Depression unveiled: a comprehensive review of pathophysiology and treatment advances

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Abstract

Depression is one of the most commonly diagnosed mental health disorders among adults and is currently the third leading cause of disease worldwide. Depression, also referred to as major depressive disorder (MDD), poses a significant global health challenge, affecting over 300 million individuals worldwide. In sub-Saharan Africa, neuropsychiatric conditions account for nearly 10% of the disease burden, with depression being the most frequently diagnosed disorder. Clinically, depression manifests through symptoms such as feelings of worthlessness, cognitive and sleep disturbances, and suicidal ideation, with major depression representing the predominant subtype. Its complex pathogenesis has been extensively investigated, incorporating hypotheses related to genetic predisposition, neurotransmitter dysregulation, and hypothalamic-pituitary-adrenal (HPA) dysfunction, among others. While both pharmacological and non-pharmacological interventions demonstrate efficacy, antidepressant medications remain the cornerstone of treatment. Untreated depression can lead to widespread emotional, behavioural, and physical health complications, significantly impairing quality of life. This review reports current hypotheses regarding the underlying pathophysiology of depression and evaluates therapeutic strategies with an emphasis on the pharmacological profile of the classes used to treat depression.

Keywords: depression, anti-anxiety, anti-depressants, major depressive disorder, selective serotonin re-uptake inhibitors

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Introduction

Major depressive disorder (MDD) is the most widespread mental health disorder worldwide.[1] It is marked by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and various physical and cognitive symptoms.[2]

It is a major contributor to the global disease-related burden among adolescents and young adults.[3] Worldwide, there has been a 59% increase in the cases of MDD observed from 172.27 million in 1990 to 274.80 million in 2019.[4] This highlights the growing burden of the disease and the need for effectual interventions.[5] The prevalence is greater in females compared to males. Adolescence and early adulthood is a developmental stage characterised by hastened biological, psychological and social changes which amplifies the vulnerability to various mental health disorders, includding MDD.[4] There are significant long-term consequences that are associated with the early onset of depression during the developmental stages. When depression remains untreated or inadequately managed, it increases the risk of chronic health problems, substance abuse, and impact on psychosocial and economic functioning.[4,5] The impact of depression is profound, significantly impairing quality of life and daily functioning.[6] It can interfere with work, education, and personal relationships. Globally, depression and anxiety account for an estimated 12 billion productive working days each year, costing the economy $333.7 billion ($382.4 billion in 2023 US dollars) annually.[7,8]

Depression is a complex condition influenced by a range of factors. Genetic predispositions, such as heritability and gene-environmental interactions, play a role.[9] Environmental influences, including early life trauma, major life stressors, and chronic illness, are also important contributors.[9,10] Psychosocial elements like poor social support, loneliness, and caregiver burden further increase the risk, as do neuroendocrine and neurochemical imbalances associated with certain brain and hormonal disorders.

Standard therapeutic approaches to the management of depression include pharmacotherapy, particularly antidepressants, and psychological therapies such as cognitive-behavioural therapy (CBT).[11] Although there are effective treatments available, depression often goes unrecognised and is insufficiently treated.[12] Historically, this has been linked to stigma and challenges in symptom detection.

Pathophysiology

The pathophysiology of depression is not fully explainable, but significant progress has been made in identifying key neurobiological systems and mechanisms (as per Figure 1), implicated in its development. The pathophysiological findings of depression include dysregulation in neurotransmitter systems, neuroendocrine and inflammatory pathways, structural and functional brain alterations, genetic and epigenetic influences, and disruptions in neuroplasticity.[13]

