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Review

Advancements Exploring Major Depressive Disorder: Insights on Oxidative Stress, Serotonin Metabolism, BDNF, HPA Axis Dysfunction, and Pharmacotherapy Advances

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Abstract: Major depressive disorder (MDD), a prevalent mental illness, is marked by a complex mixture of biological factors. This review focuses on the roles of oxidative stress, tryptophan-serotonin metabolism, brain-derived neurotrophic factor (BDNF), and the hypothalamic–pituitary–adrenal (HPA) axis in MDD's pathophysiology. Oxidative stress, defined as an imbalance between pro-oxidants and antioxidants, is closely linked to MDD's neurobiological changes. The tryptophan (TRP)-/serotonin (5-HT) metabolic pathway is also known to be crucial in mood regulation, with its dysregulation being a central aspect of MDD. Additionally, BDNF, key for neuronal growth and plasticity, often shows alterations in MDD patients, supporting its role in the disorder's progression. Furthermore, the HPA axis, which manages stress response, is frequently disrupted in MDD, further contributing to its complex pathology. In addition to exploring these biological mechanisms, this review also explores the pharmacotherapy of MDD, including new advances. These advancements in treatment strategies are crucial for managing MDD effectively. Understanding these mechanisms and the latest pharmacological interventions is essential for developing more effective treatments for MDD.

Keywords: major depressive disorder; oxidative stress; tryptophan; serotonin; brain-derived neurotrophic factor; hypothalamic–pituitary–adrenal axis; stress; pharmacotherapy

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1. Background

Depression is a mental health disease, manifesting in various forms that impact individuals uniquely. The World Health Organization (WHO) reports that approximately 280 million people worldwide suffer with depression [1]. MDD, commonly only referred to as depression, represents a debilitating condition characterized by at least one distinct depressive episode lasting a minimum of two weeks, marked by shifts in mood, anhedonia, and cognitive symptom disturbances [2]. This condition is heterogeneous, with potential consequences extending to suicide [3,4]. People suffering from MDD also have several social stigmas and high occurrences of physical health conditions like heart disease and type 2 diabetes [4]. The complexity of this disease presents a significant challenge for neuroscience, as no single established mechanism can fully elucidate its nature.

A challenge in dealing with this disease is the frequent recurrence, treatment ineffectiveness, and the absence of diagnosis and treatment options, particularly in low- and middle-income countries [1,2,5]. Nevertheless, there are viable treatment approaches, notably psychotherapy and/or the use of antidepressants [2]. Both demonstrate efficacy

in addressing MDD. Still, approximately 30% of individuals affected by MDD do not experience remission, even after multiple treatments [2,6].

Despite the complex nature of MDD, several studies support the importance of various factors, including neurotransmitters, oxidative stress and neurotrophic factors (particularly BDNF) in contributing to this condition [7,8]. Structural alterations, in brain regions such as the prefrontal cortex (PFC) and hippocampus are also significant [9]. Indeed, previous studies have shown that the hippocampus is smaller in depressed patients [10,11].

In this review, we are going to explore the role of oxidative stress, 5-HT pathway, BDNF, and HPA axis dysfunction in MDD. Additionally, we are also going to focus on the pharmacotherapy advancements of MDD in recent years. Figure 1 represents a succinct illustration of some aspects involved in depression that will be addressed in this review.

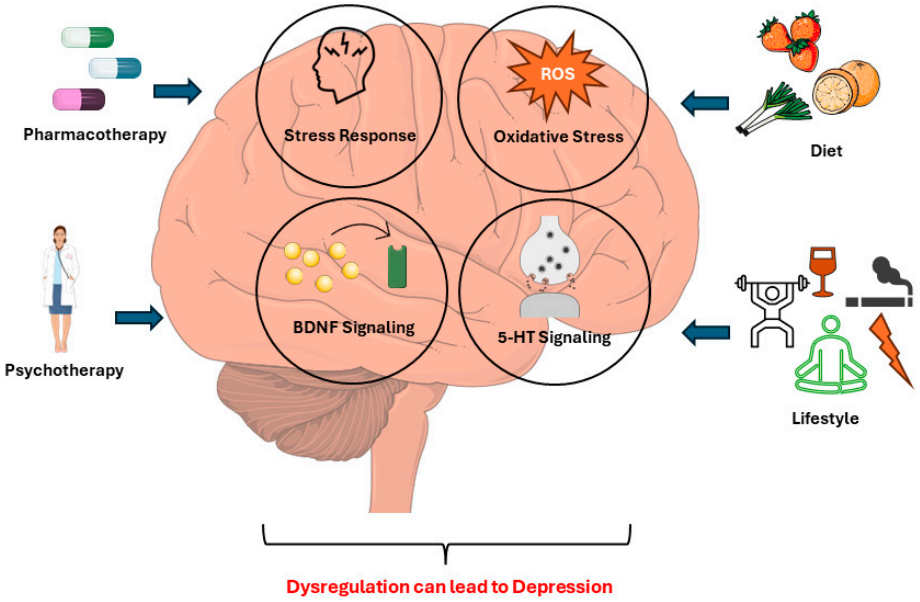

Figure 1. Stress response, oxidative stress, BDNF signaling and 5-HT signaling are crucial to depression development and progression. These systems can be influenced through diet and lifestyle factors, being managed using approaches like pharmacotherapy and psychotherapy.

2. Exploring the Role of Oxidative Stress, Tryptophan-Serotonin Metabolism, Brain-Derived Neurotrophic Factor, and Hypothalamic–Pituitary–Adrenal Axis Dysfunction in Major Depressive Disorder

2.1. Oxidative Stress as a Key Contributor to Major Depressive Disorder Pathogenesis

Oxidative stress forms from an imbalance in the equilibrium between the formation of free radicals, particularly reactive oxygen species (ROS), and antioxidants. Furthermore, the exposure to environmental stressors, like smoking or ultraviolet radiation, can accentuate the challenge of maintaining this equilibrium [12]. A balanced diet rich in antioxidants, regular exercise, and stress reduction techniques can help maintain oxidative balance [13].

