics study analyzing gut microbiota and plasma metabolites	N = 276 adults; 110 patients with MDD treated with escitalopram for 12 weeks and 166 HCs	HAMD-17	The study found that baseline gut microbial diversity and sporulation gene abundance were predictive of antidepressant remission (AUC = 0.71). Escitalopram treatment partially normalized amino acid and fatty acid metabolism while reducing gut microbial diversity, with remitters exhibiting more resilient microbiota profiles	High	Innovative approach integrating microbiota and metabolome data; results require external validation

Note: RCT: Randomized Controlled Trial; MDD: Major Depressive Disorder; CBT: Cognitive Behavioural Therapy; BCAAs: Branched-Chain Amino Acids; TAU: Treatment as Usual; HAM-D6/HAM-D17: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self-Report; IDS-SR: Inventory of Depressive Symptomatology – Self-Report; PReDICT: Predictors of Remission in Depression to Individual and Combined Treatments; PANSS:Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; CO-MED: Combining Medications to Enhance Depression Outcomes; IFN-γ: Interferon-Gamma; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self-Report; QIDS-C: Quick Inventory of Depressive Symptomatology – Clinician-Rated; IDS-C: Inventory of Depressive Symptomatology- Clinician-Rated; FIBSER: Frequency, Intensity, and Burden of Side Effects Rating; GWAS: Genome-Wide Association Study; SNPs: Single Nucleotide Polymorphisms; ALX4: ALX Homeobox 4 Agene; HC: Healthy Controls; 1H-NMR: Proton Nuclear Magnetic Resonance; ECT: Electroconvulsive Therapy; TRD: Treatment-Resistant Depression; FKBP5: FK506 Binding Protein 5; ITGA2B: Integrin Subunit Alpha 2b; IGF-I: Insulin-like Growth Factor I; GD: Geriatric Depression; LVM: Levomilnacipran; AUC: Area Under the Curve; NT-MDD: Non-Treatment-Resistant Major Depressive Disorder; DT-MDD: Difficult-to-Treat Major Depressive Disorder; HDRS-17: Hamilton Depression Rating Scale

microbiota features predictive of treatment outcome and on determining whether changes in gut microbiota are associated with successful treatment. Cross-sectional analyses between remitters and non-remitters did not result in statistically significant differences in microbiota composition at baseline; however, the application of random forest classifier, leveraging baseline gut microbiota data, demonstrated remarkable accuracy (AUC = 0.857) in predicting treatment outcome and in identifying nine bacterial genera (*Faecalibacterium, Agathobacter, Roseburia, Lachnoclostridium, Bacteroides, Ruminococcus_2, Akkermansia, Flavonifractor, and UBA1819*) as strong predictors of remission. Importantly, longitudinal analysis demonstrated significant changes in the gut microbiota of remitters from baseline to week 12, indicating a dynamic shift in microbial composition associated with successful treatment. These changes were not observed in non-remitters, underlining the potential utility of gut microbiota profiling as a potential biomarker for treatment response in geriatric depression.

Choi et al. (2021) investigated the gut microbiome's composition and functional characteristics in women with MDD, comparing it to a healthy control group. The research aims to identify potential microbial biomarkers associated with MDD, explore the relationship between gut microbiota and symptom severity, and ultimately contribute to the development of more effective diagnostic and therapeutic strategies. The findings revealed significant differences in both the composition and functional capacity of the gut microbiota between women with MDD and healthy controls. Specific phyla (Bacteroidota, Pseudomonadota and Fusobacteriota, previously known as Bacteroidetes, Proteobacteria, and Fusobacteria) were significantly enriched in the MDD group, while Bacillota and Actinomycetota (previously known as Firmicutes and Actinobacteria) were more prevalent in the control group. A random forest model demonstrated high accuracy (AUC = 0.92) in distinguishing between the groups based on a subset of 18 operational taxonomic units (OTU). Shotgun metagenomic sequencing provided additional support for these findings, revealing differences in the relative abundance of specific Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and their correlation with particular bacterial genera. The altered pathways included those associated with inflammation, lipid metabolism, and neurotransmitter biosynthesis, aligning with the existing literature on the gut-brain axis and MDD pathophysiology.

