Review Article

Newer Therapeutic Approaches in Major Depressive Disorder

Jaspreet Kaur[1], Deepika Puri[1], Karan Sachdeva[2], Prithpal S. Matreja[3]

ABSTRACT

Major depressive disorder (MDD) is a common health disorders characterized by anhedonia along with physical changes. MDD is a leading cause of disability worldwide. MDD treatment mainly focuses on improving the quality of life of the patients suffering from this disorder. Various modalities of treatment include initiating pharmacotherapy, focussed psychotherapy, or electroconvulsive therapies. The current treatment modalities focus on the monoamine hypothesis with a wide range of drugs available from tricyclic antidepressants (TCAs) to selective serotonin reuptake inhibitors (SSRIs). Despite therapy with the currently available drugs a substantial proportion of patients do not achieve full remission with full-dose titration and there is still persistence of treatment-resistant depression (TRD). The currently available antidepressants drugs are associated with frequent adverse effects with tolerance limiting their long-term adherence. Delivery of psychotherapy has its own set of limitation and one of them is in form of delivery of psychotherapy. As many patients despite optimal therapy of currently available antidepressant drugs one-third of the patients do not respond to the currently available forms of therapy. The understanding of the pathophysiology has increased our knowledge with role of neuroplasticity, disrupted signalling pathway, decreased neurotropic factor expressions and altered functional connectivity of neurocircuitry also playing its role apart from the neurotransmission theory of depression. Opening up avenues for treatment of currently unanswered area for depression which include lag in onset of effect, tolerance to therapy, treatment resistant depression and delay in achieving remission. The current review tries to highlight the various options for treatment of depression for effective treatment of depression.

Keywords: Major depressive disorder, quality of life, ketamine, opioid receptors, anhedonia

International Journal of Human and Health Sciences Vol. 10 No. 04 October'26

DOI:https://doi.org/10.31344/ijhhs.v10i4.988

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most common pervasive mental health disorders that contributes significantly to the global burden of diseases.[1,2] MDD is characterized anhedonia along with physical changes such as weight loss, tiredness and loss of appetite as well as feeling of guilt with cognitive challenges, sleep abnormalities and lack of drive.[3,4] As per the estimates of World Health Organization (WHO), it is the second-leading cause of disability worldwide across diverse demographics affecting 322 million people.[2,5-7] In the United States alone the lifetime prevalence of MDD is as high as 16.9%.[8,9] Approximately 25 million people approximately are suffering from MDD in Europe, which accounts for about 3.5% of the total population.[10] The estimated yearly prevalence of MDD in Spain is approximately 4% and is one of the most diagnosed psychiatric disorders in general population.[10-12] It is associated with high

1. Department of Physiology, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University (TMU), Moradabad, Uttar Pradesh-244001, India.
2. Intern Doctor, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University (TMU), Moradabad, Uttar Pradesh-244001, India.
3. Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University (TMU), Moradabad, Uttar Pradesh-244001, India.

Correspondence to: Prof. Prithpal S. Matreja, Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University (TMU), Moradabad, Uttar Pradesh-244001, India. Email: drpsmatreja@yahoo.co.in

rate of suicidal behaviour and mortality and is projected to be the leading cause of disability by 2030.[13,14] It is one of the leading causes of people living with disability with a significant increase in rates during the last decade,[15,16] contributing to 7.5% of all years lived with disease.[6,7] As per WHO reports major depressive disorder is the leading cause of years lost due to disability (YLD) and ninth leading cause of functional disability-adjusted life years (DALYs) in 2012.[8] Major depressive disorder costs about £27.1 billion in United Kingdom and majorly being attributed to cost of lost productivity.[17] The occurrence of MDD has increased with certain correlation with social development,[18] with a greater number of patients being diagnosed at a younger age group and women being twice at risk as compared to men, likely due to development and increase life pressure.[19] MDD is also shown to have seasonal variation with higher incidence being reported in autumn and winter.[20] The diagnostic criteria for Major Depressive Disorder has been listed in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) and International Classification of Disease-10 (ICD-10); however, early detection and prevention is difficult mostly due to lack of characteristic symptoms and objective diagnosis.[3,21-23] A patient experiencing altered mood, impaired daily activities and habits, weight changes, disturbance in sleep, loss of energy and lack of interest in pleasurable things for a period of more than 2 weeks along with social and occupational imbalance is suffering from MDD.[24,25] The management of MDD mainly focuses on improving the quality of life of the patients suffering from this disorder.[26] While the diagnosis of major depressive disorder is complicated by comorbidity and heterogeneity, there are several treatment options including both pharmacological and psychological treatments.[15,27]