The principal ROS presented in the human body are mainly produced in mitochondria, peroxisomes, and the endoplasmic reticulum, being generated through enzymatic reactions that encompass enzymes such as cyclooxygenases (COXs), nicotinamide adenine dinucleotide phosphate (NADPH), lipoxygenases and through the known Fenton reaction [14,15]. Oxidative stress damages cells primarily through the oxidation of lipids, proteins, and DNA, triggering a cascade of cellular mechanisms leading to cell damage [15,16].

To protect against the effects of increased ROS levels, cells have antioxidant defenses, such as superoxide dismutase (SOD) and catalase (CAT), important to maintain ROS homeostasis [12,17]. Exogenous antioxidant defenses may also be introduced by diet or nutritional supplementation, such as carotenoids, vitamins C and E [12,18].

High-oxidative stress levels accentuate various cellular mechanisms implicated in MDD, including the stress response, neuroinflammation, neurotransmitter signaling disturbance, and impaired neurogenesis/synaptic plasticity [19,20]. The brain is vulnerable to oxidative stress, due to its high oxygen consumption and lipid content. Also, neurons, astrocytes and microglia are rich in mitochondria and NADPH oxidase (NOX), generating high levels of ROS. This makes oxidative stress an important cause of neurodegeneration and a key factor in MDD. Addressing these changes with suitable antioxidants could be an effective strategy for treating MDD [15,20,21].

Depression is linked to reduced consumption of antioxidants like vitamins A, B, C, E, selenium, and zinc [22]. There is also evidence that high levels of lipid peroxidation in the brain lead to increased oxidative stress levels [20]. Analysis of lipid peroxidation markers in MDD (particularly malondialdehyde) demonstrated that this process was greater in MDD individuals than in controls, being connected with more severity [23]. When combined with a decrease in antioxidant defenses, these mechanisms support the role of oxidative stress as a key player in depression [20]. Also, research reported elevated levels of peroxidation biomarkers combined with reduced antioxidant activity in the plasma and serum of individuals with MDD [21,24,25]. Targeting hypoxia-related pathways may also be a promising tool for depressive disorders in the context of mitigating high-oxidative stress levels, enhanced by hypoxia [8,26]. In fact, recent findings from our investigation group revealed that hypoxia–ischemia triggers ROS elevation in neuron-like cell lines. Treatment with edaravone enhanced cell viability and decreased ROS levels, likely attributable to its free radical-scavenging characteristics [27]. Various studies have also observed reductions in antioxidant levels in both depressed patients and animal models of depression [21,28]. Furthermore, it has been demonstrated that antidepressants have antioxidant properties, and antioxidants exhibit antidepressant effects. For instance, fluoxetine and citalopram enhanced SOD activity and ascorbic acid levels, reducing malondialdehyde in MDD patients [21,29]. Research conducted on cell lines further supports the link between oxidative stress and depression. Notably, the introduction of H_2O_2 to these cells resulted in a reduction in cellular viability. However, this effect was ameliorated when serotonergic compounds such as mirtazapine and L-TRP were applied. These compounds not only enhanced cell viability in the presence of H_2O_2 but also led to a reduction in ROS levels and mitigated DNA damage following exposure to oxidative stress [30,31].

These studies support the significant role of oxidative stress as an important factor in the pathogenesis of depression and suggest that antioxidant activity holds promise as a potential therapeutic approach.

2.2. Unraveling the Hypothalamic–Pituitary–Adrenal Axis Dysregulation in Major Depressive Disorder

HPA axis is important in regulating functions such as energy balance, reproduction, and response to stress [32,33]. The elements of the HPA axis are the hypothalamus, pituitary gland and adrenal glands. The hippocampus contains neuroendocrine neurons that synthesize and secrete vasopressin and corticotropin-releasing hormone (CRH), mainly in the paraventricular nucleus (PVN). In response to stress, CRH and vasopressin are released into hypophysial portal vessels that access the anterior lobe of the pituitary gland to secrete adrenocorticotropic hormone (ACTH) via the activation of the cyclic adenosine monophosphate (cAMP) pathway, after binding to the CRH receptor 1 and vasopressin V1b (or V3) receptor, respectively. The adrenal cortex produces glucocorticoid hormones (mainly cortisol in humans) in response to stimulation by ACTH, which binds to the melanocortin type 2 receptor. These glucocorticoids regulate physiological responses and inhibit further HPA axis activation [34].

When the HPA axis is triggered, it leads to an increase in glucocorticoid levels, an important component in the body's adaptation to stress [35,36]. Different reactions to stress are observed, depending on if it is of a short-term or long-term nature. The short-term is a natural physiological response, while the long-term tends to be detrimental. Under physio-

logical settings and in a stress-free context, healthy persons release between 10 and 20 mg of cortisol on a daily basis with regular peaks [37]. Initially, there's a rise in ACTH levels, which triggers the release of cortisol. However, when someone experiences prolonged, chronic stress, cortisol levels remain elevated due to more adrenal sensitivity. [38]. Thus, when faced with uncontrollable and prolonged stress, it can lead to a range of alterations in various aspects of the CNS, contributing to neuropsychiatric and neurodegenerative conditions [35,39]. In fact, elevated cortisol secretion during stressful situations can significantly impact the functioning of the brain. This hormone has a pronounced effect on the hippocampus due to the abundance of steroid receptors it possesses [37,40]. Recurrent exposure to stress triggers alterations in neuronal structures. When stress is acute, the hippocampal atrophy that may occur is often reversible. However, chronic stress can result in the neuronal death within the hippocampus. Numerous studies suggested that conditions like depression and post-traumatic stress disorder are associated with a reduction in the volume of the hippocampus, as well as that of the PFC and amygdala [37,41].

Glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) are the intracellular nuclear receptors that respond to cortisol. GRs are found throughout the brain and peripheral tissues, while MRs are primarily located in cardiovascular tissues, the liver, kidneys, and certain brain regions like the corticolimbic areas [42]. These receptors can activate or repress the transcription of genes in the cell nucleus and also mediate non-genomic effects [43]. During the day, nuclear MRs are typically occupied by cortisol, remaining active. However, during the night, when cortisol levels are very low, these MRs become unoccupied. When cortisol levels rise significantly, both nuclear GRs and membrane-associated MRs and GRs become occupied by this hormone, leading to changes in synaptic plasticity at the cellular level [42,44].

Hyperactivity of the HPA axis is one of the most studied findings in MDD. This hyperactivity results in an increased level of glucocorticoids, which can disrupt the body's ability to regulate these hormones effectively [45].

In individuals with MDD, the GR typically becomes compromised, resulting in a diminished capacity for negative feedback regulation [46]. This dysregulation leads to an increased synthesis of glucocorticoids [47]. Antidepressant drugs, on the other hand, also work by influencing the functioning of this system. These influences can take different forms, including the regulation of the expression of the GR and post-translational modifications. As a result, the therapeutic effects of antidepressants involve, at least in part, the restoration of the function of GR [48].

High stress levels have also been associated with disturbances in 5-HT pathways, modifications in the structure of brain regions like the hippocampus and PFC, and epigenetic alterations in genes such as *BDNF* [49–51]. Long-term exposure to corticosterone has been demonstrated to induce modifications in the structure of neuronal dendrites, promoting the atrophy [52,53]. Moreover, research on postmortem tissue from individuals with depression and animal models has provided insights into the modifications at the cellular level connected with this condition, particularly structural changes in the brain, including dendritic atrophy, neuronal loss, and alterations in glial elements [54].

The connection between oxidative stress and MDD's associated stress response is also important in the context of MDD [55]. Increased production of ROS leads to the hyperactivation of the HPA axis [56]. Furthermore, the release of glucocorticoids caused by HPA axis activation increases the activity of cellular reduction-oxidation systems. When stress activates GRs, there is an increase in mitochondrial membrane potential and mitochondrial oxidation [57]. Consequently, it leads to the generation of ROS, leading to oxidative damage [15,58].

Both glucocorticoids and inflammation have been linked to the pathogenesis of depression [59]. According to the glucocorticoid resistance paradigm, less sensitivity to cortisol's anti-inflammatory properties causes increased inflammation in depression. Animal research have indicated that repeated social defeat can produce glucocorticoid-resistant monocytes, depressive-like behaviors in animal models, and enhance neuroinflammatory signal-

ing [60,61]. Human studies have concurrently observed reduced GR function/expression, HPA axis hyperactivity, and increased inflammation in depressed patients [46,60]. In fact, depressed people frequently show HPA axis hyperactivity and GR dysfunction, despite elevated inflammatory markers and the glucocorticoids' anti-inflammatory properties. This seeming paradox might be attributed to the fact that the glucocorticoid and inflammatory systems naturally coexist in equilibrium. Chronic stress may alter this balance, favoring inflammatory processes and weakening glucocorticoid signaling. Persistent stress may disrupt the homeostatic balance, causing inflammation while inhibiting the anti-inflammatory effects of glucocorticoids. Also, inflammation and glucocorticoid signaling have separate effects on the same biological processes and structures, resulting in cumulative damage that contributes to depression. In this case, these two systems may not interact directly, but they do converge on shared pathways that lead to depression. Understanding the connection is critical for finding therapy targets in depression [62].

Additionally, inflammatory changes within the brain have been linked to conditions such as dementia and MDD, highlighting the implications of these interactions [63]. Stress-induced proinflammatory cytokine production also stimulates the indoleamine 2,3-dioxygenase (IDO)/ kynurenine (KYN) pathway in cells including macrophages. IDO has an important part in the catabolism of TRP, which results in lower 5-HT levels [64]. Particularly noteworthy is the link between elevated concentrations of interleukin (IL)-1 and IL-6 and the stress response [65,66]. Indeed, an elevated production of IL-6 has been observed to play a role in MDD prognosis and how individuals respond to treatment, possibly through activation of the HPA axis [67].

The study of the stress response, which is predominantly regulated by the HPA axis, provides a road to understanding the underlying biological mechanisms that are present in depression, allowing for the development of more effective therapies.

2.3. Exploring Tryptophan/Serotonin's Role in Major Depressive Disorder

TRP is an amino acid with important implications in several physiological reactions. There are two major pathways of TRP metabolism: the KYN pathway and the 5-HT pathway [68].

The 5-HT pathway of TRP metabolization is extremely important in human physiology, influencing several physiological functions. 5-HT networks are important players in behavioral aspects, including mood regulation and memory processing. Moreover, these networks modulate motor coordination, circadian rhythm, and thermoregulation. The 5-HT pathway extends its influence on diverse physiological processes such as gastrointestinal regulation and nociception [69].

The pathway starts with the conversion of TRP to 5-hydroxytryptophan (5-HTP) by TRP hydroxylase enzymes (TPH1 or 2). 5-HTP is decarboxylated by aromatic acid decarboxylase (AADC) to produce 5-HT, which undergoes further metabolism. Specifically, 5-HT can be converted to N-acetylserotonin (NAS) by arylalkylamine N-acetyltransferase (AANAT), and then to melatonin by N-acetylserotonin O-methyltransferase (ASMT). Alternatively, monoamine oxidase (MAO) transforms 5-HT into its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) [70–73]. Interestingly, a study coordinated by our research group examining the TRP-5-HIAA axis following exposure to elevated concentrations of corticosterone and H_2O_2 have unveiled significant alterations in the levels of its metabolites, particularly 5-HT, within the extracellular environment of the cells. These findings support the impact of environmental modulation and exposure to stressors on this metabolic axis [74].

