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# Ketamine and Fluoxetine use in Chronic Unpredictable Stress-Driven Depression

**Norhan Nabil Ahmed Abdelhady [1], Ahmed Ahmed Abdelsameea[2], Laila Ahmed Mahgoub[3], Nisreen E. Elwany [4]**

1 Demonstrator in Clinical Pharmacology, Department of Pharmacology, Faculty of Medicine, Suez University, norhannabil.tia@gmail.com
2 Professor of Clinical Pharmacology, Faculty of Medicine - Zagazig University, ahmedma_72@yahoo.com
3 Professor of Clinical Pharmacology, Faculty of Medicine - Zagazig University, lailamahgoup70@gmail.com
4 Assistant Professor of Clinical Pharmacology, Faculty of Medicine - Zagazig University , Nisreenelwany@yahoo.com, NAAlwan@medicine.zu.edu.eg, Orcid No: 0000-0003-0008-8228
**Corresponding author:** Norhan Nabil Ahmed Abdelhady
**Email: norhannabil.tia@gmail.com**

**Abstract: Background**: Chronic unpredictable mild stress (CUMS) is a widely used experimental model to simulate human depression, characterized by persistent mood disturbances and impaired neurobiological function. Despite the widespread use of conventional antidepressants like fluoxetine, a selective serotonin reuptake inhibitor (SSRI), a significant proportion of patients experience inadequate responses, highlighting the urgent need for novel therapeutic approaches. Ketamine, a rapid-acting N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising antidepressant with distinct mechanisms and rapid efficacy. This review explores the potential roles of ketamine and fluoxetine in addressing depression induced by CUMS. We provide an in-depth analysis of the molecular mechanisms underlying the antidepressant effects of Ketamine and Fluoxetine. Fluoxetine exerts its antidepressant effects by enhancing serotonergic neurotransmission, modulating neuroplasticity, and promoting hippocampal neurogenesis over prolonged treatment periods. Meanwhile, ketamine exerts its effects through glutamatergic pathways, enhancing synaptogenesis, restoring synaptic connectivity, and rapidly reversing stress-induced structural deficits. Evidence suggests that ketamine may provide rapid relief of depressive symptoms, offering a critical bridge to fluoxetine's delayed therapeutic onset. Furthermore, ketamine's modulation of glutamate signaling may enhance fluoxetine's neuroadaptive effects, providing a unique synergistic approach to counteract the multifaceted neurobiological disruptions in depression. We also address potential limitations and adverse effects, including the risk of dependency with ketamine and the tolerability concerns with long-term fluoxetine use. Additionally, we explore emerging evidence on the optimal timing, dosage, and sequence of administration to maximize therapeutic outcomes. In conclusion, the review underscores the need for further research into potential roles of ketamine and fluoxetine, as well as their individual contributions to manage CUMS-induced depression. The complementary pharmacological profiles of these agents suggest promising avenues for personalized treatment strategies, offering hope for individuals with treatment-resistant depression and enhancing our understanding of depression pathophysiology. In Conclusion ketamine is a promising agent in treating CUS-driven depression, providing hope for patients with severe, stress-related depressive symptoms. However, its use requires careful consideration of safety, monitoring, and long-term implications. Fluoxetine remains a cornerstone treatment for CUS-driven depression due to its ability to modulate serotonin levels, promote neuroplasticity, and reverse stress-induced neurochemical changes. However, its delayed onset and side effect profile highlight the need for careful patient selection and management. In cases of severe, rapid-onset stress-driven depression, it may be supplemented or preceded by faster-acting interventions like ketamine.

**Keywords:** *Ketamine, Fluoxetine, Chronic Unpredictable Stress, Depression*

**Introduction.**

Depression is considered as one of the most common causes of disability all over the world [1]. It is reported by the World Health Organization [2] that it is the main contributor to worldwide disability, which affects about 322 million people. It has been listed by WHO as the third major cause of disease burden since 2008, and is expected to be the first by 2030 [3,4]. Depression is the commonest mental disorder in the U.S. [5]. Depression affects the quality of life of depressed patients [6], and it is also the principal cause of suicidal behavior [7]. Numerous clinical studies showed that the depression rate in the U.S. population rose from 6.6% in 2005 to 7.3% in 2015 [8]. The most rapid increases from 2005 to 2015 were observed among adolescents and people at the highest and lowest socioeconomic status. These increases were proportionate to race/nationality and sex, among all groups [9].

