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Current and Emerging Pharmacotherapies for Depression: A Mini Review

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Abstract

Depression is a complicated psychiatric condition with significant global health consequences. It has an impact on mood, cognition, and overall functioning, frequently resulting in significant emotional and social burdens. Pharmacotherapy is the major treatment option for mild to severe patients. Monoaminergic neurotransmission is the primary target of current antidepressants, which include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). While these medications give relief for many individuals, a substantial proportion experience poor efficacy, delayed onset, or intolerable adverse effects. To address these challenges, novel pharmacological strategies are being explored. Recent advances include fast-acting drugs like ketamine and ketamine, which alter glutamatergic transmission, as well as eurysternids like renanolone, which operate on GABA receptors. Psychedelic compounds (psilocybin) and anti-inflammatory drugs are also gaining attention for their potential antidepressant effects. Additionally, pharmacogenomics and precision medicine approaches aim for specific treatments based on individual genetic profiles, improving response and minimizing adverse effects.

Keywords: Depression; Pharmacotherapy; Antidepressants; Ketamine; Esketamine; Neurosteroids

1. Introduction

The World Health Organization (WHO) estimates that depression affects 280 million people worldwide, making it one of the most prevalent mental health conditions [1]. It is a major contributor to global disability, with important implications for quality of life, productivity, and overall well-being [2]. Depression is linked to greater morbidity, higher healthcare expenditures, and an increased risk of suicide, making it a serious public health concern [3]. The illness is characterized by persistent low mood, anhedonia, cognitive difficulties, and somatic symptoms, which often necessitate long-term treatment [4].

Depression is clinically classified into several subgroups. The most common kind is Major depressed Disorder (MDD), which is distinguished by discrete episodes of severe depressed symptoms [5]. Dysthymia, often known as persistent depressive disorder, is characterized by chronic low-grade depression that can endure for years [6]. Atypical depression is characterized by emotional reactivity as well as hypersomnia and increased hunger [7]. These subgroups may differ in etiology, clinical presentation, and therapy response, necessitating tailored management techniques [8].

Pharmacotherapy remains an important part of the treatment of depression, particularly for moderate to severe cases or when psychotherapy is insufficient [9]. Traditional antidepressants, especially those that target monoaminergic pathways, have been routinely used for decades [10]. However, the delayed onset of action, treatment resistance, and side effects in some patients underscore the present treatments shortcomings [11].

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This review attempts to give an up-to-date summary of both present and emerging pharmacotherapies for depression [12]. It outlines the mechanisms and clinical utility of traditional antidepressants while also delving into innovative and experimental drugs with potential mechanisms, such as glutamatergic modulators, eurysternids, psychedelics, and anti-inflammatory medicines [13]. Furthermore, this review discusses the role of pharmacogenomics and precision medicine in personalizing treatment methods. This review attempts to give a brief but comprehensive overview of the evolving field of depression pharmacological treatment by incorporating current developments [14].

1.1. Epidemiology of Depression

The World Health Organization (WHO) reports that depression is one of the primary causes of disability worldwide, impacting approximately 280 million people [15]. According to the Global Burden of illness Study, it is the top cause of disability among adults worldwide and a large contributor to the global illness burden [16]. Depression has a profound influence on both individuals and societies, defined by a low quality of life, poor functioning, increased morbidity, and a high suicide rate [17]. Depression imposes a significant financial burden, with depression-related healthcare costs and lost productivity accounting for a multi-billion-dollar annual cost worldwide [18].

The disorder affects all regions, with certain countries reporting higher incidence due to factors such as healthcare availability, social support, and mental health awareness [19]. Despite this, depression is still underdiagnosed in many low- and middle-income countries, emphasizing the critical need for improved mental health infrastructure and public awareness.
The prevalence of depression is significantly influenced by gender [20]. Women are constantly more at risk, according to studies, with the female to male ratio ranging from 1.5:1 to 2:1 in most locations [21]. This gap is assumed to be the result of hormonal changes, gender-based social roles, higher incidence of trauma, and increased susceptibility to stress. Furthermore, women are more likely than men to seek treatment for depression, which may help to explain the higher diagnosis rates [22].