The activity of 5-HT has precise control mechanisms regulating its synthesis, release, and metabolism. The majority of 5-HT is intracellular, ensuring a tight regulation of its concentration. Stored in intracellular vesicles, 5-HT is released into the synaptic cleft upon neuronal depolarization, where it binds to receptors on both presynaptic and postsynaptic membranes [75]. These receptors are distributed in the CNS, PNS, and peripheral tissues, such as smooth muscles. The diverse distribution of 5-HT receptors throughout the body supports the broad influence of 5-HT on human physiology and behavior. Modulating these

receptors can have significant impacts on various conditions, including mood disorders and gastrointestinal issues [76]. A summary of 5-HT receptors is presented in Table 1.

Table 1. Summary of the types of 5-HT receptors and their inhibitory/excitatory potential [77].

Receptor	Type/and Mechanism	Potential
5-HT1A-F	Gi/o-protein coupled; decrease cellular levels of cAMP	Inhibitory
5-HT2A, 5-HT2B, 5-HT2C	Gq/11-protein coupled; increase cellular levels of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG)	Excitatory
5-HT3	Ligand-gated Na + and K + cation channel; depolarize plasma membrane	Excitatory
5-HT4	Gs-protein coupled; increase cellular levels of cAMP	Excitatory
5-HT5A-B	Gi/o-protein coupled; decrease cellular levels of cAMP	Inhibitory
5-HT6	Gs-protein coupled; increase cellular levels of cAMP	Excitatory
5-HT7	Gs-protein coupled; increase cellular levels of cAMP	Excitatory

Presynaptic receptors are self-regulators, having an inhibitory influence on the release of additional 5-HT. In contrast, postsynaptic receptors modulate either excitatory or inhibitory signaling pathways, depending on the specific receptor subtype involved, through the activation of second messenger cascades. 5-HT that is reabsorbed into the originating cell via the serotonin transporter (SERT) is subsequently stored in intracellular vesicles or undergoes metabolism through the action of MAO within the cytoplasm. On the other hand, 5-HT circulating in the periphery is metabolized by the liver and lungs [75].

The involvement of monoamines in depression has been extensively researched, and 5-HT is closely connected with the depressive condition. In the present day, antidepressants designed to enhance the availability of 5-HT in the synaptic cleft, known as SSRIs, have proven to be effective and rank among the most widely prescribed medications globally [78]. Nevertheless, it is important to recognize that depression is a complex disorder, and while impaired 5-HT activity can contribute to its development, it neither represents a sole causative factor nor is it sufficient on its own [79].

Evidence from several studies supports the diverse roles played by 5-HT receptor subtypes in the development of MDD. In a general way, antagonists of 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, and 5-HT7 receptors, in addition to agonists of 5-HT1A, 5-HT1B, 5-HT2C, 5-HT4, and 5-HT6 receptors, have demonstrated the ability to promote antidepressant-like responses [80]. 5-HT1A-B and 5-HT2A are the most studied 5-HT receptors in the context of depression, despite the role of other 5-HT receptors also being a target of studies in MDD, especially 5-HT3 [81]. Our research group recently hypothesized that 5-HT3 antagonists, such as scopolamine, might combat oxidative stress by 5-HT3 interaction, despite the need of further clarification [82]. Table 2 represents a short summary of the connection between these three receptors and depression.

Table 2. Most studied 5-HT receptors in depression, as well as their connection to this disease.

5-HT Receptor	Function in Depression
5-HT1A	Agonists of 5-HT1A receptors are frequently used in the treatment of depression because they can enhance 5-HT signaling. Stimulation of the 5-HT1A receptor is an existing therapeutic target for treating depression and anxiety, using drugs such as buspirone [83].
5-HT2A	This receptor can control neuronal excitability in most networks involved in depression through interactions with the monoaminergic, GABAergic, and glutamatergic neurotransmissions [84]. Preclinical studies show that 5-HT2A receptor antagonists have antipsychotic and antidepressant properties, whereas agonist ligands possess cognition-enhancing and hallucinogenic properties [85].
5-HT3	This is an area of ongoing research. 5-HT3 receptor antagonists inhibit the binding of 5-HT to postsynaptic 5-HT3 receptor and might increase its availability to other receptors like 5-HT1A, 1B and 1D as well as 5-HT2 receptors, producing an antidepressant-like effect [86].

The 5-HT1A receptor is an abundant 5-HT receptor in the brain with presynaptic and postsynaptic subtypes. When 5-HT binds to these receptors, it induces neuronal hyperpolarization and reduces its firing rate, but the response to sustained stimulation differs between these subtypes. In depression, the 5-HT1A receptor is increased presynaptically, causing a decrease in the release of 5-HT [87]. 5-HT1A autoreceptors act as a feedback mechanism to regulate 5-HT release, being located on the 5-HT neurons in the brainstem. When 5-HT1A receptor agonists are administered, it can inhibit the firing of serotonergic neurons and thus reduce the release of 5-HT in the short term. However, with chronic administration, there's a desensitization of these presynaptic receptors, which leads to an overall increase in the release of 5-HT in the brain to bind to postsynaptic heteroreceptors, modulating the activity of the receiving neuron [88].