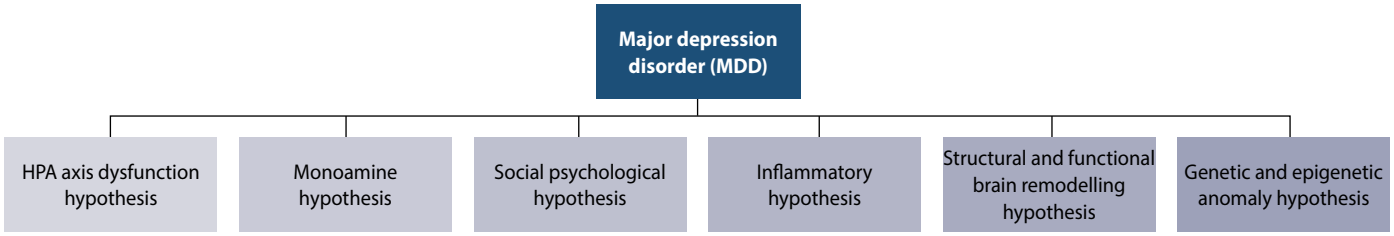

Figure 1: An outline of the hypotheses of MDD pathogenesis[40]

1. Neurotransmitter dysregulation

The **monoamine hypothesis** remains a foundational theory in the pathophysiology of depression, suggesting that deficits in central monoamines, primarily serotonin (5-HT), norepinephrine (NE), and dopamine (DA) play a critical role in symptom manifestation.[13] Reduced synaptic availability of these neurotransmitters in key brain regions such as the prefrontal cortex, hippocampus, and amygdala correlates with core symptoms of depression, including anhedonia, low mood, and cognitive disturbances. Pharmacological evidence supports this hypothesis, as most antidepressants act by increasing the synaptic concentrations of monoamines via inhibition of reuptake or enzymatic degradation.[14] Serotonin (5-HT) is widely distributed throughout the nervous system and its deficiency can lead to depression, phobias, anxiety, and other mental health disorders in patients. In the brain, dopamine (DA) is a dominant transmitter that regulates behaviour and is a precursor to epinephrine and norepinephrine (NE).[14]

There is evidence that depression is caused by an **imbalance in the GABA and glutamate** systems.[15] Glutamate is the primary excitatory neurotransmitter and contributes to synaptic plasticity, cognitive activities, and motivational and emotional behaviour in the brain. Researchers have found elevated levels of glutamate in the blood, brain and cerebrospinal fluid (CSF), of patients with depression as well as N-methyl-D-aspartate receptor (NMDAR) subunit disturbances. The inhibition of NMDAR function by ketamine for example, has antidepressant effects and protects the hippocampal neurons from stress-induced morphological changes.[15] Numerous studies have demonstrated that MDD patients have defects in GABA neurotransmission function. Brain GABA levels in MDD patients were lower than those in healthy controls in the prefrontal cortex.

2. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation

Hyperactivity of the HPA axis is one of the most consistently observed biological abnormalities in patients with depression. Chronic stress activates this system, resulting in excessive secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and ultimately cortisol.[13] The glucocorticoids interact with their receptors in multiple target tissues within the HPA axis, where they act as feedback inhibitors of both ACTH production in the pituitary corticotropes and CRH production in the hypothalamus. Disturbances of the HPA axis induced by stress have been shown to be associated with depression because of increased production of cortisol and insufficient inhibition of glucocorticoid receptor regulatory feedback.[16]

3. Inflammatory and immune system activation

Emerging evidence supports the role of immune dysregulation in depression because most patients have been seen to have increased levels of inflammatory molecules.[17] The roots of the immune hypothesis of depression can be traced back to the early 1990s, otherwise known as the 'cytokine hypothesis of depression'.[18] Increased levels of pro-inflammatory cytokines—such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)—have been observed in depressed individuals. These cytokines can alter neurotransmitter metabolism, reduce the availability of tryptophan (a serotonin precursor), and impair synaptic plasticity.[17]

4. Neuroplasticity and neurogenesis deficits

Neuroplasticity is the brain's ability to adapt structurally and functionally in response to environmental and internal stimuli. A significant body of evidence suggests that depression causes changes in neuroplasticity in specific regions of the brain which are correlated with symptom severity, negative emotional rumination as well as fear learning.[19]

Neuroimaging studies have identified structural abnormalities in several brain regions involved in emotion regulation and cognitive processing. Reductions in grey matter volume have been reported in the hippocampus, anterior cingulate cortex, and dorsolateral prefrontal cortex.[20] Functional alterations in neural circuits—such as hyperactivity in the amygdala and hypoactivity in the prefrontal cortex—are also common, correlating with heightened emotional reactivity and impaired executive function, respectively.