Both Lee and Choi made significant contributions to the growing body of research exploring the complex relationship between the gut microbiome and MDD, focusing specifically on the gut microbiome's potential as a predictor of treatment response and its association with

Table 2
Completed clinical trials.

Reference	Year	Study title	Description	Biomarkers used
Van Assche et al.	2017–2019	CERT-D RCT	Randomized controlled trial evaluating epigenetic modifications in MDD patients treated with cognitive therapy	DNA methylation
Bhattacharyya et al.	2019	PReDICT Study	Clinical trial on MDD patients treated with CBT, assessing metabolomic changes to predict treatment response	Plasma metabolites: acylcarnitines, branched-chain amino acids, lipids
Brydges et al.	2022	Metabolomic and Inflammatory Signatures of Symptom Dimensions in Major Depression	Study analyzing metabolism, inflammation, and depression symptom dimensions	Inflammatory markers (CRP, IL−6), plasma metabolites (lipids, fatty acids, gut microbiome metabolites)
Chen et al.	2021	Gut Microbiota Dysbiosis in Depressed Women	Study characterizing gut microbiota composition in depressed women	Bacterial markers (Bacteroidetes, Proteobacteria, Firmicutes, Actinobacteria), microbial metabolites
Choi et al.	2021	Discovery of Screening Biomarkers for Major Depressive Disorder in Remission by Proteomic Approach	Proteomic study identifying biomarkers for remission in MDD	Prothrombin protein as a predictive and diagnostic biomarker
Dunlop et al.	2019	GUIDED Trial	Randomized trial testing pharmacogenomics in personalized antidepressant selection	Pharmacogenomic combinatorial test (gene-drug interactions)
Gadad et al.	2018	CO-MED Trial	Study analyzing proteomic and genetic profiles for antidepressant response	Genetic polymorphisms in ALX4, SNP rs10769025
Gadad et al.	2018	CO-MED Trial	GWAS study on ALX4 gene polymorphisms in antidepressant response	SNP rs10769025 in ALX4 gene; regulatory haplotype CAAACTG associated with escitalopram monotherapy response
Greden et al.	2019	GUIDED Trial (Extension)	Large-scale study assessing pharmacogenomics impact on antidepressant selection	GeneSight® test (CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4)
Hung et al.	2021	Metabolomics-Based Discrimination of Patients with Remitted Depression from Healthy Controls	Study using NMR spectroscopy to identify metabolic differences in depression remission	Plasma metabolites: succinic acid, proline, acetic acid, creatine, glutamine, glycine, pyruvic acid, histidine
Israel-Elgali et al.	2021	Blood Transcriptional Response to Treatment-Resistant Depression during Electroconvulsive Therapy	Study analyzing transcriptional response in TRD patients undergoing ECT	FKBP5, ITGA2B, miR−24–3p
Kopzak et al.	2014	IGF-I in Major Depression and Antidepressant Treatment Response	Study measuring IGF-I levels in MDD and antidepressant response	IGF-I (insulin-like growth factor I), genetic polymorphisms in IGF1R, FOXO3
Lee et al.	2022	Intestinal Microbiota as a Predictor for Antidepressant Treatment Outcome in Geriatric Depression	Pilot study analyzing gut microbiota as a predictor of remission in geriatric depression	Gut bacterial genera: Faecalibacterium, Agathobacter, Roseburia (associated with remission)
Lee et al.	2024	Discovery and Validation of Protein Biomarkers for Monitoring the Effectiveness of Drug Treatment for Major Depressive Disorder	Study identifying serum protein biomarkers for antidepressant response using mass spectrometry	Serum proteins: Apolipoprotein A-I, Complement factor H, Complement C5, Complement C1q subcomponent B, Alpha−2-HS-glycoprotein, Vitamin D-binding protein, Corticosteroid-binding globulin
Thase et al.	2019	Impact of Pharmacogenomics on Clinical Outcomes in Patients Taking Medications with Gene-Drug Interactions (GUIDED Trial - Secondary Analysis)	Study evaluating pharmacogenomics impact on MDD clinical outcomes	GeneSight® test (CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4)
Wang et al.	2023	Multi-omics Reveal Microbial Determinants Impacting the Treatment Outcome of Antidepressants in Major Depressive Disorder	Multi-omics study identifying gut microbiota and plasma metabolites as predictors of remission	Indole−3-propionic acid (I3PA), L-tryptophan, bacterial sporulation genes, resilient gut microbiota