Stimulation of the 5-HT2A receptor in neurons can trigger effects through different signaling pathways, such as modulation of GABA and glutamate, mainly due to the high presence of this receptor in glutamatergic and GABAergic neurons [89]. In most cases, activating the 5-HT2A receptor leads to an increase in the levels of intracellular calcium. Additionally, the activation of the 5-HT2A receptor results in the phosphorylation of ERK through a variety of intracellular signaling mechanisms, mostly promoted by Src and calmodulin, a process that regulates downstream signaling components [85,90]. The ERK pathway is involved in the regulation of various cellular processes that can influence mood and behavior, playing an important role in neuroplasticity. Dysregulation of this pathway has been linked to depressive symptoms [91]. These receptors also interact with β-arrestin proteins that are multifunctional intracellular proteins that directly interact with many cellular components, contributing to multiple aspects of, for example, GPCR signaling [89,92]. Previous studies have demonstrated that these receptors coexist with β-arrestin-1 and -2 in cortical neurons. Interestingly, in mice lacking β-arrestin-2, where 5-HT2A receptors predominantly remain on the cell surface, 5-HT fails to induce behavioral responses, including head-twitching. This suggests that β-arrestin-2 mediates the internal mobility of 5-HT2A receptors within cells, which is linked to the appearance of head-twitching in response to increased 5-HT levels. DOI, a 5-HT2A-C receptor agonist, may still cause head-twitching in mice without β-arrestin-2. This suggests that β-arrestins are not necessary for DOI-mediated reactions [93,94]. These findings highlight the role of the specific ligand in determining how the receptor's signaling pathway is triggered [89]. Additionally, the dynamic regulation of signal intensity and duration in 5-HT2A receptor signaling is known to be managed through the rapid endocytosis mediated by β-arrestins [95]. Another way 5-HT2A receptor subtypes can affect signaling is by their capacity to form stable complexes with other GPCRs, such as metabotropic glutamate receptor type 2 (mGluR2) and dopamine D2 receptors. Although the function of these receptor complexes in live creatures are still to be completely understood, this process may influence how receptors attach to molecules and interact with signaling pathways [89].

The 5-HT3 receptors have permeability to various ions, namely Na^+, K^+, and Ca^{2+}. Activation of these receptors initiates the opening of ion channels, triggering rapid membrane depolarization [96,97]. The roles of 5-HT3 receptors are linked to their specific localization. The activation of nerve-terminal 5-HT3 receptors modulates the release of diverse neurotransmitters, such 5-HT, DA, or GABA. In contrast, the activation of postsynaptic 5-HT3 receptors primarily participates in rapid synaptic transmission [97,98]. Pre- and postsynaptic receptors have unique features. Notably, presynaptic 5-HT3 receptors are highly permeable to Ca^{2+} ions, but postsynaptic receptors are less permeable to Ca^{2+} in comparison to Na^+ and K^+. Presynaptic 5-HT3 receptors, which control neurotransmitter release, vary from postsynaptic receptors, which are engaged in fast synaptic transmission, due to their differential calcium permeability. Ca^{2+} influx causes neurotransmitter release into the synaptic cleft [99]. Furthermore, the 5-HT3 receptor can be composed of five identical 5-HT3A subunits (homopentameric) or a combination of 5-HT3A and one of the other four 5-HT3B, 5-HT3C, 5-HT3D, or 5-HT3E subunits (heteropentameric). The homomeric 5-HT3A receptors are equally permeable to both monovalent and divalent cations, but

heteromeric 5-HT3 receptors have lower Ca^{2+} permeability [97]. Additionally, heteromeric receptors exhibit faster activation and deactivation kinetics compared to homomeric receptors. It is worth mentioning that the affinity and efficacy of 5-HT3 receptor agonists and antagonists are dependent on the specific receptor structure [97].

Despite all the evidence that connects 5-HT signaling pathways to MDD, it is important to note that a recent comprehensive systematic umbrella review revealed that there is no robust evidence that depression is caused by lower 5-HT concentrations or activity [100], despite the fact that another very recent review was published with the aim of contradicting this review [101]. However, in recent years, specific changes in 5-HT neurotransmission have remained a viable therapeutic option for treating mood and anxiety disorders. Indeed, the efficacy of SSRIs in relieving symptoms has been extensively documented. However, the assumption that clinical depression might be traced only to the poor functioning of a single neurotransmitter is widely recognized as unlikely [102]. Evidence reveals that depleting TRP in healthy individuals, who exhibit no apparent risk factors for depression, does not result in a significant decline in mood [103]. Thus, the concept that lowering brain 5-HT levels alone is sufficient to cause depression appears to be unviable. However, in individuals who have recovered from depression and have remained free from both pharmaceutical and psychological treatments for extended periods, TRP depletion can lead to a clinically-significant reduction in mood, implying that in individuals with a history of depression, prior episodes render them vulnerable, and reductions in brain 5-HT levels can trigger clinical relapses [103]. All the complexities of the serotonergic system and depression highlight the importance of further research to clarify the effects of different drugs on the 5-HT system in MDD [73].

2.4. Exploring Brain-Derived Neurotrophic Factor in Major Depressive Disorder

BDNF is important in several aspects of human physiology and its expression is observed in both the central nervous system (CNS) and the peripheral nervous system (PNS) [104,105].

Neurons are the principal producers of BDNF, which begins as preproBDNF and then a preprotein called proBDNF [106]. ProBDNF undergoes further changes to mature form [107]. BDNF produces dimers and biologically active BDNF is typically made up of a dimer composed of two identical mature peptide chains linked together by noncovalent interactions [108].

The human BDNF gene contains 11 exons (I–IX, Vh, and VIIIh), and the production of BDNF transcripts is cell and activity specific, with different transcripts playing different roles in biochemical processes [109,110]. Exon IV is the most extensively studied, because it holds significance in the modulation of mood, cognition, and behavior [111]. The methylation status of the promoter associated with this exon has emerged as a potential biomarker for antidepressant therapy in individuals with MDD [112].

BDNF plays an important role in many processes, including neuronal survival and differentiation, synaptic plasticity, neurogenesis, neuroprotection, learning, memory, mood control, and other cognitive processes. Low BDNF levels relate to brain shrinkage, cognitive decline, and an increased risk of mental illnesses [113]. BDNF also influences the release and activity of different neurotransmitters, affecting neuronal communication and general brain function [114]. This neurotrophin is also involved in the formation of dendrites and synaptic specializations, maturation and refinement of dendritic arbors, and axon growth and differentiation [115]. Based on the actions of this neurotrophin, several therapies and techniques have been found to boost the levels of BDNF, including physical exercise, the ingestion of omega-3 fatty acids, and several antidepressants, such as SSRIs [116,117].

The relationship between BDNF and MDD is a large topic of investigation. The neurotrophic theory of depression is based on the relationship between lower BDNF levels and an increased risk of depression [118]. Table 3 summarizes the link between BDNF and MDD.