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [10], the diagnosis of major depressive disorder (MDD) is determined by the finding of five or more symptoms of these nine symptoms: bad mood, loss of interest or decreased pleasure, weight loss or weight gain, sleep disturbances, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or shame, reduced ability to think or hesitancy, and recurrent thoughts of death or recurrent suicidal ideas for 2 or more weeks. For the diagnosis of major depression, either 'depressed mood' or 'loss of interest or pleasure' must be presented [11]. So, the diagnosis of MDD depends mainly on patients' self-report, clinical examination, and evaluation of depressive symptoms [12].

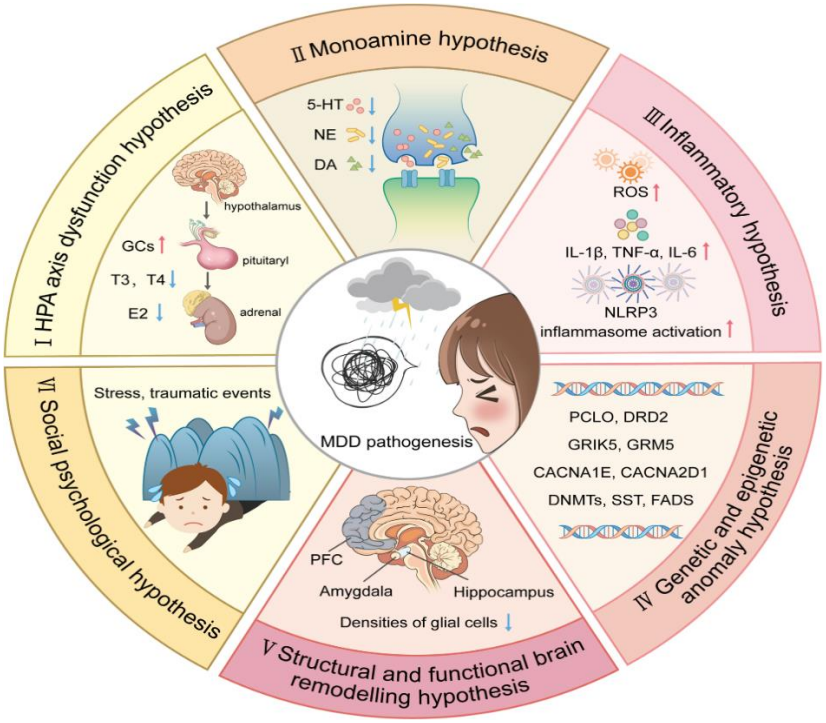


**Figure (1)** Hypotheses of depression [12].

**Monoamine hypothesis:**

The pathogenesis of MDD is explained by several hypotheses including changes in monoaminergic neurotransmission, imbalance of excitatory and inhibitory signaling in the brain, hyperactivity of the hypothalamic–pituitary adrenal (HPA) axis, inflammation, and abnormalities in normal neurogenesis [13,14]. Information transmission in the brain is mediated by molecules known as monoamines which act to create connections between presynaptic neurons and postsynaptic ones [15]. They are sorted according to their chemical structure and mechanism of action [16]. As they

have different chemical structures, each monoamine has its own specific receptor [15] and has an individual function in the brain [17-19]. For example, 5HT is a central nervous system monoamine that has a basic role in controlling appetite, circadian cycle, anxiety, memory, and learning. Dopamine is another important monoamine that is responsible for motivation and regulates pleasure, reward, and emotion. Norepinephrine (NA) is another important one that controls attention, emotions, cognition, and social interactions. The depletion of brain monoamines such as serotonin, dopamine, and NA in patients' brains is responsible for depression development [20].

So, it was hypothesized by many studies that the primary pathway of MDD pathogenesis is the depletion of monoamine neurotransmitters, such as norepinephrine and serotonin, the main neurotransmitter [21]. The monoamine hypothesis is recognized as the main theory for MDD pathophysiology, leading to the use of selective serotonin reuptake inhibitors as a treatment for depression worldwide [22].

**Oxidative stress hypothesis:**

The oxidative stress hypothesis of depression posits that an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms plays a significant role in the pathophysiology of depression [23]. It is reported by clinical studies that oxidative stress is one of the principal causes of depression [23], as the brain is more susceptible to oxidative stress (OS) because of its high oxygen demand, high lipid content, and low antioxidant mechanisms [24,25]. Oxidative stress can activate inflammatory pathways in the brain, leading to neuroinflammation. Elevated levels of pro-inflammatory cytokines (such as TNF-α and IL-1β) can disrupt neurotransmitter systems and neuronal functions, contributing to depressive symptoms [25].

Oxidative stress can significantly impact neurotransmitter systems, which are crucial for mood regulation and cognitive function, by disrupting neurotransmitter synthesis. For instance, the synthesis of serotonin from tryptophan involves the enzyme tryptophan hydroxylase, which may be impaired by oxidative damage to the enzyme or its cofactors. Oxidative stress can also deplete essential co-factors, such as tetrahydrobiopterin (BH4), necessary for the production of neurotransmitters like serotonin and dopamine. Reduced availability of these co-factors can lead to decreased levels of neurotransmitters [26].

