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Review

# The Role of Testosterone and Estrogen in Depression and Inflammation

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**ABSTRACT**

Depression, a prevalent global disorder, significantly diminishes quality of life and elevates mortality rates. Its multifactorial etiology encompasses hormonal dysregulation and inflammation. While diverse treatment modalities exist, hormonal therapy represents one such option. Notably, both testosterone and estrogen exhibit anti-inflammatory and neuroactive properties, crucial for sexual maturation, reproduction, cognition, mood regulation, and optimal brain function. Moreover, clinical conditions characterized by reduced levels of sex hormones, including menopause and hypogonadism, are frequently comorbid with depression. This review elucidates the roles of estrogen and testosterone, their respective receptors, the involvement of inflammation, their intricate relationships with depressive pathology, and available therapeutic interventions.

**Keywords:** Brain receptors, depression, estrogen, hypogonadism, inflammation, testosterone.

Depression is a widespread psychiatric disorder affecting hundreds of millions of people worldwide.[1] The condition exhibits a disproportionate effect on men and women, with adult women displaying approximately twice the prevalence rate observed in men. Notably, gender differences in depression are absent during childhood; however, this disparity emerges during puberty, a developmental stage characterized by an increase in the prevalence of both depressive symptoms and clinical depression.[2] Adolescents experiencing depression are at elevated risk for self-harm and suicidal behaviors. Furthermore, the high incidence of depression during adolescence has been linked to diminished neural reward processing.[3] Depression is also common among older adults, who face hardships such as functional decline, reduced quality of life, and increased deaths. These findings highlight the significant burden of depression among different age groups and its impact on global health.[4]

Various kinds of processes and factors involving neurotransmitter deficiency, neurogenesis, inflammation, genetics, and hormonal factors can lead to depression. Reduced serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and dopamine (DA) cause impairment in cognitive functions, depression, self-harm, and anhedonia.[5] With aging, the risk for physical and psychological disorders increases. Also, hormone levels such as testosterone, dehydroepiandrosterone, estrogen, and progesterone are reduced.[6] Declining steroid hormones such as estrogen and testosterone regulate physical and psychological factors, including depression.[7] Carrier et al.[8] observed that estrogen and testosterone therapy show beneficial effects on depression and anxiety in rodents after gonadectomy. Depression can be treated with medications and psychological therapy. When these two ways of treatment are applied together, it's very effective. Some studies state that psychological therapy is more beneficial in the long run since relapse is frequently seen in remitted patients who stop using their drugs.[9]

Generally, antidepressants are preferred to treat depressive patients; however, sexual hormone treatments might be a substitute or complementary treatment option.[10]

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## TESTOSTERONE

Testosterone is a neuroactive steroid hormone that affects neurobehavioral, somatic, and metabolic activities such as mood, appetite, libido, sexual drive, secondary male characteristics, and the central nervous system (CNS).[11] It's been reported that some depressive patients have lower testosterone levels compared to non-depressed people.

In 1889, Dr. Brown-Séquard withdrew testosterone from animal testicles and injected it into himself. He observed that his mood improved. This study raised questions about testosterone and its effect on mood, and researchers started investigating.[1]

### Testosterone Treatment

Both testosterone levels below and above the normal range can cause depression.[12] For testosterone treatment, it's important to monitor testosterone levels, severity of depression, age, dose, and treatment periods. Testosterone administration therapy can help with mental, physical, and sexual problems (such as low libido and erectile dysfunction). Studies concluded that testosterone treatment can relieve depression in older men with low levels of testosterone because low testosterone levels are related to aging and depression.[13] It was revealed that chronic diseases, excess weight gain, alcohol consumption, and some medicines can reduce androgen levels.[14] In randomized control trials, testosterone administration showed relief in depressed men. The treatment was mostly effective in patients with low testosterone levels, older hypogonadal or human immunodeficiency virus-positive men, and depressive symptoms.[15]

### Hypogonadism

Hypogonadism can be caused by testicular failure, injury, tumors, infections, genetic disorders, radiation, chemotherapy, alcohol, smoking, hypothalamus, and hypophysis anomalies. There are two types of hypogonadism: primary (hypergonadotropic hypogonadism) and secondary (hypogonadotropic hypogonadism). Hypogonadism risk increases with aging. Hypogonadism causes reduced libido, sexual dysfunction, weight gain, diabetes, hypertension, depression, drowsiness, muscle atrophy, and weak bones.[16] It's advised for hypogonadal men and men with consistently low testosterone levels to get testosterone therapy. When patients with hypogonadism received testosterone therapy for more than three months, they experienced improvements in their life, mood, and sexual functions.[17] After considering the risks and benefits, testosterone therapy is advised for keeping the secondary characteristics of males and relieving the symptoms of hypogonadism and depression.