NOTE: CERT-D RCT: Cognitive Emotional Restructuring Therapy for Depression Randomized Controlled Trial; MDD: Major Depressive Disorder; PReDICT: Predictors of Remission in Depression to Individual and Combined Treatments; CBT: Cognitive Behavioral Therapy; CRP: C-Reactive Protein; IL-6: Interleukin-6; GUIDED: Genomics Used to Improve Depression Decisions (from pharmacogenomic study); ALX4: Aristaless-Like Homeobox 4 (gene involved in treatment response); SNP rs10769025: Single Nucleotide Polymorphism rs10769025 (associated with ALX4 gene); GWAS: Genome-Wide Association Study; CO-MED: Combining Medications to Enhance Depression Outcomes; CAAACTG: Regulatory haplotype associated with escitalopram monotherapy response; CYP1A2: Cytochrome P450 Family 1 Subfamily A Member 2; CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9; CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19; CYP3A4: Cytochrome P450 Family 3 Subfamily A Member 4; CYP2B6: Cytochrome P450 Family 2 Subfamily B Member 6; CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6; HTR2A: 5-Hydroxytryptamine Receptor 2 A (Serotonin Receptor 2 A); SLC6A4: Solute Carrier Family 6 Member 4 (Serotonin Transporter Gene - SERT); NMR: Nuclear Magnetic Resonance; FKBP5: FK506 Binding Protein 5 (Regulator of Glucocorticoid Receptor Sensitivity; ITGA2B: Integrin Subunit Alpha 2b; miR-24–3p: MicroRNA-24–3p; TRD: Treatment-Resistant Depression; ECT: Electroconvulsive Therapy; IGF-I: Insulin-Like Growth Factor I; IGF1R: Insulin-Like Growth Factor 1 Receptor; FOXO3: Forkhead Box O3 (Transcription Factor Related to Aging and Cell Survival);I3PA: Indole-3-Propionic Acid.

symptom severity.

3.2. Pharmacogenomics and treatment response in major depressive disorder

Gadad et al. (2018) investigates the complex interplay between genetic variations within the *ALX4* gene and treatment response to Escitalopram, both as monotherapy and in combination with other antidepressants, in patients diagnosed with MDD. The research analyzes data from the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, a large-scale, randomized controlled trial designed to compare the efficacy of various antidepressant treatment strategies, providing a robust foundation for identifying potential pharmacogenetic predictors of treatment response. The study's focus on treatment response, rather than solely on remission, offers a more distinct and clinically relevant perspective, as response represents a significant and often clinically meaningful improvement in symptoms even if full remission isn't achieved. The genetic analysis employed a genome-wide association study (GWAS) approach, using a high-density SNP genotyping array to assess approximately 2.5 million common genetic variants across the entire genome. To gain a deeper understanding of the potential functional implications of the identified *ALX4* variants and their influence on treatment response, the researchers performed an Ingenuity Pathway Analysis (IPA). The IPA revealed that *ALX4* is indirectly associated with several genes previously implicated in MDD pathophysiology and antidepressant response, including key players in neurotransmitter systems and stress response pathways. This network analysis strongly supports the biological plausibility of the *ALX4* gene's involvement in mediating treatment response.

Greden et al. (2019) provides a robust evaluation of the clinical utility of combinatorial pharmacogenomic testing in optimizing treatment for patients with treatment-resistant MDD. The Genomics Used to Improve Depression Decisions (GUIDED) trial provides compelling evidence for the clinical utility of combinatorial pharmacogenomic testing in TRD. This study, focusing specifically on patients with TRD, the GUIDED trial ensured a more targeted and clinically relevant assessment of the pharmacogenomic intervention's efficacy. At the 8-week mark, while overall symptom improvement showed no significant difference between the pharmacogenomics-guided care arm and the treatment-as-usual (TAU) arm, the guided-care arm demonstrated significantly higher response and remission rates. This finding highlights the importance of considering not only the average symptom reduction but also the proportion of patients achieving clinically significant improvement or full recovery. A post-hoc analysis further strengthened this conclusion, demonstrating even more dramatic improvements in outcomes among patients initially prescribed medications incongruent with their pharmacogenomic profiles who subsequently switched to congruent medications by week 8. This result directly supports the clinical utility of pharmacogenomic testing in identifying and mitigating the adverse effects of gene-drug interactions. The positive impact of pharmacogenomic-guided care proved remarkably durable, with continued improvements in patient outcomes observed through the 24-week study duration.

