Title: The Necessity for Biomarker-based Personalized Medicine in Major Depression Disorders: A Comprehensive Literature Review

Running Title: A Review on Major Depressive Disorder

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Abstract:

Background: Major depressive disorder (MDD) is a mental disorder characterized by alterations in mood, cognition, neurovegetative functions, and psychomotor activity. Millions of people worldwide suffer from this disease. There is no diagnosis based on laboratory tests for major depression. Even though there are varieties of treatments for MDD, often antidepressants are used to treat patients. There is a wide range of different responses to antidepressant drugs. Treatment-resistant depression (TRD) is a big challenge in the treatment of this disease.

Purpose: This article's goal is to review the current knowledge of MDD in order to show the deficiencies related to this disease in various fields of diagnosis and treatment, which shows the essential need for molecular studies to find new biomarkers related to this disease.

Method: This review uses two search strategies: a literature search using keywords (major depressive disorder, or MDD) and articles on each study topic. Animal experiments, pediatric MDD, and postpartum depression are excluded. For parts requiring more study, specific keywords are used.

Result: Biological approaches can help with a better understanding of the MDD pathogenesis mechanism, which is needed for diagnosis, treatment, and prediction of treatment response.

Conclusion: Despite the fact that there are a variety of treatments and diagnoses for MDD, they are not sufficient, and it appears more investigations and research are needed. Finding a specific and sensitive panel of biomarkers for these aims is more helpful for accelerating the clinical development of new diagnoses and therapeutics for MDD patients.

Keywords: Major depressive disorder, Major depression, MDD, Diagnostic criteria, Biomarker

Highlights:

- There are still many unresolved issues with MDD.
- In psychiatry, personalized medicine is lowering death and morbidity rates.
- Systems biology studies can play a significant role in the disease's future.

Plain Language Summary:

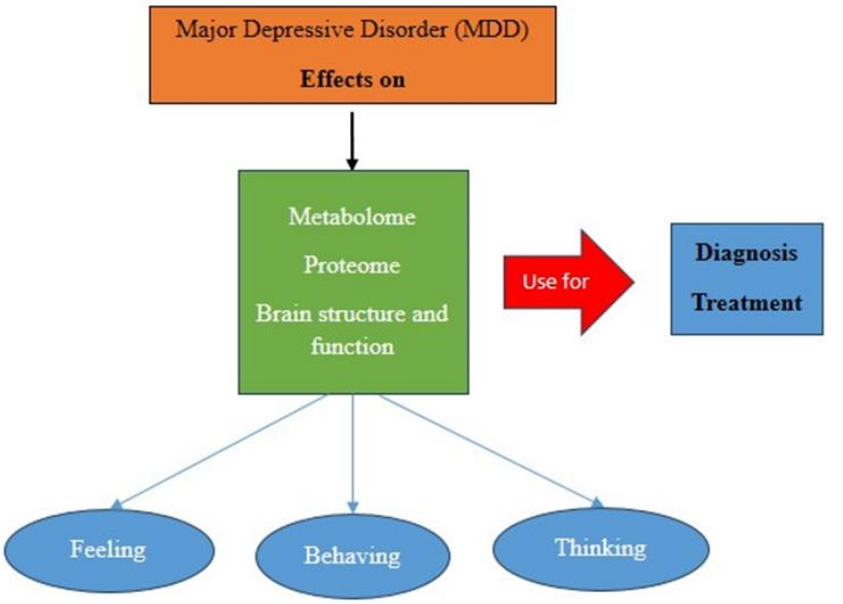
Major depressive disorder is a mental disorder that affects how you feel, think, and behave and can cause a number of emotional and physical issues. Major depressive disorder is characterized by a prolonged sense of sadness and loss of interest, disturbed sleep and appetite, unwarranted guilt and feelings of worthlessness, and agitation or retardation. Various emotional and physical issues can develop as a result of these symptoms.

In this paper, we reviewed the current understanding of MDD's pathophysiology, diagnosis, treatment, and drug resistance. There is no diagnosis based on laboratory tests for major depression. A mental status examination, the patient's self-reported experiences, and behavior noted by family or friends are the main diagnostic criteria for MDD. There are varieties of treatments for MDD, but often antidepressants are used to treat patients, and in addition, psychological counseling is more important. There is a wide range of different responses to antidepressant drugs. Treatment-resistant depression (TRD) is a big challenge in the treatment of this disease.

This article's goal is to review the current knowledge of MDD in order to show the deficiencies related to this disease in various fields of diagnosis and treatment, which shows the essential need for molecular studies to find new biomarkers related to this disease.

Despite the fact that there are a variety of treatments and diagnoses for MDD, they are not sufficient, and it appears there are still many unresolved issues in this field. So, more investigations and research are needed.

Our results indicate that biological approaches can help with a better understanding of the MDD pathogenesis mechanism, which is needed for diagnosis, treatment, and prediction of treatment response. Also, finding a specific and sensitive panel of biomarkers based on biological approaches is more helpful for accelerating the clinical development of new diagnoses and therapeutics for MDD patients. Systems biology studies can play a significant role in the disease's future. Also, a more comprehensive and multivariable strategy that combines several approaches, including proteomics, metabolomics, and neuroimaging techniques, would allow the diagnosis and treatment of depression to be personalized and help us better understand the neurobiology of different depression subtypes.A graphical abstract of the study is shown below.



Introduction:

Depression is a heterogeneous disorder. Depression includes numerous diseases with different causes and pathophysiologies (Nestler et al., 2002). There is a broad range of spectrum from minor/sub-threshold to major (Jani et al., 2015). Major depression (MDD) is a serious disorder of enormous sociological and clinical relevance. MDD patients present a wide range of symptoms like low energy, depressed mood, lack of interest or pleasure, guilt or feelings of low self-worth, abnormal sleep or appetite, and poor concentration, all of which can cause significant distress and loss of normal function. A person cannot be diagnosed as having MDD, following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), unless they show five of the aforementioned symptoms, one of which must be a depressed mood or anhedonia that impairs their ability to function in social or occupational settings (Bains & Abdijadid, 2022; Brigitta, 2022; Marcus, Yasamy, van Ommeren, Chisholm, & Saxena, 2012). The origins of depression and melancholia are known to have originated in Hippocrates' writings in the 5th century B.C., the father of modern medicine (Spielberger, Ritterband, Reheiser, & Brunner, 2003).

Depression is the most prevalent psychiatric disorder and represents one of the most important causes of disability in the world(Newby, McKinnon, Kuyken, Gilbody, & Dalgleish, 2015; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). According to the World Health Organization, MDD will account for 13% of the overall global burden of disease by 2030, displacing cardiovascular disease, with a lifetime prevalence of between 10% and 15% (Lopizzo et al., 2015). Given its widespread prevalence, it has been called the "common cold" of mental illness (Spielberger et al., 2003). Every year, approximately one million people die in Western societies due to a lack of comprehension of disease pathophysiology and a lack of laboratory tests to help with accurate diagnosis and antidepressant treatment strategies (Daniel Martins-de-Souza et al., 2012).