Treatment with antidepressant drugs during the acute stage of the disease aims to help the patient achieve a remission state with gradual return to baseline level of functioning. Various modalities of treatment are given during the acute phase of the disease which include initiating pharmacotherapy, focussed psychotherapy, or electroconvulsive therapies (ECT).[13] The conventional treatment of Major Depressive Disorder has largely been based on monoamine hypothesis. This hypothesis has implicated an imbalance in the neurotransmitters for the pathophysiology of depression. The neurotransmitter majorly implicated are noradrenaline, serotonin, and dopamine.[28] This hypothesis has been the guiding principle for treatment of depression for the past several decades. The treatment of MDD with the various classes of drugs available ranging from tricyclic antidepressants (TCAs) to selective serotonin reuptake inhibitors (SSRIs) there is still persistence of treatment-resistant depression (TRD). A substantial proportion of patients suffering from MDD cannot achieve full remission despite dose titration with the currently available therapy.[1,29] The Sequenced Treatment to Relieve Depression (SART*D) study demonstrated that patients on first line antidepressant drugs achieved a remission rate of approximately 30%, the study further showed that the cumulative remission rate in patients receiving four step treatment was only 67%.[30-32] The patient who experiences of recurrence of major depressive disorder often tend to come with complaints of fatigue, low mood, loss of interest in life, delayed thinking and fluctuation in mental state.[31] The present therapy undermines the complexity of the disorder and hence there is need for newer strategies to treat depression.[8] The current modalities of treatment of MDD have delayed onset of the therapeutic action posing a significant challenge in the treatment during the stage of acute illness. Apart from their slow response.[8] The antidepressants drugs are associated with frequent adverse effects which include gastrointestinal disturbances, sexual dysfunctions, and tolerance limited their long-term adherence.[25,32]

Prescription of drugs used for major depressive disorder has increase to more than fivefold in United States alone since the introduction of SSRIs. The percent of adults in the United States between 2015 and 2018 on medication for depression have increased more than five folds to 13.2% compared to time between 1988 and 1994.[33,34] Drugs for depressive disorders are amongst the most prescribed medications in adults between 20 to 59 years of age in the United States.[33,35]

Delivery of Psychotherapy has its own set of limitation and one of them is in form of delivery practices. The use of information technology can delve into the problem of delivery of psychotherapy in the form of internet-delivered psychological treatments. These treatments

have been found to work at par and sometimes as a replacement for face-to-face treatments.[36] Internet based psychotherapy – internet-delivered cognitive behavioural therapy (ICBT) has been in use for the past more than two decades and has yielded long-term effects as with cognitive behavioural therapy (CBT).[37,38]

As the clarity on pathophysiology further unfolds apart from the neurotransmission theory of depression, the role of disrupted signalling pathway and neuroplasticity also play their part in depression. In patients suffering from depression there has been role of reduced neurotropic factor expressions and altered functional connectivity of neurocircuitry,[39] which could be potential new therapeutic target in the treatment of depression. Studies have found that the current treatment with antidepressant drugs might exert their effect by increasing neural plasticity.[40,41] Long-term administration of fluoxetine can enhance synaptic plasticity and increase postsynaptic spine density.[8,41]

NEWER THERAPEUTIC APPROACH IN DEPRESSIVE DISORDERS

Ketamine and Esketamine: Ketamine when given in sub-anaesthetic doses leads to rapid effect and has thus challenged the role of monoaminergic hypothesis of pathophysiology of depression.[42] The focus now shifts on the glutamatergic dysfunction as one of the pathophysiology of depression. One of the primary excitatory neurotransmitters, glutamate has a role in synaptic plasticity as well as learning and memory. Synaptic plasticity has been implicated to have an important role in normal emotional functioning and cognition[43] through the N-methyl-D-aspartate (NMDA) and alpha amino-3-hydroxy-5-methyl-4-isoxzole propionic acid (AMPA) receptors.[1] The NMDA is a heteromeric ionotropic receptor with binding sites for both glutamate and glycine (NR2 and NR1 subunits respectively) and being kept in inhibitory control by magnesium ion – ketamine binds to NR2 subunit non-selectively as an antagonist.[24] Ketamine in sub-anaesthetic doses facilitates psychotherapeutic process and is involved in fear extinction, restructuring of traumatic memories and new memory formation.[44,45]