In their investigation of pharmacogenomics and TRD, Thase et al. (2019) employed the Genomics Used to Improve Depression Decisions (GUIDED) trial to provide compelling evidence for the clinical utility of combinatorial pharmacogenomic testing in TRD. The study utilized a sophisticated, third-generation combinatorial pharmacogenomic test (GeneSight Psychotropic), analyzing 59 genetic variants across eight genes influencing drug metabolism and response. This comprehensive approach, unlike simpler single- gene or multi-gene tests, provided a far more accurate assessment of gene-drug interactions and their effects on treatment outcomes. Multiple validated outcome measures (HAM-D17, QIDS-C16, PHQ-9) were assessed at frequent intervals (weeks 0, 4, 8, 12, and 24), providing a rich dataset for analyzing treatment effects on various aspects of clinical improvement. Although the primary endpoint (overall symptom improvement at 24 weeks) in the intent-to-treat analysis did not achieve statistical significance, secondary endpoints revealed compelling clinically meaningful results, particularly within the subset of patients with baseline gene-drug interactions. These patients demonstrated significant improvements in response and remission rates in the pharmacogenomic-guided arm compared to the TAU with these positive effects proving extremely durable over the 24-week study period. This enduring benefit provides strong evidence supporting the clinical utility of pharmacogenomic testing in identifying and mitigating adverse gene-drug interactions.

3.3. Metabolomic approaches to understanding MDD heterogeneity

Wang et al. (2023) conducted a comprehensive metabolomics study investigating the impact of escitalopram (ESC) treatment on the gut microbiome and plasma metabolome in patients with MDD.

The findings revealed a significant impact of ESC on the plasma metabolome of MDD patients. Specifically, the treatment resulted in a marked upregulation of several amino acids, including L-tryptophan, L-tyrosine, L-methionine, and L-alanine, which were depleted in MDD patients at baseline. Concurrently, a significant downregulation of various fatty acids was observed. These metabolic shifts were considerably more pronounced in patients who achieved remission (R) compared to those who did not (NR), suggesting a potential link between metabolic recovery and treatment success. The increase in L-tryptophan, a precursor to serotonin and capable of crossing the blood-brain barrier, is particularly noteworthy, as is the substantial upregulation of indole-3-propionic acid (I3PA), a gut microbiota-derived metabolite with reported neuroprotective properties. ESC treatment also reduced gut microbial richness and diversity, though baseline richness was significantly higher in remitters (Clostridium disporicum, Turicibacter sanguinis, Eubacterium hallii, Coprococcus comes and Clostridium perfringens). ML models, integrating multi-omics data, revealed previously unknown associations between plasma metabolites and microbial taxa, highlighting the personalized nature of this interplay. A predictive model for remission, based solely on baseline sporulation gene abundance, demonstrated high accuracy. This research strongly suggests a complex interplay between ESC treatment, gut microbiome, and metabolic alterations in MDD, with the potential to utilize readily available genetic information for more effective personalized treatment strategies.