### Dorsal Raphe, Serotonin, and Testosterone

The dorsal raphe nucleus is located along the midline of the brainstem, extending through the midbrain, pons, and medulla. These nuclei mainly consist of serotonergic neurons that release 5-HT. The serotonin reuptake transporter facilitates its reuptake into the presynaptic neuron. Serotonin is primarily broken down by monoamine oxidase (MAO). A reduction in serotonergic input and neurogenesis to the limbic system has been considered for the development of depression.[18,19] A study that was done on animals with removed gonads showed improvement in depressive symptoms with testosterone administration because testosterone activates 5-HT release in the dorsal raphe nuclei. Testosterone-induced 5-HT increases hippocampal volume and protects the hippocampus. Thus showing antidepressant activity.[20]

### Testosterone and the Brain

Depression can develop due to various factors, such as alterations in the coding of the genes for monoamine regulators, corticotropin-releasing hormone (CRH), and brain-derived neurotrophic factor (BDNF).[21] Over-activation of the immune system in the CNS causes higher astrocyte and microglia numbers.[22] Some changes in the brain were detected in postmortem imaging of people who were depressed, such as shrinkage of the hippocampus and prefrontal cortex, and a decrease in gray matter volume and glial density.[23,24] So by treating and targeting these areas, depression can be treated since testosterone acts as an antidepressant with the downregulation of the immune system in the CNS. For instance, Garcia-Estrada et al.[25] saw that testosterone therapy remarkably reduced reactive astrocytes and microglia around a neural injury. They stated that the reduction of gliosis might be the neuroprotective effect of testosterone administration. The antidepressant effect of testosterone may be due to direct stimulation of neurogenesis in the dentate gyrus of the hippocampus.[26]

Another study showed that testosterone administration in an adult bird induced vascular endothelial growth factor production. This increases new capillary formations, which also increases BDNF production and neurogenesis.[27]

### Receptor Polymorphism and Depression

Genetic trait markers of androgen receptor (AR) functions, like the CRH-activating gene CAG repeating length, might be affecting T levels and depression in men. It's suggested that men with shorter CAG repeat length may experience a more noticeable link between testosterone levels and depression, likely due to greater AR sensitivity; however, men with longer CAG repeat length might not have the same degree of sensitivity to testosterone, which could explain the lack of association between testosterone levels and depression in this group.[28]

### Contraindications

Androgenic steroid hormones can create some side effects, including cardiovascular system, muscle, skeletal system, neuronal, mental, liver, and reproductive system diseases. Testosterone therapy is not recommended in patients who are planning to have children or patients with breast cancer, prostate cancer, high hematocrit levels, sleep apnea, urinary tract infections, heart diseases, or thrombophilia.[10,16]

### Conflicting Views

There are different opinions about depression treatment with testosterone, and present pieces of evidence show conflicting results. Seidman et al.[29] accept testosterone administration as a psychotherapy product. However, they state that efficacy is limited to a small group, especially hypogonadism. They suggested that the effectiveness of testosterone as an antidepressant is not backed up well enough. Still, they suggested that some situations, such as polymorphisms and prenatal androgenization, may make men more likely to experience the effects of testosterone.[30]

## ESTROGEN

Estrogen is a steroid hormone. Estrogen has roles in many physiological functions, such as the maturation of reproductive organs, the menstrual cycle, and maintaining bone density. There are different types of estrogens. Estrone (E1), estradiol (E2; 17β-estradiol), estriol (E3), and estetrol (E4). Estradiol is the predominant estrogen. Estrogen is synthesized in the ovaries and can also be synthesized from other organs such as the heart, liver, adipose tissue, and brain.[31] Estrogen also affects neurotransmitters in the brain: DA, 5-HT, and glutamate. It highly affects cognition and mood.[32]

The relationship between estrogen and dopaminergic systems is highly involved in various psychiatric and neurodegenerative disorders, as well as memory and reward processing.