Oxidative stress is evidenced by an increase in the levels of oxidative stress markers in the blood of depressed patients [27]. The most common markers in the enzymatic antioxidant process are the levels of catalase (CAT) and superoxide dismutase (SOD) [28]. The main marker for the non-enzymatic antioxidant defense mechanism is glutathione (GSH). SOD transforms superoxide anion radicals into hydrogen peroxide, thereby decreasing the interaction between superoxide anion and nitric oxide to form reactive peroxynitrite [28]. CAT is an important antioxidant enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen [29], effectively reducing the levels of this potentially harmful ROS. By converting $H_2O_2$ into non-toxic byproducts, catalase prevents oxidative damage to cellular components, including lipids, proteins, and DNA [30].

SOD and CAT are crucial enzymes in the cellular defense against oxidative stress. Their sequential and complementary actions help to maintain redox balance and protect cells from oxidative damage. Understanding the interplay between SOD and CAT can inform potential therapeutic strategies aimed at enhancing antioxidant defenses and alleviating oxidative stress-related conditions [31].

Malondialdehyde (MDA) is the main product of lipid peroxidation, a process in which ROS attack lipids in cell membranes, leading to cell damage. MDA is a highly toxic aldehyde that serves as a biomarker for oxidative damage [32]. Studies on lipid peroxidation in depressed patients revealed an increase in the levels of MDA and other lipid peroxidation products [33,34]. Furthermore, patients with depression showed a decrease in the SOD, and CAT levels and an increase in MDA levels. Besides their main role in increasing monoamine levels, antidepressants, especially SSRIs, are effective in reducing oxidative damage in depressed patients [28].

**HPA axis dysfunction hypothesis:**

The HPA axis and oxidative stress hypothesis are two important concepts in understanding the body's response to stress and its implications on health. The HPA axis is a complex set of interactions among the hypothalamus, pituitary gland, and adrenal glands that regulate various body functions, including the stress response. On exposure to stressors,

the hypothalamus releases corticotropin-releasing hormone (CRH), stimulating the pituitary gland to release adrenocorticotropic hormone (ACTH) [35]. This, in turn, triggers the adrenal glands to produce cortisol. Chronic stress can lead to dysregulation of the HPA axis, resulting in altered cortisol levels, which may contribute to mental health disorders, obesity, cardiovascular diseases, and metabolic syndrome. Chronic activation of the HPA axis can lead to increased production of ROS [25].

Increased cortisol levels can exacerbate oxidative stress, leading to potential cellular damage. Additionally, prolonged activation of the HPA axis due to chronic stress can enhance oxidative stress, creating a feedback loop that may further dysregulate the HPA axis and exacerbate health problems. Targeting both the HPA axis and oxidative stress pathways can be beneficial in treating conditions related to stress, such as anxiety and depression. Treatment of depressed patients with antidepressants inhibits the HPA axis and normalizes elevated cortisol levels associated with depression [23,36,37]. Many antidepressants improve the negative feedback mechanism of the HPA axis, which may be impaired in depressed individuals. This can lead to a reduction in CRH and ACTH secretion, ultimately decreasing cortisol production [38].

**The inflammatory hypothesis of depression**

The inflammatory hypothesis of depression suggests that chronic low-grade inflammation plays a central role in the development and persistence of depressive symptoms. This theory is supported by evidence showing elevated levels of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) in individuals with depression. These inflammatory mediators can cross the blood-brain barrier and influence central nervous system (CNS) function, leading to alterations in key neural pathways. For example, inflammation can dysregulate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hypercortisolemia, and disrupt neurotransmitter systems such as serotonin, norepinephrine, and dopamine. Additionally, cytokines can decrease the availability of tryptophan, a precursor for serotonin synthesis, by activating the kynurenine pathway, ultimately reducing serotonin levels and contributing to depressive symptoms [25].

Neuroinflammation also affects synaptic plasticity and neural connectivity, particularly in brain regions like the prefrontal cortex, hippocampus, and amygdala, which are critical for mood regulation. Pro-inflammatory cytokines impair neurogenesis by inhibiting brain-derived neurotrophic factor (BDNF) signaling and promoting neuronal apoptosis. Moreover, inflammation-induced oxidative and nitrosative stress further damages neurons and glial cells, exacerbating the neurobiological changes associated with depression. This hypothesis explains why some patients with depression, especially those resistant to conventional antidepressants, may benefit from treatments targeting inflammation. Anti-inflammatory agents, such as NSAIDs, cytokine inhibitors, and even lifestyle interventions like diet and exercise, have shown promise in reducing depressive symptoms in these cases, further supporting the link between inflammation and depression [25].