There are two major hypotheses based on the classical monoaminergic hypothesis of depression: one of them is the cytokine hypothesis (dysfunction in the immune-inflammatory system), and another is the neurotrophic hypothesis (neuronal plasticity) (Cattaneo et al., 2015). Epidemiologic studies indicate that approximately 40% and 50% of depression risk is hereditary (Nestler et al., 2002). Generally, genetic, epigenetic, physiological, and psychological components make up the biological basis of mood disorders (Saltiel & Silvershein, 2015) . Genetic research indicates that polygenes with small effects and infrequent mutations are probably the genetic causes of the

condition (K. Y. Lee et al., 2014). Moreover, non-genetic factors are important. These variables are extremely diverse. A variety of these factors range from stress and emotional trauma to viral infections and even random processes during brain development (Nestler et al., 2002). Additionally, there is undeniable documentation that indicates that people with physical disorders—and particularly those with numerous physical disorders—are more likely to develop depression (Kang et al., 2015). Moreover, socioeconomic status is shown to be a risk factor for depression (Liang et al., 2012).

Based on the Diagnostic and Statistical Manual's symptomatic criteria, depression has been classified as "major depression" since the 1960s. From these criteria, it is clear that the diagnosis of depression, in contrast to the majority of disorders of other organ systems, i.e., cancer and diabetes, is not based on quantitative clinical testing like serum chemistry, organ imaging, and biopsies but rather on symptoms that are highly variable (Lakhan, Vieira, & Hamlat, 2010; Nestler et al., 2002).

The clinical overlap of Alzheimer's-type dementia, vascular dementia, fronto-temporal dementia, and MDD presents considerable diagnostic problems (Braaten, Parsons, McCUE, Sellers, & Burns, 2006). Also, patients with bipolar disorder clearly experience significant depressive symptoms (Chang, 2009; Lin, Perils, & Wan, 2008).

If depression isn't controlled, significant aftereffects, such as economic, social, physical, and psychological consequences, will be seen. Several studies demonstrate that treating depression is both efficient and cost-effective (Evans-Lacko et al., 2016; Greenberg et al., 2003). There are several factors that contribute to the economic burden of depression, including the prevalence of the disease, the rate and degree of impairment, and the treatment rate (Greenberg et al., 2003). In 1990, studies indicated an average loss of 5.6 productive hours per week for depressed workers in the United States. On the other hand, treatment has its costs. The same studies estimated that the annual economic burden for direct treatment, missed wages, indirect workplace costs, and labor costs related to short- and long-term disability ranges from $44 to $53 billion (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003; Tierney, 2007). According to estimates, indirect costs to society are seven times greater than direct costs (Organization, 2005).

The additional direct cost per person decreased between 2010 and 2018, despite a rise in the entire population of MDD sufferers. In the meantime, the percentage of people with MDD who received

therapy stayed the same over the preceding ten years, indicating that this population still has significant unmet treatment needs (Greenberg et al., 2021).

Up to now, attempts to define biomarkers for MDD have not yet led to robust biomarkers. This is due to an incomplete knowledge of the molecular mechanisms underlying MDD and how these mechanisms react and interact in a dynamic environment, and it is obvious that further studies are required in order to fully understand the MDD pathophysiology.

Researchers are looking for new approaches to treat psychiatric problems because the available traditional treatments are not ideal (Larijani et al., 2021). Moreover, due to the overlapping clinical features of mental disorders and MDD, the diagnosis and treatment of depression and determining its subgroups are facing many problems. Even though significant findings have been made relating to the effective treatment of depression, there are still large gaps in our understanding. Understanding the neurobiological basis of MDD remains one of the most important challenges for modern psychiatry. A better understanding of the molecular mechanisms of MDD can open new windows in the management, treatment, and remission of patients who suffer from this disease. The aim of the current study was to highlight the significance of identifying novel biomarkers for the diagnosis and prediction of treatment responses, as well as evaluate MDD and its subtypes.

Search strategy:

The search strategies for this review are divided into two sections. A different set of search techniques is used for each of the two sections of this evaluation. At first, a literature search was conducted through PubMed and Google Scholar using the ("major depressive disorder" OR "MDD") search keywords up to June 1, 2022. The second part included articles on each part of the study topic. PubMed and Google Scholar were extensively searched utilizing combinations of the following keywords: (MDD [AND] history), (MDD [AND] mechanism), (MDD [AND] diagnosis), (MDD [AND] treatment), (MDD [AND] drug resistance), and (MDD [AND] biomarker). Each retrieved study's title and abstract were checked to see if they adhered to the inclusion or exclusion criteria. For each part of the research strategy, animal experiments, pediatric MDD, and postpartum depression were excluded. Subsequently, for the parts that needed more study, a search was made with more specific keywords. Schematic 1 represents the workflow of the study.

History:

Depression and melancholia concepts can be traced back to the 5th century B.C. in Hippocrate's writings, the father of modern medicine. "Black mood" is a description for the Greek-Latin term "melancholia," which Hippocrates attributed to excessive black bile in the brain (Marsella, Hirschfeld, & Katz, 1987; Onions, 1966). Melancholia was regarded as a mental disorder characterized by prolonged sadness and fear, "despondency, sleeplessness, irritability, restlessness," and an aversion to food (Hirshbein, 2009).

In the 2nd century A.D., Galen's restatement of Hippocrates' description of melancholia prevailed for the next 1,500 years. Galen believed that, in contrast to earlier authorities, yellow bile, nutritional deficiencies, the suppression of menstrual or hemorrhoidal flow, and emotional elements might also contribute to melancholia's origin (Ariza, Merino, & Linero, 2010; Marsella et al., 1987). During the 17th and 18th centuries, more modern, occasional theories of melancholy began to appear by physicians and Christian Church pastors in Europe. The Latin verb deprimere, which inspired the current English term for depression, means "to press down" (Kanter, Busch, Weeks, & Landes, 2008; Roystonn et al., 2021).

Five writers—Griesinger, Sankey, Maudsley, Krafft-Ebing, and Kraepelin—addressed the issue of the root of delusional melancholy during the 1860s and 1880s. The authors all came to the same conclusion—that melancholia was a basic mood disorder—and maintained that the delusions naturally resulted from the aberrant mood. During this century, the model for explaining delusional melancholia in terms of faculty psychology inverted itself from one that linked intellect to mood to one that linked mood to intellect (Kendler, 2020). In the 1980s and late 1970s, many researchers looked at the effects of norepinephrine, precursors tyrosine and phenylalanine as well as serotonin precursors L-tryptophan and 5-hydroxytryptophan (5-HTP), on depressive patients (Meyers, 2000). Depressive illness was thought of as a recurrent episodic disorder with full remission between episodes for several decades in the 20th century (Ban, 2014). At the end of the 20th century, depression, or melancholy, was recognized as a true illness of the time, comparable to the hysteria Charcot had witnessed at the Salpêtrière Hospital in Paris in the 19th century (Barroso, 2003).

