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Review Paper

Pharmacological Management of Depression in the Modern Era: Established Therapies and Future Drug Targets

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ABSTRACT

Depression is a very common and debilitating psychiatric disorder that carries a high emotional, cognitive, physical, social and economic burden. The underlying mechanism of its pathophysiology is multi-faceted and involves many interconnected mechanisms linked to monoaminergic imbalance, hypothalamic–pituitary–adrenal axis (HPA axis) dysregulation, neuroinflammation, glutamatergic dysfunction, decreased neuroplasticity, decreased brain-derived neurotrophic factor (BDNF) signaling, and altered gut–brain axis communication. Pharmacological treatment still relies on the use of conventional antidepressants: antidepressants that inhibit the uptake of serotonin (SSRIs), or serotonin–norepinephrine (SNRIs), or tricyclic, or monoamine oxidase, or melaninergic, or atypical. They work for many people, but some have a slow onset of action, side effects, poor response, relapse and treatment-resistant depression. The monoamine hypothesis of depression has been superseded by novel mechanism-based

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targets in recent studies. Innovative therapies involve NMDA receptor modulators, AMPA receptor potentiators, GABAergic neurosteroid modulators, orexin receptor antagonists, kappa opioid receptor antagonists, anti-inflammatory drugs, neurotrophic factor-based drugs, and gut microbiota-targeted drugs. Antidepressant response has been revealed as a crucial role for glutamatergic signaling and synaptic plasticity, now captured by rapid-acting therapeutics like ketamine and esketamine. The future therapeutic approaches are likely to include the development of more rapidly acting drugs, greater safety profiles, biomarker-directed treatment, pharmacogenomics, faster drug discovery using artificial intelligence and personalized medicine. In conclusion, current pharmacological treatment of depression is a trend toward a more integrated and precision-driven strategy that targets enhanced remission rates, tolerability, decreased relapse rates and sustainable functional improvements

INTRODUCTION

1.1 Background of Depression

Depression is a frequent, chronic, and disabling mental health condition that is defined by a persistent depressed mood, loss of interest or pleasure, decreased energy, sleep disturbances, difficulty with concentration, feelings of guilt or worthlessness, psychomotor changes, appetite disturbance and, in severe cases, thoughts of suicide [1]. It's not just a passing, emotional response to stressful or sad circumstances, it's a mental health condition characterized by emotional, cognitive, behavioral and biological symptoms. Depression can be a one-off event; however for many people, depression can be a recurring or prolonged condition which is a significant challenge for health professionals and public health systems. Most people have a general idea that major depression is a multi-factorial disorder. It is a process that is highly complex and involves a combination of genetic susceptibility, environmental stressors, neurochemical imbalance, endocrine dysfunction, inflammatory processes, impaired neuroplasticity, and psychosocial factors [2]. Previous theories of depression have centered on low levels of monoamine neurotransmitters, including serotonin, norepinephrine and dopamine. But modern research indicates that depression is not due to a single neurotransmitter abnormality. The mechanisms known so far to be affected are alteration of hypo-pituitotropic axis, neuroinflammatory cytokines, neurotransmission involved, brain-derived neurotrophic factor, circadian rhythm and gut–brain axis [3]. Depression symptoms are different for each person. Most patients present with sadness and hopelessness, but some with more prominent anxiety, irritability, fatigue, sleep disturbance, or body pain, or with cognitive slowing. Other illnesses that commonly accompany depression include diabetes, cardiovascular disease, chronic pain, neurological disorders and substance use disorders. This overlap leads to a complex diagnosis and treatment [4]. Importantly, depression lowers a person's quality of life, affects his/her academic and occupational performance, impacts his/her relationships, and increases the likelihood of self-harm and suicide. Depression may result in suicide and there is effective depression treatment for mild, moderate and severe depression, according to the World Health Organization. Pharmacological therapy is the mainstay of treatment in moderate to severe depression [5]. While psychotherapy, lifestyle changes, social support and neuromodulation treatments are also significant, antidepressant medications are the backbone of biological therapy. The goal of antidepressant treatment is to reduce symptoms, achieve remission, prevent relapse, return to function and enhance quality of life. But, delayed effects, incomplete responses, side effects, interactions, non-compliance and treatment-resistant depression remain significant treatment challenges [6].

1.2 Global burden and clinical significance

Depression is a major component of the disease burden worldwide. According to the World Health Organization, around 5.7% of all adults in the world have depression, and women are more likely to develop depression than men. Depression is also known as a major cause of disability globally, so it causes significant loss of years lived with disability, loss of productivity and significant long-term social and economic loss [7]. These statistics illustrate depression as not only a psychiatric disease but also as a public health problem. The clinical importance of depression is very widespread as it impacts persons across all age groups, socioeconomic status and regions. Depression can affect adolescents' and young adults' educational, social, self-esteem and future occupational functioning. It has been linked to work absenteeism, decreased productivity, poor family functioning and increased utilization of health-care facilities among adults [8]. Depression can also occur in older adults in combination with cognitive impairment, chronic medical disease, feelings of loneliness, and disability. Depression can also adversely impact treatment adherence, exacerbate the impact of chronic physical diseases on lifestyle behaviors, and further contribute to increased perceived disease burden, leading to poor outcomes in patients with chronic physical diseases. Depression has significant economic consequences. The direct costs are the cost of physician visits, medications, hospitalizations, psychotherapy, emergency department visits, and long-term management. Indirect costs involve loss of work productivity, unemployment, burden on caregivers, and premature death. Depression is also emotionally and financially stressful to families, particularly if it is recurring or not responding to treatment [9]. The true burden may be higher than reported estimates, as many patients may not seek care because of stigma, lack of awareness, difficulty accessing mental health services or financial constraints. Clinically, depression is important as an untreated or poorly treated condition can become chronic and recurrent. Early diagnosis and timely treatment of appropriate therapy is a great aim of modern depression management. The treatment of depression should be tailored to the individual based on symptom profile, severity, comorbid conditions, history of response to antidepressants, safety, tolerability, patient preference, cost, and risk for drug interactions [10]. This personalized treatment is particularly crucial, since few antidepressants work for everyone. One of the most challenging fields of clinical practice is treatment-resistant depression. It is usually used when the patient has not responded to at least two properly selected antidepressant drugs for sufficient length of time. These cases are linked to increased disability, health-care expenses, and risk of suicide. Recent reviews suggest that both ketamine and intranasal esketamine have emerged as valuable therapeutic options for the treatment of TRD, particularly due to their rapid antidepressant effects. Thus, contemporary pharmacologic treatment should involve both traditional and newer mechanism-based antidepressant treatments [11].

1.3 Evolution of Antidepressant Pharmacotherapy

In recent decades, the management of depression with drugs has significantly changed. The development of antidepressants was a lot of a serendipity. The first big classes of drugs given for depression were monoamine oxidase inhibitors and tricyclic antidepressants. These medications yielded significant clinical results and helped to demonstrate the potential of using pharmacological manipulation of brain neurotransmitters to enhance clinical symptoms of depression [12]. Their use was restricted due to some drawbacks such as adverse effects, dietary

restrictions, toxic effects in larger doses and poor tolerability. This early time in antidepressant drug development is referred to as the beginnings of modern antidepressant pharmacotherapy, according to a review. The next big step was the development of selective serotonin reuptake inhibitors. SSRIs like fluoxetine, sertraline, paroxetine, citalopram and escitalopram were widely adopted due to their relative safety and tolerability compared to tricyclic antidepressants and monoamine oxidase inhibitors [13]. Their arrival prompted a change to long-term outpatient care of depression. Serotonin–norepinephrine reuptake inhibitors, norepinephrine–dopamine reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, serotonin modulators, and melatonergic antidepressants added to the options. These agents enabled the clinician to choose a medicine based on the symptoms that were present, including anxiety, fatigue, insomnia, pain, sexual dysfunction, or weight-related issues. However, traditional antidepressants have many drawbacks. Most take the benefit several weeks. A significant number of patients have partial response or non-response. Adherence can be impacted by adverse effects like gastrointestinal disturbance, sexual dysfunction, weight gain, sedation, insomnia, blood pressure changes, and discontinuation symptoms. Such restrictions led to the quest for more rapid-acting and more specific treatments. The monoamine hypothesis, a longstanding paradigm of depression pharmacotherapy, is no longer sufficient. New avenues of therapeutic exploration include glutamate, gaba, neurosteroids, inflammatory pathways, neuroplasticity, circadian biology and the gut-microbiome [14]. The use of the spray for treatment resistant depression is significant as it offers a new and novel glutamate-targeted approach for treatment-resistant depression; this use is mentioned in the FDA Approval Letter for Spravato in 2019. In the same vein, treatment with neurosterols has become a new avenue of research, especially in postpartum depression [15]. In March 2019, Brexanolone became the first medication approved by the FDA specifically for postpartum depression; zuranolone was approved as the first pill specifically approved for postpartum depression in adults in August 2023. Therefore, the treatment of depression by antidepressant drugs has evolved from a wide-range of monoamine-based treatment to a more mechanism-based and personalized one. Future directions in the management of depression may include more rapid acting medications, targeting depression through the use of biomarkers, pharmacogenomics, combination treatments, and the development of new targets to address the biological heterogeneity of depression.

2. Pathophysiology of Depression

Depression is a heterogeneous neuropsychiatric disorder, without any single biological causes. These are the contemporary findings that show that multiple biological systems, such as monoaminergic neurotransmission, neuroendocrine stress regulation, immune-inflammatory pathways, glutamatergic signaling, neuroplasticity, and the gut–brain axis, can contribute to the development of major depressive disorder. These mechanisms do not act independently, but rather they affect one another and interact to create disturbances in mood, cognition, sleep, appetite, motivation, stress response and emotional regulation. The latest reviews characterize depression as a disorder associated with monoaminergic dysfunction, loss of function in the hypothalamic–pituitary–adrenal axis, decreased levels of BDNF, neuroplasticity changes, inflammation, and gut microbiome imbalance [15].

2.1 Monoamine Hypothesis

One of the most widely accepted and well-known theories suggesting the biological basis of depression is the monoamine hypothesis. It suggests that the symptoms of depression are linked to a decrease in the activity of monoamine neurotransmitters, particularly serotonin, norepinephrine and dopamine, in specific areas of the brain associated with mood. These neurotransmitters play a role in emotional well-being, rewarding behavior, motivation, attention, sleep, appetite and stress. Serotonin is related to mood, anxiety, sleep and impulse control, norepinephrine to alertness, concentration, energy and adaptation to stress and dopamine to reward, pleasure, motivation and psychomotor activity [16]. This hypothesis became important because numerous antidepressant medications have been found to enhance monoaminergic neurotransmission. The five main classes of antidepressants all have different effects on serotonin and other monoamines, with selective serotonin reuptake inhibitors (SSRIs) raising serotonin levels, serotonin–norepinephrine reuptake inhibitors (SNRIs) boosting both serotonin and norepinephrine, tricyclic antidepressants (TCAs) blocking serotonin and other monoamine reuptakes, monoamine oxidase inhibitors (MAOIs) blocking the enzymatic degradation of serotonin and other monoamines, and bupropion enhancing serotonin and other monoamines. Thus, clinical activity of these drugs lends further support to the role of monoamines in depression. The monoamine hypothesis is no longer seen as a comprehensive understanding of depression, however. A major drawback is that antidepressants raise levels of monoamines in the synapse within hours, but it takes weeks for clinical improvement to occur. The delay indicates that adaptive changes downstream, such as receptor regulation and/or intracellular signaling, neuroplasticity, and gene expression are required to produce the antidepressant response. Moreover, not every patient is responsive to monoamine drugs and many patients will have partial response or resistance. The monoamine hypothesis is thus updated in a modern fashion. The serotonin deficit theory is not the only theory to consider when discussing depression. A systematic umbrella review raised doubts about the robustness of the serotonin-deficiency theory of depression, and other expert discussions suggested that serotonin still has a role to play and is part of a larger, multifactorial theory of depression. Therefore, a dysfunction of monoamines is significant in depression, but in concert with hormones of stress, inflammation, glutamate signaling, neurotrophic processes, and environment [17].