**Other factors implicated in the pathogenesis of depression:**

Depression can be a complication of some diseases such as obesity [39], diabetes [40], anxiety [41], Alzheimer's disease (AD), and schizophrenia [42,43]. There are a lot of theories that explain the pathogenesis of depression, such as genetic disposition and changes in brain structure or function [44]. The cause of depression is unclear, but it is thought that MDD depends on several factors such as social, psychological, genetic, and biological factors [45]. Long-term exposure to psychological or physical stress is one of the most common predisposing factors for major depressive disorder [46]. Chronic stress causes dysregulation of HPA axis activity, decreases neurotrophic factors (such as Nerve Growth Factor (NGF) and BDNF), and increases inflammatory mediators (such as IL-6, TNF-α, and iNOS) [47-49]. These pathological events can cause atrophic changes and volume reduction in brain regions responsible for emotional and stress responses, like the prefrontal cortex, hippocampus, and amygdala [50].

**Experimental induction of depression:**

Depression can be induced by several methods including drugs such as clonidine [51] and reserpine [52], which irreversibly inhibit vesicular reuptake of monoamines [53]. Reserpine is commonly used in experimental animal models via intraperitoneal (IP) injection for the induction of depression [54]. Another way to induce depression is by

the chronic administration of lipopolysaccharides (LPS) intraperitoneally [55]. Additionally, depression can be induced by subcutaneous administration of Monosodium Glutamate (MSG), which is a food additive [56]. Recently, depression can be induced by exposure to chronic unpredictable mild stressors (CUMS) [57], one of the most widely used and popular models of depression, providing the best attempt to simulate the human depressive state [58]. These mild stressors include food deprivation for 24 hours, water deprivation for 24 hours, cage tilting for 24 hours, wet bedding overnight, overcrowding of the cage, and reversal of the light-dark cycle [59].

**Treatment of depression:**

Treatment for MDD involves psychological or pharmacological treatments, or a combination of both. In the majority of cases, patients prefer psychological treatment over pharmacological treatment [60], although patients with severe depressive symptoms must be treated with drug-based therapy [61]. A variety of antidepressant agents exist with different mechanisms of action, but they share common aims. It is evidenced by preclinical and clinical studies that antidepressant drugs such as monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) have antioxidant actions by increasing the antioxidant capacity [62].

From the perspective of the monoamine hypothesis, the primary mechanism of antidepressant drugs is to increase the availability of key neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) in the synaptic cleft. These drugs include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), norepinephrine–dopamine reuptake inhibitors (NDRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). However, this hypothesis does not fully explain the complexity of depression, as the therapeutic effects of these drugs often take weeks to manifest despite rapid increases in neurotransmitter levels [63].

According to the inflammatory hypothesis of depression, elevated levels of pro-inflammatory cytokines and systemic inflammation are associated with the onset and persistence of depressive symptoms. Anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may help alleviate depressive symptoms, either directly by reducing inflammation or indirectly by enhancing the efficacy of conventional antidepressants, particularly in treatment-resistant depression [64–66].

Shortly after the discovery of SSRIs, they became a basic treatment for different psychiatric disorders. Their mechanism of action is through the inhibition of presynaptic serotonin reuptake at the serotonin transporter, leading to increased serotonin at the postsynaptic membrane in the synaptic gap. Nowadays, there are six major SSRIs on the market (fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine), which have different chemical structures but similar mechanisms of action. Each SSRI has unique pharmacokinetics, pharmacodynamics, and side effects [67].

The therapeutic effects of selective serotonin reuptake inhibitors (SSRIs) are not solely explained by their inhibition of the serotonin transporter (SERT). While SSRIs increase serotonin availability in the synaptic cleft shortly after administration, their full therapeutic effects typically take four to six weeks to manifest. This delay is attributed to secondary mechanisms, including neuronal adaptation and changes in brain homeostasis. SSRIs induce neuronal stress and activate downstream signaling pathways, leading to increased neuroplasticity, enhanced brain-derived neurotrophic factor (BDNF) expression, and remodeling of synaptic connections. These processes are thought to underlie the long-term antidepressant effects, highlighting the complexity of their action beyond the initial modulation of serotonin flux [68].

SSRI studies initially targeted depression, but these drugs are also effective for anxiety disorders. SSRIs are preferred over TCAs due to better compliance and a favorable side effect profile [69]. However, SSRIs still have a range of adverse effects that need to be monitored, including common side effects like nausea, vomiting, sleep disturbances, dizziness, and headaches, and less common effects such as serotonin syndrome, QT prolongation, and birth defects [67,70].