Any change wither in the expression of function of NMDA or AMPA receptor could potentially contribute to depressive symptoms.[1] Another factor implicated to be reason for depressive symptoms is decreased levels of neurotrophic factors like BDNF (Brain-derived Neurotrophic factor) and glutamate is linked to expression of neurotrophic factors supporting growth, survival, and function of neurons.[46] Glutamate causes modulation glutamatergic system via antagonism at NDMA receptor and activation at AMPA receptor thereby relieving depressive symptoms quickly.[47] Ketamine when used to treat depression is delivered over a period of 30-40 minutes with monitoring of blood pressure, heart rate and temperature monitoring through either the intravenous, intramuscular or intranasal route in a dose range of 0.5 mg/kg to 1 mg/kg along with conventional treatment.[1,48] Ketamine when given by the intravenous route reduces the suicidal ideation in patient with depression for up to five days after a single dose [6, 49]. In comparison to treatment with midazolam, ketamine had better glutamate receptor modulator with effects seen at 24 hours and lasting up to 14 days.[49-51]

Several studies have showed that treatment of patients with an intravenous infusion of ketamine have demonstrated effectiveness in improvement in symptoms, even in patients who are resistant to standard treatment.[1,52] Another study a meta-analysis of either use of ketamine/esketamine showed an improved rate of response, higher remissions and decrease in the severity of depressive symptoms as compared to placebo. The number of adverse events were like placebo.[53] Another systematic review demonstrated ketamine to have rapid onset of action in extremes of age groups (<18 years and >60 years).[54] Another meta-analysis of involving 1877 patients showed that racemic ketamine demonstrated greater overall response and remission rates with lower dropouts.[55] A double-blind withdrawal study on treatment resistant depressive (TRD) showed that continuous treatment of esketamine nasal spray along with conventional antidepressants was superior to placebo and delayed relapse in patients.[56] Intranasal esketamine has been approved by US-FDA in 2019 for patients with treatment resistant depression.[57] Common side effects of ketamine in the treatment of depression include dissociation, hallucinations, confusion, elevation of blood pressure and heart rate, nausea, vomiting, and dizziness.[1,6,58] Use of esketamine has its own set

of adverse effects with patients reporting with urinary pain, hyperhidrosis, suicidal ideation and dissociation limiting its clinical applications in treatment resistant depressive patients.[59-61] One of the major clinical limitations for the administration of ketamine to patients suffering from treatment resistant depression is the short duration of action and frequent administration by an interventionist.[24,62]

Nitrous Oxide: Like Ketamine, Nitrous oxide (N_2O) is also an NMDAR antagonist which has shown to restore synaptic plasticity and activate the neuronal nitric oxide synthase Nitrous oxide has shown to decrease the depressive like behaviour in mice has shown to have increase expression of BNDF with a high response rate in treatment resistant depressive patients though its adverse effect and inconvenient mode of administration limits its widespread use . Another NMDAR antagonist Memantine has shown effect with combination therapy specifically in elderly population. Many drugs acting on the NMDAR pathway have shown to be effective in antidepressant therapy namely Riluzole, Amantadine, Lanicemine and MK-801.[1,6,24]

Anti-inflammatory Drugs: Studies have also demonstrated that an imbalance in the immune system especially the response to inflammation could have a plausible role in depression. Patients with depressive symptoms have invariably had an increased levels of cytokines like interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C- reactive protein (CRP). The raised level of these cytokines could possibly disrupt the process of neuroregulation and trigger neuroinflammation.[63] As inflammation is presumed to play a role, study done on the use of anti-inflammatory drugs in major depressive disorder have shown to reduce symptoms better as compared to placebo. Further analysis has shown that anti-inflammatory drugs have produced a greater response rate as compared to placebo with a better remission rate, moreover sub-group analysis have shown to be effective as either monotherapy or adjuvant to other drugs. A wide variety of drugs have shown to be effective for their effects including NSAIDs (non-steroidal anti-inflammatory drugs), statins, minocycline's and omega-3 fatty acids.[64]

Neuropeptide Y: Neuropeptide Y has been seen to be reduced in patients with major depressive disorder and when neuropeptide Y was administered with other antidepressants demonstrated significant effect within 24 hours of administration, but the effect was not persistent.[6]