Another crucial aspect is age, as depression affects people at all stages of life. Depression usually begins in adolescence or early adulthood, but it can strike at any age. Depression is more common in older persons, particularly those who have chronic illnesses or are experiencing cognitive deterioration [23]. Poverty, low education, and unemployment are all closely linked to an increased risk of depression. People in low socioeconomic status frequently experience chronic stress, limited access to mental health care, and increased rates of adversity, all of which increase the likelihood of developing depression [24].

2. Pathophysiology of Depression

2.1. Neurochemical Basis: Monoamine Hypothesis

The monoamine hypothesis has long been considered important to understanding depression. Depression is thought to be caused by deficits in the neurotransmitter's serotonin, norepinephrine, and dopamine [25]. These chemicals regulate mood, arousal, and cognition. Reduced availability or malfunctioning of receptors or transporters in brain regions such as the prefrontal cortex and limbic system has been linked to the development of depressive symptoms. This idea has resulted in the creation of numerous antidepressant drugs, such as SSRIs, SNRIs, and TCAs, which try to raise the amounts of these neurotransmitters in the synaptic cleft [26].

2.2. HPA Axis Dysfunction

The hypothalamic-pituitary-adrenal (HPA) axis regulates the body's stress response. Chronic stress causes HPA axis dysregulation, which results in high levels of cortisol, a crucial stress hormone [27]. Prolonged cortisol levels can reduce neuronal plasticity and induce atrophy in mood-regulating brain regions, particularly the hippocampus. This HPA axis malfunction has been connected to the development of depressive symptoms and may aggravate stress-induced brain function, adding to the depression cycle [28].

2.3. Neuroinflammation and Cytokines

Neuroinflammation appears to play an important role in depression. Depressed people have higher amounts of pro-inflammatory cytokines in their blood and cerebrospinal fluid, including IL-6, IL-1β, and TNF-α[29]. These cytokines can influence neurotransmitter metabolism, limit neurotrophic factor availability, and hinder neurogenesis. Inflammatory pathways also have an effect on brain regions involved in mood regulation, such as the prefrontal cortex and amygdala, which contribute to depressed symptoms [30].

2.4. Neurotrophic Factors (BDNF)

Brain-derived neurotrophic factor (BDNF) is an important protein that regulates synaptic plasticity, neuronal survival, and neurogenesis. Lower BDNF levels have been repeatedly linked to depression, particularly in brain regions that control mood and memory, such as the hippocampus and prefrontal cortex [31]. Chronic stress and high cortisol levels can inhibit BDNF expression, resulting in decreased synapse function and lower neural resilience. This BDNF drop is thought to contribute to the neuronal atrophy seen in depression and may explain why some patients resist treatment [32].

2.5. Glutamate Hypothesis and Role of Neuroplasticity

According to the glutamate hypothesis, dysregulated glutamatergic signaling, particularly through NMDA receptors, is a major contributor to depression. Glutamate is the brain's principal excitatory neurotransmitter, involved in synaptic transmission and plasticity [33]. Overactivity of NMDA receptors and changes in glutamate release can cause excitotoxicity and disrupt neuroplasticity, which is necessary for learning, memory, and mood control. Recent research has found that NMDA antagonists, such as ketamine, can quickly reduce depressed symptoms, underlining the therapeutic promise of regulating glutamate transmission in treatment resistant depression [34].

2.6. Symptoms of Depression

Depression causes a variety of emotional, cognitive, and physical symptoms. Emotional symptoms often include chronic sorrow, feelings of hopelessness, shame, and a loss of interest or pleasure in formerly rewarding activities, also known as anhedonia. People suffering from depression frequently experience emotional numbness, irritability, or excessive tears [35].

Cognitive symptoms are common in depression, with individuals having difficulties concentrating, making decisions, and remembering things. These cognitive impairments are commonly known as brain fog and can have a major influence on daily functioning. Depressive moods are characterized by negative thought patterns such as self-criticism, excessive rumination, and distorted thinking [36].