2.2 Neuroendocrine Dysregulation and HPA Axis

The central neuroendocrine system that controls the body's response to stress is called the hypothalamic–pituitary–adrenal axis. Corticotropin-releasing hormone is secreted from the hypothalamus during stress. This activates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) that activates the adrenal cortex to produce cortisol. Cortisol is responsible for helping the body cope with stress, it's a regulator of metabolism, immune system, heart and blood pressure, and brain arousal. In normal conditions, cortisol also negatively regulates the hypothalamus and pituitary to avoid over-activation and interestingly, cortisol levels are elevated during exercise [18]. In normal conditions, cortisol also has a negative influence on the hypothalamus and pituitary to avoid excessive stress activation, and interestingly, cortisol increases during exercise. During depression, this stress-regulating system can go awry. An increased level of cortisol, a disruption in the negative feedback loop, an alteration in cortisol's circadian rhythm, and a

prolonged activation of the HPA axis are seen in many depressed patients. The chronic stress is one of the most important environmental risk factors for depression, due to the prolonged exposure to cortisol can affect the brain areas related to mood and cognition, such as the hippocampus, prefrontal cortex, and amygdala. Several reviews of the pathophysiology of depression outline the importance of HPA-axis hyperactivity in the onset and maintenance of depressive symptoms. The HPA-axis activity is normally regulated by the hippocampus to dampen down excessive activity. Chronic stress and high levels of cortisol can, however, inhibit neurogenesis in the hippocampus, decrease the plasticity of the synapses, and decrease the volume of the hippocampus. This results in less control of cortisol production and a vicious circle of over-activation of the stress system [19]. The prefrontal cortex that plays a role in emotional control and decision-making can also become less effective in managing stress. Meanwhile, hyperactivity in the amygdala (structure associated with fear and emotional salience) could result in heightened stress reactivity, negative emotional bias, and anxiety. Other biological mechanisms also contribute to the interaction with the HPA-axis dysregulation. Too much cortisol can cause inflammation, change serotonin and dopamine function, disrupt sleep, upregulate oxidative stress, and downregulate BDNF expression. These effects lead to decreased mood, fatigue, cognitive dysfunction, anhedonia and lack of tolerance for stress. Thus, depression can be seen as a disorder of maladaptive stress biology, in which the brain and body continue to be activated in a state of chronic stress after the stressor has subsided.

2.3 Neuroinflammation and Immune Mechanisms

The role of neuroinflammation in the current literature of depression. Importance of neuroinflammation to modern understanding of depression. While previous studies concentrated primarily on neurotransmitters, recent research suggests that immune and inflammatory systems play an important role in mood and brain function. Depression is associated with elevated levels of inflammatory markers including interleukin-6, tumour necrosis factor-alpha, interleukin-1 beta and C reactive protein [20]. These inflammatory signals can be the result of chronic stress, infection, obesity, poor diet, sleep disturbance, autoimmune disease, metabolic disorders, or psychosocial adversity. The brain can become inflamed in various ways. Peripherally generated cytokines can reach the brain via the blood–brain barrier, vagus nerve signaling, endothelial activation and trafficking of immune cells. Once inflammatory signals arrive at the central nervous system, they can trigger damage of the resident immune cells of the brain, the microglia. The activated microglia release cytokines, ROS and other factors which can modify neuronal functions, synaptic plasticity and neurotransmitter metabolism [21]. Neuroinflammation, peripheral inflammation and gut dysbiosis are considered three important mechanisms in the pathophysiology of MDD according to reviews. Tryptophan metabolism is one of the important inflammatory pathways during depression. Tryptophan is an amino acid that can be used to make serotonin. Inflammation can lead to activation of the enzyme indoleamine 2,3-dioxygenase and change the metabolism of tryptophan away from serotonin to the kynurenine pathway. Some kynurenine metabolites like quinolinic acid can promote glutamatergic excitotoxicity by binding to NMDA receptors; others have been shown to modulate oxidative stress and neuronal survival. This mechanism connects inflammation and decreased serotonin synthesis, glutamate dysregulation and impaired neuroplasticity. Inflammation impacts dopamine

and reward pathways as well. Dopamine synthesis, release and receptor activation in brain reward pathways can be lowered by pro-inflammatory cytokines [22]. This could lead to anhedonia, loss of motivation, psychomotor slowing, and fatigue, typical symptoms of depression. Futhermore, inflammatory mediators can disrupt sleep, heighten sensitivity to pain, cause cognitive impairment and exacerbate anxiety. The immune hypothesis of depression does not imply that depression is always caused by inflammation. Rather, it suggests there's a subset of patients that may exhibit depressive symptoms as a result of inflammation. This is clinically relevant as these patients may be different in their response to conventional antidepressant therapy and may be susceptible to treatment strategy based on anti-inflammatory or immunomodulatory therapies in the future. This correlation between stress, inflammation and depression also helps to understand why, chronic physical diseases, obesity, autoimmune diseases and chronic psychosocial stress are linked to an increased risk of depression [23].

2.4 Glutamatergic Dysfunction

Glutamate is a major excitatory neurotransmitter in the brain critical to synaptic transmission, learning and memory, and the process of neuroplasticity. Recently, defects in glutamatergic function have been implicated in depression, and these defects are considered to be relevant to mood disturbances. The glutamate hypothesis differs from the monoamine hypothesis, which primarily accounts for the delayed antidepressant effects, in that it helps to elucidate the immediate antidepressant effects, particularly those noted with ketamine and esketamine. Glutamate targets multiple receptor systems, such as NMDA receptors, AMPA receptors and metabotropic glutamate receptors. A balance between the activity of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA is important for normal brain function. Depression, chronic stress, inflammation and excess cortisol can mess up this balance. Too much glutamate release or decreased clearance can cause excitotoxicity leading to nerve damage and synapse damage [24]. Conversely, weakened glutamate transmission in some of these circuits could disrupt connectivity between mood, cognition and motivation regions of the brain. In depression, dysfunction of the NMDA receptor is of special significance. Excitotoxic damage and decreased neuroplasticity may be due to overactivation of NMDA receptors, and modulation of the NMDA receptor can lead to a rapid antidepressant effect. The NMDA receptor antagonist ketamine has been reported to rapidly improve depressive symptoms in some treatment-resistant depression patients. It is believed to exert an antidepressant-like effect by increasing AMPA receptor signaling, activation of intracellular mechanisms like mTOR, augmentation in synaptic formation and normalization of functional connections in circuits involved in mood. Medication-free major depression has been the focus of modern reviews of depression pathophysiology, which have found abnormalities in glutamate and GABA to be significant. There are also links between glutamatergic dysfunction and inflammation and neuroplasticity [25]. Inflammation can elevate the production of quinolinic acid that can activate NMDA receptors and can lead to excitotoxicity. Long-term stress can cause a decrease in the function of the glial cells, in the ability to take up the glutamate, and in the ability to regulate the energy metabolism of the neurons. The alterations may play a role in the loss of synapses in the prefrontal cortex and hippocampus, both of which have been involved in depression. This has shifted the paradigm of antidepressant drug discovery focusing on the role of glutamate in depression. The traditional

antidepressants mainly target monoamines, whereas recent studies are directed to glutamate modulators, AMPA receptor potentiators, NMDA receptor modulators and drugs that restore excitatory-inhibitory balance. This is particularly significant for patients with treatment-resistant depression, suicidal ideation, and severe depression, which may benefit from more rapid symptom relief [26].

2.5 Neuroplasticity and BDNF Signaling

Neuroplasticity is the property of the brain to adapt, reorganize, form new synaptic connections and change neural circuits as a result of experience, stress, learning, and treatment. Depression is seen more and more as a disease of dysplastic brain. Under chronic stress, inflammation, excess cortisol, oxidative stress and diminished neurotrophic support can result in neuronal atrophy, synaptic loss, a diminished capacity for neurogenesis, and changes in connectivity in mood-regulating brain regions [27]. One of the most essential molecules in neuroplasticity is the BDNF. BDNF promotes long-term potentiation, dendritic branching, neuron survival, and synaptic growth, as well as neurogenesis. Specifically it is important in the hippocampus, the prefrontal cortex and other regions associated with mood, memory and cognitive flexibility. Depression is associated with decreased BDNF signaling, and successful antidepressant therapy is associated with increased BDNF activity and enhanced synaptic plasticity. The recent reviews provide a summary of the correlation of BDNF, neuroplasticity and antidepressant responsiveness in depression. With chronic stress, the expression of BDNF might decrease, particularly in the hippocampus and prefrontal cortex. This can lead to a decrease in hippocampal volume, memory difficulties, negative cognitive bias, poor emotional regulation and less resilience to stress. If the level of BDNF is low, the neurons may be less able to respond to environmental demands [28]. This could be why negative thinking is a common symptom of depression, along with a lack in problem solving and inability to bounce back from stressful situations. Part of the improvements that antidepressants provide for depression is that they help restore the neuroplasticity of the brain. While SSRIs and SNRIs are associated with early changes in monoamines, the therapeutic effects of these drugs could be mediated by subsequent changes in gene expression, BDNF signaling, synaptic remodeling and network adaptation. This may help to account for the delayed effects of traditional antidepressants [29]. Conversely, ketamine is a fast-acting antidepressant that can show more immediate effects by promoting rapid changes in synaptogenesis and functional connectivity via glutamate-mediated plasticity pathways. Neuroplasticity also creates a connection between pharmacological and non-pharmacological treatments. BDNF activity and neuroplasticity can also be affected by psychotherapy, physical exercise, good sleep, cognitive training and stress reduction. The neuroplasticity model thus reinforces the idea of a holistic approach to the management of depression, in which pharmaceuticals provide a neurological landscape that can enhance the brain's ability to heal, while psychological and lifestyle treatments can mold more favorable neural circuits [30].

2.6 Gut–Brain Axis in Depression

The gut/ brain axis is a system that connects the gut, gut microorganisms, immune, endocrinal, vagus nerve, and central nervous system in a two-way pathway. This axis has been a growing focus in recent years for studies of depression. The gut microbiota may interact with brain function by generating neurotransmitter like substances, short chain fatty acids, immune mediators, metabolic

products, and modulate the metabolism of tryptophan. Any change in gut microbes balance (dysbiosis) can help to cause inflammation, changes in your body's response to stress, and symptoms of mood disorders. There are several mechanisms that might account for the involvement of the gut–brain axis in depression. First, the gut dysbiosis can lead to leakiness, or open gut, such that bacterial products like lipopolysaccharide can enter into the blood stream and induce systemic inflammation [31]. This inflammatory activation may impact the brain, and play a role in depressive symptoms. Second, gut bacteria affects tryptophan metabolism which impacts serotonin synthesis and kynurenine pathway activity. Third, metabolites of microbes, including short-chain fatty acids, can influence blood–brain barrier function, microglial activity and neuroplasticity. Fourthly, the vagus nerve directly connects the gut and the brain, affecting emotional control and stress responses. There is also a possibility of the gut microbiota affecting the HPA axis. A well-balanced microbiome seems to help to maintain normal stress regulation, while dysbiosis may play a role in heightened cortisol responses and low stress resilience. Its role in connecting a diet, stress, inflammation, and depression has become an important connection. Human and animal research have found the composition of gut microbiota may be different in people with depression, but the specific patterns are inconsistent and not yet clear. The imbalance in gut microbiome is described recently as one of the biological processes that are involved in the pathogenesis of depression. The gut–brain axis is a clinically relevant pathway that presents opportunities for prevention and treatment [32]. In addition to conventional therapies, supportive interventions such as diet quality, probiotics, prebiotics, psychobiotics, anti-inflammatory nutrition and microbiota-targeted interventions are under investigation for depression. Such methods are not to be used in place of proven treatment for moderate to severe depression. Instead, they are hopeful adjunctive methods that can be helpful in individual patients with gastrointestinal symptoms, inflammation, metabolic disease, and/or depression related to stress conditions. The overall pathogenesis or pathobiology of depression can be considered as an interaction of different biological pathways [33]. Monoamine dysfunction accounts for some of the therapeutic efficacy of existing antidepressants and HPA-axis dysfunction accounts for the correlations between stress and depression. Immune activation is associated with changes in neurotransmitters and alterations in plasticity, which are linked to neuroinflammation. Excitatory – inhibitory imbalance and fast acting antidepressant mechanisms are explained by glutamatergic dysfunction. Impaired neuroplasticity and reduced BDNF signaling are responsible for structural and functional changes in the brain, and are linked to the gut–brain axis, which links microbiota, metabolism, immunity, and regulation of mood. Thus, depression is a complex condition and not a neurotransmitter deficiency [34].