GABA Inhibitors: Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter acting via metabotropic and ionotropic receptors and an alteration in the GABAergic system could possibly cause an imbalance in excitation/ inhibition thereby leading to depression.[65-68] Pre-clinical studies have predicted that drugs acting on the metabotropic GABAergic receptors have antidepressant activity which includes muscimol, valproic acid diazepam, oxcarbazepine and carbamazepine. GABAergic system plays a role in the serotonergic system, glutamate changes and the excitatory-inhibitory balance of cortex contributing to antidepressant action of ketamine.[24] Metabotropic receptors seem to be involved in affective disorders with dysregulated GABAergic pathway leading to decrease in GABA synthesizing neurons in the orbitofrontal complex.[69] This decrease is also seen in patients suffering from postpartum depression and treatment resistant depression.[70,71] Brexanolone is an allosteric modulation at the $GABA_A$ receptor which have potential to be used as a therapeutic option for major depressive disorder. Brexanolone resembles allopregnanolone which tends to increase the GABA mediated signalling through positive allosteric modulation.[72] Brexanolone was approved by FDA for postpartum depression in March 2019, provided at healthcare facilities with intravenous administration monitoring and adherences to REMS.[73] A study has demonstrated that brexanolone when given in women with postpartum depression showed greater response, and higher remission rates as compared to placebo. On infusion of brexanolone the response commenced within 24 hours with a peak at 36 hours and was present for 7 days. The adverse effect profile and tolerance to brexanolone were like placebo.[74]

Opioids Receptors: The various opioid receptors the – delta (DOR), kappa (KOR), and mu (MOR) are responsible for regulation of reward process, mood and stress response which is mediated by GPCR. Buprenorphine a partial agonist-antagonist had been approved for the treatment of withdrawal symptoms due to opioid dependence and as an analgesic for moderate-to-severe pain.[75,76] Buprenorphine has been found effective in improving symptoms in treatment resistant depression with improved mood and reduced

suicidal behaviour and anxiety without any serious adverse effect.[77,78] Nalmefene another agonist-antagonist on opioid receptor tends to decrease hyperactivity in HPA axis and increases BNDF expression thereby preventing inflammation-induced depressive-like behaviors in rodents.[79] Tianeptine possess antidepressant action and is an opioid receptor agonist with minimal effect on sleep, memory or cognitive function.[80] Evidence suggests that there is reduced inflammatory markers in hippocampus and prefrontal cortex and decreased depressive-like behaviour in rodents.[81] Reports suggest that the efficacy of tianeptine is increased when used in combination with other drugs, combining with cannabinoids has shown reduced depressive-like behaviour in mice.[82] Targeting the opioid receptor as it plays a role in stress, mood, reward as well as cellular inflammations could play futuristic role in treatment, but the liability of abuse potential and tolerance remains the major challenge in its usage.[83-85]

Psychedelics: Psychedelics like lysergic acid diethylamide (LSD), 3,4-methylenedioxy-N-methylamphetamine (MDMA) and psilocybin are known to exert their effect through the serotonin receptors (5-HT_{2A}) and can have a potential role in treatment of depressive disorders. Psychedelics modulate the serotonin receptors which could possibly lead to varied neural connectivity pattern, greater neuroplasticity and change in default mode network (DMN) activity.[86] In a systematic review and meta-analysis, the use of psychedelics with psychological support showed a reduction in symptoms at variable times from as early as 1-day to 1-week to 3-5 weeks but there were several limitations in these studies which included poor study design, small sample size hence the generalizability is difficult to predict.[87] Though psychedelics are well-tolerated, there are always possibility of dependence potential, exacerbation of pre-existing mental disorders and acute psychological distress always are potential alarms hence there is need for rigorous screening protocol with supportive therapeutic setting.[88]

PPAR Agonist: Peroxisome Proliferator-Activated Receptors have their implications on glucose regulation, inflammation, energy homeostasis and metabolism of lipids. The three subtypes of PPAR – alpha, beta/ delta and gamma (α, β/δ, and γ) are decreased in depressive behaviors, could potentially be one of the targets for management of depression.[89] Further evidence suggest shows that there is reduced neurogenesis, behavioural changes and neuronal differentiation are seen in knockdown mice in the PPAR-γ in hippocampus.[90] Role of PPAR gains further importance as few antidepressant drugs like venlafaxine are activated for their action in depression.[91] Combination of simvastatin with PPAR-γ agonist – Pioglitazone/ Rosiglitazone has demonstrated anti-inflammatory effect with reduced levels of expression of TNF-α, IL-6, and IL-1β, and in astrocytic activation in hippocampus as well as improved behaviour in rat model of depression.[92]