### Estrogen Receptors and Brain

There are special regions in the brain for estrogen synthesis. This indicates that estrogen has essential functions in the brain. Estrogen is synthesized from the hippocampus, cerebellum, hypothalamus, amygdala, and cortex of the brain by neurons and astrocytes.[33] In certain psychiatric disorders, estrogen signaling pathways are disturbed. Estrogen administration has therapeutic effects on these disorders.[34]

Estrogen can exert different responses when it binds to different receptors. Major estrogen receptors are estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled estrogen receptor (GPER).[35] Estrogen influx to the cell membrane can create a direct effect. Estrogen receptors inside the nucleus bind to the estrogen-responsive element (ERE) of ERα and ERβ directly. Or estrogen can indirectly produce an effect by an intracellular cascade. Hence, estrogen signaling can be genomic (directly binding to ERE) and nongenomic (intracellular signaling cascade activation). Estrogen can act as a neurotransmitter through nongenomic and fast effects. This way, it doesn't require gene alteration.[36] Estrogen receptor α and ERβ receptors are abundant in the brain. They are located in the prefrontal and temporal cortex. Receptors show different predominant distributions. Estrogen receptor α is predominantly expressed in the amygdala and hypothalamus, whereas ERβ is predominantly expressed in the somatosensory cortex, hippocampus, thalamus, and cerebellum. Brain scans showed that those regions are often involved in psychiatric disorders. Both estrogen receptors are found in the basal ganglia and cortico-striato-thalamo-cortical circuit of the brain, where DA-producing neurons are also located.

Studies have shown sex differences in the expression of these receptors, with men displaying a higher density of nuclear ERβ receptors than women.[37] Usually, Erα is responsible for the reproductive system and also affects some hypothalamic regions that regulate temperature and metabolism. Estrogen receptor β controls nonreproductive functions such as depression, locomotion, emotions, and cognitive behavior. The receptor also highly impacts motor learning in the cerebellum by enhancing neuroplasticity and synapse formation in the cerebrum. Research suggests that the adjustment of estrogen through signaling pathways, receptors, and neurotransmitters in the human brain affects the

formation of mental disorders such as depression and cognitive functions.[38] Estrogen shows neuroleptic functions.[39] This resembles drugs that are used for psychiatric disorders. Therefore, estrogen has therapeutic potential.

### Estrogen, Dopamine, and Serotonin

Dopamine and 5-HT synthesis relieve depression. Estrogens regulate dopaminergic neurotransmissions and induce DA synthesis in the nucleus accumbens and striatum, decreasing degradation in the nucleus accumbens.[40] Estrogen also regulates 5-HT pathways by increasing the activity of tryptophan hydroxylase, inducing 5-HT production, and regulating 5-HT receptors that highly impact depression. Estrogen acts like an antidepressant by prolonging neural transmission and decreasing 5-HT uptake into cells. When 5-HT gets into presynaptic neurons, MAO inhibitors are degraded, and 5-HT metabolism is reduced.[41]

### Estrogen Replacement Therapy

Depression risk in women especially increases during postpartum, menopause, and menstruation due to highly diminished estrogen levels. Estrogen replacement therapy (ERT) can be preferred in depressive patients and those who have undergone ovariectomy. The therapy also helps with memory and cognition. In perimenopausal or postmenopausal women with depression, ERT showed improvements in depressive symptoms. Hormone replacement therapy (HRT) is composed of estrogen and progestin. It was revealed that early treatment with HRT and ERT together reduces cardiometabolic risks associated with menopause by improving lipid, insulin sensitivity, and inflammatory mediators.[42] Meanwhile, the same treatment, when administered 10 years after menopause, exerted cardiovascular risk-enhancing effects.

### Adverse Effects of Estrogen

Estrogen administration can cause breast hyperplasia, embolism, hot body temperature, and thrombosis. Due to its feminizing effects, estrogen therapy is not recommended for use in men.[43] Selective estrogen receptor modulators (SERMs) include risks such as uterine cancer, thrombosis, and embolism, and can cause death because of increased stroke risk in postmenopausal women.