Many different treatment approaches have been tried in the treatment of depressive states. Historically, there have been three phases in the development of the psychiatric treatment of depression:

The first phase, which lasted until the mid-1930s, was characterized by ineffective somatic treatment and psychotherapy. Although many different drugs and physical techniques are used, none of these treatments have a consistent therapeutic effect, even though they occasionally appear to benefit specific people. The second phase is convulsive therapy and lobotomy, which lasts from the mid-1930s to the mid-1950s of the twenty-first century. Convulsions brought on either chemically by pentamethylenetrazol (Metrazol) or electrically by a current sent through the brain at this phase of psychotherapy development comprise, for all intents and purposes, the sole therapy recommended in acute severe depressions. Around the same time, frontal lobotomies were invented, and they were successful in treating depressive disorders, especially chronic ones that had resisted electroconvulsive therapy (ECT). The third phase is pharmacotherapy. This phase began in the middle of 1950, and the development of this phase has not yet been completed (Ban, 2014; Lehmann, 1965; López-Muñoz & Alamo, 2009). An improved comprehension of the molecular mechanisms of MDD can help in the discovery of useful treatments for this disease.

Mechanism:

Identifying the cause of the pathogenesis of MDD or the prediction of the treatment response in these patients is more important, and for achieving these aims, understanding biological changes during MDD is necessary. MDD may be associated with neurotransmitters and biochemical factors, such as neurophysiologic markers, neuroimaging markers, and inflammatory markers. The main neurotransmitters involved in depression include the serotonergic system, and the noradrenergic and dopaminergic systems (H.-Y. Lee & Kim, 2013). Patients with depression have been found to have decreased hippocampal volume, which is strongly correlated with the frequency and duration of depressive episodes. Despite structural abnormalities in the brain, the neurobiology of MDD is also thought to be influenced by changes in brain neuronal function (Saltiel & Silvershein, 2015). Positron emission tomography (PET) studies in mood disorders have discovered several abnormalities in regional cerebral blood flow (CBF) and glucose metabolism in limbic structures and the prefrontal cortex (PFC) (Mössner et al., 2007). Most neurotransmitter synthesis is regulated by the brain (Meyers, 2000). Also, these brain regions' structure and function are controlled by monoaminergic neurotransmission (Saltiel & Silvershein, 2015). Monoamine neurotransmitters, particularly serotonin (5-HT), dopamine (DA), and noradrenaline (NA), have been shown to be hypoactive in MDD patients' midbrains, and these agents have received more attention because nearly all of the antidepressant drugs' mechanisms of action are through these

systems (Drevets, Price, & Furey, 2008; Werner & Covenas, 2010). In addition to the classical neurotransmitters, neuropeptides are also changed in specific brain regions during major depression. Major depression has been shown to be associated with the hyperactivity of some neuropeptides, including substance P corticotropin-releasing hormone and thyrotropin-releasing hormone, and the hypoactivity of other neuropeptides, including neuropeptide Y and galanin. (Werner & Covenas, 2010). Although the monoamine transmitter is very important, to fully comprehend the pathophysiology of the disease, the monoamine theory is insufficient on its own. Many studies indicate that immune mechanisms, especially cytokines, are implicated in depression's pathogenesis (Sahin & Aricioglu, 2013). The cytokine hypothesis of depression posits that the cytokines have a critical function in its cause. Cytokines are immune system hormones. They are composed of proteins and glycoproteins that are secreted by immune cells and act as signals among the immune cells (Dunn, Swiergiel, & de Beaurepaire, 2005). Several clinical studies reveal that people with depression indicate higher plasma levels of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α (Dunn et al., 2005). The interaction between peripheral inflammation and the central nervous system has been thoroughly studied. There are several mechanisms for entering cytokines, particularly TNF-α and IL-1β, in the brain that influence central neuronal function and cause behavioral alterations known as "sickness behavior". These mechanisms include passing through circumventricular organs, projection with peripheral vagal nerve afferents, uptake by active transport systems, crossing of cytokine induced immune cells like macrophages, monocytes, and T cells directly through the blood brain barrier and direct passage. These cytokines, after entering the brain, trigger their own production, particularly in the amygdala, dentate gyrus of the hippocampus, hypothalamus, and other parts of the brain. Also, recent studies indicated that the Toll-Like Receptors (TLRs), which have a role in neuronal function and the production of cytokines and chemokines in response to inflammation or stressful situations, have altered protein and mRNA levels in the hypothalamus of people with depression (Cattaneo et al., 2015; Sahin & Aricioglu, 2013). The neurotoxic mechanisms and the modulation of neurotransmitter metabolism are two examples of the many ways that cytokines in the brain can have an impact on brain function (Capuron & Dantzer, 2003; Cattaneo et al., 2015).

It has been suggested that the pro-inflammatory cytokines IL-1β and IL-6, which increase during infection, are crucial for synaptic plasticity, neurogenesis, and neuromodulation. These pro-inflammatory cytokines stimulate the paraventricular nucleus of the hypothalamus to secrete

corticotropin-releasing hormone (CRH), activate the hypothalamic-pituitary-adrenal (HPA) axis, and encourage the release of adreno-corticotrophin hormone (ACTH) and glucocorticoids. Understanding how IL-1β functions in the pathophysiology of depression may help explain how it affects changes in amine metabolism, neurogenesis, and neuroinflammation (Farooq, Asghar, Kanwal, & Zulqernain, 2017; Jeon & Kim, 2016; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011).

Additionally, it has been demonstrated that cytokines can cause dysfunction of the neurotrophic system and decrease neurogenesis in a number of brain regions, most notably in hippocampus. Free radicals, oxidants, and glucocorticoids are overproduced as a result of the excessive inflammatory response sparked by pro-inflammatory cytokines in the peripheral nervous system, which can disrupt glial cell activities and damage neurons in the brain. As a result, neural plasticity may eventually decline, which is a key component of depression-related dysfunction. The term "neuronal plasticity" describes several mechanisms that are essential for brain function, including the capacity to recognize, respond to, and adapt to a wide range of external and internal stimuli. It is believed that these processes can be dysfunctional in a variety of psychiatric diseases, which may ultimately increase disease vulnerability (Ariza et al., 2010; Cattaneo et al., 2015).

Furthermore, the stress hormones cortisol, ACTH, and CRH can all be increased by cytokines. These hormones have been linked to HPA dysfunction and have been found to be elevated in depressed patients. Disrupted microglia function has been linked to neurologic and psychiatric disease and could have a significant impact on neuronal activity and function (Cattaneo et al., 2015; Pariante & Miller, 2001; Zunszain et al., 2011).