3. Established Pharmacological Therapies

Pharmacological treatment continues to be one of the mainstays in the treatment of moderate to severe depression. The choice of antidepressant is influenced by symptom severity, prior antidepressant response, comorbid anxiety and/or pain, sleep, appetite, risk of suicide, drug interactions, adverse-effect profile, cost, and patient preference. Shared decision making, periodic review after initiation of antidepressant therapy, assessment for side effects, and maintenance antidepressant therapy for long enough after remission of symptoms to minimize the risk of relapse, are the areas in which current treatment guidelines place particular emphasis. NICE guidance suggests that discussions with

patients around treatment options should take place, and that treatment should be tailored to the clinical need and the patient's preference; in more severe depression, antidepressant medications and a combination of antidepressant and psychological therapy are recommended [35].

3.1 Selective Serotonin Reuptake Inhibitors

Some of the most frequently prescribed first line antidepressants are selective serotonin reuptake inhibitors. This class is composed of fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. SSRIs primarily work by blocking the presynaptic nerve terminal serotonin transporter. This blockade prevents serotonin from being taken back up into the presynaptic terminal, which leads to more serotonin in the postsynaptic receptor. According to StatPearls, SSRIs bind to the serotonin transporter (SERT) and prevent serotonin from being removed from the synaptic cleft, as well as having fewer adrenergic, cholinergic, and histaminergic effects and fewer side effects than older antidepressants. The therapeutic benefit of SSRIs stems from their effectiveness, tolerability, safety in overdose, and their utility in comorbid anxiety disorders. They are usually recommended for patients with depression and anxiety, panic symptoms, obsessive thoughts, irritability, and emotional instability [36]. Fluoxetine is long acting and can be helpful when eliminating symptoms are an issue, and sertraline is a broad spectrum drug that is widely used due to its balanced tolerability profile. The use of escitalopram is sometimes preferred because of its relatively good tolerance and easy dosing. While effective, paroxetine more often causes anticholinergic effects, weight gain, sedation, sexual dysfunction and withdrawal symptoms. SSRIs tend to be well tolerated, but they do come with some side effects. Side effects consist of nausea, diarrhea, headache, insomnia, somnolence, tremor, sweating, sexual dysfunction and emotional blunting. Adherence can be lowered by sexual side effects including decreased libido, decreased speed of ejaculation, anorgasmia, and erectile dysfunction. Another side effect of SSRIs is hyponatremia, particularly in older adults or diuretic users. During the onset of treatment, some may feel more anxious, restless or unable to sleep. In sensitive patients, therefore, it is helpful to begin with low doses and a slow titration [37]. One of the biggest drawbacks of using SSRIs clinically is their time lag before they begin to have a significant impact on mood. Serotonin reuptake inhibition is fast, but clinical effects take several weeks. This delay is believed to be attributed to adaptive changes in receptor sensitivity, intracellular signaling, gene expression and neuroplasticity. Not all patients respond to SSRIs equally and only a partial response (or no response) occurs in many of them. Therefore, treatment should be reassessed following a suitable trial, and/or treatment adjustment, switch or augmentation may be considered if there is an inadequate response [38].

3.2 Serotonin–Norepinephrine Reuptake Inhibitors

The serotonin–norepinephrine reuptake inhibitors (SNRIs) are antidepressant drugs that enhance the activity of both serotonin and norepinephrine. A number of the important drugs in this class are venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran. They are believed to work by blocking the serotonin and norepinephrine transporters, which leads to more serotonin and norepinephrine available in the synapse. The dual mechanism is clinically relevant since serotonin is involved in emotional control, anxiety and mood and Norepinephrine is involved in alertness, energy, concentration and pain modulation. SNRIs are effective in treating depressed patients with psychomotor slowing, poor concentration, low energy, fatigue or painful

physical symptoms. Duloxetine has other indications for neuropathic pain, fibromyalgia and chronic musculoskeletal pain [39]. High dose venlafaxine can have more noradrenergic activity; low dose venlafaxine more serotonin-dominant. The active metabolite of venlafaxine, desvenlafaxine, is simpler metabolized. Due to their noradrenergic activity, SNRIs may also be useful if SSRI's do not lead to a sufficient increase in energy or motivation. SNRIs have an adverse-effect profile similar to that of SSRIs, but with the addition of noradrenergic effects. Side effects are nausea, dry mouth, sweating, insomnia, dizziness, constipation, sexual dysfunction and raised blood pressure. Venlafaxine, especially when used at higher doses, may elevate blood pressure, therefore should be monitored in patients at risk for elevated blood pressure or who have hypertension. When venlafaxine and desvenlafaxine are suddenly stopped, a person may have withdrawal effects like getting dizzy, irritated, electric shock-like feelings, feeling sad, not sleeping well, nausea, and flu-like symptoms [40]. So, it is advisable to wean off therapy slowly. SNRIs are typically used when SSRIs are not effective or if there is a patient symptom picture that indicates there is some benefit to the noradrenergic component. They are particularly important in depression with pain syndromes, low energy or an inadequate response to SSRIs. These however should be used with caution in those with uncontrolled hypertension, marked cardiac disease, anxiety activation and sensitivity to the stimulant-like side effects. They should be taken alone, as with SSRIs, because of the potential risk of serotonin syndrome when used with monoamine oxidase inhibitors [41].

3.3 Tricyclic Antidepressants

The tricyclic antidepressants are older antidepressants still clinically used; especially in severe depression, melancholic depression, chronic depression or treatment-resistant depression. These include amitriptyline, imipramine, clomipramine, nortriptyline, desipramine and doxepin. The primary mechanism of action of TCAs is inhibition of norepinephrine and serotonin reuptake; they also inhibit muscarinic cholinergic, histaminergic H1, and alpha-adrenergic receptors. These are very general receptor functions that underlie their therapeutic properties but also their high adverse effect profile. TCAs are effective antidepressants but are generally not first line treatment, as they are not tolerated or are not considered safe due to their side effects [42]. The efficacy of TCAs is similar to that of SSRIs in the treatment of major depressive disorder, but they are more likely to cause adverse effects (anticholinergic activity) and have a lower risk of overdose. For these reasons, TCAs are usually reserved for patients who have not responded to more recent antidepressants, or patients who have particular symptoms, such as insomnia, neuropathic pain, migraine prophylaxis requirements, or chronic pain. The negative side effects of TCAs are significant. Common side effects of anticholinergic drugs are dry mouth, blurred vision, constipation, urinary retention, tachycardia, and cognitive impairment. Histamine blockade may lead to sleepiness and weight gain and alpha-adrenergic blockade may lead to postural hypotension and dizziness. TCAs can also have an effect on cardiac conduction, causing QT prolongation, arrhythmia, and severe toxicity on over-dose [43]. Therefore they should be used with caution in patients with cardiovascular disease, elderly, patients at risk of falls and patients with suicidal ideation. Although these are some of the limitations, TCAs are useful in certain clinical scenarios. When depression is accompanied by chronic pain, insomnia, and/or migraine, antidepressants such as amitriptyline and nortriptyline are often prescribed. Clomipramine exhibits potent serotonergic properties; it is very

effective for the obsessive-compulsive component, but may have side effects that decrease its usefulness. Compared to the tertiary amine TCAs (such as amitriptyline or imipramine), nortriptyline and desipramine are sometimes reported as being more tolerable. For some TCAs, therapeutic drug monitoring could be helpful to maximize effectiveness and prevent toxicity [44].

3.4 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are one of the first antidepressant medications. Countries that have phenelzine, tranylcypromine, isocarboxazid, and moclobemide included in this class are the countries where these medications are registered. The mechanism of action of MAOIs is to block monoamine oxidase (the enzyme that breaks down serotonin, norepinephrine and dopamine). The enzymes that inhibit these neurotransmitters make them more available in the brain. StatPearls states that while MAOIs are the oldest class of antidepressants known, they are not first-line treatment as a result of side effects and drug–drug interactions [45]. MAOIs are particularly useful in atypical depression, unresponsive depression and depression cases that are characterized by rejection sensitivity, excessive sleepiness, increased appetite, leaden paralysis, and mood reactivity. They can also be helpful in people who've tried several antidepressant medications and are not helped by any of them. Their use has been, however, decreasing, due to the need for careful dietary restrictions, medication review, patient education, and monitoring. The most important safety issue with MAOIs is the build-up of tyramine leading to a hypertensive crisis. Nonselective MAOIs may cause dangerous hypertension when taken with certain preserved foods (aged cheese, some alcoholic drinks, cured meats, some fermented foods), red wine, and other foods that are high in tyramine. MAOIs also have serious drug interaction risks [46]. The use of MAOIs with SSRIs, SNRIs, TCAs, some opioids, sympathomimetics or serotonergic agents may lead to a serotonin syndrome or a hypertensive reaction. StatPearls cautions against the possibility of drug–drug and drug–food interactions with MAOIs, and against the use of MAOIs in combination with SSRIs due to the risk of serotonin syndrome. Due to these dangers, MAOIs must be "washout" before starting or stopping other antidepressants. Most antidepressant medications have a washout period of 14 days or more; for fluoxetine, the washout period is longer since the half-life is very long. Clinicians experienced in using MAOIs are therefore usually the ones who prescribe them. Today they are not as widely used, but are still valuable for certain patients who have failed to improve from other treatments [47].

3.5 Atypical Antidepressants

Atypical antidepressants are a diverse category of medications that do not easily fall into one of the four categories listed above: SSRIs, SNRIs, TCAs, and MAOIs. These include bupropion, mirtazapine, trazodone, vortioxetine, vilazodone, and possibly other drugs based on classification. The therapeutic actions, clinical uses, and side effects of these drugs are diverse. On a molecular level, they vary in a way that allows them to be used in individual treatments especially when patients don't respond to standard serotonergic drugs or when they have intolerable side effects [48]. The mechanism of action of bupropion is mainly the blocking of the reuptake of norepinephrine and dopamine with little direct serotonergic action. According to StatPearls, bupropion is a dopamine/norepinephrine reuptake inhibitor that acts at the presynaptic cleft. Clinically it can be helpful in depression where there is fatigue, hypersomnia, decreased motivation, poor concentration or sexual

dysfunction from using an SSRI. Less likely to lead to sexual dysfunction or weight gain than other serotonergic antidepressants. It can cause insomnia, anxiety, tremor, dry mouth, and a higher risk of seizures, particularly at higher doses or in individuals with eating disorders or seizure history, however. The mechanism of action of Mirtazapine is primarily through antagonism of presynaptic alpha-2 adrenergic receptors, increasing norepinephrine and serotonin release. Also inhibits 5-HT2 and 5-HT3 receptors with high antihistaminic activity. This profile makes mirtazapine useful in depression with insomnia or anxiety, poor appetite or weight loss or nausea [49]. The common side effects are sedation and weight gain. Lower doses may lead to more sedative effects because of the histamine blocking effects. Mirtazapine can be especially helpful in frail patients who have trouble sleeping and don't have much appetite; however, it may not be the best option for patients worried about weight gain or metabolic changes. Trazodone belongs to a class of drugs known as serotonin antagonists and reuptake inhibitors. It acts as an inhibitor of serotonin type 2 receptors and has low inhibitory activity on the serotonin reuptake. It also has antihistaminic and alpha-1 adrenergic blocking properties, leading to sedation and postural hypotension. According to StatPearls, trazodone is an antidepressant drug that blocks the serotonin transporter and serotonin type 2 receptors. Trazodone is frequently prescribed for insomnia with a depression at low dose in the real world, but at a higher dose for complete antidepressant activity. Sedation, dizziness, orthostatic hypotension and occasionally priapism are all important adverse effects. Vortioxetine is multimodal antidepressant with activity that encompasses serotonin reuptake inhibition and modulation of multiple serotonin receptor subtypes. May be helpful with cognitive aspects of depression (concentration, executive functioning). According to guidance from NICE vortioxetine is a treatment choice when there is no or limited response to at least two antidepressant drugs during the current episode. Vilazodone is a serotonin reuptake inhibitor with partial 5-HT1A receptor agonist activity that could be considered in certain individuals, but may have gastrointestinal side effects [50].