Brydges et al. (2022) presents a detailed analysis of the statistical relationships between three distinct symptom dimensions of MDD and a composite measure of inflammation. The three symptom dimensions considered: Immunometabolic (IMD), Melancholia, and Anxious distress—represent distinct clinical presentations within MDD, reflecting the disorder's considerable heterogeneity. The use of these distinct dimensions is critical to understanding the complex interplay between different symptom clusters and underlying biological processes. The inflammation index is a composite measure calculated from pre- treatment plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6), two well-established markers of systemic inflammation. This study reveals distinct metabolomic signatures associated with three symptom dimensions of MDD: IMD, Melancholia, and Anxious distress. IMD correlated positively with gut-derived tryptophan metabolites (indoxyl sulfate, indole-3-lactate), propane-1,3-diol, butyric acid, and fumaric acid; inversely with short-chain acylcarnitines (C3:1, C4:1, C10) and long-chain saturated fatty acids (C16, C17, C18). Melancholia inversely correlated with long-chain phosphatidylcholines (PCs) and lysoPCs, several amino acids, and saccharic acid; positively with indoxyl sulfate and 2-hydroxyvaleric acid. Anxious distress inversely correlated with medium- and long-chain fatty acids (including omega-3 and omega-6), positively with citrulline, glutamate, valine, kynurenine, and gut-derived secondary bile acids. Indoxyl sulfate was the only metabolite positively correlated with all three dimensions. The limited overlap in metabolites across dimensions, confirmed by ChemRICH analysis, highlights the biochemical heterogeneity of MDD.

3.4. Predicting antidepressant treatment response in MDD: the role of biomarkers and genetic factors

Kopczack et al. (2014) investigated IGF-I's role as a potential biomarker for predicting antidepressant treatment response in MDD, also exploring the influence of genetic factors. Using data from the Psychiatric Genomics Consortium (PGC), they analyzed polymorphisms in ten IGF-I system genes (*IGF1*, *IGF1R*, *IGFBP1-IGFBP7*, *IGFBPL1*) and four additional genomic regions (FOXO3, IGFBP3, RPA, SPOCK2) known to affect IGF-I levels. Elevated baseline IGF-I levels were significantly associated with MDD in the study cohort, persisting after six weeks of treatment and being significantly higher in non-remitters at baseline. In remitters, changes in IGF-I levels correlated significantly with cortisol changes, suggesting HPA axis involvement.

Lee et al. (2024) investigates the identification and validation of serum protein biomarkers that can objectively monitor the effectiveness of antidepressant treatment for MDD. The research directly addresses the significant unmet need for improved methods of assessing treatment response in MDD, acknowledging the limitations of relying solely on subjective clinical scales like the HAM-D. While the HAM-D remains a valuable tool, it does not directly measure a return to a healthy state, hindering the precise evaluation of a medication's impact on recovery. The researchers posit that identifying and validating robust protein biomarkers offers a crucial pathway towards more objective and precise assessment of treatment efficacy. The study identified eight serum proteins exhibiting consistent differential expression patterns across the three groups (control, NT-MDD, and DT-MDD): Apolipoprotein A-I, Complement factor H, Complement C5, Complement C1q subcomponent subunit B, Alpha-2-HS-glycoprotein, Complement C1q subcomponent subunit C, Vitamin D-binding protein, and Corticosteroid-binding globulin.

The observation that the expression levels of these proteins in the MDD group closely resembled those of the control group is a significant finding, implying that alterations in these proteins may directly reflect the impact of drug treatment and potentially serve as robust indicators of successful treatment response. The involvement of these proteins in pathways related to complement activation and immune response further supports their potential utility as biomarkers. The identification of these eight proteins, coupled with their involvement in biologically relevant pathways, strongly suggests their potential as valuable biomarkers for objectively monitoring the effectiveness of antidepressant treatment in MDD.

Gadad et al. (2018) provides a comprehensive analysis of plasma inflammatory from participants to the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This longitudinal design, coupled with the measurement of a broad array of inflammatory markers, including acute-phase reactants. The specific inflammatory markers included in the analysis are: alpha-2-macroglobulin (A2M), C-reactive protein (CRP), serum amyloid P component (SerAmyP), basic fibroblast growth factor (bFGF), eotaxin-1 (CCL11), granulocyte colony-stimulating factor (G-CSF), interferon gamma (IFN-γ), interleukin 13 (IL-13), interleukin 17 A (IL-17A), interleukin 1 beta (IL-1β), interleukin 1 receptor antagonist (IL-1ra), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 9 (IL-9), interleukin 10 (IL- 10), macrophage inflammatory protein 1-alpha (MIP-1α), macrophage inflammatory protein 1-beta (MIP- 1β), platelet-derived growth factor BB (PDGF-BB), regulated on activation, normal T cell expressed and secreted (RANTES), and tumor necrosis factor alpha (TNF-α).(e.g., CRP, Serum Amyloid P), cytokines (e.g., IL-6, IFN-γ, IL-1β, IL-4, IL-5, IL-10, TNF-α), chemokines (e.g., Eotaxin-1/CCL11, RANTES), and growth factors (e.g., bFGF, PDGF-BB), allowed for a thorough and unbiased assessment of inflammatory status in the context of antidepressant treatment for MDD. Six markers showed significant changes ($p < .10$) from baseline to week 12: Serum Amyloid P, IL-5, IFN-γ, Eotaxin-1, RANTES, and IL-13. Only Eotaxin-1 and IFN-γ changes significantly predicted remission at week 12. Increased Eotaxin-1 levels were associated with remission, while decreased IFN-γ levels were associated with non-remission. The lack of significant associations for the other markers suggests that Eotaxin-1 and IFN-γ may be particularly valuable predictors of treatment outcome.