Human studies have demonstrated a positive link between peripheral blood levels of BDNF and both hippocampal size and cognitive function [119,120]. Low BDNF levels are consistently associated with an increased prevalence of depressive symptoms, neuronal loss, and atrophy in key brain regions [121]. A study highlighted that patients experiencing their first episode of drug-free MDD and responding to SSRI treatments exhibited elevated serum BDNF levels [122]. Moreover, antidepressant-treated individuals have shown increased BDNF expression in the hippocampus when compared to their untreated counterparts [123]. Postmortem examinations of brains from patients with depression, including suicide cases, have revealed reduced BDNF mRNA levels, confirming this trend [124,125]. Animal models of depression also aligned with this evidence, showing that chronic stress and depression lead to diminished BDNF levels, increased cell death, and reduced neurogenesis in the hippocampus, alongside decreased BDNF expression in other brain areas [126,127]. A genetic variation known as Val66Met, which naturally occurs in the BDNF gene, is also linked with MDD [128]. Recent research has linked this polymorphism to MDD and its potential use as a biomarker for predicting a patient's response to antidepressants and electroconvulsive therapy [129]. Various forms of physical exercise have also been found to stimulate the production of this neurotrophin, leading to cognitive enhancement and a reduction in symptoms associated with depression and anxiety [105,130].

Table 3. Summary of the BDNF and MDD connection. Adapted from [105].

Feature	Explanation
Levels of BDNF	Reduced BDNF levels have been observed in individuals with MDD [118].
Structure and function	Deficiencies or imbalances in BDNF levels contribute to depression by promoting structural and functioning changes [131].
5-HT	BDNF is affected by 5-HT, and 5-HT stimulation can increase BDNF production and release. 5-HT receptors can also control BDNF production, which influences neuronal function and, consequently, mood modulation [132].
Neuroplasticity	BDNF has a role in neuroplasticity, which is essential for synaptic connections and structural changes in the brain connected to MDD [133].
Oxidative stress	Oxidative stress can impair BDNF production and signaling pathways. The link between oxidative stress and BDNF levels is critical in the development and progression of depression [15].
HPA axis dysregulation	Stress-induced HPA axis hyperactivity and the subsequent increase in glucocorticoid levels diminish BDNF expression, which plays an important role in the development of depression [134].

3. Pharmacological Interventions in the Management of Major Depressive Disorder

3.1. An Overlook of Pharmacotherapy for Major Depressive Disorder

The global economic impact of depression is significant, and it has consistently remained the third leading contributor to the worldwide disease burden, as designated by the WHO since 2008 [135]. Thus, there is the need for advancements in research.

The first advancement in the treatment of depression was made in the early 1950s, when researchers developed iproniazid as a drug for tuberculosis which also proved to be effective in alleviating symptoms of depression, being a type of MAOI [136]. Around the same time, another class of antidepressants known as tricyclics (TCAs) appeared. Imipramine was the first TCA, approved in 1959 by the Food and Drug Administration (FDA) for the treatment of MDD. Like MAOIs, TCAs were developed in the 1950s and were found to elevate monoamine levels, primarily by blocking the reuptake of 5-HT and noradrenaline [84,137]. While these discoveries represented important advancements, the acceptance and use of these early antidepressants were impeded by public stigma and

severe side effects [137]. By the late 1980s, SSRIs offered a more targeted approach to depression treatment. As previously referred, they function by inhibiting the reuptake of 5-HT into neurons within the raphe nuclei, resulting in increased 5-HT. These drugs were found to have improved side effect profiles. The introduction of SSRIs led to an increase in the use of antidepressants among adults. Despite being developed several decades ago, SSRIs remain some of the most prescribed drugs in the world [84,138]. However, approximately 33% of patients with MDD do not respond to treatment with these commonly used drugs, and 67% do not achieve remission with this first-line approach [84]. Today, several classes of antidepressants are present in the market. Besides the previously mentioned, serotonin–noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine, block 5-HT and NA reuptake in the synapse, serotonin modulators (e.g., vilazodone) and atypical antidepressants (e.g., mirtazapine) are also widely used [139]. In recent years, research has shifted its focus towards potential new therapies, including noncompetitive NMDA receptor antagonists [84].

Depression treatment approaches include both pharmaceutical interventions and non-pharmaceutical options, such as psychotherapy, electroconvulsive therapy, and transcranial magnetic stimulation [135]. Psychotherapy has demonstrated its efficacy in alleviating depressive symptoms and enhancing the overall quality of life for individuals with depression [140]. Consequently, numerous clinical guidelines are progressively endorsing the use of psychotherapy either as a standalone treatment or in combination with antidepressants [135].

3.2. Antidepressant Breakthroughs: Advancements in Pharmacotherapy for Depression

While most antidepressants are considered safe and effective, they have limitations, including a delayed onset of action and side effects that can impact a patient's adherence to treatment, such as weight gain, sexual dysfunction, dizziness, headaches, anxiety, psychosis, and cognitive impairments. Over the past few decades, several efforts in antidepressant research have been directed towards discovering drugs that act more rapidly, with greater safety [135,141].

The most common type of new drugs is based on NMDA receptor properties [135,141,142]. The interest in these receptors comes from the studied role of glutamate in depression. Glutamate is an excitatory neurotransmitter in the brain, important in synaptic plasticity, cognitive functions, and emotional and reward processes. Ionotropic receptors (NMDA, AMPA, and kainate receptors), as well as metabotropic receptor mGluR, have been demonstrated to play a role in regulating mood and related functions that are compromised in individuals with depression [143]. Clinical investigations and animal research observed dysfunction within the glutamatergic system in diverse limbic and cortical regions of the brains of individuals experiencing depression [144].