3.6 Melatonergic Antidepressants

Melatonergic antidepressants are a unique class of antidepressant drugs that affect both the regulation of circadian rhythms and monoaminergic modulation. Agomelatine is the main drug in this category. It is a melatonin MT1 and MT2 receptor agonist and antagonist at 5-HT2C receptors. This synergic effect may contribute to the re-entrainment of the circadian system as well as stimulate the release of norepinephrine and dopamine in the frontal cortex. According to a pharmacological review, agomelatine is a strong MT1/MT2 receptor agonist and neutral 5-HT2C receptor antagonist [51]. The mechanism behind melatonergic therapy is the fact that depression often is accompanied by circadian rhythm disturbance. Insomnia, early morning awakening, hypersomnia, diurnal mood variation, fatigue and disruption of sleep–wake cycles may occur in patients. Agomelatine acts on melatonin receptors, and may help to enhance sleep quality and circadian rhythm, with a lesser risk of sexual dysfunction than many SSRIs. It is also a 5HT2C antagonist which could also improve dopaminergic and noradrenergic transmission in those brain regions where they play a role in mood and motivation. Agomelatine might be indicated in depressed patients with insomnia, dysregulated sleep-wake rhythm or a sensitivity to serotonergic side effects. It does have some safety factors, however. Liver function monitoring is recommended as agomelatine can lead to increases in hepatic transaminases and rarely to clinically

significant hepatotoxicity. Should not be used in patients with active liver disease or important hepatic impairment. For this reason, the introduction of agomelatine represents a novel mechanism and a sexual side-effect profile that is favorable, but appropriate patient selection and laboratory monitoring is required before taking this drug [52]. This suggests that pharmacotherapy for depression is not restricted to augmenting monoamines in the synapse, as shown by melatonergic antidepressants. Rather, contemporary established treatment also acknowledges the position of sleep structure, circadian regulation and biological rhythms in mood issues. This is especially relevant since sleep disturbances are both a symptom and risk factor for the persistence or recurrence of depression [53].

3.7 Combination and Augmentation Therapy

Patients who respond partially or do not respond sufficiently, have recurrent depression, have a psychotic depression, or have a treatment-resistant depression are treated with combination therapy and augmentation therapy. The usual definition of combination therapy is the use of two antidepressants, and the usual definition of augmentation is the addition of a non-antidepressant agent to enhance a response [54]. These strategies are not first-line treatment for all patients as they are more complicated, more expensive, require more monitoring, and have higher adverse effect burden. They are however important if patients don't respond to standard monotherapy. The most frequent combination approach is the use of mirtazapine or trazodone, in combination with an SSRI or SNRI, particularly if insomnia, anxiety, loss of appetite or partial response is a concern. Alternatively, changing the antidepressant class if the first antidepressant is not effective or is poorly tolerated. The use of two or more serotonergic drugs needs to be careful since it may lead to serotonin syndrome. In general, combinations of SSRIs, SNRIs and TCAs with MAOIs should be avoided due to the risk of serious interaction. The NICE guidance for depression with no or inadequate response includes changing antidepressant drugs, adding another antidepressant, or modifying treatments into a combination of psychological therapies and antidepressant drug use; it also cautions against certain combinations of antidepressants - for instance, combinations of SSRI, SNRI or TCA with MAOI - being potentially hazardous [55]. One of the most well-known treatment-resistant depression augmentation strategies is lithium. Lithium may act as a modulator of antidepressant treatment effects via modulation of monoaminergic transmission, 2nd messengers, neuroprotection, circadian regulation, and suicide-risk reduction mechanisms. It does need to be carefully monitored though. Prior to lithium treatment, and monitoring for lithium levels after commencement and dose adjustments, the following should be measured in accordance with NICE guidance: Weight, renal function, thyroid function, and calcium levels. Lithium toxicity may manifest as diarrhea, vomiting, tremor, ataxia, confusion, and seizures and is exacerbated by dehydration, renal impairment, NSAIDs, ACE inhibitors, angiotensin receptor blockers, and diuretics. Also, 2nd generation antipsychotics have been employed as augmentation agents, especially in treatment resistant depression, and in depression with psychotic features. Medications include aripiprazole, quetiapine, olanzapine, and risperidone [56]. These agents could act by modulating dopamine and serotonin receptors which could lead to better mood. Partial dopamine agonist activity is the reason that aripiprazole is sometimes used, and quetiapine may be helpful if there is a lot of anxiety and insomnia. Antipsychotic augmentation is, however, associated with a number of potential side-effects

including weight gain, dyslipidaemia, hyperglycemia, sedation, extrapyramidal symptoms, elevation of prolactin, and QT prolongation. Pulse, BP, weight, glucose/HbA1c, lipids and adverse effects are recommended as parameters to be monitored at baseline and follow-up in the case of the use of antipsychotics in depression. Other augmentation therapies involve thyroid hormone, lamotrigine in some patients and psychostimulants in some patients, and electroconvulsive therapy (ECT) in the most severe and treatment-resistant depression [57]. Futher-line treatment includes second generation antipsychotics, specialist input, lithium, electroconvulsive treatment, lamotrigine and triiodothyronine, and is included in the NICE treatment algorithms. In clinical application, augmentation should be tailored to the patient's clinical presentation, physical status, drug interaction, prior response and risk. In summary, there are many classes of antidepressant medications with a variety of mechanisms, effects, and drawbacks. SSRI's stay as a first line choice due to tolerability and safety. SNRIs can be useful if you want to increase noradrenaline activity or to help to control pain. TCAs and MAOIs are effective but have a limited use due to side effects and concerns. Atypical antidepressants can be used to select the antidepressants more specifically according to the type of symptoms, whereas melatonergic drugs can be used to treat circadian disturbance. Partial responders and treatment-resistant cases should be treated with combination and augmentation strategies. This modern clinical practice is not just to prescribe an antidepressant, but to choose, monitor, tailor, and individualize treatment until remission and functional recovery are realized [58].

Table 1: Commonly Used Antidepressant Drugs

Drug Name	Class	Main Mechanism of Action	Common Clinical Use	Common Adverse Effects
Fluoxetine	Selective Serotonin Reuptake Inhibitor	Inhibits serotonin reuptake and increases serotonin level in synaptic cleft	Major depression, anxiety disorders, OCD, bulimia nervosa	Nausea, insomnia, headache, sexual dysfunction, anxiety, GI upset
Sertraline	Selective Serotonin Reuptake Inhibitor	Blocks serotonin reuptake transporter and enhances serotonergic neurotransmission	Depression with anxiety, panic disorder, PTSD, OCD	Diarrhea, nausea, tremor, insomnia, sexual dysfunction
Escitalopram	Selective Serotonin Reuptake Inhibitor	Selectively inhibits serotonin reuptake	Major depressive disorder and generalized anxiety disorder	Nausea, fatigue, sweating, sleep disturbance, sexual dysfunction
Paroxetine	Selective Serotonin Reuptake Inhibitor	Increases serotonin concentration by blocking serotonin reuptake	Depression, anxiety disorders, panic disorder	Weight gain, sedation, dry mouth, sexual dysfunction, withdrawal symptoms
Venlafaxine	Serotonin–Norepinephrine Reuptake Inhibitor	Inhibits reuptake of serotonin and norepinephrine	Depression, anxiety disorders, treatment-resistant depression	Nausea, sweating, insomnia, increased blood pressure, withdrawal symptoms

Duloxetine	Serotonin–Norepinephrine Reuptake Inhibitor	Enhances serotonin and norepinephrine transmission	Depression with neuropathic pain, fibromyalgia, chronic pain	Dry mouth, nausea, dizziness, fatigue, sweating, increased BP
Amitriptyline	Tricyclic Antidepressant	Blocks serotonin and norepinephrine reuptake; also blocks muscarinic, histamine, and alpha receptors	Depression with insomnia, chronic pain, migraine prophylaxis	Sedation, dry mouth, constipation, weight gain, postural hypotension, cardiac toxicity
Nortriptyline	Tricyclic Antidepressant	Inhibits norepinephrine and serotonin reuptake	Depression, neuropathic pain, elderly patients when TCA is needed	Dry mouth, constipation, dizziness, sedation, arrhythmia risk
Bupropion	Atypical Antidepressant / NDRI	Inhibits dopamine and norepinephrine reuptake	Depression with fatigue, low motivation, smoking cessation	Insomnia, dry mouth, anxiety, tremor, seizure risk at high dose
Mirtazapine	Atypical Antidepressant / NaSSA	Blocks alpha-2 receptors and increases norepinephrine and serotonin release	Depression with insomnia, anxiety, weight loss, poor appetite	Sedation, increased appetite, weight gain, dry mouth
Trazodone	Serotonin Antagonist and Reuptake Inhibitor	Blocks 5-HT2 receptors and weakly inhibits serotonin reuptake	Depression with insomnia	Sedation, dizziness, orthostatic hypotension, rare priapism
Vortioxetine	Multimodal Antidepressant	Inhibits serotonin reuptake and modulates serotonin receptors	Depression with cognitive symptoms such as poor concentration	Nausea, headache, dizziness, sexual dysfunction
Agomelatine	Melatonergic Antidepressant	MT1/MT2 receptor agonist and 5-HT2C receptor antagonist	Depression with sleep and circadian rhythm disturbance	Headache, dizziness, nausea, liver enzyme elevation
Phenelzine	Monoamine Oxidase Inhibitor	Inhibits monoamine oxidase enzyme and increases serotonin, norepinephrine, and dopamine	Atypical depression, treatment-resistant depression	Weight gain, postural hypotension, sexual dysfunction, hypertensive crisis with tyramine foods
Tranylcypromine	Monoamine Oxidase Inhibitor	Irreversibly inhibits monoamine oxidase and increases monoamines	Severe or resistant depression	Insomnia, agitation, hypertension risk, drug and food interactions

4. Emerging Drug Targets in Depression

The drug treatment of depression has traditionally centered on monoaminergic neurotransmitters, including serotonin, noradrenaline and dopamine. While this is the case with SSRI's, SNRI's, TCA's, and atypical anti-depressants, there is still a significant number of patients who experience delayed responses, partial success, relapse, and/or treatment resistance. This restriction has been a driving force for the evolution of newer antidepressant approaches that aim to modulate mechanisms beyond the monoaminergic

pathways. In the current treatment of depression, the glutamatergic system, the GABAergic system, neurosteroid pathways, orexin receptors and systems of opioid receptors, immune-inflammatory pathways, neurotrophic signaling, and the gut–brain axis are increasingly the focus of drug discovery. A systematic review of approved and pipeline treatments indicated that a large proportion of the developments of antidepressant drugs in recent years and in late-stage clinical trials target mechanisms beyond the classical monoamine hypothesis, including the NMDA receptor, the GABA-A receptor, and the kappa-opioid receptor [59].