Depression is correlated with atrophy of neurons in the cortical and limbic brain regions that control mood and emotion. High levels of plasmatic cortisol have been observed to suppress neuroplasticity in the hippocampus. Decreased expression of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus and prefrontal cortex, is associated with reduced synaptic connectivity, impaired learning, and mood regulation. Antidepressant pharmacotherapy has been shown to upregulate BDNF which activates the tyrosine kinase receptors and triggers an intracellular cascade involving cAMP-dependent protein kinase A, mitogen-activated protein kinase as well as other signalling molecules.[21]

5. Genetic and epigenetic influences

Major depressive disorder is likely to have a heritability rate of approximately 31–42%.[22] Several depression risk loci have been identified. This evidence shows that depression is influenced by genetic factors.[23,24] Gene-environment interactions, particularly involving early-life stressors, play a crucial role in modulating vulnerability through epigenetic mechanisms such as DNA methylation and histone modification.[20]

Clinical manifestation

Depression presents a combination of psychological and somatic symptoms. Core features include persistent depressed or irritable mood and/or lack of interest or pleasure in activities.[25] Patients often report feelings of guilt, worthlessness or hopelessness, and reduced energy or fatigue. Cognitive symptoms such as diminished ability to think or concentrate and indecisiveness are common.[25] Somatic features include changes in appetite or weight, insomnia or hypersomnia, and psychomotor agitation. Many patients also have recurrent thoughts of suicidal ideation. In children and adolescents, mood may present more as irritability than classic sadness.

Depression also presents with substantial functional impairment. A South African survey showed that over 90% of respondents with depression reported significant disruption in work, social, or home activities.[26] The burden of depression is seen in disability and suicide with about one in eight deaths worldwide in young adults are linked to suicide, many of which involve depression.[27] A major depressive episode must last ≥ 2 weeks by definition, but many episodes extend for months if untreated. Untreated mental health disorders escalate patient morbidity leading to functional impairment and increases the risk of suicide attempts.[28,29] Furthermore, if antidepressant pharmacotherapy is initiated later than six months since the first onset of a depression episode, the chance of the patient attaining remission significantly decreases.[30] The importance of early recognition and treatment of depression in patients is highly emphasised.[30]

Persistent depressive disorder (PDD), also known as dysthymia, involves chronic depressive symptoms lasting two years or more.[31] The severity of symptoms is lower than in acute MDD but often includes low energy, low self-esteem, hypersomnia or insomnia, appetite changes, and difficulty concentrating. By definition an individual living with PDD has not gone more than two months symptom-free.[31] Due to its chronic nature, PDD tends to cause cumulative impairment and it "is often more disabling than episodic major depression".[32]

Other notable subtypes include seasonal affective disorder (SAD), a pattern of MDD episodes that recur seasonally. This typically manifests as depressive episodes in late autumn/winter that remit by spring.[33] Prevalence of SAD varies by latitude and study methods but is generally estimated around 1–10%.[34,35]

Postpartum depression (PPD), is a form of perinatal depression which refers to MDD onset during pregnancy or the first year after childbirth.[36] Common symptoms include mood swings, mild elation, irritability, tearfulness, fatigue, and confusion.[37] A recent global meta-analysis found PPD in about 17% of new mothers worldwide, with the highest rates of approximately 40% reported in Southern Africa.[36]

Atypical depression is defined by a specifier of mood reactivity plus ≥ 2 "reversed" neurovegetative symptoms.[38] Diagnosis of atypical depression requires mood reactivity (ability to feel better temporarily in response to a positive life event) plus at least two of the following symptoms: significant overeating (hyperphagia), weight gain, excessive sleep, or a heavy, leaden feeling in the limbs.[38]