Brain-derived neurotrophic factor (BDNF) has received the greatest attention as a growth factor in MDD. In the central and peripheral neurological systems, BDNF controls neuronal plasticity, migration, and survival. It is hypothesized that decreased levels of BDNF in depression are likely caused by higher corticosteroid dosages because activation of the glucocorticoid receptors (GRs) has a negative effect on the BDNF gene. Although BDNF levels in MDD may serve as a diagnostic and prognostic marker, there are still unresolved issues, such as whether peripheral BDNF is able to pass the blood-brain barrier and whether it can cause behavioral effect (Hacimusalar & Eşel, 2018).

According to neuroimaging research, depression affects a number of structurally and functionally dysfunctional brain regions, the majority of which are related to the limbic system, default mode

network, central execution network, and salience network. Together, they contribute to a number of clinical depressive symptoms (Dai, Zhou, Xu, & Zuo, 2019).

The lateral prefrontal cortex's activity is abnormally decreased in MDD patients, particularly during express voluntary control, at the point when the emotional experience is already taking place. On the other hand, it is possible that (medicated) MDD patients can control their emotions in the early, automatic stages by drawing on additional lateral prefrontal neuronal resources. Medial may act as a mediator in this plan of action (Rive et al., 2013).

The neuropharmacological mechanisms that have been proposed as the final common pathways for antidepressant responses are as follows: (1) increases in the gene expression of BDNF and other neurotrophic/neuroprotective factors in the hippocampus and PFC; (2) enhancement of postsynaptic serotonin type 1A (5-HT1A) receptor function; and (3) attenuation of the sensitivity or transmission of NMDA-glutamatergic receptors (Drevets et al., 2008).

Diagnoses:

Comprehensive evaluation and accurate diagnosis are essential components of managing depression. The evaluation must be based on a thorough history, physical exam, and mental state examination. All sources, especially the family, must be consulted for history. The diagnosis must be noted using the most recent diagnostic criteria (Gautam, Jain, Gautam, Vahia, & Grover, 2017).

The diagnosis of MDD is made using internationally accepted diagnostic criteria. The International Classification of Diseases (Mental and Behavioral Disorders, ICD-10) and the classification of the American Psychiatric Association (DSM-IV) are two of the most commonly used criteria (Farah & Gillihan, 2012). The ICD-10 classifies depression as mild, moderate, or severe (with or without psychotic symptoms) based on a list of ten depressive symptoms (Ariza et al., 2010; Kessing, 2004). The disease essentialism of the DSM-IV has come under harsh criticism from Steven E. Hyman (2011), a former director of the National Institute of Mental Health (NIMH), who stated: "The problem is that the DSM has been introduced into an understudied area, which has been accepted without question." It was formed with a focus on a paradigm shift in the system. Disclose the DSM-IV's limitations, advance research questions beyond disease essentialism, and adopt etiologically and pathophysiologically sound diagnostic systems (Kim & Park, 2021). The ICD-10 and DSM-IV diagnostic criteria for depressive episodes overlap, but there are some

differences in emphasis. ICD-10 requires that the patient exhibit two of the first three symptoms (depressed mood, loss of interest in daily activities, and decreased energy). and at least two of the remaining seven symptoms, while for DSM-IV, At least five of the nine symptoms must be present in the patient, and at least one of the first two symptoms (depressed mood and loss of interest). For both diagnostic methods, a diagnosis may only be made when the symptoms have existed for at least two weeks (Nonetheless, it might be shortened for the ICD-10 if symptoms are very severe or present quickly). Both ICD-10 and DSM-IV require that symptoms result in functional impairment that increases with the episode's severity (Health, 2010). Table 1 shows the diagnostic criteria of ICD-10.

Table1: diagnostic criteria of deppresive episode according to ICD-10:

A: somatic symptom may or may not be present: The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as:

- loss of interest and pleasurable feelings
- waking in the morning several hours before the usual time
- depression worst in the morning
- marked psychomotor retardation
- agitation
- loss of appetite
- weight loss
- loss of libido

B: Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe.

- **Mild depressive episode:** Two or three of the above symptoms are usually present. The patient is usually distressed by these but will probably be able to continue with most activities.

- **Moderate depressive episode:** Four or more of the above symptoms are usually present and the patient is likely to have great difficulty in continuing with ordinary activities.

- **Severe depressive episode without psychotic symptoms:** An episode of depression in which several of the above symptoms are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of "somatic" symptoms are usually present.

C: The episode not due to psychotropic substance abuse or organic mental disorder

Incl.: single episodes of:

- depressive reaction
- psychogenic depression
- reactive depression

Excl.:

- adjustment disorder
- recurrent depressive disorder
- associated with conduct disorders

Derived from WHO ICD-10 version 2019

Some minor changes were made to the DSM-IV diagnostic criteria for some disorders, which have made it easier for attending physicians and psychologists to make diagnoses. The goal of the DSM-5 Task Force was to make a subtle shift towards "bridging the gap between etiology-based symptomatology and identifiable pathophysiological etiology"(Kupfer & Regier, 2011; Svenaeus, 2014). Table 2 indicates the diagnostic criteria for DSM-5.

Table 2. Major depressive disorder diagnostic criteria according to a DSM 5

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanie episode.
Derived from Diagnostic and statistical manual of mental disorders fifth edition DSM-5,2013.

First, in the context of mood disorders, depressive disorders are considered a separate entity from bipolar disorders. Second, diagnostic thresholds for MDD were lowered in DSM-5 compared with those in DSM-IV. The term "hopelessness" was changed to a more individualized way of describing depressed mood, and the term "bereavement exclusion" was removed from the diagnostic criteria. In the ICD-10 diagnostic criteria for depressive episodes, the deletion of the item 'bereavement exclusion' was partially supported because clinical or genetic aspects of major depressive episodes caused by bereavement were not significantly different from those caused in other contexts of major depressive episodes. Thirdly, the transdiagnostic specifiers, such as those with psychotic features, those with mixed features, and those with anxious features, were adjusted in DSM-5. This was done to show the quantitative, not qualitative, overlapping symptoms of major depressive disorder related to anxiety disorder, schizophrenia, and bipolar disorder. According to the severity-psychosis hypothesis, the specifier was coded with psychotic features only in MDD. This hypothesis emphasizes psychotic symptoms as factors that depend on the severity of MDD. By rejecting the severity-psychosis hypothesis in several studies, the DSM-5, encoding the specifier with psychotic features, was approved for major depressive disorder as well as mild and moderate MDD and dysthymic disorder (Kim & Park, 2021; Svenaeus, 2014).

The inclusion and exclusion criteria for each diagnostic category are being reevaluated and revised in light of recent discoveries. The addition of genetic and neurobiological measures has been taken into consideration in regard to this most recent adjustment (Farah & Gillihan, 2012).

The progression of depression and how effectively a patient responds to treatment are significantly influenced by a wide range of biological, psychological, and social aspects that are not well recognized by existing diagnostic frameworks. When doing a diagnostic examination, it is crucial to take into account both the patient's past experiences with depression as well as any family history of the condition (Depression, 2009).

Brain imaging is already used by some practitioners to make psychiatric diagnoses (Farah & Gillihan, 2012).