4.1 NMDA Receptor Modulators

N-methyl-D-aspartate receptors are glutamate ionotropic receptors that play a role in synaptic plasticity, learning, memory, excitatory neurotransmission, and remodeling of neural circuits. There has been a strong association of abnormal glutamatergic transmission to the pathophysiology of depression, particularly treatment-resistant depression. Excessive glutamate exposure, due to the effects of chronic stress, inflammation, and impaired glutamate uptake by cells of the glia, can disrupt the balance of glutamate and cause either excitotoxicity or a decrease in adaptive synaptic signaling. So, NMDA receptor modulation is one of the most significant novel strategies for antidepressant drug discovery [60]. The most famous NMDA receptor modulator that has rapid antidepressant properties is Ketamine. Ketamine is a noncompetitive NMDA receptor antagonist that may result in rapid improvement of depressive symptoms for certain patients with treatment-resistant depression. Antidepressant effect goes beyond just NMDA blockade. Existing models propose that ketamine specifically targets NMDA receptors on GABAergic interneurons and causes a brief release of glutamate. This glutamate release leads to activation of glutamate receptors, including AMPA receptors, and is followed by an activation of intracellular pathways, including mTOR, BDNF and signaling related to synaptogenesis. These changes at the outlet may reset the normal connections that exist in the prefrontal cortex and other parts of the brain involved with mood. Ketamine and esketamine are reported to be paradigm examples of swift-acting glutamatergic antidepressants, with NMDA and AMPA receptors being key targets for rapid antidepressant effects. The S-enantiomer of Ketamine is an important clinical example of NMDA receptor targeting therapy (Esketamine). According to the FDA-approved label, Spravato is a noncompetitive NMDA receptor antagonist labeled for treating treatment-resistant depression as a monotherapy or in combination with an antidepressant medication in adults; and treatment of depressive symptoms in adults with major depressive disorder and acute suicidal ideation or behavior. The change in depression pharmacotherapy is very significant due to the mechanism of action of esketamine, which is glutamatergic rather than serotonin or norepinephrine transporter. But limitation is there with the modulation of NMDA receptor. Ketamine and esketamine do need clinical supervision because of their dissociative, sedative effects, blood pressure elevation, potential for abuse, and need for monitoring. Some of the side effects listed on the FDA label for Spravato include sedation, somnolence, tachycardia, vertigo and dissociation effects. As such, future development of NMDA targeted antidepressants will rely on the development of more orally active, non-dissociative, safer and more selective compounds that would retain the rapid antidepressant efficacy, but with reduced adverse effects [61]. NMDAR-dependent Long-term Depression (LTD) Mechanism mentioned in **Fig.1**.

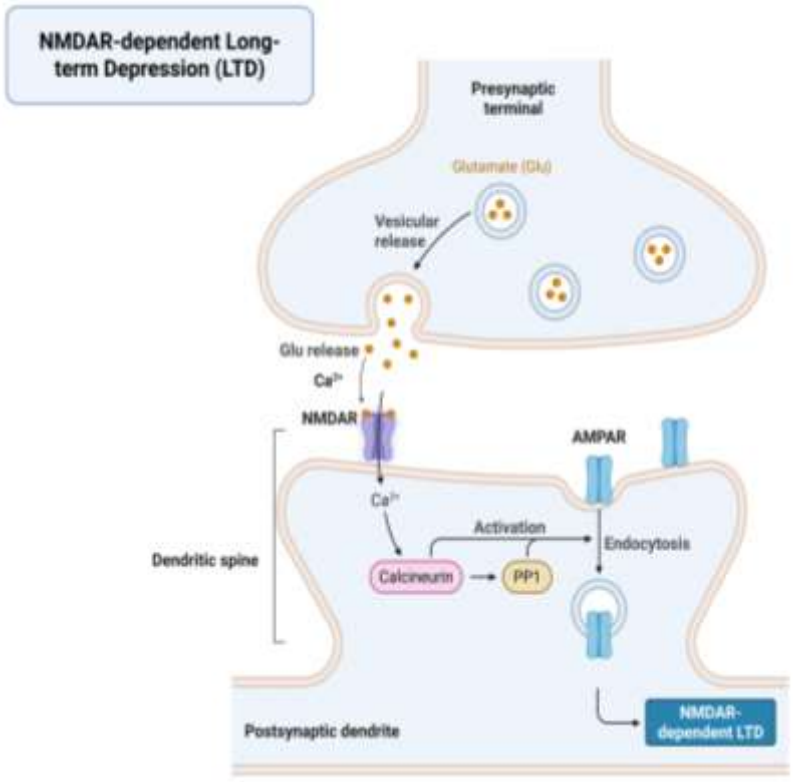

Fig.1: NMDAR-dependent Long-term Depression (LTD) Mechanism

4.2 AMPA Receptor Potentiators

There is another large class of ionotropic glutamate receptors known as the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. AMPA receptors are crucial for synaptic strengthening, neuronal communication, and neuroplasticity and play a key role in fast excitatory synaptic transmission. Key abnormalities in depression involve impaired synaptic plasticity and decreased connectivity in circuits involved in the regulation of mood. AMPA receptor potentiation is intended to correct these deficits by increases in the activation of excitatory synapses and adaptive plasticity. Activation of AMPA receptors seems to be required for the fast antidepressant effects of ketamine. The release of glutamate caused by NMDA receptor blockade activates the AMPA receptor, which turns on downstream molecular pathways that promote BDNF release, mTOR signalling, dendritic spine growth and synaptogenesis. These processes may repair or reverse stress-induced loss of synapses in these areas. The reviews of rapid antidepressant drugs highlight that there are several pathways through which they exert their rapid antidepressant effects that converge on NMDA/AMPA/BDNF-induced plasticity [62]. AMPA receptor potentiators, also referred to as "ampakines," are currently being investigated as a novel class of antidepressant medications due to their potential to directly stimulate AMPA receptor signaling without causing the dissociative effects seen with NMDA receptor blockade by ketamine. The theoretical benefit of AMPA potentiation is that it could reinforce synapse function, enhance cognitive symptoms and facilitate repair of the neural system. Depression is associated with cognitive impairment, low motivation, decreased emotional flexibility, and poor executive function; adding that to a patient's depression symptoms would make AMPA-based therapies useful. Depression continues to be a largely

investigational area for AMPA receptor potentiators, despite the biological rationale. Challenges include ensuring that receptors are optimally activated, that excitotoxicity does not occur, that there is long-term safety, and that patients who will benefit most are selected. However, a high AMPA activation can be detrimental, and future drugs designed to target the AMPA receptor will need to improve plasticity without neurotoxicity or seizures. The AMPA receptor pathway is thus, better known as a potential promising downstream mechanism of rapid antidepressant activity, rather than as an established class of clinical treatments [63].

4.3 GABAergic System Targets

The predominant inhibitory neurotransmitter in the central nervous system is GABA. Emotional regulation demands a balance between excitatory (glutamatergic) and inhibitory (GABAergic) signaling. During depression, this excitatory-inhibitory balance can be disturbed, leading to increased anxiety, insomnia, emotional over-reactivity, rumination, decreased ability to tolerate stress, and changes in the activity of the cortical networks. The GABAergic system is a potential target for treatment because GABA levels were found to be decreased in several neurobiological models of depression and because GABAergic signaling is impaired [64]. One of the most clinically relevant advances in the field of depression is the identification of the development of allosteric modulators of the GABA-A receptor which are neuroactive steroids. Neurosteroid drugs that modulate GABA-A receptor are examples of such drugs, including Brexanolone and zuranolone. The significance of Zuranolone is that in August 2023, it became the first oral drug approved by the FDA for treating postpartum depression in adults. According to reviews zuranolone is an oral neuroactive steroid antidepressant and a positive allosteric modulator of GABA-A receptor. There is a strong rationale for modulation of GABA-A receptors in postpartum depression due to the rapid hormonal shifts that occur following delivery, which could impact on neurosteroid levels and GABAergic function. Allopregnanolone is a neurosteroid that has a positive effect on the GABA-A receptor and is involved in the regulation of stress, mood and neuronal inhibition. Disruptions in the neurosteroid system can predispose to the development of mood symptoms. Zuranolone and related drugs are designed to restore inhibitory tone and enhance mood faster than traditional antidepressant medications. GABAergic drugs have other applications in addition to postpartum depression. Inpatients with major depression often suffer from insomnia, agitation, anxiety and stress-related hyperarousal. GABA-A modulators increase inhibitory neurotransmission and could help dampen the hyperactivity of neural circuits, which in turn could help to regulate mood. GABAergic drug development, however, must be done with caution to prevent the undesirable effects of sedation, cognitive slowing, dependence, respiratory depression and abuse potential. Neuroactive steroid modulators can offer an alternative mechanism, but somnolence and dizziness are clinically significant adverse events. A Cochrane review of zuranolone for postpartum depression published in 2025 suggests that it may be effective for the treatment of depression response and remission, but also may be associated with an increase in maternal adverse events, compared with placebo treatment [65].

4.4 Orexin Receptor Modulators

The lateral hypothalamus synthesizes the neuropeptides called orexins (or hypocretins). They control sleep-wake cycles, arousal, food intake, reward processing, stress and energy balance. Sleep disturbance is often seen with depression, such as insomnia, waking up too early,

hypersomnia, nonrestorative sleep and circadian rhythm disturbances. Sleep and mood regulation are tightly intertwined, and the orexin system has become an attractive target in the context of depression, particularly those patients with major depression with insomnia [66]. The Orexin receptor antagonists (ORAs) were initially created for insomnia. These agents inhibit wake-promoting orexin signaling, and enhance the initiation and maintenance of sleep. In more recent studies, it has been evaluated whether orexin receptor antagonists can also be used directly or indirectly to alleviate depressive symptoms, via their effect on sleep and circadian regulation. A systematic review in 2025 found that orexin receptor antagonist are predominantly insomnia medications, but there is preliminary evidence for their effectiveness in major depression. Seltorexant is an investigational agent on a list of drugs that are the most important in this area. It is an orexin-2 receptor antagonist which is being investigated as an adjunctive treatment in depression with insomnia symptoms. The biological logic is that hyperarousal, perhaps related to overactive orexins, could exacerbate sleep problems and stress response, anxiety, and depressive symptoms. Orexin-2 receptor antagonism potentially can enhance sleep quality and mood effects through the decreases in pathological hyperarousal. We were introduced to the orexin receptor antagonists in a narrative review that described and summarized their use as a novel class of drugs originally developed for insomnia, and used as add-on treatments in depressed patients who were resistant to, or who did not respond optimally to, conventional antidepressants. Insomnia is especially pertinent in the context of the orexin target because insomnia is not simply a symptom of depression, but can also be a predictor of depression relapse, negatively influence on antidepressant treatment effectiveness, and be a risk factor for suicide. A drug that enhances sleep architecture (REM/Stage 4) along with a reduction of depressive symptoms could have useful clinical properties. Orexin receptor modulators are not yet proven to be conventional antidepressants, however. There are also emerging data and a need for additional large, long-term trials to identify the most responsive patient populations, to clarify how these drugs will be used in combination with antidepressants, and to answer the question of whether the antidepressant effect is sleep independent [67].