Bipolar disorder, previously known as manic depressive illness, is a severe chronic mood disorder characterised by episodes of mania, hypomania, and alternating or intertwining episodes of depression.[39] In a worldwide mental health survey, the prevalence of bipolar disorders was consistent across diverse cultures and ethnic groups, with an aggregate lifetime prevalence of 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, 1.4% for subthreshold bipolar disorder, and 2.4% for the bipolar disorder spectrum. Bipolar I disorder presents with at least one manic episode, although major depressive episodes are typical but they are not required for diagnosis.[39] Bipolar II disorder presents with at least one hypomanic episode and one major depressive episode.

Additionally, other less prevalent DSM-defined mood disorders include premenstrual dysphoric disorder, disruptive mood dysregulation disorder, and substance/medical-induced depressive disorder.[40]

Management

1. Non-pharmacological management

1.1 Psychotherapy

Psychotherapy is an essential part of the treatment of depression. It is considered the first treatment for mild depression, when used in combination with pharmacotherapy, improves treatment response, quality of life and reduces the risk of relapse. Effective psychotherapy techniques include CBT, inter-personal therapy (IPT)**,** and other structured psychotherapies, have strong evidence of effectiveness and can support evidence that psychotherapy can be as effective for many patients as drug therapy.[41,42] Evidence suggests that psychotherapy and antidepressant pharmacotherapy have broadly similar effects on the severity of depression, although some analyses suggest a slight superiority of the pharmacotherapy on average. Importantly, psychotherapy also offers long-term benefits such as improved resistance skills and relapse prevention.[41,42]

1.2 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) is a psychological therapy that deals with the treatment of depression and other mental health

disorders. It involves applying electrical energy to the scalp to induce seizures. ECT increases the concentration of GABA in the cortex and increases the function of serotonin, making it more effective than antidepressants pharmacotherapy, although it is usually a reserved treatment due to its higher risk of side effects.[43] The decision to use ECT varies depending on severity and patient preferences. Although ECT is more effective than antidepressant pharmacotherapy, it is usually reserved for case-resistant treatments due to the relatively high risk of side effects.[43,44]

1.3 Complementary therapies

Other approaches, such as naturopathy, can be integrated into a comprehensive treatment plan, but the evidence is inconclusive, therefore these methods should not replace standard care.[12]

2. Pharmacological management

Pharmacotherapy is the cornerstone of the treatment of moderate to severe depression. The primary aim during the acute phase of a major depression episode is to achieve symptom remission and restore the functional baseline. The mechanism of action and adverse effect profiles vary depending on the class of antidepressants.

2.1 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmaceutical treatments due to their proven efficacy and safety. They work by inhibiting the reabsorption of serotonin and thus increasing the level of serotonin in the brain. SSRIs are generally well tolerated, with common side effects, including sexual dysfunction and gastrointestinal symptoms.[45-47]

2.2 Serotonin-norepinephrine reuptake inhibitors (SNRIs)

SNRIs are also used as first-line options. They exert their effect by inhibiting the reuptake of both serotonin and norepinephrine, making them effective for both depression and chronic pain conditions.[45]

2.3 Tricyclic antidepressants (TCAs)

TCAs inhibits the reabsorption of serotonin and norepinephrine, but they are also associated with action on muscarinic, histaminic and alpha-adrenergic receptors. This results in more side-effects than SSRIs. They are indicated for major depression, anxiety, sleep disorders and chronic pain. Common side effects include constipation, dry mouth, dizziness, weight gain, orthostatic hypotension and sedation.[35,48]

2.4 Monoamine oxidase inhibitors (MAOIs)

MAOI were one of the first antidepressants to be developed. They act by inhibiting the monoamine oxidase enzymes (MAO-A and MAO-B) increasing levels of neurotransmitter. Similar enzymes break down dopamine, norepinephrine, and serotonin. Due to safety and nutrition concerns MAOIs are rarely used due to dietary