Depression is frequently accompanied by physical symptoms such as exhaustion, appetite changes, sleep difficulties, and physical aches and pains. Depression can also cause psychomotor agitation or retardation, in which the individual becomes restless or physically slows down [37].

3. Risk Factors for Depression

3.1. Genetic Predisposition

Genetic factors considerably increase the likelihood of experiencing depression. According to family research, people who have a first-degree relative suffering from depression are more likely to get the condition themselves. Twin and adoption studies indicate a heritability of 40-50%. Specific genes involved in the serotonin and dopamine systems have been linked, but no single gene has been definitively found [38].

3.2. Environmental Stressors

Environmental variables, particularly trauma and chronic stress issues or relationship, are significant risk factors for depression. These stressors can alter brain chemistry and function, increasing sensitivity to depressive episodes. Long-term stress can disrupt the HPA axis, raising cortisol levels and decreasing brain plasticity, further predisposing people to depression [39].

3.3. Comorbid Conditions

Depression is frequently accompanied by other psychiatric diseases, such as anxiety and substance abuse problems. Anxiety and depression have similar neurological pathways, and people who have one are more likely to develop the other. Substance misuse, particularly alcohol and illegal drugs, is common in people suffering from depression, as substances can be used as a kind of self-medication to reduce depressive symptoms, but this typically worsens the condition [40].

3.4. Diagnosis and Assessment Tools

Depression is diagnosed based on clinical examination and defined diagnostic criteria. The assessment techniques listed below are routinely used to examine the intensity and range of depression symptoms:

Beck Depression Inventory (BDI): A self-reported questionnaire for determining the severity of depressive symptoms, including mood, behavior, and somatic symptoms. It is commonly used for screening and monitoring therapy progress [41].

Hamilton Depression Rating Scale (HDRS): A clinically administered scale used to determine the severity of depression in patients. It encompasses several areas, including mood, sleep patterns, hunger, and physical symptoms. This scale is frequently used in clinical trials and for more severe symptoms of depression [42].

Patient Health Questionnaire-9 (PHQ-9): The Patient Health Questionnaire-9 (PHQ-9) is a basic and extensively used screening tool for identifying depression. It consists of nine questions that assess the frequency of symptoms during the last two weeks, which match to the DSM-5 criteria [43].

Table 1 Overview of Current and Emerging Pharmacotherapies for Depression

Pharmacotherapy	Mechanism of Action	Clinical Applications	Clinical consideration
Selective Serotonin Reuptake Inhibitors (SSRIs)	Inhibit serotonin reuptake, increasing serotonin availability at synapses	First-line treatment for moderate to severe depression	Well-tolerated; delayed onset of action (2-4 weeks)
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Inhibit reuptake of serotonin and norepinephrine	Effective in major depressive disorder (MDD), especially with somatic symptoms	Common side effects: nausea, insomnia, sexual dysfunction
Tricyclic Antidepressants (TCAs)	Inhibit reuptake of serotonin and norepinephrine; block histamine and acetylcholine receptors	Used in treatment-resistant depression and certain pain syndromes	High side effect burden: anticholinergic effects, weight gain, sedation
Monoamine Oxidase Inhibitors (MAOIs)	Inhibit monoamine oxidase, increasing levels of serotonin, norepinephrine, and dopamine	Used in atypical depression and treatment-resistant depression	Potentially serious food-drug interactions (tyramine)
Atypical Antidepressants	Various mechanisms: e.g., dopamine reuptake inhibition (bupropion), 5HT2 antagonism (mirtazapine)	For patients with specific symptom profiles (e.g., low energy, weight gain)	Bupropion: stimulant-like effects; mirtazapine: sedative, weight gain
Antipsychotic Augmentation	Dopamine and serotonin receptor antagonism	Used for treatment-resistant depression, often alongside SSRIs/SNRIs	Side effects: sedation, weight gain, metabolic risks
Lithium Augmentation	Modulates serotonin and dopamine receptors	Augments antidepressant effects in treatment-resistant depression	Narrow therapeutic index; monitoring required