### Inflammation and Depression

Recent clinical evidence shows that neuroinflammation, excessive cytokine production, diminished 5-HT levels, dysregulation of the hypothalamus-pituitary-adrenal axis, and alterations in neurogenesis in the hippocampus are associated with depression.[44] People with higher interferon 1, interleukins, interferon-alpha, and elevated tumor necrosis factor alpha (TNFα) levels in the hippocampus and striatum are also associated with anxiety and depression. Inflammation causes decreased neurogenesis in the hippocampus and induces glutamate release from microglia.[45]

### Inflammation and Testosterone

Blood-brain barrier (BBB) dysfunction is associated with neurological and inflammatory disorders. A study on mice showed that BBB permeability increased in testosterone-deficient male mice. Disorganized tight junctions and decreased tight junction proteins such as claudin-5 and ZO-1 were seen along with the activation of astrocytes and microglia and upregulation of inflammatory molecules such as interleukin (IL)-1 beta, cyclooxygenase 2, inducible nitric oxide, and TNF. Testosterone administration in the mice restored BBB permeability, tight junction integrity, and decreased inflammatory cytokines. This shows the neuroprotective and anti-inflammatory properties of testosterone.[46]

### Inflammation and Estrogen

Estrogen deficiency is closely associated with depression and anxiety. The pathogenesis of these effects mainly involves hippocampal neuroinflammation. A study showed the changes in female mice after ovariectomy. Ovariectomy resulted in elevated levels of IL-18 and IL-1β as inflammatory cytokines and upregulation of the NOD-like receptor protein 3 inflammasome components, along with activated caspase-1. Furthermore, ovariectomy also caused upregulation of toll-like receptor (TLR)-2 and TLR-4 and active nuclear factor kappa B and thus, initiated neuroinflammation. All the changes, such as inflammation, elevated cytokines in the hippocampus, and depressive behaviors, were relieved with the inflammasome inhibitor VX-765 treatment. Moreover, administration of E2 and ERβ agonists reversed the inflammatory and behavioral changes, while an ERα agonist had no significant effect. Ovariectomy also caused increased P2X7 receptor and P2X7R expression, which was reversed by E2 and the ERβ agonist.[47]

Estrogen protects neurons from glutamate-mediated neurotoxicity in cortical and hippocampal neurons and induces BDNF synthesis. This pathway protects the brain from inflammation

and stress. Essential for neuron survival, neurogenesis, and neuroplasticity, BDNF plays a key role in the development and progression of psychiatric disorders. Estrogen also modulates glucose metabolism and provides more energy to neurons.[48-52]

Selective estrogen receptor modulators bind to ERα, ERβ, and GPER. These compounds further initiate genomic and nongenomic signaling pathways. These pathways are critical for cognitive function and neuroprotection in the brain. Improving cognition and memory, enhancing neuroprotection, and exhibiting anti-inflammatory and antioxidant effects in the brain are among the key benefits of SERMs. They may also contribute to a reduced risk of breast cancer.

In conclusion, depression is a common psychiatric disorder that affects people globally. It can be caused by chemical, genetic, hormonal, neurological, and inflammatory factors. Testosterone and estrogen therapy are alternative treatment choices for depression. Testosterone therapy can be beneficial in males with depressive low testosterone levels and hypogonadal men. Estrogen hormone treatments, such as HRT and ERT, show potential for alleviating depression, mostly in perimenopausal women. Estrogen and testosterone possess anti-inflammatory and neuroprotective effects and have impacts on cytokines. These effects imply that sexual hormones and their effects on inflammation may also be a contributor to depression development or the opposite; these hormones, when they are at healthy levels, can protect the brain from depression and inflammation. Clinicians should carefully weigh the risks and benefits of hormone therapy, considering individual patient profiles to optimize its use in managing depression.