Table I: Antidepressant drug classes, examples and common side-effects[45-47]

Class	Generic names	Mechanism	Indications	Side Effects
Monoamine oxidase inhibitors (MAOI)	• Moclobemide • Tranylcypromine	• Inhibits monoamine oxidase which degrades dopamine, norepinephrine and serotonin.	• Major depressive disorder • Anxiety	• Drowsiness • Fatigue • Decreased sexual function • Hypertensive crisis
Selective serotonin reuptake inhibitors (SSRIs)	• Citalopram • Escitalopram • Fluoxetine • Sertraline	• Inhibits reuptake of serotonin	• Major depressive disorder • Anxiety disorders	• Headache • Drowsiness • Suicidal ideation • Chanes in sexual behaviour
Serotonin norepinephrine reuptake inhibitors (SNRIs)	• Duloxetine • Desvenlafaxine	• Inhibits reuptake of serotonin and norepinephrine	• Major depressive disorder • Anxiety disorders • Diabetic peripheral neuropathic pain	• Dizziness • Fatigue • Orthostatic hypotension
Tricyclic antidepressants	• Amitriptyline • Imipramine • Nortriptyline	• Inhibits reuptake of serotonin and norepinephrine	• Major depressive disorder • Anxiety disorders • Sleep disorders • Chronic pain syndromes	• Dry mouth, blurred vision • Weight gain • Sedation • Sexual dysfunction
Triazolopyridine	• Trazodone	• Inhibits reuptake of serotonin and serotonin receptor antagonist	• Depression • Mixed anxiety	• Priapism
Phenylpiperazine	• Nefazodone	• Moderately inhibits serotonin and norepinephrine inhibitor	• Major depressive disorder	• Hepatotoxicity
Aminoketone	• Bupropion	• Selectively inhibits reuptake of dopamine and norepinephrine	• Depression • Smoking cessation	• Tremors • Dose-dependent seizures • Sweating
	• Mirtazapine	• Blocks presynaptic ά2-adrenergic autoreceptors, 5-HT2 and 5-HT3	• Major depressive disorder	• Sedation

restrictions therefore are reserved for treatment-resistant cases.[45,46] Table I gives a summary of the antidepressant classes, examples in each medication class, indications and common side effects.

In the event where the patient experiences treatment-resistant depression (TRD), augmentation strategies are recommended after two failed antidepressant trials.[49] The Food and Drug Administration (FDA)-approved adjunctive agents include atypical antipsychotics such as aripiprazole, quetiapine, olanzapine/fluoxetine, risperidone which all significantly increase response and remission rates when added to an antidepressant.[50] Lithium augmentation has strong evidence and is a guideline first-line augmenter for TRD since it significantly improves response and reduces suicide risk. Thyroid hormone (T3) augmentation is also evidence-based, showing higher response rates than placebo when added to antidepressants.[50] Other augmenters with evidence include stimulant-like agents such as modafinil and second-generation antipsychotics such as aripiprazole and quetiapine which are supported for TRD. Lastly, ketamine (an NMDA antagonist) produces rapid antidepressant effects in TRD.[51] Intravenous ketamine has been shown to significantly improve symptoms in TRD, often within hours, though durability is limited.[51]

New antidepressant medications have been introduced recently. Gepirone extended-release (a 5-HT1A partial agonist) received FDA approval in 2023 for MDD based on clinical trials showing moderate efficacy.[45] Lumateperone, an atypical antipsychotic with serotonin and dopamine modulation, showed significant benefit in clinical trials of mixed-feature depression and is being explored for the treatment of MDD.[52] However, these medications are not yet on the market.