GABAergic modulators are also promising novel targets for antidepressants. GABA, the primary inhibitory neurotransmitter, is important in balancing brain function by counteracting glutamate [135]. Studies revealed that individuals with depression often exhibit GABA-related neurotransmission impairments [145]. A recent study analyzed the status and research trends of the GABAergic system in depression from 2004 to 2020, revealing that GABA levels in the PFC, anterior cingulate cortex, and occipital lobe are decreased in patients with MDD [146]. Nonetheless, while GABAergic ligands have shown effectiveness in treating depression, directly influencing the GABA pathway, they can lead to side effects like drowsiness or sedation, which can impede daily functioning. Therefore, the balance seems to be shifting in favor of glutamate receptor ligands [141].

More optimism regarding MDD pharmacotherapy appeared when researchers discovered the antidepressant properties of intravenous ketamine, a NMDA receptor antagonist [142]. This drug blocks NMDA receptors on GABA interneurons, releasing the inhibition of glutamate release, a process that activates AMPA receptors on glutamatergic cells and increases BDNF and glutamate, increasing synaptic efficiency [147]. The administration of ketamine to depressed patients resulted in a sustained three-day reduction in

depressive symptoms [148]. This discovery led to the search for related medications like S-ketamine (esketamine), which was developed for intranasal use and FDA-approved as an adjunctive treatment for treatment-resistant depression in 2019. Notably, both intravenous ketamine and intranasal esketamine have shown promise in rapidly alleviating MDD symptoms, leading to esketamine's second FDA-approved indication in 2020. Despite these promising aspects, the benefits of ketamine and esketamine must be weighed against their costs and potential side effects, such as sedation and dissociation [142,149]. Additionally, combining electroconvulsive therapy with antidepressants has been a known approach, and recent findings regarding its use with esketamine have shown great promise and high effectiveness, particularly in cases of drug-resistant depression [141,150].

The combination of bupropion and dextromethorphan also resulted in a significant reduction in depression scores. Dextromethorphan is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, a class of drugs that is recognized for their potential to facilitate synaptic plasticity and neuronal resilience, primarily through their capacity to upregulate BDNF secretion [151]. Bupropion inhibits the reuptake of both NA and DA, as well as CYP2D6 enzymes, increasing the bioavailability of dextromethorphan. This drug combination was approved only in the USA in August 2022 for the treatment of MDD in adults (currently, is only used off-label in Europe [152]). In clinical trials, this combination was generally well tolerated, and was not associated with a signal for increased psychotomimetic effects or weight gain [153].

Another trial explored the use of adjunctive esmethadone, another uncompetitive NMDA receptor antagonist [154]. This trial demonstrated rapid and robust reductions in depressive symptoms, although this was not consistently replicated in a subsequent phase 3 trial. Additional phase 3 studies are currently ongoing to confirm the initial findings [142,155].

Neurosteroids like brexanolone and zuranolone represent another class of potential antidepressants [142]. These drugs modulate GABA neurotransmission. Brexanolone, which was approved by the FDA in 2019 for postpartum MDD, demonstrated rapid and long-lasting reductions in depression symptoms [156]. Zuranolone is also being studied across various MDD cases, with positive results from clinical trials. Indeed, this drug demonstrated enhanced efficacy in alleviating depressive symptoms by day 15, exhibiting a rapid onset of action by day 3, and exhibiting a favorable safety profile [157].

A relatively new category of antidepressants includes orexin receptor antagonists and compounds that act through two neuropeptides (orexin-A and orexin-B) and two GPCRs (the orexin type 1 and 2 receptors). The dysfunction of the orexin system has been implicated in the pathophysiology of depression in human and animal studies, although the exact mechanism of this dysfunction remains unclear. Nevertheless, ligands for type 1 and 2 receptors can modulate various aspects such as feeding, sleep, motivated behavior, anxiety, and addiction, making them potentially influential in regulating different facets of depression. Orexin receptor antagonists are being investigated as potential treatments for MDD, with several ongoing clinical trials [158].

New drugs like ansofaxine (a potential triple reuptake inhibitor of 5-HT, NA, and DA) exhibit side effects that are quite similar to traditional antidepressants. These side effects are generally mild to moderate, with slightly different frequency patterns compared to drugs like SSRIs. Notably, this drug does not seem to cause sexual dysfunction, typically associated with conventional antidepressants [141,159]. In September of 2023, FDA also approved gepirone, for the treatment of MDD. This drug is a 5-HT1A receptor agonist, and an active metabolite of gepirone, 1-(2-pyrimidinyl)piperazine, is an α 2-adrenergic receptor antagonist. This drug has the big advantage of not causing sexual dysfunction or weight gain, as well as inducing less sedation and minimal withdrawal symptoms [160].

Psychedelic drugs have also gained attention as potential alternative antidepressants. Preliminary findings suggest that psilocybin, derived from mushrooms, may lead to sustained antidepressant effects in patients with treatment-resistant depression and terminal cancer [142]. In individuals suffering from treatment-resistant depression, the administra-

tion of a single dose of psilocybin, combined with psychological support in conjunction with SSRI treatment, exhibited a generally positive safety profile and displayed significant therapeutic effectiveness as assessed through a diverse array of clinician-conducted evaluations and self-reported measures [161]. In fact, a recent study suggests that a single, moderate dose of psilocybin significantly reduces depressive symptoms compared to a placebo, for at least two weeks [162].

The cholinergic system is increasingly recognized as having a significant role in mood regulation. Acetylcholine, a neurotransmitter, is implicated in mood disorders with depressive symptoms, although its exact role remains unclear. Recent evidence, such as the rapid and sustained antidepressant effects of scopolamine in depressed individuals, has induced the interest in the cholinergic system's involvement in MDD and bipolar disorder, being suggested that excessive cholinergic activity can trigger MDD. This hypothesis is supported by studies showing that drugs increasing acetylcholine activity can induce depressive symptoms [163]. However, understanding of the efficacy and mechanism of treatments targeting the reversal of acetylcholinesterase increase using acetylcholinesterase inhibitors (AChEIs) remains limited [164].