4.5 Kappa Opioid Receptor Antagonists

Reward, pain, stress response, emotional regulation, motivation, and social bonding are all functions of the opioid system. In particular, the kappa opioid receptor has garnered particular interest in the field of depression, as it is stimulated by dynorphin, an endogenous opioid peptide that is secreted during times of stress. Hyperactive Dynorphin-Kappa Opioid Receptor Signaling is linked to dysphoric mood, anhedonia, stress-induced changes in behavior, and decreased sensitivity to reward. Anhedonia is one of the most fundamental symptoms of depression, making the kappa opioid receptor antagonists an emerging potential drug target. The kappa opioid receptor antagonists are developed to block the negative affective states that result from dynorphin effects. These agents could help to normalize the functioning of the reward pathway and alleviate symptoms like loss of pleasure, loss of motivation, emotional numbing and stress-induced depressive behaviors caused by excessive kappa signaling [68]. It works differently to standard antidepressants, which primarily act on monoamine reuptake, and instead works on stress-reward circuitry. Selective kappa opioid receptor antagonists include aticaprant and navacaprant that have been studied in the treatment of major depressive disorder. In 2024, a systematic review indicated that both aticaprant (as an adjunctive

therapy) and navacaprant (as a monotherapy) were under development for major depressive disorder and that both agents had been able to demonstrate a reduction in depressive symptoms in clinical trials, with tolerable adverse events. Navacaprant has also been investigated as a highly selective kappa opioid receptor antagonist in adult patients with major depression. This field is also an example of the ambiguity of emerging targets. Progress in clinical development has been mixed with some late-stage trials failing to meet their earlier expectations. In March 2025, Reuters reported that Johnson & Johnson would abandon late-stage trials of aticaprant for the treatment of major depressive disorder because of its lack of effectiveness. Thus, kappa opioid receptor antagonism is a biologically interesting, but clinically unproven, strategy. The future of its use may rely on improved patient selection, including using patients with higher levels of anhedonia, stress-related depression, or biomarkers for activation of the dynorphin pathway [69].

4.6 Anti-inflammatory Targets

Inflammation has come to be regarded as a key biological factor in a subset of depressed patients. Many studies have found increased inflammatory markers such as C-reactive protein, interleukin-6, tumor necrosis factor-alpha, interleukin-1 beta, and other cytokines in some patients with major depressive disorder. Blood–brain barrier signaling, vagal pathways, immune cell trafficking, microglial activation, and altered neurotransmitter metabolism are all inflammatory signals that can impact the brain. An overview of 2024 noted that neuroinflammation, peripheral inflammation, gut dysbiosis are all significant mechanisms in major depressive disorder's pathophysiology [70]. Cytokines, inflammatory enzymes, microglial activation pathways, oxidative stress pathways, and inflammasomes are anti-inflammatory targets in depression. An important pathway is the NLRP3 inflammasome, a protein complex that activates the cytokines interleukin-1 beta and interleukin-18. Mechanisms of Anti-Inflammatory in CNS-related diseases mentioned in Fig.2. NLRP3 inflammasome components and pro-inflammatory cytokines have been found to be increased in people with major depression, and the inflammasome is suggested to be a therapeutic target for major depression. Depression symptoms may occur in inflammation for a number of reasons. There are two separate mechanisms by which cytokines can decrease serotonin availability: firstly, they might affect the metabolism of tryptophan and cause it to follow the kynurenine pathway, and secondly, they can inhibit the production of serotonin by blocking its synthesis. This could raise levels of neurotoxic metabolites like quinolinic acid that can activate NMDA receptors and promote glutamatergic excitotoxicity. Second, inflammation may decrease activity in reward pathways, resulting in anhedonia, fatigue, psychomotor slowing and low motivation. Third, cytokines may disrupt BDNF signaling and neuroplasticity, resulting in less neuronal resiliency. Finally, chronic inflammation can stimulate microglia and lead to oxidative stress, which can harm synapses and neural networks. The use of nonsteroidal anti-inflammatory drugs, cytokine inhibitors, minocycline, omega-3 fatty acids, statins and NLRP3 related drugs as adjunctive treatments in depression has been explored [71]. A systematic review and meta-analysis published in 2024 indicate that anti-inflammatory medications, when used as an adjunct to antidepressant treatment, have demonstrated antidepressant effects in comparison to the placebo group, although there is a concern for heterogeneity and the selection of patients. A clinical future for this area is likely to depend on the identification of an ‘inflammatory subtype' of depression, based on biomarkers like CRP, IL-6, TNF-alpha, immune gene signatures or

others. It is not recommended to use anti-inflammatory medications as a general treatment for depression. Depression is also heterogeneous and not all patients have clinically significant inflammation. The most logical way to do this is to use biomarker-directed treatment, using anti-inflammatory agents in individuals who have high inflammatory markers or inflammatory conditions like obesity, autoimmune disease, metabolic syndrome, or chronic pain [72].

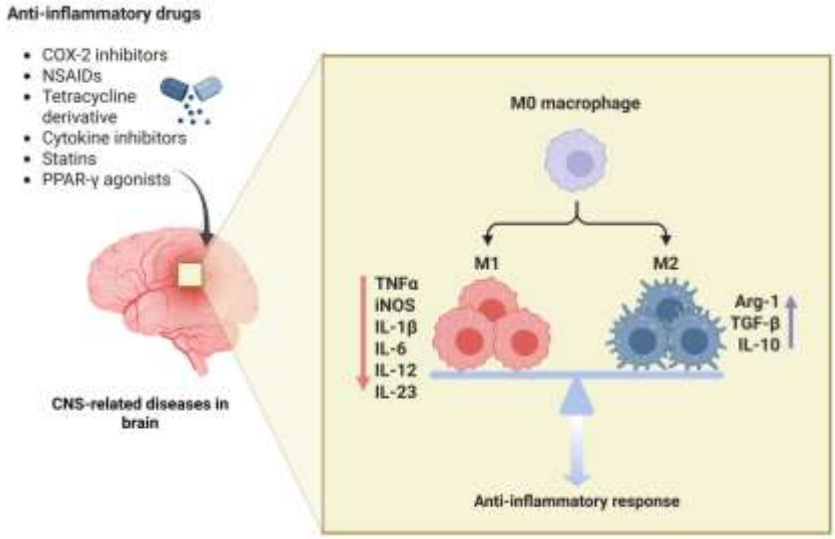

Fig.2: Mechanisms of Anti-Inflammatory Response in CNS-Related Diseases

4.7 Neurotrophic Factor-Based Targets

Neurotrophins are proteins which promote neuronal survival, growth, differentiation, synaptic plasticity and remodeling of brain circuits. Of these, the best studied is brain-derived neurotrophic factor (BDNF). BDNF is required for neurogenesis in the hippocampus, formation of dendritic spines, strengthening of synapses and emotional learning. Impaired neuroplasticity has been linked to depression, and chronic stress has been shown to decrease BDNF signaling in areas of the brain, including hippocampus and prefrontal cortex. The neurotrophic hypothesis suggests that depression is associated with loss of neurotrophic support and synaptic plasticity and that therapeutic antidepressant treatment improves neuroplasticity. BDNF is a key factor in neuronal survival and growth and is involved in synaptic communication and plasticity. Low BDNF levels also have been linked with depression, and antidepressant medications can elevate BDNF levels, thereby promoting neurogenesis and better mood [73]. Targets based on the role of the neurotrophin include BDNF, the TrkB receptor, downstream mTOR signaling, CREB-mediated gene expression, dendritic spine formation pathways, and synaptic proteins. The rapid antidepressant effect of Ketamine may be related to the release of BDNF and activation of pathways that promote the growth of synapses. Likewise, the use of conventional antidepressants could attempt to enhance depression, very likely by slowly raising BDNF expression and neuroplastic adaptation over the course of weeks. That is why it sometimes takes time to respond to antidepressants despite rapid changes in neurotransmitter levels. Direct BDNF therapy is challenging due to the large size of BDNF and its lack of good penetration of the blood–brain barrier, as well as its complex receptor action. Hence, the majority of pharmacological approaches in drug development target indirect pathways of increasing BDNF–TrkB signaling or increasing downstream plasticity. Possible therapeutic targets are TrkB

agonists, positive modulators of neurotrophic signaling, mTOR pathway modulators, glutamatergic agents that promote BDNF release, and agents that counteract the neurotrophic impairments caused by stress. Neurotrophic targets are significant because they target the structural and functional changes in the brain that are associated with depression. The strategies are not about just boosting neurotransmitter concentrations, but about correcting the distorted circuits, enhancing emotional flexibility and restoring cognitive function. Too much or unregulated stimulation of growth pathways, however, could pose dangers; thus, future therapies will need to produce targeted and controlled plasticity enhancement [74].

4.8 Gut Microbiota-Based Therapeutic Targets

The gut microbiota is now recognized as a crucial regulator of mood, stress response, immunity, metabolism and brain function. The gut–brain axis is the link between the gastrointestinal tract and the central nervous system via neural, immune, endocrine and metabolic pathways. The activity of gut bacteria can affect neurotransmitter production, short chain fatty acid production, metabolism of tryptophan, signaling through the vagus nerve, integrity of the intestinal barrier, and inflammatory responses. When microbial balance is disrupted (dysbiosis) it could play a role in the development of depression by increasing inflammation, disrupting the regulation of stress hormones, and affecting neuroplasticity [75]. Experimental targets are the use of probiotics, prebiotics, synbiotics, psychobiotics, dietary fibre, fermented food, postbiotics, short-chain fatty acid pathways and faecal microbiota transplantation. Psychobiotics are live microbes or one that targets the microbiota and thus can have a beneficial effect on mental health via gut–brain signaling. First, beneficial bacteria can help lower systemic inflammation by helping to maintain gut barrier function and limit translocation of inflammatory bacterial products. Second, the microbiota affect intestinal metabolism of tryptophan, affecting the synthesis of serotonin and the activity of kynurenine pathway [76]. Lastly, bacterial metabolites, including short-chain fatty acids, may impact microglial function, blood–brain barrier integrity, and neuroplasticity [77]. Fourth, gut bacteria communicate with the HPA axis and can impact cortisol's reaction to stress. Fifth, signals run directly from the gut to the brain via the vagus nerve. The use of microbiota-based therapy is appealing as it could have fewer safety and tolerability issues than a number of the pharmacologic treatments, and may also be more tolerated [78]. It could be particularly important in patients with depression who experience gastrointestinal symptoms, inflammatory disease, metabolic dysfunction, poor diet, taking antibiotics, and stress-induced dysbiosis. But it's still a developing field. At present, there is insufficient evidence to recommend using probiotics or microbiota intervention as a substitute for traditional antidepressant treatment for moderate to severe depression. There are several significant drawbacks, such as strain-specific effects, inconsistent formulations, and small trials, inconsistent dosing, and a lack of clarity about long-term results. As a whole, the new targets that emerged for depression treatment demonstrate a significant transition from a monoamine-based approach to a systems-based approach to the regulation of mood [79]. NMDA receptor modulators and AMPA receptor pathways are associated with rapid synaptic plasticity, GABAergic neurosteroid modulators are associated with restoring an inhibitory balance, orexin receptor antagonists are associated with sleep-wake and arousal dysfunction, kappa opioid receptor modulators are associated with anhedonia in stress-related depression, anti-inflammatory drugs are associated with immune-mediated

depression, neurotrophic approaches are associated with repairing impaired plasticity, and gut microbiota-based therapies are associated with the connection between metabolism, immunity, and brain function. These are all encouraging targets that aim to tackle various biological forms of depression, but a lot of them are yet to be validated, patient-specific using biomarkers and extensively tested for safety and efficacy over a long period of time before they become available as a standard clinical treatment [80].