Conclusion

The management of depression requires a comprehensive, patient-centred approach that integrates both non-pharmacological and pharmacological strategies. Psychotherapy, including CBT and interpersonal therapy, offer significant benefits in symptom reduction, coping skill development, and relapse prevention, particularly in mild to moderate cases. For treatment-resistant or severe depression, electroconvulsive therapy remains a valuable and highly effective option. Pharmacological interventions are essential, especially for moderate to severe or persistent depression. First-line agents such as SSRIs and SNRIs are favoured for their efficacy and tolerability, whilst TCAs and MAOIs may be considered in specific clinical contexts, despite their more complex side effect profiles. The choice of treatment should be guided by the severity of symptoms, patient preferences, previous treatment responses, and the presence of comorbidities. Ultimately, a collaborative, tailored treatment plan that may include both pharmacotherapy and psychotherapy offer the best outcomes in achieving remission and restoring quality of life for individuals living with depression.

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References

1. Marx W, Penninx BWJH, Solmi M, et al. Major depressive disorder. Nat Rev Dis Prim. 2023;9(1):1–21. https://doi.org/10.1038/s41572-023-00454-1.
2. Schnurr PP, Chard KM, Ruzek JI, et al. Comparison of prolonged exposure vs cognitive processing therapy for treatment of posttraumatic stress disorder among US veterans: A randomized clinical rrial. JAMA Netw Open. 2022;5(1):1–15. https://doi.org/10.1001/jamanetworkopen.2021.36921.
3. Thapar A, Eyre O, Patel V, Brent D. Depression in young people. Lancet. 2022;400(10352):617–631. https://doi.org/10.1016/S0140-6736(22)01012-1.
4. Zhang Y, Li Z, Feng Q, et al. Global, regional and national burdens of major depression disorders and its attributable risk factors in adolescents and young adults aged 10–24 years from 1990 to 2021. BMC Psychiatry. 2025;25(1). https://doi.org/10.1186/s12888-025-06772-w.
5. Liu J, Ning W, Zhang N, Zhu B, Mao Y. Estimation of the global disease burden of depression and anxiety between 1990 and 2044: An analysis of the Global Burden of Disease Study 2019. Healthc. 2024;12(17). https://doi.org/10.3390/healthcare12171721.
6. Kupferberg A, Hasler G. The social cost of depression: Investigating the impact of impaired social emotion regulation, social cognition, and interpersonal behavior on social functioning. J Affect Disord Reports. 2023;14:100631. https://doi.org/10.1016/j.jadr.2023.100631.
7. Pathak S. Mental health: Who bears the cost at the workplace? Hindustan Times [Internet]. 2023;1–3. Available from: https://pure.jgu.edu.in/id/eprint/6448/%0Ahttps://pure.jgu.edu.in/id/eprint/6448/1/hindustantimes.com-Mental health Who bears the cost at the workplace.pdf.