Traditional Plants: Ayahuasca, a traditional plant medicine, is in use as a part of the indigenous cultures for centuries in Amazon rainforest contains alkaloid dimethyltryptamine (DMT) which possess hallucinogenic properties. DMT is a serotonin receptor agonist and possess sigma-1 receptor agonist activity which acts on the neurotransmission of dopamine.[93] Studies have shown that patients of major depressive disorder treated with ayahuasca showed significant antidepressant effect which increased from day 1 to day 7 as compared to placebo with vomiting being the most common adverse effect experienced by patients.[94]

Microbiota: The gut microbiota has the potential to influence mental health via the gut-brain axis with prebiotics and probiotics are helpful in alleviating the symptoms of depression.[95] Probiotics strains like Lactobacillus and Bifidobacterium when administered can alter the gut microbiome, impacting the mental health. Probiotics are believed to have neuroprotective effect and anti-inflammatory action with potential to alleviate symptoms of depression. Probiotics play a role in metabolism and synthesis of serotonin and GABA thereby having potential to impact mood.[95] The non-digestible fibre in prebiotics like lactulose and galactose derivatives tend to selectively stimulate growth of gut bacteria that increases microbial diversity leading to production of short chain fatty acids (SCFAs). SCFAs have a neuroinflammatory and mood modulatory role.[95] A study revealing the gut microbiota showed that patients with altered gut clostridial population was associated with depression and reduced Bacteroides was associated with anxiety.[96] Another study revealed that participants receiving probiotics (Bifidobacterium) had significant increase in BNDF along with lower stress scores and greater mental flexibility.[97]

CONCLUSION

As our understanding to the pathophysiology of depression has greatly increased so also have the newer modalities of treatment of depression which have shown significant evidence of improvement for patients suffering from depression. To conclude many treatment modalities have shown considerably proof of evidence for treatment of depression with drugs varying from ketamine and esketamine which act on the glutamate pathway. Ketamine in sub-anaesthetic doses facilitates psychotherapeutic process and leads to fear extinction, restructuring of traumatic memories and new memory formation. Treatment with an intravenous infusion of ketamine have demonstrated effectiveness in improvement in symptoms with major limitations being the administration of ketamine. Nitrous Oxide acting via NMDAR pathway increases expression of BNDF with a high response rate in treatment resistant depression. A wide variety of anti-inflammatory drugs have shown to be effective. Brexanolone, an allosteric modulator at the $GABA_A$ receptor which have potential to be used as a therapeutic option for major depressive disorder. PPAR Agonist could potentially be benefit for treatment of depression and so also is the role of gut microbiota. Though preliminary evidence suggests the benefits of most of these drugs but still long-term studies are required for more conclusive evidences.

Conflict of interest: None declared.

Funding source: Nil.

Ethical considerations: Not applicable.

Authors' contribution: All authors were equally involved in conceptualization, literature search, review, compilation and analysis as well as manuscript writing, editing and final submission.

REFERENCES

1. Jagtiani A. Novel treatments of depression: bridging the gap in current therapeutic approaches. Explor Neurosci. 2024;3:272-86.
2. World Health Organization (WHO). Depressive Disorder (depression). Geneva: WHO; 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/depression (Accessed February 24, 2026).
3. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther. 2024;9(1):30.
4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. 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):1789-858.
5. Nagy C, Maitra M, Tanti A, Suderman M, Théroux JF, Davoli MA, et al. Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons. Nat Neurosci. 2020;23(6):771-81.
6. Njenga C, Ramanuj PP, de Magalhães FJC, Pincus HA. New and emerging treatments for major depressive disorder. BMJ. 2024;386:e073823.
7. Moreno-Agostino D, Wu YT, Daskalopoulou C, Hasan MT, Huisman M, Prina M. Global trends in the prevalence and incidence of depression: a systematic review and meta-analysis. J Affect Disord. 2021;281:235-43.
8. Huang YJ, Lane HY, Lin CH. New Treatment Strategies of Depression: Based on Mechanisms Related to Neuroplasticity. Neural Plasticity 2017;1;4605971.
9. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119-38.
10. Pérez-Sola V, Roca M, Alonso J, Gabilondo A, Hernando T, Sicras-Mainar A, et al. Economic impact of treatment-resistant depression: a retrospective observational study. J Affect Disord. 2021;295:578-86.
11. Gabilondo A, Rojas-Farreras S, Vilagut G, Haro JM, Fernández A, Pinto-Meza A, et al. Epidemiology of major depressive episode in a southern European country: results from the ESEMeD-Spain project. J Affect Disord. 2010;120(1-3):76-85.
12. Vieta E, Alonso J, Pérez-Sola V, Roca M, Hernando

T, Sicras-Mainar A, et al. Epidemiology and costs of depressive disorder in Spain: the EPICO study. Eur Neuropsychopharmacol. 2021;50:93-103.