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## REFERENCES

1. Anderson DJ, Vazirnia P, Loehr C, Sternfels W, Hasoon J, Viswanath O, et al. Testosterone Replacement Therapy in the Treatment of Depression. Health Psychol Res. 2022 Nov 26;10:38956.
2. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. Psychol Bull. 2017;143:783-822.
3. O'Callaghan G, Stringaris A. Reward processing in adolescent depression across neuroimaging modalities: A review. Z Kinder Jugendpsychiatr Psychother. 2019;47:535-41.
4. Luppa M, Sikorski C, Luck T, Ehreke L, Konnopka A, Wiese B, et al. Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. J Affect Disord. 2012 Feb;136:212-21.
5. Jesulola E, Micalos P, Baguley IJ. Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - are we there yet? Behav Brain Res. 2018;341:79-90.
6. Walther A, Ehlert U. Steroid secretion and psychological well-being in men 40+. In: Rice T, Sher L, eds. Neurobiology of Men's Mental Health. Nova; 2015:287-322.
7. Walther A, Philipp M, Lozza N, Ehlert U. The rate of change in declining steroid hormones: A new parameter of healthy aging in men? Oncotarget. 2016;7:60844-57.
8. Carrier N, Saland SK, Duclot F, He H, Mercer R, Kabbaj M. The anxiolytic and antidepressant-like effects of testosterone and estrogen in gonadectomized male rats. Biol Psychiatry. 2015;78:259-69.
9. Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: A meta-analysis. Depress Anxiety. 2009;26:279-88.
10. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103:1715-44.
11. Peng R, Li Y. Associations between tenascin-C and testosterone deficiency in men with major depressive disorder: A cross-sectional retrospective study. J Inflamm Res. 2021;14:897-905.
12. Booth A, Johnson DR, Granger DA. Testosterone and men's depression: The role of social behavior. J Health Soc Behav. 1999;40:130-40.
13. Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: The Rancho Bernardo Study. J Clin Endocrinol Metab. 1999;84:573-7.
14. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002 Feb;87:589-98.
15. Walther A, Breidenstein J, Miller R. Association of testosterone treatment with alleviation of depressive symptoms in men: A systematic review and meta-analysis. JAMA Psychiatry. 2019;76:31-40.
16. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. Int J Clin Pract. 2010;64:682-96.
17. Elliott J, Kelly SE, Millar AC, Peterson J, Chen L, Johnston A, et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. BMJ