3.5. Transcriptomic biomarkers of treatment response in treatment-resistant depression

Israel-Elgali et al. (2021) shows a comprehensive investigation into the transcriptional response of peripheral blood mononuclear cells (PBMCs) to various treatments for TRD, offering novel insights into potential biomarkers for predicting treatment outcome. Electroconvulsive therapy (ECT) induced distinct transcriptional changes in PBMCs from individuals with TRD, differing significantly from those observed with standard antidepressant treatment (TAU) or ketamine. The gene *FKBP5*, previously associated with antidepressant response, showed significantly higher expression in TRD patients compared to controls, with the most marked elevation in the ECT group, particularly among those who responded to treatment. This strongly suggests *FKBP5* as a potential biomarker for ECT responsiveness. In contrast, *ITGA2B*, a gene not previously linked to MDD, exhibited differential expression patterns across treatment modalities, showing higher expression in the TAU group and lower expression in the ECT group (particularly in responders). These opposing trends in *FKBP5* and *ITGA2B* expression across treatments strongly suggest distinct underlying biological mechanisms. Further investigation revealed a significant inverse correlation between miR-24–3p and *ITGA2B* expression. "In vitro" experiments using SH-SY5Y cells confirmed that miR-24–3p directly targets and downregulates *ITGA2B* expression, implicating this microRNA in mediating ECT's effects on *ITGA2B*. The findings presented here highlight the potential of FKBP5, *ITGA2B*, and miR-24–3p as candidate biomarkers for predicting ECT response in TRD. The unique transcriptional responses to ECT, compared to TAU or ketamine, indicate that ECT may operate via biological mechanisms different from those of other antidepressants.

4. Discussion

4.1. Towards personalized treatment through multi-omics and biomarkers

MDD presents a significant clinical challenge, characterized by both its diverse clinical manifestations and the complex interplay of underlying biological mechanisms (Berk et al., 2023). The considerable heterogeneity of MDD, coupled with the frequent occurrence of treatment resistance, underscores the critical need for more effective and, crucially, personalized therapeutic approaches (Njenga et al., 2024). Progress toward this goal hinges on a multi-pronged strategy that integrates several key advancements. First, the inherent complexity of MDD demands a holistic, multi-omics approach (Stolfi et al., 2024). Rather than relying on single-layer analyses (e.g., focusing solely on genomics), a more comprehensive understanding requires integrating data from genomics, transcriptomics, proteomics, metabolomics, and metagenomics (Thase et al., 2019; Resurreccion and Fong, 2022; Wang et al., 2023). This integrated approach captures the interplay of biological factors, providing a more complete picture of MDD pathophysiology.

This broader biological understanding of MDD is crucial for identifying reliable biomarkers and measurable indicators that can directly reflect the disease state. By comprehensively studying the various molecular and metabolic pathways involved in MDD, researchers can pinpoint specific changes in the body that correlate with the disorder's onset, progression, and response to treatment. Reliable biomarkers could include alterations in the levels of specific metabolites, proteins, or gene expression patterns that are consistently observed in individuals with MDD. These biomarkers could be detected in easily accessible biological samples, such as blood, saliva, or cerebrospinal fluid, providing objective and non-invasive tools for diagnosis and disease monitoring. Furthermore, the identification of such biomarkers can aid in predicting treatment outcomes, enabling personalized approaches that optimize therapeutic interventions. A deeper biological understanding of MDD enables earlier diagnosis, better monitoring, and more effective interventions.