13. Karrouri R, Hammani Z, Benjelloun R, Otheman Y. Major depressive disorder: validated treatments and future challenges. World J Clin Cases 2021; 9(31): 9350-67.
14. Lépine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat. 2011;7(Suppl 1):3-7.
15. Andersson G. The latest developments with internet-based psychological treatments for depression. Expert Rev Neurother. 2024;24(2):171-6.
16. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. J Psychiatr Res. 2020;126:134-40.
17. McDaid D, Park AL, Davidson G, John A, Knifton L, McDaid S, et al. The economic case for investing in the prevention of mental health conditions in the UK. London: London School of Economics and Political Science and Mental Health Foundation, 2022.
18. Albert KM, Newhouse PA. Estrogen, Stress, and Depression: Cognitive and Biological Interactions. Annu Rev Clin Psychol. 2019;15:399-423.
19. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617-27.
20. Monteleone P, Maj M. The circadian basis of mood disorders: recent developments and treatment implications. Eur Neuropsychopharmacol. 2008;18(10):701-11.
21. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. JAMA Psychiatry. 2018;75(4):336-46.
22. Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G, et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat Commun. 201816;9(1):1470.
23. Kovacs M, Lopez-Duran N. Prodromal symptoms and atypical affectivity as predictors of major depression in juveniles: implications for prevention. J Child Psychol Psychiatry. 2010;51(4):472-96.
24. Elias E, Zhang AY, Manners MT. Novel Pharmacological Approaches to the Treatment of Depression. Life (Basel). 2022;12(2):196.
25. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 2015;23(1):1-21.
26. Ferenchick EK, Ramanuj P, Pincus HA. Depression in primary care: part 1-screening and diagnosis. BMJ. 2019;365:l794.
27. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, et al. Time for united action on depression: a Lancet-World Psychiatric Association Commission. Lancet. 2022;399(10328):957-1022.
28. Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry. 2000;61(Suppl 6):7-11.
29. Valenstein M. Keeping our eyes on STAR*D. Am J Psychiatry. 2006;163(9):1484-6.
30. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.
31. Monroe SM, Harkness KL. Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol Rev. 2005;112(2):417-45.
32. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369-88.
33. Kovich H, Kim W, Quaste AM. Pharmacologic Treatment of Depression. Am Fam Physician. 2023;107(2):173-81.
34. Brody DJ, Gu Q. Antidepressant Use Among Adults: United States, 2015-2018. NCHS Data Brief. 2020;(377):1-8.
35. Martin CB, Hales CM, Gu Q, Ogden CL. Prescription Drug Use in the United States, 2015-2016. NCHS Data Brief. 2019;(334):1-8.
36. Andersson G. Internet-delivered psychological treatments. Ann Rev Clin Psychol. 2016;12:157-79.
37. Andersson G, Topooco N, Havik O, Nordgreen T. Internet-supported versus face-to-face cognitive behavior therapy for depression. Expert Rev Neurother. 2016;16(1):55-60.
38. Andersson G, Rozental A, Shafran R, Carlbring P. Long-term effects of internet-supported cognitive behaviour therapy. Expert Rev Neurother. 2018;18(1):21-8.
39. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med. 2016;22(3):238-49.
40. Santarelli L, Saxe M, Gross C, Surget A, Battaglia

F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003;301(5634):805-9.