Table 2 Emerging Therapies for Depression

Pharmacotherapy	Mechanism of Action	Clinical Applications	Clinical consideration
Ketamine/Esketamine (NMDA antagonists)	Blocks NMDA receptors, increasing glutamate activity at synapses	Rapid-acting for treatment-resistant depression	Fast onset (within hours); nasal esketamine for outpatient use
Psilocybin (Psychedelic)	5HT2A receptor agonist; induces neural plasticity and altered perception	Treatment-resistant depression, research phase	Controlled environments; potential for long-lasting effects after one or two sessions
Renanolone (Eurysternid)	Enhances GABAergic signaling, modulating neurotropic receptors	Approved for postpartum depression	Rapid onset; intravenous infusion; expensive and requires monitoring
Uranologer (Eurysternid)	Modulates GABA-A receptors and neurotropic pathways	Major depressive disorder (MDD) and postpartum depression (in trials)	Oral formulation; potential for outpatient use
Anti-inflammatory Agents	Reduce inflammatory cytokines (e.g., IL-6, TNF-α)	For depression with high inflammatory biomarkers	Ongoing trials; may benefit patients with inflammation-driven depression
Pharmacogenomics	Specific antidepressant therapy based on genetic profiles (e.g., CYP450 enzymes)	Personalized treatment for depression	Personalized medicine approach; still in development phase

Table 3 Augmentation and Combination Therapies

Pharmacotherapy	Mechanism of Action	Clinical Applications	Clinical consideration
Antidepressant + Antipsychotic	Combined mechanisms of action: serotonin, dopamine modulation	Used for treatment-resistant depression	Improved efficacy, but higher risk of side effects like sedation and weight gain
Antidepressant + Lithium	Enhances serotonin, dopamine modulation	Augmentation in treatment-resistant depression	Narrow therapeutic index for lithium; regular monitoring required
Antidepressant + Thyroid Hormones	Modulates thyroid hormone levels that affect mood regulation	Augmenting antidepressant effects in depression	Particularly useful in treatment-resistant or hypothyroid patients

4. Future Directions

Advances in neuroscience, technology, and medicine are paving the way for a transformation in depression therapy. One possibility is the discovery of novel pharmaceutical targets, like as orexin and sigma receptors, which may serve as alternatives to classic monoaminergic pathways. These targets could lead to antidepressants that are faster acting and more effective, with fewer adverse effects [44].

Artificial intelligence (AI) and machine learning are becoming important in drug discovery, allowing for faster identification of interesting compounds and prediction of treatment effects. AI can also help with specific treatment strategies by assessing patient data and recommending the best drugs based on genetic, biochemical, and clinical characteristics [45].

Digital psychiatry is emerging as an important tool for controlling depression, providing smartphone-based monitoring, telepsychiatry, and digital therapies to supplement pharmaceutical interventions. When combined with medication, this synergy can help with adherence, early diagnosis of relapse, and specific therapy [46]. In addition, long-acting and specific formulations are being developed to improve convenience, reduce dosage frequency, and limit drug level changes. Depot injections and specific drug delivery systems are examples of innovations aimed at improving long-term outcomes, particularly for treatment resistant or noncompliant patients. These future trends highlight a shift towards more accurate, efficient, and patient-centered care in depression management [47].

5. Conclusion

Depression is a complex and challenging mental health disorder, but considerable advances in pharmacological treatments provide new hope. From classic monoaminergic medications to new medicines targeting glutamate, orexin, and sigma receptors, the therapeutic landscape is rapidly changing. Emphasizing a patient-centered and specialized strategy is critical for improving outcomes, particularly in treatment-resistant patients. Innovations in digital psychiatry, AI-powered drug research, and long-acting formulations all contribute for effective and sustainable therapy. As science continues to elucidate the neuroscience of depression, the future of antidepressant therapy is bright, with more focused, fast-acting, and personalized medicines on the way.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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