Regarding other targets, previous studies have found that treatments aimed at regulating the HPA axis, such as GR antagonists, do not effectively alleviate the symptoms of depressed patients [141]. Nevertheless, this is a subject of research interest, and a recent study revealed that antalarmin, a CRH receptor 1 antagonist, alleviated LPS-induced depression-like behavior in mice [165]. Therapies regarding the direct manipulation of KYN pathways are also still not available in the common medical practice for MDD [166].

Drug repurposing, the exploration of new uses for existing market-available drugs, is gaining attention in research. These drugs have passed safety evaluations, undergone formulation development, and successfully completed preclinical and clinical testing, substantially reducing the risk of failure [167]. Table 4 represents examples of widely studied drugs with the potential to be repurposed in the context of depression, their original indication, as well as evidence in depression that supports their potential use in this disease.

Table 4. Main indication, known mechanism of action and relevance in depression of potential to be repurposed in the context of this disease.

Drug	Main Indication and Mechanism of Action	Relevance in Depression
Statins	Management and treatment of hypercholesteremia. Selective, competitive inhibitor of hydroxymethylglutaryl-CoA (HMG-CoA) reductase [168].	Demonstrated antidepressant effects, useful as add-on therapy in patients with cardiovascular disease, with MDD [169]. Beneficial effect through positive actions on 5-HT neurotransmission, neurogenesis, and neuroplasticity, HPA axis regulation and modulation of inflammation [170].
Scopolamine	Postoperative nausea and vomiting and motion sickness. Competitive antagonist of 5-HT3 receptors and nonselective muscarinic antagonist [171].	Evidence of antidepressant effects in patients with MDD and bipolar depression [172]. Added to antidepressants can effectively relieve the symptoms of patients with severe depression [173]. Currently, 2 clinical trials in MDD and bipolar disorder are ongoing (NCT04719663 and NCT04211961 [174]). Studies in rodents have revealed that the antidepressant-like effects are connected to mTORC1 signaling in the PFC. This activation of mTORC1 seems to be initiated by a glutamate surge in the PFC, resulting from the disinhibition of glutamatergic neurons. This increased glutamate transmission leads to the activation of AMPA receptors, that raises the levels of BDNF, which then stimulates mTORC1 signaling and promotes synaptogenesis processes [175].

Table 4. *Cont.*

Drug	Main Indication and Mechanism of Action	Relevance in Depression
Valproic Acid	Treatment/management of epilepsy. Mechanism of action not fully understood: Inhibits voltage-gated sodium channels, GABA transaminase, increases the expression and activity of glutamic acid decarboxylase (GAD), inhibits the action of histone deacetylases (HDAC) enzymes, notably HDAC1, modulates the activity of various calcium channels [176].	Demonstrated efficacy in preventing mood recurrence and enhancing the quality of life for individuals with bipolar disorder when used as a maintenance therapy [177]. Supplementary use of this drug resulted in significant and sustained clinical enhancement over a prolonged duration in individuals with severe treatment-resistant depression [178].
Lamotrigine	Treatment/management of epilepsy. Mechanism of action for lamotrigine is not entirely understood; selectively binds and inhibits voltage-gated sodium channels, stabilizing presynaptic membranes and inhibiting presynaptic glutamate release [179].	Used off-label for bipolar disorder [179]. Could potentially offer an effective option in addressing individuals with treatment-resistant persistent depressive disorder, being a viable substitute for the combination of antidepressant and benzodiazepine therapies in this disorder [180].
Pioglitazone	Treatment of type 2 diabetes mellitus. Peroxisome proliferator-activated receptor (PPAR)-gamma and PPAR-alpha agonist [181].	Pioglitazone, alone or as add-on therapy to conventional treatments, could induce remission of depressive episodes [182]. Evidence of enhancing antidepressant response among people with comorbid MDD and type 2 diabetes [183]. Induced the neuroprotective phenotype of microglia in chronic mild stress-treated mice, mediated by PPARγ [184], and antidepressant effect in LPS injected rats [185].
N-acetyl cysteine	Therapy for acetaminophen toxicity. Serves as a prodrug to L-cysteine, a precursor to glutathione [186].	Evidence as an adjunctive therapy to reduce symptoms of Bipolar Affective Disorder, MDD, and Schizophrenia [187]. Enhanced coping mechanisms, not only for addressing acute stressors but possibly also for mitigating the impact of persistent stress-inducing factors [188].
Minocycline	Tetracycline antibiotic, anti-infectious activity against both Gram-positive and Gram-negative bacteria. Bind to the 30S ribosomal subunit of bacteria, preventing protein synthesis [189].	Potential novel treatment for treatment-resistant depression [190]. May improve depressive symptoms and augment response to treatment in patients with treatment-resistant depression [191]. Inhibits both the IDO and the p-38 components of inflammation-induced depression [192].
Nimodipine	Prevent vasospasm secondary to subarachnoid hemorrhage. Blocks voltage-gated L-type calcium channels [193].	This drug has been shown to be effective in treating mood symptoms for bipolar and unipolar depression [194]. An old clinical trial revealed that this drug in the context of vascular depression, augmentation of fluoxetine with nimodipine led to better treatment results and lower rates of recurrence [195].
Quetiapine	Schizophrenia and acute manic episodes. Antagonist for D2 receptors and 5-HT2A receptors [196].	Quetiapine monotherapy in older adults with MDD was found to be effective [197]. Quetiapine augmentation may be a useful intervention for MDD with comorbid anxiety [198]. Adjunctive quetiapine was effective in patients with MDD who had shown an inadequate response to antidepressant treatment [199].
Celecoxib	Analgesic for patients with osteoarthritis and rheumatoid arthritis. Selective inhibition of COX-2 [200].	A recent meta-analysis demonstrated that celecoxib could be effective for improving depressive symptoms [201]. Antidepressant efficacy was demonstrated when used as an add-on treatment for MDD and mania, possibly by reducing inflammatory markers [202].

Drug repurposing in the treatment of depression represents an essential approach in the world of mental health. It offers the potential for rapid and cost-effective solutions, while also reducing the risks and challenges associated with developing entirely new drugs.

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