Although the pathoanatomic foundation of mental diseases could be defined significantly with the use of modern imaging, a key challenge in using neuroimaging for psychiatric diagnosis is that the clinical usefulness of such tests depends in part on their ability to differentiate between variuos conditions. As the number of diagnostic categories regarded as clinically important increases, generally, both inter-subject and intra-subject variability in interpretation rises (Depression, 2009;

Savitz, Rauch, & Drevets, 2013). Multiple anomalies in regional cerebral blood flow (CBF) and glucose metabolism in different brain regions have been identified by positron emission tomography (PET) imaging research. Recent studies on neuroimaging have concentrated on the neurobiological abnormalities related to MDD, such as malfunctioning or structural variations in cerebral regions. Due to reactive microglia's association with a number of molecular modifications that can be detected by different radiotracers, morphological and functional changes in reactive microglia allowed for in vivo detection of microglial activation as a biomarker of central inflammation in a variety of pathological conditions, including MDD (Gritti, Delvecchio, Ferro, Bressi, & Brambilla, 2021; H.-Y. Lee & Kim, 2013).

Single photon emission computed tomography (SPECT) is the functional imaging method used as an ancillary diagnostic tool in clinical psychiatry. In particular, it helps to differentiate depression from neurodegenerative diseases when making a differential diagnosis of depression. In this imaging technique, regional cerebral blood flow is measured by tracers that emit gamma rays in the blood. A low-resolution, three-dimensional image of brain activity is created from this local blood flow data (Cho et al., 2002; Farah & Gillihan, 2012; Nagafusa et al., 2012).

The following conditions can be measured with magnetic resonance imaging (MRI): brain structure volume (structural MRI); white matter integrity and density [diffusion tensor imaging (DTI)]; or functional metabolic activity patterns (fMRI), either at rest or in response to a specific task or challenge. Moreover, fMRI can be utilized to investigate activity in specific brain regions or in coordinated temporal patterns of activity across several regions (fcMRI)(Dunlop & Mayberg, 2014; Pilmeyer et al., 2022).

Treatments:

Achieving full remission in MDD is difficult because of the chronic nature of this disease. Typical response rates in antidepressant trials are 60 to 70 percent, while remission rates are much lower (between 30 and 50%) (McIntyre & O'Donovan, 2004; Trivedi & Daly, 2008).

There are three phases of depression: mild, moderate, and severe. These three phases can be divided into two general group treatment strategies for achieving remission in MDD: one is a pharmacological treatment strategy, and the other is a non-pharmacological treatment strategy (Trivedi & Daly, 2008).

There are numerous distinct pharmacologic classes of medications that may be utilized to treat depression, and each of them can modulate depression symptoms via different mechanisms. The mechanisms of action of these drugs are apparently all involved with or dependent upon the alteration of a number of neuromediators. The neurotransmitters serotonin and norepinephrine are the main targets of most major classes of antidepressants (Gold, Machado-Vieira, & Pavlatou, 2015; Tierney, 2007).

In spite of higher acquisition costs, combination therapy for MDD can be cheaper than monotherapy. Any initial monotherapy has a low remission rate, and antidepressant combinations are currently utilized in practice at the second or following steps when relapse occurs over a longer period of time, or, in some situations, even acutely as a first step where rapidity of impact is a clinical priority. These combinations, if employed as initial therapies, may be more effective than monotherapy in terms of higher rates of remission, lower attrition, or longer-term benefits (McIntyre & O'Donovan, 2004; Trivedi & Daly, 2008).

First-line antidepressant treatment is ineffective in up to half of MDD patients, and two or more treatments are ineffective in one-third of them. Non-pharmacological treatments can be used as treatment options for treatment-resistant patients (Trivedi & Daly, 2008).

Non-pharmacological treatments can be divided into two groups include somatic treatments and psychotherapy. Somatic treatment covering vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, magnetic seizure therapy, electroconvulsive therapy (ECT), and ablative neurosurgery (Moreines, McClintock, & Holtzheimer, 2011; Trivedi & Daly, 2008) .

The creation of novel therapeutic alternatives that are based on the pathophysiology of a certain psychiatric condition and permit a more targeted approach to treatment is one of the main objectives. Invasive or non-invasive brain and/or cranial nerve stimulation procedures are one group of such therapy possibilities. VNS uses an implanted pulse generator in the left anterior chest wall to deliver intermittent electrical stimulation to the left cervical vagus nerve. The US Food and Drug Administration (FDA) granted approval for VNS in 2005 for "the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments"(Christmas, Steele, Tolomeo, Eljamel, & Matthews, 2013; Cimpianu, Strube, Falkai, Palm, & Hasan, 2017; Nemeroff et al., 2006).

To stimulate the cerebral cortex with rTMS, an electric coil is used to produce a magnetic field. Contrary to ECT, it is well tolerated by patients, doesn't require the use of anesthetics, and doesn't appear to have any adverse effects on cognitive function. The US FDA has approved using 3,000 stimuli each day to treat MDD (or 15,000 stimuli per week) (Mirabzadeh & Khodaei, 2012; Pan et al., 2020).

Usual treatments for severe TRD have some known side effects that may limit their use. ECT and ablative neurosurgery are two common solutions for severe TRD. Under general anesthesia, electrical current is serially administered through the brain in the ECT procedure in order to cause a generalized tonic-clonic seizure. Gray matter volume in the medial temporal lobes significantly increased after ECT, indicating that ECT may have a neurotrophic effect that contributes to its therapeutic efficacy. Also, the longitudinal experience with ablative techniques demonstrates that precise, distinct lesions continue to play a significant role in the disruption of affective circuitry in the management of TRD (Moreines et al., 2011; Ota et al., 2015; Volpini et al., 2017).

The earliest surgical attempt to treat TRD was an ablative neurosurgery technique. Today, there are several surgeries, including anterior cingulotomy, anterior capsulotomy, limbic leucotomy, and subcaudate tractotomy (Moreines et al., 2011). According to the evidence, even after surgeries, residual symptoms remain frequently, which leads to psychosocial dysfunction. The chances of making a full recovery are reduced when patients remain more symptomatic. There are numerous ongoing initiatives to deploy cutting-edge ablative therapy for the brain. Recent advances in cerebral ablation techniques have led to the development of new methods that enable precise targeting, accurate thermal dose delivery, and real-time visualization of induced tissue damage. Examples of these methods include magnetic resonance-guided focused ultrasound and laser interstitial thermal therapy. The accuracy of ablative operations may be further enhanced by new modalities, including MRgFUS, while safety is increased by avoiding open-brain surgery. This technique has gained popularity over the past ten years, and its therapeutic uses are expanding. Nonetheless, more traditional procedures like stereotactic radiosurgery and radiofrequency thermal ablation continue to play a crucial part in the treatment of numerous neurological illnesses (Franzini, Moosa, Prada, & Elias, 2020; Franzini et al., 2019; Volpini et al., 2017).