Open. 2017 Nov 16;7:e015284.
18. Erbaş O, Ergenoglu AM, Akdemir A, Yeniel AÖ, Taskiran D. Comparison of melatonin and oxytocin in the prevention of critical illness polyneuropathy in rats with experimentally induced sepsis. J Surg Res. 2013 Jul;183:313-20.
19. Hornung JP. The human raphe nuclei and the serotonergic system. J Chem Neuroanat. 2003 Dec;26:331-43.
20. Gould TD, Georgiou P, Brenner LA, et al. Animal models to improve our understanding and treatment of suicidal behavior. Transl Psychiatry. 2017;7:e1092.
21. Wuwongse S, Chang RCC, Law ACK. The putative neurodegenerative links between depression and Alzheimer's disease. Prog Neurobiol. 2010;91:362-75.
22. Sorgun O, Çakır A, Bora ES, Erdoğan MA, Uyanıkgil Y, Erbaş O. Anti-inflammatory and antioxidant properties of betaine protect against sepsis-induced acute lung injury: CT and histological evidence. Braz J Med Biol Res. 2023 Nov 13;56:e12906.
23. Czéh B, Lucassen PJ. What causes the hippocampal volume decrease in depression? Eur Arch Psychiatry Clin Neurosci. 2007;257:250-60.
24. Barreto G, Veiga S, Azcoitia I, Garcia-Segura LM, Garcia-Ovejero D. Testosterone decreases reactive astroglia and reactive microglia after brain injury in male rats: Role of its metabolites, estradiol and dihydrotestosterone. Eur J Neurosci. 2007;25:3039-46.
25. Garcia-Estrada J, Del Rio JA, Luquin S, Soriano E, Garcia-Segura LM. Gonadal hormones down-regulate reactive gliosis and astrocyte proliferation after a penetrating brain injury. Brain Res. 1993;628:271-8.
26. Spritzer MD, Roy EA. Testosterone and adult neurogenesis. Biomolecules. 2020;10:225.
27. Chen Z, Ye R, Goldman SA. Testosterone modulation of angiogenesis and neurogenesis in the adult songbird brain. Neuroscience. 2013;239:139-48.
28. Seidman SN, Araujo AB, Roose SP, McKinlay JB. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. Biol Psychiatry. 2001;50:371-6.
29. Seidman SN, Orr G, Raviv G, Levi R, Roose SP, Kravitz E, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. J Clin Psychopharmacol. 2009 Jun;29:216-21.
30. Pope HG, Amiaz R, Brennan BP, et al. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. J Clin Psychopharmacol. 2010;30:126-34.
31. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med. 2002;346:340-52.
32. Almey A, Milner TA, Brake WG. Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. Horm Behav. 2015;74:125-38.
33. Denley MCS, Gatford NJF, Sellers KJ, Srivastava DP. Estradiol and the development of the cerebral cortex: An unexpected role? Front Neurosci. 2018;12:245.
34. Crider A, Pillai A. Estrogen signaling as a therapeutic target in neurodevelopmental disorders. J Pharmacol Exp Ther. 2017;360:48-58.
35. Filardo EJ, Thomas P. Minireview: G protein-coupled estrogen receptor-1, GPER-1: Its mechanism of action and role in female reproductive cancer, renal and vascular physiology. Endocrinology. 2012;153:2953-62.
36. Balthazart J, Ball GF. Is brain estradiol a hormone or a neurotransmitter? Trends Neurosci. 2006;29:241-9.
37. Hwang WJ, Lee TY, Kim NS, Kwon JS. The role of estrogen receptors and their signaling across psychiatric disorders. Int J Mol Sci. 2020 Dec 31;22:373.
38. Bacqué-Cazenave J, Bharatiya R, Barrière G, Delbecque JP, Bouguiyoud N, Di Giovanni G, Cattaert D, De Deurwaerdère P. Serotonin in animal cognition and behavior. Int J Mol Sci. 2020;21:1649.
39. Kulkarni J, Butler S, Riecher-Rössler A. Estrogens and SERMs as adjunctive treatments for schizophrenia. Front Neuroendocrinol. 2019;53:100743.
40. Becker JB. Estrogen rapidly potentiates amphetamine-induced striatal dopamine release and rotational behavior during microdialysis. Neurosci Lett. 1990;118:169-71.
41. Holschneider DP, Kumazawa T, Chen K, Shih JC. Tissue-specific effects of estrogen on monoamine oxidase A and B in the rat. Life Sci. 1998;63:155-60.
42. Dwyer JB, Aftab A, Radhakrishnan R, et al. Hormonal treatments for major depressive disorder: State of the art. Am J Psychiatry. 2020;177:642.
43. Baik SH, Baye F, McDonald CJ. Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses. Menopause. 2024 May 1;31:363-71.
44. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C, Camus V. Neuroinflammation and depression: A review. Eur J Neurosci. 2021 Jan;53:151-71.
45. Lee CH, Giuliani F. The role of inflammation in depression and fatigue. Front Immunol. 2019;10:1696.
46. Atallah A, Mhaouty-Kodja S, Grange-Messent V. Chronic depletion of gonadal testosterone leads to blood-brain barrier dysfunction and inflammation in male mice. J Cereb Blood Flow Metab. 2017 Sep;37:3161-75.
47. Xu Y, Sheng H, Bao Q, Wang Y, Lu J, Ni X. NLRP3 inflammasome activation mediates estrogen deficiency-induced depression- and anxiety-like behavior and hippocampal inflammation in mice. Brain Behav Immun. 2016 Aug;56:175-86.
48. Kajta M, Lasoń W. Oestrogen effects on kainate-induced toxicity in primary cultures of rat cortical neurons. Acta Neurobiol Exp. 2000;60:365-9.
49. Erbaş O, Akseki HS, Eliküçük B, Taşkıran D. Antipsychotic-like effect of trimetazidine in a rodent model. ScientificWorldJournal. 2013 Oct 22;2013:686304.
50. Harb M, Jagusch J, Durairaja A, Endres T, Leßmann V, Fendt M. BDNF haploinsufficiency induces behavioral endophenotypes of schizophrenia in male mice that

are rescued by enriched environment. Transl Psychiatry. 2021 Apr 22;11:233.

51. Yildirim N, Simsek D, Kose S, Yildirim AGS, Guven C, Yigitturk G, et al. The protective effect of Gingko biloba in a rat model of ovarian ischemia/reperfusion injury: Improvement in histological and biochemical parameters. Adv Clin Exp Med. 2018 May;27:591-7.
52. Aykan K, Altuntaş İ, Erbaş O. DNA repair mechanisms: DNA repair defects and related diseases. D J Med Sci 2022;8:130-40.