41. Ampuero E, Rubio FJ, Falcon R, Sandoval M, Diaz-Veliz G, Gonzalez RE, et al. Chronic fluoxetine treatment induces structural plasticity and selective changes in glutamate receptor subunits in the rat cerebral cortex. Neuroscience 2010;169(1):98-108.
42. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-4.
43. Pal MM. Glutamate: the master neurotransmitter and its implications in chronic stress and mood disorders. Front Hum Neurosci. 2021;15:722323.
44. Collo G, Merlo Pich E. Ketamine enhances structural plasticity in human dopaminergic neurons: possible relevance for treatment-resistant depression. Neural Regen Res. 2018;13(4):645-6.
45. Drozdz SJ, Goel A, McGarr MW, Katz J, Ritvo P, Mattina GF, et al. Ketamine Assisted Psychotherapy: A Systematic Narrative Review of the Literature. J Pain Res. 2022;15:1691-1706.
46. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci. 2019;13:363.
47. Jagtiani A, Khurana H, Malhotra N. Comparison of efficacy of ketamine versus thiopentone-assisted modified electroconvulsive therapy in major depression. Indian J Psychiatry. 2019;61(3):258-64.
48. Andrade C. Ketamine for Depression, 4: In What Dose, at What Rate, by What Route, for How Long, and at What Frequency? J Clin Psychiatry. 2017;78(7):e852-7.
49. Su TP, Li CT, Lin WC, Wu HJ, Tsai SJ, Bai YM, et al. A Randomized, Double-Blind, Midazolam-Controlled Trial of Low-Dose Ketamine Infusion in Patients with Treatment-Resistant Depression and Prominent Suicidal Ideation. Int J Neuropsychopharmacol. 2023;26(5):331-9.
50. Dean RL, Hurducas C, Hawton K, Spyridi S, Cowen PJ, Hollingsworth S, et al. Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. Cochrane Database Syst Rev. 2021;9(9):CD011612.
51. Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med. 2015;45(16):3571-80.
52. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-64.
53. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Expert Opin Drug Saf. 2022;21(6):853-66.
54. Di Vincenzo JD, Siegel A, Lipsitz O, Ho R, Teopiz KM, Ng J, et al. The effectiveness, safety and tolerability of ketamine for depression in adolescents and older adults: a systematic review. J Psychiatr Res. 2021;137:232-41.
55. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542-55.
56. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients with Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019;76(9):893-903.
57. Kim J, Farchione T, Potter A, Chen Q, Temple R. Esketamine for treatment-resistant depression – first FDA-approved antidepressant in a new class. N Engl J Med. 2019;381(1):1-4.
58. Acevedo-Diaz EE, Cavanaugh GW, Greenstein D, Kraus C, Kadriu B, Zarate CA, et al. Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. J Affect Disord. 2020;263:568-75.
59. Turner EH. Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. Lancet Psychiatry. 2019;6(12):977-9.
60. Zimmermann KS, Richardson R, Baker KD. Esketamine as a treatment for paediatric depression: questions of safety and efficacy. Lancet Psychiatry. 2020;7(10):827-9.
61. Kaur U, Pathak BK, Singh A, Chakrabarti SS. Esketamine: a glimmer of hope in treatment-resistant depression. Eur Arch Psychiatry Clin Neurosci. 2021;271(3):417-29.
62. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H-U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21(3):169-84.
63. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013;246:199-

229.