According to the theoretical base, brief psychotherapy interventions can be divided into four primary categories: psychodynamic therapy (grounded in psychoanalytic principles), interpersonal

therapy (IPT), supportive counseling (Rogerian person-centered therapy), and cognitive behavioral therapy (CBT) (Möller & Henkel, 2005).

Two effective short-term psychotherapies for major depression are IPT and CBT (Aronson & Ayres, 2000). Specifically, in depression, CBT seems to decrease residual symptoms and lead to reduce the risk of relapse. Also, for the first-line treatment of MDD in children and adolescents, CBT is the most efficient and cost-effective approach. It has been proposed that combining antidepressant medication with psychotherapy may be more successful than using either approach separately (Haby, Tonge, Littlefield, Carter, & Vos, 2004; Trivedi & Daly, 2008).

According to IPT, there is a correlation between interpersonal issues and depressive symptoms that has a major impact on the development and maintenance of depressive disorders. Hence, the primary therapy goals of this strategy are interpersonal issues. The definition of four interpersonal difficulty areas includes interpersonal role disputes, role transitions, complicated bereavement, and interpersonal deficits (Brakemeier & Frase, 2012).

Despite the fact that both CBT and IPT can be successful therapies for MDDs, it is still unclear which therapy is superior to the other (Zhou, Hou, Liu, & Zhang, 2017).

Clinical decision-making is made easier and more consistent by the use of treatment algorithms, which offer specific steps. In psychiatry, treatment algorithms were designed to enhance patient outcomes by reducing prescribing variance, boosting the appropriateness of medications and dosages, and avoiding "pseudoresistance"(Vaccarino & Kennedy, 2022). Treatment algorithms (TAs), which are made up of sequential treatment strategies and standardized instructions for therapeutic choices, have been created as a solution to this issue. These TAs are made to prevent treatment resistance and to increase the quality of care in order to improve results (Ricken et al., 2018). The Texas Medication Algorithm Project (TMAP) compared the clinical and financial results of algorithm-guided treatment (ALGO) and treatment as usual (TAU) using predetermined medication algorithms, clinical support, and a predetermined patient and family educational package. Based on clinician-rated and patient-reported symptoms as well as total mental functioning during a year, the ALGO intervention package was more effective for patients with MDD than TAU (Trivedi et al., 2004).The ALGO group included patients who needed to start antidepressant therapy or change their antidepressant medications. Initially, the TAU group followed similar criteria, but because less frequently did the TAU group's medication need to be

changed,if the patient's Brief Psychiatric Rating Scale total score was higher than the median for the clinic's regular quarterly evaluation of each patient, they also joined (Trivedi, 2007).

Drug resistance:

Antidepressants, in turn, ameliorate many of the neurobiological disturbances in depression and thereby alleviate depressive symptoms, but multiple therapies are ineffective for up to one-third of individuals with MDD who are receiving sufficient care (Anacker, Zunszain, Carvalho, & Pariante, 2011; De Carlo, Calati, & Serretti, 2016). MDD patients responses to antidepressant drugs are different (table 3) (El-Hage, Leman, Camus, & Belzung, 2013).

Table 3: Types of response to antidepressants in MDD patients

non-response	only minimum improvement is achieved
partial response	score on the standardized instrument decreases by 25–50%
Response	when a decrease of at least 50% is obtained
Remission	only residual clinical symptoms are reported
Derived from El-Hage W et al 2013	

Despite the fact that first-line antidepressant (AD) therapy significantly alleviates the symptoms of depression in numerous cases, only fifty to sixty percent of MDD patients respond to the treatment. In addition, thirty to forty percent of MDD patients never get symptom remission after taking standard AD medication (Rogóż, 2013). Numerous definitions of treatment-resistant depressed (TRD) patients have been proposed, and there is no validated consensus definition of TRD. To define depressed disorders that did not sufficiently remit following treatment, one of the most basic TRD concepts was proposed. Resistance is most commonly defined as the inability of a current depressive episode to respond to at least two sufficient trials (Berlim & Turecki, 2007; El-Hage et al., 2013; Guilloux et al., 2012). TRD is described by the European Agency for the Evaluation of Medicinal Products as the inability to respond to two medications from different classes that have been administered for long enough at a sufficient dose without any particular mention of an appropriate dosage or duration by regulatory authorities. TRD is not defined by the US FDA (Mathew, 2008).TRD is widespread, increasing the risk of suicide, disability, and patient suffering (Moreines et al., 2011).

Numerous comprehensive studies have been conducted on the issue of AD-resistant depression (Rogóż, 2013). There are some strategies for dealing with these problems. Combination therapy is one of these strategies, and it involves giving patients who only partially respond to one antidepressant a second medication. This strategy is commonly used to improve the response to initial treatment (Ables & Baughman III, 2003). Also, for patients who have only partially responded, adding a non-antidepressant medication to an antidepressant is a helpful method. Thyroid hormone, Lithium, beta-blocker pindolol (Visken), and buspirone (Buspar) are four substances that are widely used in augmentation therapy. lithium and triiodothyronine (T3) are the best document options. Studies indicated that lithium decreased the activity of post-synaptic serotonin or 5-HT receptors and leading to enhances serotonin transmission.T_3 may be used to improve the effects of tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRIs) (Ables & Baughman III, 2003; Cadieux, 1998; Joffe, Sokolov, & Levitt, 2006).

The more successful treatment for individuals who have severe resistance to antidepressant therapy or those with psychotic depression is electroconvulsive therapy, a nonpharmacological intervention that is routinely evaluated as a measure of TRD (Ables & Baughman III, 2003; Trevino, McClintock, Fischer, Vora, & Husain, 2014).

Four staging methods have been proposed for classifications of TRD, these classifications include the "Thase and Rush staging method" (Thase & Rush, 1997), which involves graduating stages of resistance according to response to one or more different therapeutic approaches (table 4).

Table 4: Thase and Rush staging method

Stage	**Description**
Stage 0	Any medication trials, to date, determined to be inadequate
Stage I	No response to ≥1 adequate trial of 1 major class of antidepressants
Stage II	No response to ≥2 adequate trials of ≥2 distinctly different classes of antidepressants
Stage III	Stage II + non-response to an adequate trial of a TCA
Stage IV	Stage III + non-response to an adequate trial of a MAOI
Stage V	Stage IV + non-response to electroconvulsive therapy
Adapted from Thase and Rush 1997	

The "Massachusetts General Hospital staging method (MGH-S)"(Fava, 2003) is based on the number of antidepressant trials carried out and their possible alteration, but disregards the variation in pharmacological classes among the trials. The MGH-S method evaluates the dose and duration of each prior therapy to take into account the intensity and optimization of that particular treatment (table 5).