**Role of Ketamine in chronic unpredictable mild stress**

Chronic unpredictable mild stress (CUMS) serves as a robust preclinical model to induce depressive-like behaviors in animals. It mimics the multifactorial nature of human depression, encompassing environmental, genetic, and neurochemical factors. CUMS-induced alterations in behavior and neurobiology make it an ideal platform to evaluate novel antidepressant strategies [71-74].

Ketamine, a dissociative anesthetic and a N-methyl-D-aspartate (NMDA) receptor antagonist, has gained significant attention for its rapid-acting antidepressant effects in treatment-resistant depression (TRD). Its discovery has revolutionized psychiatric therapeutics, offering a new dimension to managing depressive disorders, particularly in scenarios where conventional treatments fail [71].

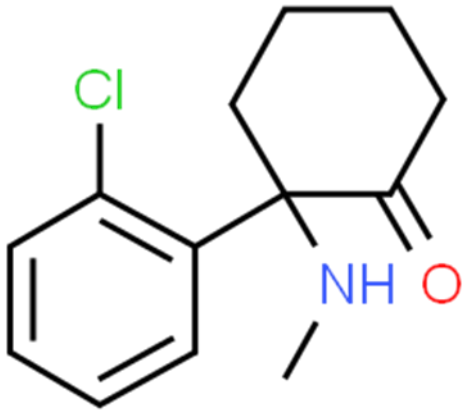


**figure (2)** chemical formula of ketamine. [72].

The chemistry of ketamine reveals its structural uniqueness as a phencyclidine derivative. Ketamine exists as a racemic mixture of R- and S-enantiomers, with the S-enantiomer (esketamine) exhibiting higher NMDA receptor affinity. Its lipophilic nature facilitates blood-brain barrier penetration, enhancing its central nervous system activity and its efficacy in clinical applications [72].

Pharmacokinetically, ketamine exhibits rapid absorption following intravenous, intramuscular, or intranasal administration. Its hepatic metabolism primarily involves cytochrome P450 enzymes, producing active metabolites such as norketamine, which contribute to its therapeutic effects. The half-life of ketamine ranges from 2-3 hours, facilitating rapid onset [73,74].

The pharmacodynamics of ketamine highlight its role as a non-competitive NMDA receptor antagonist. Ketamine binds to the phencyclidine site within the NMDA receptor channel, inhibiting calcium influx and modulating glutamatergic neurotransmission. This action is thought to underlie its rapid antidepressant effects, particularly in synaptic plasticity and neurogenesis [75].

The mechanism of action of ketamine extends beyond NMDA receptor antagonism. Emerging evidence suggests that ketamine enhances synaptic connectivity through increased BDNF release and activation of the mammalian target of rapamycin (mTOR) pathway. These effects contribute to rapid alleviation of depressive symptoms and resilience against stress [76,79].

Adverse events associated with ketamine include dissociation, transient hypertension, and potential for misuse due to its psychotomimetic properties. Despite these concerns, careful monitoring and dosing adjustments mitigate these risks in clinical settings, ensuring safety and efficacy [81].

Clinical studies evaluating ketamine's efficacy in CUMS-induced depression highlight its ability to rapidly reverse depressive-like behaviors. Animal models demonstrate improvements in sucrose preference, mobility in forced swim tests, and normalization of hippocampal BDNF levels, emphasizing its potential in stress-induced depression [83].

**Role of Fluoxetine in chronic unpredictable mild stress**

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is a cornerstone in the pharmacological management of depression. By inhibiting serotonin reuptake, fluoxetine increases serotonin levels in the synaptic cleft, leading to improved neurotransmission and mood regulation. [73].

Fluoxetine, characterized by its extensive half-life (4-6 days for the parent compound and up to 16 days for its active metabolite, norfluoxetine), provides prolonged therapeutic effects. Metabolized by CYP2D6, fluoxetine demonstrates interindividual variability influenced by genetic polymorphisms, potentially affecting its pharmacokinetic profile when combined with ketamine [75:78].