64. Bai S, Guo W, Feng Y, Deng H, Li G, Nie H, et al. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2020;91(1):21-32.
65. Cutler AJ, Mattingly GW, Maletic V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. Transl Psychiatry. 2023;13(1):228.
66. Sieghart W. Structure and pharmacology of gamma-aminobutyric acid A receptor subtypes. Pharmacol Rev. 1995;47(2):181-234. PMID: 7568326.
67. Sieghart W, Fuchs K, Tretter V, Ebert V, Jechlinger M, Höger H, et al. Structure and subunit composition of GABA(A) receptors. Neurochem Int. 1999;34(5):379-85.
68. Olsen RW, Sapp DW. Neuroactive steroid modulation of GABAA receptors. Adv Biochem Psychopharmacol. 1995;48:57-74.
69. Sundman-Eriksson I, Allard P. [(3)H]Tiagabine binding to GABA transporter-1 (GAT-1) in suicidal depression. J Affect Disord. 2002;71(1-3):29-33.
70. Epperson CN, Gueorguieva R, Czarkowski KA, Stiklus S, Sellers E, Krystal JH, et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacology (Berl). 2006;186(3):425-33.
71. Kosel M, Rudolph U, Wielepp P, Luginbühl M, Schmitt W, Fisch HU, et al. Diminished GABA(A) receptor-binding capacity and a DNA base substitution in a patient with treatment-resistant depression and anxiety. Neuropsychopharmacology. 2004;29(2):347-50.
72. Edinoff AN, Odisho AS, Lewis K, Kaskas A, Hunt G, Cornett EM, et al. Brexanolone, a $GABA_A$ modulator, in the treatment of postpartum depression in adults: a comprehensive review. Front Psychiatry. 2021;12:699740.
73. Patatanian E, Nguyen DR. Brexanolone: a novel drug for the treatment of postpartum depression. J Pharm Pract. 2022;35(3):431-6.
74. Zheng W, Cai DB, Zheng W, Sim K, Ungvari GS, Peng XJ, et al. Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. Psychiatry Res. 2019;279:83-89.
75. Davis MP, Pasternak G, Behm B. Treating chronic pain: an overview of clinical studies centered on the buprenorphine option. Drugs. 2018;78(12):1211-28.
76. Shulman M, Wai JM, Nunes EV. Buprenorphine treatment for opioid use disorder: an overview. CNS Drugs. 2019;33(6):567-80.
77. Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov J, et al. Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial. Am J Psychiatry. 2016;173(5):491-8.
78. Bodkin JA, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol. 1995;15(1):49-57.
79. Callaghan CK, Rouine J, Dean RL, Knapp BI, Bidlack JM, Deaver DR, et al. Antidepressant-like effects of 3-carboxamido seco-nalmefene (3CS-nalmefene), a novel opioid receptor modulator, in a rat IFN-α-induced depression model. Brain Behav Immun. 2018;67:152-62.
80. Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine: a review of its use in depressive disorders. CNS Drugs. 2001;15(3):231-59.
81. Trojan E, Chamera K, Bryniarska N, Kotarska K, Leśkiewicz M, Regulska M, et al. Role of Chronic Administration of Antidepressant Drugs in the Prenatal Stress-Evoked Inflammatory Response in the Brain of Adult Offspring Rats: Involvement of the NLRP3 Inflammasome-Related Pathway. Mol Neurobiol. 2019;56(8):5365-80.
82. Poleszak E, Wośko S, Sławińska K, Wyska E, Szopa A, Świąder K, et al. Influence of the CB_1 and CB_2 cannabinoid receptor ligands on the activity of atypical antidepressant drugs in the behavioural tests in mice. Pharmacol Biochem Behav. 2020;188:172833.
83. Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. Trends Neurosci. 2013;36(3):195-206.
84. Van't Veer A, Carlezon WA Jr. Role of kappa-opioid receptors in stress and anxiety-related behavior. Psychopharmacology (Berl). 2013;229(3):435-52.
85. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. Br J Pharmacol. 2011;164(4):1322-34.
86. Gattuso JJ, Perkins D, Ruffell S, Lawrence AJ, Hoyer D, Jacobson LH, et al. Default Mode Network Modulation by Psychedelics: A Systematic Review. Int J Neuropsychopharmacol. 2023;26(3):155-88.
87. Ko K, Kopra EI, Cleare AJ, Rucker JJ. Psychedelic therapy for depressive symptoms: a systematic review and meta-analysis. J Affect Disord. 2023;322:194-204.
88. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al. Psychedelics and Psychedelic-Assisted Psychotherapy. Am J Psychiatry. 2020;177(5):391-410.

89. Mirza AZ, Althagafi II, Shamshad H. Role of PPAR receptor in different diseases and their ligands: physiological importance and clinical implications. Eur J Med Chem. 2019;166:502-13.

90. Chen F, Yu X, Meng G, Mei Z, Du Y, Sun H, et al. Hippocampal Genetic Knockdown of PPARδ Causes Depression-Like Behaviors and Neurogenesis Suppression. Int J Neuropsychopharmacol. 2019;22(6):372-82.

91. Chen C, Shen JH, Xu H, Chen P, Chen F, Guan YX, et al. Hippocampal PPARα is involved in the antidepressant-like effects of venlafaxine in mice. Brain Res Bull. 2019;153:171-80.

92. Lam YY, Tsai SF, Chen PC, Kuo YM, Chen YW. Pioglitazone rescues high-fat diet-induced depression-like phenotypes and hippocampal astrocytic deficits in mice. Biomed Pharmacother. 2021;140:111734.

93. Hamill J, Hallak J, Dursun SM, Baker G. Ayahuasca: Psychological and Physiologic Effects, Pharmacology and Potential Uses in Addiction and Mental Illness. Curr Neuropharmacol. 2019;17(2):108-28.

94. Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med. 2019;49(4):655-63.

95. Saravanan D, Khatoon B S, Winner G J Sr. Unraveling the interplay: exploring the links between gut microbiota, obesity, and psychological outcomes. Cureus. 2023;15(11):e49271.

96. Mason BL, Li Q, Minhajuddin A, Czysz AH, Coughlin LA, Hussain SK, et.al. Reduced anti-inflammatory gut microbiota are associated with depression and anhedonia. J Affect Disord. 2020;266:394-401.

97. Kim CS, Cha L, Sim M, Jung S, Chun WY, Baik HW, et al. Probiotic Supplementation Improves Cognitive Function and Mood with Changes in Gut Microbiota in Community-Dwelling Older Adults: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. J Gerontol A Biol Sci Med Sci. 2021;76(1):32-40.