FUTURE PERSPECTIVES

Pharmacological treatment of depression is taking a newer and more personalized direction with quick, safe and efficient treatments. Conventional antidepressants, including SSRIs, SNRIs, tricyclic and atypical antidepressants, are helpful, but have several drawbacks such as slow onset of action, partial response, adverse effects, treatment resistance, and relapse. Thus, alternative models of drug development beyond the monoamine hypothesis need to be developed in the future. Pioneered by the rapid-acting antidepressants like ketamine and esketamine, this research direction has sparked a new focus on glutamatergic signaling, synaptic plasticity, and the modulation of NMDA receptors. New compounds that are safer NMDA receptor modulators, AMPA receptor potentiators, or drugs with both BDNF neuroplasticity activity but no dissociation or abuse potential are likely to be added to future therapies. GABAergic neurosteroid modulators are important too and particularly for depression related to hormonal shifts, stress dysregulation and inhibitory neurotransmission dysfunctions. A second promising treatment is the one based on inflammation. A subpopulation of depressed patients has elevated inflammatory markers, suggesting that anti-inflammatory and immunomodulatory medications may prove to be beneficial in biomarker-selected patients. Likewise, the gut–brain axis is a new avenue of therapy, and probiotics, prebiotics, psychobiotics, and microbiota-based therapies could be used as adjuncts to conventional antidepressant treatment. The field of personalised medicine will be a big part of future depression management. The use of Pharmacogenomics, Biomarker guided therapy, Neuroimaging, Digital monitoring and AI can help to predict drug response, reduce side effects and choose optimal therapy for the individual. Future treatment can be guided by biological subtype and symptom profile, genetic background, inflammatory status and patient-specific risk factors rather than trial and error. In general, it is expected to be a combination of existing psychotropic drugs and novel mechanism-based, lifestyle-based, psychotherapy, and precision medicine-based treatment approaches that will be combined in the future to achieve faster antidepressant remission, improved tolerability, and long-term functional recovery.

CONCLUSION

Depression is a psychiatric disorder that impairs mood, cognition, behavior, physical health, social functioning and quality of life and is a complex and heterogeneous disorder. Multiple interrelated mechanisms have been proposed to underlie its pathophysiology, such as monoaminergic imbalance, dysregulated HPA axis functioning, neuroinflammation, dysfunction of glutamatergic neurotransmitter systems, dysfunction of neuroplasticity, reduction of BDNF signaling, and a dysfunction of communication between the gut and the brain. Thus, depression cannot be considered solely as a mere lack of serotonin or other monoamines. A number of the existing drugs used for depression remain relevant to clinical practice, including selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, atypical antidepressants, and

melatonergic drugs. These medicines work well for many people, and are still the mainstay of drug treatment. The major drawbacks are however delayed onset of action, side effects, non-responsiveness to treatment, recurrence and treatment resistance. There have been some recent developments in understanding depression beyond the monoamine treatments. There are novel targets including NMDA receptors, AMPA receptors, GABAergic systems, orexin receptors, kappa opioid receptors, inflammatory pathways, neurotrophic factors and gut microbiota which may provide directions for future drug development. Emerging evidence of the role of glutamatergic signaling and synaptic plasticity in antidepressant response has been provided by rapid-acting agents like ketamine and esketamine. In general, the current pharmacological treatment of depression is moving towards mechanism-based and personalized therapy. Future research directions should include the development of more rapidly acting drugs, better safety, treatment based on biomarkers, pharmacogenomic, and a combination of pharmacological treatment and psychotherapy and lifestyle modification. Clinicians will better be equipped to select appropriate therapy, optimize remissions, minimize relapse and optimize functional recovery into the future with a better understanding of the biological diversity of depression.

REFERENCES

1. Li Y, Wang F, Chen G, Zhai S. Pharmacological treatment of adolescent depression: Current advances and future perspectives. Letters in Drug Design & Discovery. 2026 Feb 2:100278.
2. Heesen SH, Chang MH, Wehr MC, Rossner MJ. Revitalizing psychopharmacology in the GWAS era: the potential of barcoded screening in drug discovery. Current Opinion in Genetics & Development. 2026 Feb 1;96:102425.
3. Englisch S, Zink M. New Pharmacological Treatment Approaches for Schizophrenia: Navigating the Post-iclepertin Landscape. CNS drugs. 2026 Jan 29:1-25.
4. Li L, Yao M, Meng J, Zhong Z, Nan N, Kazemi AH, Guo J, Liu C, Jiang Y. Advances in calcium signalling research for the diagnosis and treatment of depression. Annals of medicine. 2026 Dec 31;58(1):2620329.
5. Nishonov EJ. Contemporary Perspectives on Hypertension in Internal Medicine: From Risk Stratification to Personalized Management in the Digital Era. International Journal of Clinical & Translational Medicine. 2026 Apr 16;1(3):90-9.
6. Marques-Garcia F, Martinez-Bravo C. A review of pharmacogenomics in the individualization of pharmacological treatment: present and future. Journal of Laboratory and Precision Medicine. 2026 Jan 30;11.
7. Taylor JJ, Li J, Lin C, Jones E, Frandsen S, Becker CR, Drew W, Haj-Darwish D, Jabbour S, Leach J, Palm S. Circuit-targeted modulation of anxiety symptoms in individuals with major depression: A randomized head-to-head TMS trial. Molecular psychiatry. 2026 Mar 30:1-0.
8. Lennon MJ, Sachdev PS. Vascular cognitive impairment and dementia: Prevention, treatments, mechanisms and management options for the future. Neuropsychopharmacology. 2026 Jan 19:1-4.
9. Mujica-Parodi LR, Öngür D, Richardson RM. Opportunities and Challenges in Precision Neurotherapeutics. Annual Review of Biomedical Engineering. 2026 Jan 16;28.
10. Bose MM, Govindula A, Nampoothiri M, Arora D, Mudgal J. The HPA axis and kynurenine pathway: exploring the role of

stress and neuroinflammation in treatment-resistant depression. Pharmacological Reports. 2026 Apr;78(2):374-90.

11. Alkhateeb M, Nayeem A, Ahmed A, Alsahli M, Sheikh J, Abd-Alrazaq A. AI for Detecting and Predicting Postpartum Depression: Scoping Review. Journal of Medical Internet Research. 2026 Jan 8;28:e77376.
12. Erdelyi-Hamza B, Torok D, Eszlari N, Bagdy G, Juhasz G, Gonda X. Three shades of gloom: investigating the genetic background of current depressive symptoms associated with different severity of current stress exposure in a general population. European Neuropsychopharmacology. 2026 Jan 1;102:17-25.
13. Yuan X, He Y, Cao Q, Hu Y, Li X, Ran Z, Li Y, He J, Yan C, Xiong J. Sex-specific global, regional and national burden of dysthymia and major depression disorder in older adults from 1990 to 2021: a systematic analysis of the global burden of disease 2021 study. European Archives of Psychiatry and Clinical Neuroscience. 2026 Jan 7:1-0.
14. Tian W, Yan G, Xiong S, Zhang J, Peng J, Zhang X, Zhou Y, Liu T, Zhang Y, Ye P, Zhao W. Burden of depressive and anxiety disorders in China and its provinces, 1990–2021: findings from the global burden of disease study 2021. The British Journal of Psychiatry. 2026 Jan;228(1):18-28.
15. Yu Q, Xue F, Wik SL, Gao M, Adebisi YA, Lucero-Prisno III DE, Zhong CC, Wong MC, Huang J, Global Health Focus Epidemiology Group. Mapping disease burden of major depressive disorder and its risk factors in low- and middle-income countries. Psychotherapy and psychosomatics. 2026 May 20;95(2):153-63.
16. Wojciechowska K, Zajkowska I, Zabrocka P, Martowska J, Choroszewska E, Baran J, Warych W. The Role of Gut Microbiota in the Pathophysiology of Depression: A Narrative Review. Quality in Sport. 2026 Jan 11;49:67803-.
17. Nathan MD, Bondy E, Walsh M, Gibson K, Schiller CE. The impact of estradiol dynamics during the menopause transition on depression risk: A narrative review of estradiol's neurobiological mechanisms. Biological Psychiatry. 2026 Feb 10.
18. Akif A, Islam MR. The Microbiota-Gut-Brain Axis in the Pathophysiology of Major Depressive Disorder: A Mechanistic Review. Comprehensive Physiology. 2026 Feb;16(1):e70100.
19. Subba R, Ellappan S, Banerjee S, Mondal AC. Astroglia and depression: A gliocentric perspective from rodent models to therapeutic insights. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2026 Jan 27:111627.
20. Laboute T, Zucca S, Sial OK, Sharma M, Brunori G, Singh S, Nageswar KV, Peng H, Rader C, Becker JA, Le Merrer J. Targeting mGlyR with nanobodies for depression. Nature Communications. 2026 Jan 26;17(1):831.
21. Jones B, Miller J, Lopez AS, Norris JL, Green CL, Sollers III JJ, Wood M, Bryson WJ, Sollers IV JJ, Barker CS, Bynum Z. Kinesiophobia and depression in patients with sickle cell disease: A review of gender differences, pathophysiology, and clinical implications. Journal of the National Medical Association. 2026 Jan 9.
22. Bose MM, Govindula A, Nampoothiri M, Arora D, Mudgal J. The HPA axis and kynurenine pathway: exploring the role of stress and neuroinflammation in treatment-resistant depression. Pharmacological Reports. 2026 Apr;78(2):374-90.
23. Zhou Y, Zou Y, Zhong X, Li H, Yang J, Meng H, Xie W, Yao P, Wu X, Cai H, Li L.

Development of a novel HDAC6 PET imaging agent uncovers associations between HDAC6 overexpression and neuroinflammation in depression. Redox Biology. 2026 Jan 12:104014.
24. Parise EM, Nestler EJ. The neurobiological and molecular underpinnings of depressive phenotypes.
25. Sultana A, Hussain MS, Maqbool M, Agrawal M, Bisht AS, Khurana N, Singh G, Kumar R. The gut connection: a narrative review on the in-depth analysis of gut microbiota and metabolites in depression. Current reviews in clinical and experimental pharmacology. 2026 Feb;21(1):25-51.
26. Glasbauer ND, Pirola CJ. Olfaction Under the Shadow of Depression: Objective Evidence from a Comprehensive Meta-Analysis. Advances in Geriatric Medicine and Research. 2026 Jan 23;8(1).
27. Wang H, Chen Y, Zhao A, Shen Z, Zhang Y. The role of probiotics in modulation of the gut-brain axis: A prospective therapy for depression and mood disorders. Frontiers in Pharmacology. 2026 Jan 26;16:1709060.
28. Medeiros GC, Gould TD, Demo I, Goes FS, Zarate CA. Neurotransmitters and neuropeptides in depression.
29. Zhao C, Lao J, Cao J, Yang Y, Liu C, Tang F. Advances in gut microbiome and metabolomics research in the comorbidity of inflammatory bowel disease and depressive disorder. Journal of Gastroenterology and Hepatology. 2026 Jan;41(1):54-60.
30. Li P, Gao Y, Zhao X. The Bone–Brain Axis: Novel Insights into the Bidirectional Crosstalk in Depression and Osteoporosis. Biomolecules. 2026 Jan 31;16(2):213.
31. Ansari M, Balali-Dehkordi S, Rahimi-Madiseh M, Zarean E, Amini-Khoei H. Environmental enrichment by targeting hippocampal claudins attenuates depressive-like behaviours in maternally separated male mice. The World Journal of Biological Psychiatry. 2026 Jan 2;27(1):58-69.
32. Zhong Y, Nie Y, Mao Y, Liu Y, Zou T, Liao X, Zhao L. The Relationship Between Trace Elements and Depression. Nutrients. 2026 Feb 1;18(3):484.
33. Yan F, Zan S, Xu J, Zhao S, Wang Z, Yang F. Cognitive and clinical dimensions of structural and functional insula alterations in patients with depression: a resting-state fMRI study. International Journal of Neuroscience. 2026 Jan 2;136(1):67-76.
34. Khan R, Faizan M, Tatode A, Premchandani T, Hussain UM, Qutub M. Rap1-Dependent pathways in depression: Genetic, Epigenetic, and neuroinflammatory mechanisms shaping synaptic resilience. Molecular Biology Reports. 2026 Dec;53(1):182.
35. Gao J, Liang Y, Wang Y, Chen H. Auricular Stimulation Therapy: An Evidence-based Practice Strategy for Depression. Current Opinion in Pharmacology. 2026 Jan 20:102607.
36. Otobo E, Nguyen JD, Saeed F, Torpoco Rivera M, Sinnott S, Mehta PK, Seligowski AV, Abohashem S, Osborne MT. Depression, anxiety, and bipolar disorder and atherosclerosis. Current Atherosclerosis Reports. 2026 Dec;28(1):41.
37. Jang YJ, Chang JH, Moon DU, Jeon HJ. Cognitive Impairment, Dementia and Depression in Older Adults. Journal of Clinical Medicine. 2026 Jan;15(3):1198.
38. Kellner CH, Sartorius A, Espinoza RT. The evidence base for electroconvulsive therapy (ECT) in geriatric depression. The American Journal of Geriatric Psychiatry. 2026 Jan 1;34(1):134-5.
39. Li Y, Wang F, Chen G, Zhai S. Pharmacological treatment of adolescent depression: Current advances and future

perspectives. Letters in Drug Design & Discovery. 2026 Feb 2:100278.