8. Greenberg P, Chitnis A, Louie D, et al. The economic burden of adults with major depressive disorder in the United States (2019). Adv Ther. 2023;40(10):4460–79. https://doi.org/10.1007/s12325-023-02622-x.
9. Remes O, Francisco J, Templeton P. Biological, psychological, and social determinants of depression: A review of recent literature. Brain Sci. 2021;11(12). https://doi.org/10.3390/brainsci11121633.
10. Herrera PA, Campos-Romero S, Szabo W, et al. Understanding the relationship between depression and chronic diseases such as diabetes and hypertension: A grounded theory study. Int J Environ Res Public Health. 2021;18(22). https://doi.org/10.3390/ijerph182212130.
11. Menon S, Bhagat V. Literature study on the Efficacy of antidepressants with CBT in the treatment of depression. Res J Pharm Technol. 2022;15(6):2775–87. https://doi.org/10.52711/0974-360X.2022.00465.
12. Ormel J, Hollon SD, Kessler RC, Cuijpers P, Monroe SM. More treatment but no less depression: The treatment-prevalence paradox. Clin Psychol Rev. 2022;91:102111. https://doi.org/10.1016/j.cpr.2021.102111.
13. Tian H, Hu Z, Xu J, Wang C. The molecular pathophysiology of depression and the new therapeutics. MedComm. 2022;3(3):1–36. https://doi.org/10.1002/mco2.156.
14. Gammoh OS, Bashatwah R. Potential strategies to optimize the efficacy of antidepressants: Beyond the monoamine theory. Electron J Gen Med. 2023;20(5). https://doi.org/10.29333/ejgm/13295.
15. Sarawagi A, Soni ND, Patel AB. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. Front Psychiatry. 2021;12(April). https://doi.org/10.3389/fpsyt.2021.637863.
16. Keller J, Gomez R, Williams G, et al. HPA axis in major depression: Cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry. 2017;22(4):527–36. https://doi.org/10.1038/mp.2016.120.
17. Hayley S, Hakim AM, Albert PR. Depression, dementia and immune dysregulation. Brain. 2021;144(3):746–60. https://doi.org/10.1093/brain/awaa405.
18. Roman A, Kreiner G, Nalepa I. Macrophages and depression – A misalliance or well-arranged marriage? Pharmacol Reports. 2013;65(6):1663–72. https://doi.org/10.1016/S1734-1140(13)71528-7.
19. Rădulescu I, Drăgoi A, Trifu S, Cristea M. Neuroplasticity and depression: Rewiring the brain's networks through pharmacological therapy (Review). Exp Ther Med. 2021;22(4):1–8. https://doi.org/10.3892/etm.2021.10565.
20. Cheng Z, Su J, Zhang K, Jiang H, Li B. Epigenetic mechanism of early life stress-induced depression: focus on the neurotransmitter systems. Front Cell Dev Biol. 2022;10:1–13. https://doi.org/10.3389/fcell.2022.929732.
21. Castrén E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021;90(2):128–36. https://doi.org/10.1016/j.biopsych.2021.05.008.
22. Flint J, Kendler KS. The genetics of major depression. Neuron. 2014;81(3):484–503. https://doi.org/10.1016/j.neuron.2014.01.027.
23. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668–81. https://doi.org/10.1038/s41588-018-0090-3.