Biomarkers enable earlier, more accurate diagnosis and faster treatment initiation. Furthermore, biomarkers enable clinicians to design personalized treatment strategies, maximizing therapeutic efficacy while minimizing potential adverse effects. Finally, biomarkers provide a means for continuously monitoring treatment efficacy, allowing for timely adjustments to ensure optimal patient outcomes. The ultimate aim is to move beyond the traditional "one-size-fits-all" approach to treatment toward a truly personalized medicine model (Drugan and Leucuța, 2024). This necessitates tailoring therapies to individual patient characteristics, encompassing their genetic profile, unique clinical presentation, and personal lifestyle factors.

Reliable biomarkers help clinicians select effective, safe treatments from the outset. Central to this effort is the identification of potential therapeutic targets. This requires in-depth research into specific genes (*ALX4*, *FKBP5*, *ITGA2B*, and *SLC6A4*, among others) and key biological pathways (serotonin transport, cytochrome P450 enzyme activity, inflammatory responses, tryptophan and lipid metabolism, and gut microbiota composition and function) implicated in MDD pathophysiology (Gadad et al., 2018). Understanding the interaction between these pathways, such as the gut-brain axis and the significant influence of inflammation, is vital for developing innovative treatments that effectively address the root causes of the disorder (Choi et al., 2021). The development and validation of reliable biomarkers represent a paradigm shift in the diagnosis and treatment of MDD, offering transformative potential for improving patient outcomes. Biomarkers facilitate earlier and more accurate diagnosis, differentiating MDD from conditions sharing overlapping symptoms, enabling timelier interventions and improved outcomes (Lee et al., 2024). Their predictive capabilities guide the selection of optimal initial antidepressant medications, minimizing trial-and-error, shortening the duration of untreated illness, and potentially reducing adverse events (Greden et al., 2019). Furthermore, biomarkers can identify individuals more likely to respond positively to specific treatments or those at higher risk for treatment resistance, facilitating the design of tailored treatment strategies based on individual characteristics and predictions, ultimately leading to better outcomes (Greden et al., 2019).

4.2. Biological pathways and clinical monitoring

Objective biological markers provide a more precise and reliable measure of treatment efficacy than subjective clinical scales (e.g., HAM-D), enabling clinicians to effectively monitor treatment progress and make timely adjustments for optimization (Lee et al., 2024). Moreover, the integration of multi-omics data reveals key biological pathways involved in MDD, leading to the identification of novel therapeutic targets and the development of more effective treatments (Gadad et al., 2018; Wang et al., 2023). Prognostic biomarkers offer the additional benefit of predicting disease trajectory and relapse risk, enabling clinicians to implement preventative strategies, thus enhancing long-term outcomes and improving patients' overall quality of life (Lee et al., 2022). This also offers substantial healthcare cost savings. Improved diagnostic accuracy, reduced trial-and-error treatment approaches, enhanced response rates, and decreased relapse rates—all facilitated by the effective use of biomarkers—offer the potential to significantly reduce the overall costs associated with MDD. Rigorous assessment using clinical scales and biomarkers is essential to evaluating treatment response. (Lee et al., 2024; Kopczack et al., 2014; Israel-Elgali et al., 2021). This data-driven approach is fundamental for advancing our understanding of MDD and fostering the development of more effective and truly personalized treatment strategies. On these grounds, the path towards improved outcomes in MDD involves a sophisticated, multi-faceted strategy that integrates the power of multi-omics, predictive biomarkers, personalized treatment plans, a thorough understanding of key biological pathways, and objective measurement of treatment success. The goal is not just symptom reduction but sustained remission and improved quality of life. This review synthesizes existing literature on the multifaceted nature of MDD, focusing on remission and treatment response.