40. Chehadi AC, Pereira de Lima E, Detregiachi CR, Santos de Argollo Haber R, Catharin VM, Fornari Laurindo L, Engracia Valenti V, Machado Galhardi C, Tanaka M, Maria Barbalho S. Harnessing Dietary Tryptophan: Bridging the Gap Between Neurobiology and Psychiatry in Depression Management. International Journal of Molecular Sciences. 2026 Jan 1;27(1):465.
41. Brzozowska A, Garbacz AI, Majszyk TJ, Głuski J, Borowiecka PA, Węglarz A, Kosiorek P, Niezgoda A, Olborska A, Wrochna BM, Radziwonka A. Lifestyle modification and selected pharmacological therapies in Polycystic Ovary Syndrome: current evidence and emerging approaches. Quality in Sport. 2026 Feb 6;51:68457-.
42. Yang L, Wang Y, Wan H, Feng H, Liu Y, Xue G, Zhi Y, Zhang F, Liu Y, Zhang Z. Research Progress on the Application and Mechanisms of Baihe Dihuang Decoction in Major Depressive Disorder. Drug Design, Development and Therapy. 2026 Dec 31:1-8.
43. Lima VF, Silva VA, Pelosof R, Malfatti V, Cretaz E, Vidal KS, Brunoni AR, Cavenaghi VB. Non-implantable neuromodulation therapies compared to conventional treatments for major depression. Expert Review of Clinical Pharmacology. 2026 Feb 1(just-accepted).
44. Qiu N, Becker B. Integrating artificial intelligence and noninvasive brain stimulation: toward precision interventions for depression. Brain-Apparatus Communication: A Journal of Bacomics. 2026 Dec 31;5(1):2620894.
45. Huhulea EN, Frishman WH, Aronow WS. Emerging and Established Pharmacotherapies for Smoking Cessation: A Review. Cardiology in Review. 2026 Jan 13:10-97.
46. Gettman LC. Hypothyroidism: An Established and Evolving Disorder-Clinical Foundations, Pharmacotherapy, and the Expanding Role of the Pharmacist.
47. Yue C, Wang N, Zhai H, Yuan Z, Cui Y, Quan J, Zhou Y, Fan X, Wang H, Wu Z, Mi H. Adenosine signalling drives antidepressant actions of ketamine and ECT. Nature. 2026 Jan 8;649(8096):423-31.
48. Bose MM, Govindula A, Nampoothiri M, Arora D, Mudgal J. The HPA axis and kynurenine pathway: exploring the role of stress and neuroinflammation in treatment-resistant depression. Pharmacological Reports. 2026 Apr;78(2):374-90.
49. Frycz BA, Dutsch-Wicherek M, Płaza O, Szulc A, Bijata M, Wlodarczyk J, Dzwonek J. The synaptic triad in depression: how stress-related pathways converge on BDNF, NMDA receptor, and MMP-9. Pharmacological Reports. 2026 Jan 28:1-23.
50. Wang H, Chen Y, Zhao A, Shen Z, Zhang Y. The role of probiotics in modulation of the gut-brain axis: A prospective therapy for depression and mood disorders. Frontiers in Pharmacology. 2026 Jan 26;16:1709060.
51. Singh A, Davis F, Anwar AI, Hirsch JD, Barrie SA, Tirumala S, Shekoohi S, Ahmadzadeh S. Review and Update of Anesthetic Management for Electroconvulsive Therapy: A Narrative Review. Neuropsychiatric Disease and Treatment. 2026 Dec 31:1-1.
52. Swainson J, Brietzke E, Khullar A, McIntyre RS, Soares CN. Ketamine, Psychedelics, and Psychotherapy: Reframing, Redefining, Renaming Treatment Models. The Canadian Journal of Psychiatry. 2026 Feb;71(2):83-8.
53. Miller CH, Hickman A, Baten C, Ali Z, Kahlon SK, Klassen AM, Zamora G, Shepherd JH, Venegas G, Miller JA, Woo E. Ketamine pharmacotherapy for major

depressive disorder: A narrative review. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2026 Feb 27:111651.
54. Yoon S. Treatment Strategies for Perinatal Depression Beyond Conventional Antidepressants: A Narrative Review. Clinical and Experimental Obstetrics & Gynecology. 2026 Jan 16;53(1).
55. Necyk C, Eberhardt T, Mahmoud SH. Depression Assessment. InPatient Assessment in Clinical Pharmacy: A Comprehensive Guide 2026 Jan 2 (pp. 249-272). Cham: Springer Nature Switzerland.
56. Cai Y, Ren X, Ding C. Impacts of non-pharmacological interventions on post-intensive care syndrome: An umbrella review of systematic reviews and meta-analyses of randomized controlled trials. Intensive and Critical Care Nursing. 2026 Apr 1;93:104326.
57. Benito A, Jiménez-Murcia S, Tirado-Muñoz J, Adan A. WADD-SEPD Consensus on psychological treatment of dual disorders I: General recommendations, most used therapies, and severe mental disorders. Journal of Clinical Medicine. 2026 Jan 16;15(2):730.
58. Nivetha K, Karuveettil V, Pillai AS, Jayachandran M, Pallaty PL. Effectiveness of artificial intelligence–enhanced cognitive behavioral therapy compared to alternative non-pharmacological therapies for treating depression or anxiety among adults: a systematic review protocol. JBI Evidence Synthesis. 2026 Jan 1;24(1):184-92.
59. De Zoysa AI, Govinnage J, Giorlando F, Dodd S, Narayanaswamy JC, Berk M. Emerging neurobiological targets in psychiatric treatment. European Neuropsychopharmacology. 2026 Apr 1;105:112767.
60. Huang J, Huang C, Ji Y, Zhang Q, Hu S, Wei Y, Hashimoto K, Xu X, Yang C. Neuropsychiatric drug development in China: Current status and emerging trends. Molecular Psychiatry. 2026 Feb 6:1-9.
61. Li Y, Wang F, Chen G, Zhai S. Pharmacological treatment of adolescent depression: Current advances and future perspectives. Letters in Drug Design & Discovery. 2026 Feb 2:100278.
62. Lewandrowski KU, Blum K, Schmidt S, Alvim Fiorelli RK, Gold MS, Mohankumar K, Sharafshah A, Bagchi D, Pinhasov A, Lorio MP, Modestino EJ. The Emerging Crisis in Non-Prescribed Ketamine Use: A Rapid Attenuation of Depression in Face of Abuse and "Chill-out" or Escapism Drug. Substance Use & Misuse. 2026 Jan 5:1-8.
63. Munguba H, Arefin A, Hasegawa R, Posa L, Romano GR, Peddada TN, Donatelle A, Singh A, Gutzeit VA, Vijay A, Vaddi P. Mechanism-guided identification of antidepressant G protein-coupled receptor drug targets. Cell. 2026 Apr 30;189(9):2612-32.
64. Li L, Yao M, Meng J, Zhong Z, Nan N, Kazemi AH, Guo J, Liu C, Jiang Y. Advances in calcium signalling research for the diagnosis and treatment of depression. Annals of medicine. 2026 Dec 31;58(1):2620329.
65. Yamamoto M, Hirakata H, Toda K. Neural signaling mechanisms in depression: bridging classical monoamine hypotheses, animal models, and emerging antidepressant strategies. Frontiers in Cell and Developmental Biology. 2026 Mar 25;14:1777975.
66. Rychlik N, Jüngling K, Meuth SG, Budde T, Méndez-Couz M. Channel Dysfunction as the Basis for Comorbidities in Multiple Sclerosis and Depression. Archiv der Pharmazie. 2026 Jun;359(6):e70273.
67. Parker N, Koch E, Shadrin AA, Fuhrer J, Hindley GF, Stinson SE, Jaholkowski P,

Tesfaye M, Dale AM, Wingo TS, Wingo AP. Leveraging the genetics of psychiatric disorders to prioritize potential drug targets and compounds. Neuropsychopharmacology. 2026 Mar 7:1-0.

68. Wolitzky-Taylor K, Wen A, Freimer N, Craske MG. Anxiety and depression in emerging adults: The STAND program as a model of scalable screening and intervention. Neuropsychopharmacology. 2026 Jan;51(1):244-58.
69. Huang FW, Bello ST. Role of Neuronal Cholecystokinin Receptor: An Emerging Therapeutic Target for Ameliorating Neurological Diseases. Molecular Neurobiology. 2026 Jan;63(1):296.
70. Abebe E, Mulugeta A, Madakkattel I, Stacey D, Hyppönen E. Uncovering plasma protein biomarkers linked to depression: A differential abundance analysis and Mendelian randomization using large-scale data. Journal of Affective Disorders. 2026 Jan 5:121134.
71. Yoosefian M, Bayramzadeh H, Abass KS, Mokhtari T. Potent LeuBAT inhibitors designed in silico as next-generation duloxetine analogs for enhanced major depressive disorder treatment. Scientific Reports. 2026 Jan 12.
72. Hu J, Shi M, Tian M, Xie B, Tan Y, Zhou D, Qian T, Qin D. Nanomedicine-Driven Therapeutic Strategies for Rheumatoid Arthritis-Associated Depression: Mechanisms and Pharmacological Progress. Pharmaceuticals. 2026 Jan 4;19(1):94.
73. Gholami M. Identification of Shared Genetic Variants and Haplotypes Associated With Schizophrenia and Depression. Brain and Behavior. 2026 Jun;16(6):e71554.
74. Khan R, Faizan M, Tatode A, Premchandani T, Hussain UM, Qutub M. Rap1-Dependent pathways in depression: Genetic, Epigenetic, and neuroinflammatory mechanisms shaping synaptic resilience. Molecular Biology Reports. 2026 Dec;53(1):182.
75. Ye B, Fu Z, Zhou X, Wang S, Ouyang L, Chen Z, Deng G. Low-Grade Inflammation: Pathophysiological Mechanisms and Drug Targets in Irritable Bowel Syndrome with Diarrhea. Journal of Inflammation Research. 2026 Dec 31:1-22.
76. Jin Y, Wu F, Jin M, Tang L, Chen Y, Xu Z, Wang W, Wu J. Shared mechanisms and integrated management of post-stroke pain and depression: A comprehensive review. Pain and Therapy. 2026 Feb;15(1):19-39.
77. May L, Dwivedi Y. MicroRNA-425-3p: A Promising Biomarker and Candidate for Pharmacological Intervention in Neuropsychiatric Disabilities with Relevance to Major Depressive Disorder. Neuropsychiatric Disease and Treatment. 2026 Dec 31:611548.
78. Wang JX, Zhang LL, Liu CX, Zhang XN, Xiao YQ, Zheng Y, Chang X. New Strategies for Treating Depression with Chinese Medicine: Focusing on NLRP3-Mediated Mechanisms. Chinese Journal of Integrative Medicine. 2026 Jan 15:1-0.
79. Heesen SH, Chang MH, Wehr MC, Rossner MJ. Revitalizing psychopharmacology in the GWAS era: the potential of barcoded screening in drug discovery. Current Opinion in Genetics & Development. 2026 Feb 1;96:102425.
80. Liu Y, Chen B, Yang Y, Li Y, Xia X, Yan K, Xu H, Li Y, Tan X. Insights into the interplay between stroke and depression through lipid metabolism-related diagnostic genes. Molecular Brain. 2026 Jan 18.

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