24. Li X, Luo Z, Gu C, et al. Common variants on 6q16.2, 12q24.31 and 16p13.3 are associated with major depressive disorder. Neuropsychopharmacology. 2018;43(10):2146–53. https://doi.org/10.1038/s41386-018-0078-9.
25. Kale H, Shepherd J, Dwibedi N, et al. Disease burden associated with prominent anhedonia in patients with major depressive disorder from Adelphi Depression Disease Specific Programme. JnJMedicalConnect. 2024;21(Mdd):2023. Available from: https://www.jnjmedicalconnect.com/media/attestation/congresses/neuroscience/2024/psych/disease-burden-associated-with-prominent-anhedonia-in-patients-with-major-depressive-disorder-mdd-fr.pdf.
26. Tomlinson G, Slater D. Types of depression. Depression. 2018;6(1):157–61. https://doi.org/10.4324/9781315171616-21.
27. World Health Organisation. Mental Health Atlas 2020 [Internet]. WHO Publication. 2021. 1–136 p. Available from: https://www.who.int/publications/i/item/9789240036703.
28. Fries GR, Saldana VA, Finnstein J, Rein T. Molecular pathways of major depressive disorder converge on the synapse. Mol Psychiatry. 2023;28(1):284–97. https://doi.org/10.1038/s41380-022-01806-1.
29. Sher L. Individuals with untreated psychiatric disorders and suicide in the COVID-19 era. Brazilian J Psychiatry. 2021;43(3):229–30. https://doi.org/10.1590/1516-4446-2020-1210.
30. Bukh JD, Bock C, Vinberg M, Kessing LV. The effect of prolonged duration of untreated depression on antidepressant treatment outcome. J Affect Disord. 2013;145(1):42–8. https://doi.org/10.1016/j.jad.2012.07.008.
31. Woldu H, Murrough JW, Iosifescu D V. Depressive Disorders. Mount Sinai Expert Guides: Psychiatry. 2016. 59–73 p. https://doi.org/10.1002/9781118654231.ch10.
32. Hintz AM, Gomes-Filho IS, Loomer PM, et al. Depression and associated factors among Brazilian adults: the 2019 national healthcare population-based study. BMC Psychiatry. 2023;23(1):1–15. https://doi.org/10.1186/s12888-023-05133-9.
33. McCarter G. Depression overview. MD Conf Express. 2007;7(2):28-9. https://doi.org/10.1177/155989770700700213.
34. Melrose S. Seasonal affective disorder: An overview of assessment and treatment approaches. Depress Res Treat. 2015;2015. https://doi.org/10.1155/2015/178564.
35. Rosen LN, Targum SD, Terman M, et al. Prevalence of seasonal affective disorder at four latitudes. Psychiatry Res. 1990;31(2):131–44. https://doi.org/10.1016/0165-1781(90)90116-M.
36. Wang Z, Liu J, Shuai H, et al. Mapping global prevalence of depression among postpartum women. Transl Psychiatry. 2021;11(1). https://doi.org/10.1038/s41398-021-01692-1.
37. Atias K. Postpartum depression during breastfeeding within a year after birth. Psychol Res (in Balkans). 2024;27(2):133–40. https://doi.org/10.7546/PsyRB.2024.27.02.05.
38. Greenspan H, Hussain A, Aginah O, et al. Treatment challenges of atypical depression: A case report. Psychiatr Ann. 2013;43(11):523–4. https://doi.org/10.3928/00485713-20131105-08.
39. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016;387(10027):1561–72. https://doi.org/10.1016/S0140-6736(15)00241-X.
40. Cui L, Li S, Wang S, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduction and Targeted Therapy. Springer US; 2024;9. https://doi.org/10.1038/s41392-024-01738-y.
41. Boschloo L, Bekhuis E, Weitz ES, et al. The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis. World Psychiatry. 2019;18(2):183–91. https://doi.org/10.1002/wps.20630.
42. Kovich H, Kim W, Quaste AM. Pharmacologic treatment of depression. Am Fam Physician. 2023;107(2):173–81.
43. Sanacora G, Mason GF, Rothman DL, et al. Increased cortical GABA concentrations in depressed patients receiving ECT. Am J Psychiatry. 2003;160(3):577–9. https://doi.org/10.1176/appi.ajp.160.3.577.
44. Lisanby SH. Electroconvulsive therapy for depression. N Engl J Med. 2007;357(19):1939–45. https://doi.org/10.1056/NEJMct075234.
45. Lucido MJ, Dunlop BW. Emerging medications for treatment-resistant depression: A review with perspective on mechanisms and challenges. Brain Sci. 2025;15(2). https://doi.org/10.3390/brainsci15020161.
46. Skosana PP, Shirindza N, Abraham V. Mental health update - update on depression with a focus on escitalopram. 2024;91(4). https://doi.org/10.36303/SAPJ.0811.
47. Karrouri R, Hammani Z, Otheman Y, Benjelloun R. Major depressive disorder: Validated treatments and future challenges. World J Clin Cases. 2021;9(31):9350–67. https://doi.org/10.12998/wjcc.v9.i31.9350.
48. Skosana PP, Mokhele S, Andrew J. Management of post-traumatic stress disorder: a review of anxiety disorders and PTSD. 2024;91(4):39–45. https://doi.org/10.36303/SAPJ.0746.
49. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540–60. https://doi.org/10.1177/0706743716659417.
50. Nuñez NA, Joseph B, Pahwa M, et al. Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. J Affect Disord. 2022;302:385–400. https://doi.org/10.1016/j.jad.2021.12.134.
51. Medeiros GC, Demo I, Goes FS, Zarate CA, Gould TD. Personalized use of ketamine and esketamine for treatment-resistant depression. Transl Psychiatry. 2024;14(1). https://doi.org/10.1038/s41398-024-03180-8.
52. Durgam S, Kozauer SG, Earley WR, et al. Lumateperone for the treatment of major depressive disorder with mixed features or bipolar depression with mixed features: A randomized placebo-controlled trial. J Clin Psychopharmacol. 2025;45(2):67–75. https://doi.org/10.1097/JCP.0000000000001964.