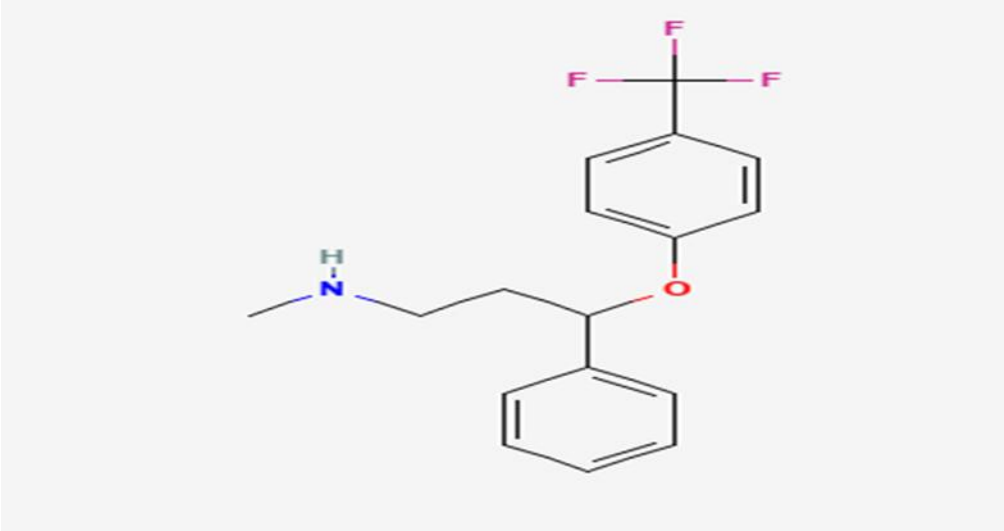


**Figure (3)** shows chemical structure of fluoxetine. [73].

Fluoxetine's pharmacodynamics involve the blockade of the serotonin transporter (SERT), reducing serotonin reuptake. This leads to increased serotonin availability in the synaptic cleft and sustained receptor activation. Additionally, fluoxetine exhibits downstream effects on neuroplasticity, including brain-derived neurotrophic factor (BDNF) upregulation, complementing ketamine's mechanisms [76].

Fluoxetine's mechanism involves both acute and chronic effects on serotonergic neurotransmission. Over time, it induces receptor desensitization and downstream signaling cascades, including activation of the extracellular signal-regulated kinase (ERK) pathway. [80].

Fluoxetine's side effect profile includes nausea, insomnia, and sexual dysfunction, which can affect patient adherence. When used in combination with ketamine, monitoring for additive effects, particularly on the central nervous system, becomes critical to optimize therapeutic outcomes [81, 82].Fluoxetine's role in CUMS models involves gradual amelioration of depressive symptoms through serotonin-mediated pathways. [84,85].

In Conclusion: ketamine offers a breakthrough in treating CUS-driven depression, providing hope for patients with severe, stress-related depressive symptoms. However, its use requires careful consideration of safety, monitoring, and long-term implications. Fluoxetine remains a cornerstone treatment for CUS-driven depression due to its ability to modulate serotonin levels, promote neuroplasticity, and reverse stress-induced neurochemical changes. However, its

delayed onset and side effect profile highlight the need for careful patient selection and management. In cases of severe, rapid-onset stress-driven depression, it may be supplemented or preceded by faster-acting interventions like ketamine.

**References**

1. Metrics IFH, Evaluation. GBD Compare. Seattle, WA: IHME, University of Washington; 2015.
2. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: WHO; 2017.
3. Dadi AF, Miller ER, Bisetegn TA, Mwanri L. Global burden of depression and its association with chronic diseases in South Africa, 2008-2015. Psychiatr Clin North Am. 2020;43(3):161-172.
4. Zhu S, Zhao L, Fan Y, et al. Interaction between TNF-α and oxidative stress status in first-episode drug-naïve schizophrenia. Psychoneuroendocrinology. 2020;114:104595.
5. Collaborators GBD. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789-1858.
6. Lépine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat. 2011;7(Suppl 1):3-7.
7. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry. 2016;3(2):171-178.
8. Weinberger AH, Gbedemah M, Martinez AM, et al. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol Med. 2018;48(8):1308-1315.
9. Twenge JM, Cooper AB, Joiner TE, et al. Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005–2017. J Abnorm Psychol. 2019;128(3):185-199.
10. Svenaeus F. Depression and the self: meaning, control and loss. Med Health Care Philos. 2014;17(3):363-370.
11. Park SC, Kim D. The centrality of depression and anxiety symptoms in major depressive disorder determined using a network analysis. J Affect Disord. 2020;271:19-26.
12. Daria S, Proma MA, Shahriar M, et al. Serum interferon-gamma level is associated with drug-naïve major depressive disorder. SAGE Open Med. 2020;8:2050312120974169.
13. Maes M, Bosmans E, Meltzer HY, et al. Interleukin-1 beta: a putative mediator of HPA axis hyperactivity in major depression? Am J Psychiatry. 1993;150(8):1189-1193.
14. Emon MPZ, Das R, Nishuty NL, et al. Reduced serum BDNF levels are associated with the increased risk for developing MDD: a case-control study with or without antidepressant therapy. BMC Res Notes. 2020;13:1-6.
15. Südhof TC. The cell biology of synapse formation. J Cell Biol. 2021;220(7):e202103052.
16. Edmondson D, Mattevi A, Binda C, Li M, Hubalek F. Structure and mechanism of monoamine oxidase. Curr Med Chem. 2004;11(15):1983-1993.
17. Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. J Clin Psychiatry. 2008;69(Suppl E1):4-7.
18. Kulkarni S, Dhir A, Akula KK. Potentials of curcumin as an antidepressant. Sci World J. 2009;9:1233-1241.
19. Moret C, Briley M. The importance of norepinephrine in depression. Neuropsychiatr Dis Treat. 2011;7(Suppl 1):9-13.
20. Freis ED. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. N Engl J Med. 1954;251(25):1006-1008.
21. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry. 2000;61(6):4-6.
22. Pastis I, Santos MG, Paruchuri A. Exploring the role of inflammation in major depressive disorder: beyond the monoamine hypothesis. Front Behav Neurosci. 2024;17:128224
23. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol. 2008;11(6):851-876.
24. Khan MS, Muhammad T, Ikram M, Kim MO. Dietary supplementation of the antioxidant curcumin halts systemic LPS-induced neuroinflammation-associated neurodegeneration and memory/synaptic impairment via the JNK/NF-κB/Akt signaling pathway in adult rats. Oxid Med Cell Longev. 2019;2019:7860654.

25. Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. Drug Discov Today. 2020;25(7):1270-1276.
26. Correia AS, Cardoso A. Oxidative Stress in Depression: The Link with the Stress Response, Neuroinflammation, Serotonin, Neurogenesis, and Synaptic Plasticity. Antioxidants (Basel). 2023;12(2):470.
27. Pinto RJ, Correia-Santos P, Costa-Leite J, et al. Cortisol awakening response among women exposed to intimate partner violence. Psychoneuroendocrinology. 2016;74:57-64.
28. Maritim AC, Sanders RA, Watkins JB. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol. 2003;17(1):24-38.
29. Nandi A, Yan LJ. Stability and activation of catalase. Arch Biochem Biophys. 2019;673:108-118.
30. Chelikani P, Fita I, Loewen PC. Diversity of structures and properties among catalases. Cell Mol Life Sci. 2004;61(2):192-208.
31. Anwar S, Alrumaihi F. Exploring therapeutic potential of catalase: strategies in disease prevention and management. Biomolecules. 2024;14(6):697.
32. Caiaffo V, Oliveira BD, de Sá FB, Evêncio Neto J. Anti-inflammatory, antiapoptotic, and antioxidant activity of fluoxetine. Pharmacol Res Perspect. 2016;4(3):e00231.
33. Tsuboi H, Tatsumi A, Yamamoto K, et al. Possible connections among job stress, depressive symptoms, lipid modulation, and antioxidants. J Affect Disord. 2006;91(1):63-70.
34. Gałecki P, Szemraj J, Bieńkiewicz M, et al. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. Pharmacol Rep. 2009;61(3):436-447.
35. McKay MS, Zakzanis KK. The impact of treatment on HPA axis activity in unipolar major depression. J Psychiatr Res. 2010;44(3):183-192.
36. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):676-692.
37. Zhang Z, Deng T, Wu M, Zhu A, Zhu G. Botanicals as modulators of depression and mechanisms involved. Chin Med. 2019;14:1-10.
38. Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol. 2006;20(4_suppl):79-84.
39. Gibson-Smith D, Bot M, Snijder M, et al. The relation between obesity and depressed mood in a multi-ethnic population. Soc Psychiatry Psychiatr Epidemiol. 2018;53(6):629-638.
40. Bădescu S, Tătaru C, Kobylinska L, et al. The association between diabetes mellitus and depression. J Med Life. 2016;9(2):120-125.
41. Zhou Y, Cao Z, Yang M, et al. Comorbid generalized anxiety disorder and its association with quality of life in patients with major depressive disorder. Sci Rep. 2017;7:40511.
42. Samsom JN, Wong AH. Schizophrenia and depression co-morbidity: what we have learned from animal models. Front Psychiatry. 2015;6:124728.
43. Ryu SH, Jung HY, Lee KJ, et al. Incidence and course of depression in patients with Alzheimer's disease. Psychiatry Investig. 2017;14(3):271-278.
44. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry. 2010;9(3):155-161.
45. Li JH, Vicknasingam B, Cheung YW, et al. To use or not to use: an update on licit and illicit ketamine use. Subst Abuse Rehabil. 2011;2:11-20.
46. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology. 2008;33(1):88-109.
47. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464-468.
48. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140(3):774-815.
49. Dahlman AS, Blennow K, Zetterberg H, et al. Growth factors and neurotrophins in patients with stress-related exhaustion disorder. Psychoneuroendocrinology. 2019;109:104415.
50. Liu W, Ge T, Leng Y, et al. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural Plast. 2017;2017:6871087.
51. Antkiewicz-Michaluk L, Romańska I, Wąsik A, Michaluk J. Antidepressant-like effect of 1MeTIQ in clonidine-induced depression: behavioral and neurochemical studies. Neurotox Res. 2017;32(1):94-106.