Table 5: Massachusetts General Hospital staging method

Stage	**Description**
1	Nonresponse to each adequate (at least 6 weeks of an adequate dose of antidepressant) trial of a marketed antidepressant generates an overall score of resistance (1 point per trial)
2	Optimization of dose, optimization of duration, and augmentation/ combination of each trial (based on the MGH or Antidepressant Treatment Response Questionnaire) increase the overall score (.5 point per trial per optimization/strategy)
3	ECT increases the overall score by 3 points
Derived from Fava 2003	

The "European Staging Method" (Souery et al., 1999) includes both classification and staging approaches to TRD as well as chronic aspects of resistance (table 6).

Table 6: European Staging Method

Stage	Description
A	Non-responder to: TCA, SSRI, MAOI, SNRI, ECT, and Other antidepressant(s) • Non response to one adequate antidepressant trial • Duration of trial: 6–8 weeks
B	Treatment Resistant Depression (TRD) • Resistance to 2 or more adequate antidepressant trials • Duration of trial(s): TRD 1: 12–16 weeks TRD2: 18–24 weeks TRD3: 24–32 weeks TRD4: 30–40 weeks TRD5: 36 weeks–1 year
C	Chronic Resistant Depression (CRD) • Resistance to several antidepressant trials, including augmentation strategy. • Duration of trial(s): at least 12 months
Adapted from Souery et al 1999	

"Maudsley Staging Method (MSM)"(Fekadu et al., 2009) includes the number of unsuccessful treatment trials, the chronicity of the disease, and, in addition, incorporates measurements of disease severity as a significant cofactor (table 7) (Guilloux et al., 2012; Trevino et al., 2014).

Table 7: Maudsley Staging Method

Parameter	specification	Score
Duration	Acute (≤12 months)	1
	Sub-acute (13 to 24 months)	2
	Chronic (>24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures	Level 1: 1–2 medications	1
Antidepressants	Level 2: 3–4 medications	2
	Level 3: 5–6 medications	3
	Level 4: 7–10 medications	4
	Level 5: >10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
Total		(15)
Derived from Fekadu et al 2009		

In contrast to treatment restistance, there is pseudoresistance. pseudoresistance can result from inadequate dosage or treatment length, patient noncompliance, or uncommon pharmacokinetics, as well as a misdiagnosis of the primary disorder due to failure to recognize a secondary mood disorder or a depressive subtype (Mirabzadeh & Khodaei, 2012). Differentiating between true treatment-resistant depression and psoudoresistance is the clinician's initial task. During the clinical assessment, three areas are concentrated on in order to rule out pseudoresistance: 1) physician-related factors, 2) patient-related factors, and 3) accuracy of diagnosis (Kornstein & Schneider, 2001)

Discussion:

Clinical observations of behavioral changes are often used to characterize psychiatric disorders (Niciu et al., 2014). Clinical medicine is really interested in the development of objective,

biologically-based tests for psychiatric disorders (First et al., 2018). Obtaining personalized medicine in psychiatry is a valuable goal because its success could result in a significant decline in morbidity and mortality(Ozomaro, Wahlestedt, & Nemeroff, 2013). MDD is a major contributor to disability worldwide and an important risk factor for noncompliance with medical treatment. It is a complicated phenotype driven by multiple biological disruptions and may result in numerous physiological changes (J. Lee et al., 2015; D Martins-de-Souza et al., 2014).

It is clear from our study that pro-inflammatory cytokines enter the brain through various mechanisms, affecting central neuronal function and causing "sickness behavior." These cytokines trigger their own production in the brain's regions, including the amygdala, dentate gyrus of the hippocampus, hypothalamus, and other parts of the brain. Also, PET studies have identified abnormalities in regional CBF and glucose metabolism in limbic structures and PFC in mood disorders. So to create a more comprehensive understanding of the brain circuitry underlying MDD, more research to integrate studies on the different parts of the brains like the hippocampus and amygdala, and hypothalamic circuits are needed.

Our study revealed that decreased levels of BDNF in MDD may serve as a diagnostic marker, but unresolved issues remain, such as whether peripheral BDNF is able to pass the blood-brain barrier and whether it can cause behavioral effects. According to the study, electroconvulsive treatment (ECT) increased the levels of serum BDNF in patients with depression (Rocha et al., 2016). Also, there are a number of studies that show antidepressants may be crucial in activating TrkB receptors and raising brain levels of BDNF (Rana, Behl, Sehgal, Srivastava, & Bungau, 2021). Depressive behaviors do not appear to be caused by genetic disruption of the signaling pathways involving BDNF and its receptor, the tyrosine kinase TrkB, but it does reduce the effectiveness of antidepressant medications. Therefore, while BDNF is not the only mediator of depression or anxiety, it may be a target for antidepressants (Martinowich, Manji, & Lu, 2007).

Despite all the advancements made thus far, as summarized in Table 8, there are still a lot of unanswered issues that need to be answered in the future (Brigitta, 2022).

Table 8: A summary table of the findings that are part of this literature review

	category	Summary of findings
Mechanisms		
1	neurotransmitters and biochemical factors	Neurotransmitters: the serotonergic system and, the noradrenergic and dopaminergic systems biochemical factors: neurophysiologic markers, neuroimaging markers, and inflammatory markers
2	structurally and functionally dysfunctional brain regions	decreased in hippocampal volume, decreased in lateral prefrontal cortex's activity
3	changes in brain neuronal function	abnormalities in regional CBF and glucose metabolism in limbic structures and PFC
4	immune mechanisms	Increased in plasma levels of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α
5	growth factor	decreased in the BDNF levels
Diagnoses		
1	Comprehensive evaluation	thorough history, physical exam, and mental state examination
2	internationally accepted diagnostic criteria	ICD-10 DSM-IV
3	Brain imaging	PET SPECT MRI
Treatments		
1	pharmacological treatment strategy	Monotherapy combination therapy
2	non-pharmacological treatment strategy	psychotherapy (psychodynamic therapy, interpersonal therapy, supportive counseling, and cognitive behavioral therapy somatic treatments (VNS, rTMS, deep brain stimulation, magnetic seizure therapy, ECT, and ablative neurosurgery)

The pharmaceutical treatments that are currently available are generally designed to improve monoamine-dependent neurotransmission, but pharmacotherapy is not always effective, so new non-monoamine-based approaches such as melatonergic mechanisms and glutamate methods are becoming increasingly important. Other therapies, including psychotherapy, electroconvulsive therapy, magnetic transcription, activating the vagus nerve system, and deep brain stimulation, are unclear but, to varying degrees, effective (Malik, Singh, Arora, Dangol, & Goyal, 2021). Also, a staging model for TRD should ideally be able to categorize patients based on their level of MDD treatment resistance. Psychopathological and biological indicators for staging TRD, similar to those used in oncology, may help to better predict the course and prognosis of the disease (Ruhé, van Rooijen, Spijker, Peeters, & Schene, 2012). The lack of biomarkers that can effectively diagnose MDD and predict treatment responses, as well as evaluate MDD and its subtypes, is

critical in clinical practice and continues to be a bottleneck in the pharmaceutical industry (Ding et al., 2014; Huang & Lin, 2015; Mora, Zonca, Riva, & Cattaneo, 2018).