4.3. Limitations and future directions

While clinically relevant, this focus inherently presents limitations in fully capturing the complexity of MDD's diverse symptom presentations and underlying pathophysiological mechanisms. The inherent heterogeneity across studies, in terms of design, methodologies, and the characteristics of the enrolled populations, precludes a rigorous quantitative meta-analysis, necessitating a narrative synthesis approach to integrate and interpret the findings. This approach, while providing a valuable overview of current knowledge, inherently limits the ability to draw definitive conclusions regarding the relative importance or effect size of various factors. Further research is needed to clarify the complex, still unclear biological mechanisms of MDD. Identifying genes and pathways is promising but incomplete without considering epigenetics and their interactions. Finally, translating the findings of this review into specific and effective clinical interventions represents a significant challenge. The current state of knowledge, while pointing towards promising directions, necessitates further investigation and validation through large-scale, rigorously designed, and well-controlled clinical trials. Such trials should use multi-omics methods and control for confounders. Without such rigorous clinical validation, the clinical implications of the synthesized research remain speculative. The complex and evolving understanding of MDD requires a continued, collaborative research effort involving both preclinical and clinical studies to move toward more precise and personalized treatments that improve both remission rates and overall patient outcomes.

5. Conclusion

This review synthesizes the growing body of research into the complex and heterogeneous nature of MDD, underscoring the urgent need for a paradigm shift towards personalized medicine in order to optimize treatment and achieve sustained remission. MDD is characterized by substantial variability in its clinical presentation and underlying pathophysiology, which presents significant challenges for the application of generalized therapeutic approaches. This variability highlights the limitations of traditional, one-size-fits-all treatments, which often fail to provide effective relief for many patients. Addressing the complexity of MDD requires a multi-omics strategy, which integrates diverse datasets, including genomic, transcriptomic, proteomic, metabolomic, and metagenomic information. While this approach aims to identify robust biomarkers, challenges remain in achieving earlier and more accurate diagnosis, guiding personalized treatment, predicting individual responses, and objectively monitoring treatment efficacy. A comprehensive understanding of the intricate interplay between genetic factors, key biological pathways—including inflammatory, neurotransmitter, lipid metabolism, and gut-brain axis processes— and how these pathways influence treatment response is essential for the development of novel, targeted therapies. Continued research in these areas is critical to advancing our knowledge of MDD and translating these findings into truly personalized, patient-centered care.

Advancing molecular insights into MDD will enable tailored interventions and reduce disease burden.

CRediT authorship contribution statement

Giulio Corrivetti: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Francesco Monaco**: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Annarita Vignapiano**: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Alessandra Marenna**: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ernesta Panarello**: Writing – review & editing, Writing – original draft, Data curation, Bibliographic research. **Benedetta Di Gruttola**: Writing – review & editing, Writing – original draft, Data curation, Bibliographic research. **Stefania Landi**: Writing – review & editing, Writing – original draft, Data curation, Bibliographic research. **Raffaele Malvone**: Writing – review & editing, Writing – original draft, Data curation, Bibliographic research. **Corrado Vecchi**: Writing – review & editing, Writing – original draft, Data curation, Statistical analysis. **Stefano Leo**: Writing – review & editing, Writing – original draft, Data curation, Bibliographic research, Statistical analysis. **Pietro Castellini**: Writing – review & editing, Writing – original draft, Bibliographic research. **Luca Steardo**: Writing – review & editing, Writing – original draft, Data curation. **Marco Solmi**: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Riccardo Panella**: Writing – review & editing, Writing – original draft, Data curation. **Alessio Fasano**: Writing – review & editing, Writing – original draft, Formal analysis, Data curation.

Consent for publication

All authors have reviewed and approved the final manuscript and consent to its publication. Each author has confirmed their substantial contribution to the work and agrees to be held accountable for the content of the paper.

Author contributions statement

Designed research: G.C., F.M., A.V., A.M., E.P., B.D.G., S.L., R.M., C. V., S.L., P.C. Conducted research: L.S.jr, M.S., R.P., A.F., F.M., A.V., A. M., E.P., B.D.G., S.L.,P.C. Performed statistical analysis: C.V. Wrote paper: F.M., A.V., L.S. jr., E.P., R.P., M.S.,. Primary responsibility for final content: F.M., A.V., E.P., P.C., S.L., C.V., M.S., R.P., G.C., A.F.

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The authors state that generative AI and AI-assisted technology was not used in the preparation of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no competing interests. This includes any financial, professional, or personal relationships that could have influenced the design, conduct, analysis, interpretation, or reporting of this work. All authors have completed and submitted a competing interests declaration form, and none reported any conflicts.

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