52. El-Marasy SA, El Awdan SA, Hassan A, et al. Anti-depressant effect of cerebrolysin in reserpine-induced depression in rats. Chem Biol Interact. 2021;334:109329.
53. Nasrolahi A, Mahmoudi J, Akbarzadeh A, et al. Neurotrophic factors hold promise for Parkinson's disease treatment. Rev Neurosci. 2018;29(5):475-489.
54. Khadrawy YA, Sawie HG, Hosny EN, Mourad HH. Assessment of the antidepressant effect of caffeine using a rat model of depression induced by reserpine. Bull Natl Res Centre. 2018;42:1-9.
55. Yin R, Zhang K, Li Y, et al. Lipopolysaccharide-induced depression-like model in mice: meta-analysis and systematic evaluation. Front Immunol. 2023;14:1181973.
56. Yang F, Zhu W, Cai X, et al. Minocycline alleviates NLRP3 inflammasome-dependent pyroptosis in monosodium glutamate-induced depressive rats. Biochem Biophys Res Commun. 2020;526(3):553-559.
57. Zeldetz V, Natanel D, Boyko M, et al. A new method for inducing a depression-like behavior in rats. JoVE. 2018;(132):e57137.
58. Markov DD, Novosadova EV. Chronic unpredictable mild stress model of depression: possible sources of poor reproducibility. Biology (Basel). 2022;11(11):11621.
59. Salari M, Sharifi-Bakhtiar M, Soltani H, et al. Chronic unpredictable mild stress model for inducing depression-like behaviors in rodents. Iran J Basic Med Sci. 2023;26(1):1-9.
60. McHugh RK, Whitton SW, Peckham AD, et al. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders. J Clin Psychiatry. 2013;74(6):595-602.
61. Magnani M, Sasdelli A, Bellino S, et al. Treating depression: what patients want. Psychosomatics. 2016;57(6):616-623.
62. Behr GA, Moreira JC, Frey BN. Antioxidant effects of antidepressants: implications for the pathophysiology of MDD. Oxid Med Cell Longev. 2012;2012:609421.
63. Zakaria FH, Samhani I, Mustafa MZ, et al. Pathophysiology of depression: stingless bee honey promising as an antidepressant. Molecules. 2022;27(16):5091.
64. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. J Clin Psychiatry. 2001;62(Suppl 16):18-25.
65. Akhondzadeh S, Jafari S, Raisi F, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression. Depress Anxiety. 2009;26(7):607-611.
66. Müller N. The role of anti-inflammatory treatment in psychiatric disorders. Psychiatr Danub. 2013;25(3):298-305.
67. Edinoff AN, Akuly HA, Hanna TA, et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurol Int. 2021;13(3):387-401.
68. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden. Drugs Context. 2015;4:212290.
69. Edwards JG, Anderson I. Systematic review and guide to selection of SSRIs. Drugs. 1999;57(4):507-533.
70. Schmider J, Greenblatt DJ, Von Moltke LL, et al. Inhibition of CYP2C9 by SSRIs: studies of phenytoin p-hydroxylation. Br J Clin Pharmacol. 1997;44(5):495-498.
71. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry. 2018;23(4):801-811.
72. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther. 1965;6(3):279-291.
73. Wong DT, Bymaster FP. Development of the SSRI fluoxetine. Nat Rev Drug Discov. 2002;1(9):689-695.
74. Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology. 2005;52(2):90-110.
75. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
76. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin in action. J Affect Disord. 1998;51(3):215-235.
77. Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, an active metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur J Pharmacol. 1997;333(1):99-104.
78. Preskorn SH. Clinical pharmacology of SSRIs. Depression. 1997;5(4):14-30.
79. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011;475(7354):91-95.

80. Castrén E, Rantamäki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev Neurobiol. 2010;70(5):289-297.
81. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. Lancet Psychiatry. 2018;5(1):65-78.
82. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. Prim Care Companion J Clin Psychiatry. 2001;3(1):22-27.
83. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864.
84. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010;329(5994):959-964.
85. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012;338(6103):68-72.