In recent years, there has been a lot of interest in the application of omics technology to determine the underlying mechanisms of diseases and find biomarkers (Gilanchi et al., 2020). A "systems biology"-based method can be helpful for discovering predictive biomarkers in mood disorders because it compiles and integrates a number of hierarchical levels or domains, making it a useful tool for future studies (Niciu et al., 2014). Diagnostic categories based on symptom patterns that have a distant relationship to biological mechanisms restrict the development of biomarkers for mental disorders. In disorders with high heritability (schizophrenia, autism, and Alzheimer's disease), genomic research has produced significant genome-wide association study (GWAS) results, whereas in disorders with moderate heritability (anxiety disorders, unipolar major depression), the development of symptoms relies more on environmental risk factors. Methods to identify biologically more homogeneous subgroups are needed to advance biomarker research (Bagdy & Juhasz, 2013). For the purpose of better comprehending the mechanisms driving brain phenotypes and neuropsychiatric disorders, a field known as "neuroimaging genomics" has emerged that combines genomic and imaging data (Mufford et al., 2017). Significant genetic-neuroimaging connections were discovered for the monoaminergic, BDNF, glutamatergic, HPA axis, and other common genes, which were in line with theories about the pathophysiology of MDD (Zhang, Mellor, & Peng, 2018).

Further information regarding the function of the genome may be provided by proteomic research. Systems biology analysis can be used to evaluate proteome-generated data in order to better understand the origins and effects of complex psychiatric disorders like MDD (Daniel Martins-de-Souza, Harris, Guest, Turck, & Bahn, 2010). A proteomic study on the brains of post-mortem depression patients in 2012 discovered changes in the expression of arachidonic acid and phospholipase D2 (PLD2), both of which are components of membrane structure and function and are key components of synaptic vesicle membranes, and these changes have also been linked to depression (Daniel Martins-de-Souza et al., 2012). Proteomics is a helpful tool for identifying disease-specific biomarkers in body fluids by examining global protein profiling (Amiri-Dashatan, Koushki, Abbaszadeh, Rostami-Nejad, & Rezaei-Tavirani, 2018). In 2012, Ditzen et al. researched MDD CSF and found 11 differentially expressed proteins as biomarker candidates for MDD (Ditzen et al., 2012). A proteome study of the plasma presented by Xu and colleagues identified

nine proteins that are expressed differently in MDD patients and the control group (Xu et al., 2012). However, most proteomic studies have actually provided an understanding of the molecular aspects of MDD, and very limited studies have identified differentially expressed proteins as candidate biomarkers for MDD. It is still possible to identify proteins in the field of proteomic research that may aid in not only diagnosis but also patient classification according to various types of MDD (such as atypical depression and psychotic depression), prognosis, treatment monitoring and response evaluation, and potential drug targets to be used (Daniel Martins-de-Souza, 2012). Moreover, recent investigations have revealed changes in epigenetic markers in suicide victims, raising the possibility that there is a connection between epigenetics and depression. Advances in proteomic technology have made it possible to explore epigenetic mechanisms in a high-throughput way (Xu et al., 2012). In addition, to functionally validate changes in protein expression, targeted analysis of metabolites has been used (Daniel Martins-de-Souza et al., 2010). Also, in MDD patients, the use of neuroimaging techniques to predict anticipated therapeutic results is quickly evolving. The fronto-insular cortex's pretreatment resting state metabolic activity may be able to distinguish between individuals who are likely to respond to psychotherapy and those who are more likely to respond to medication, and it may serve as a biomarker for treatment selection (Dunlop & Mayberg, 2022).

Also Many scientists in medicine have been interested in bioinformatics, particularly in the investigation of disease-related protein networks. Many bioinformatics studies have been conducted on a variety of diseases thus far in an attempt to identify therapeutic and diagnostic biomarkers. There have been some studies done on diseases, including psychological disorders and depression. This method may result in new diagnostic guidelines for the early identification and assessment of these conditions (Maghvan et al., 2017). Considering disease conditions change the biological pathways by which proteins are expressed, studying these changes in tissue, blood, urine, or other biological samples could reveal disease markers (Amiri-Dashatan et al., 2018). Also disease-related tissue damage may sometimes alter body fluids' metabolic profiles (Khalkhal et al., 2021).

since tissue alterations are known to manifest in body fluids. Considering that human brain samples cannot be obtained and because of the heterogeneity of MDD, patients' brains undergo extensive changes. In order to identify biomarkers, it will be very helpful to examine all body fluids, including cerebrospinal fluid, serum, plasma, and urine. Moreover, because psychiatric disorders

are so diverse, a single biomarker is insufficient to determine the cellular and molecular pathways involved in a specific person. The most efficient method for diagnostic and treatment decision-making will be to identify a panel of biomarkers with high sensitivity and specificity for different disease subtypes based on their underlying biological mechanisms.

These findings opened a new window to personal medicine because these data suggest that new biomarkers may make it possible to divide MDD patients into different subtypes. Validating such robust biomarkers might result in novel personalized medicine strategies that are based on patient classification. However, it would be a mistake to limit the study to non-imaging markers, as imaging techniques offer the most accurate evaluation of the organ that is the origin of the disease, but identifying new biomarkers for MDD using molecular profiles may also result in drug discovery and more targeted treatment for MDD patients.

It is important to point out that the current review contains certain limitations. For instance, some methodological considerations, such as the gender of the patients in studies, were not taken into account while determining the inclusion/exclusion criteria. Also, as studies do not always clarify the drug treatment of patients, this information was not considered for the inclusion or exclusion criteria of the study.

Conclusion:

Our findings provide a comprehensive profile of the MDD. The results of this study demonstrated that, despite the high prevalence of MDD, there are still many unresolved issues with regard to the diagnosis, the course of treatment, and the identification of the primary mechanisms underlying the disease. Our study indicated there is a need to find novel biomarkers for this disease because, due to the lack of biomarkers based on physiological measures or diagnostic tests, objective diagnosis and prognosis in MDD remain difficult. Additionally, in order to identify biomarkers with high accuracy, high-quality and prospective studies are necessary. Systems biology studies can play a significant role in the disease's future. Also A more comprehensive and multivariable strategy that combines several approaches, including bioinformatics, proteomics, metabolomics, and neuroimaging techniques, would allow the diagnosis and treatment of depression to be personalized and play a significant role in monitoring therapy efficacy and follow-up of disease. Also, biomarkers help us better understand the neurobiology of different depression subtypes.

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The authors declare that they have no conflict of interest.

Author Contributions:

Conceptualization, Mostafa Rezaei Tavirani, Samira Gilanchi ; Methodology, Mostafa Rezaei Tavirani, Samira Gilanchi ; Investigation, Samira Gilanchi, Mahyar Daskareh; Writing – Original Draft, Samira Gilanchi, Mostafa Rezaei Tavirani; Writing – Review & Editing, all authors; Funding Acquisition, No funding was provided by any sources for this paper; Supervision, samira gilanchi

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